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

Summary

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

Results information

Result version number	v2
This version publication date	04 June 2022
First version publication date	18 April 2022
Version creation reason	

Trial information

Trial identification

Sponsor protocol code	2693-CL-0302

Additional study identifiers

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

Notes:

Sponsors

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

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	23 April 2021
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	23 April 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

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

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator: -

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

Notes:

Population of trial subjects

Subjects enrolled per country

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

Notes:

Subjects enrolled per age group

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

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

Subject disposition

Recruitment

Recruitment details:

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

Pre-assignment

Screening details:

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

Period 1

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

Arms

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

Arm description:

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

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

Dosage and administration details:

Participants received fezolinetant matching placebo orally, QD.

Arm title	Double-blind Period: Fezolinetant 30 mg

Arm description:

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

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

Dosage and administration details:

Participants received fezolinetant 30 mg orally, QD.

Arm title	Double-blind Period: Fezolinetant 45 mg

Arm description:

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

Arm type	Experimental

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

Dosage and administration details:

Participants received fezolinetant 45 mg orally, QD.

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

Period 2

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

Arms

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

Arm description:

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

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

Dosage and administration details:

Participants received fezolinetant 30 mg orally, QD.

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

Arm description:

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

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

Dosage and administration details:

Participants received fezolinetant 45 mg orally, QD

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

Arm description:

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

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

Dosage and administration details:

Participants received fezolinetant 30 mg orally, QD.

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

Arm description:

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

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

Dosage and administration details:

Participants received fezolinetant 45 mg orally, QD

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

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

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

Baseline characteristics

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

Reporting group values	Double-blind Period: Placebo	Double-blind Period: Fezolinetant 30 mg	Double-blind Period: Fezolinetant 45 mg
Number of subjects	168	166	167
Age categorical Units:			
Age Continuous Units: Years			
arithmetic mean	54.6	53.9	54.3
standard deviation	± 4.6	± 4.9	± 5.4
Sex: Female, Male Units: Participants			
Female	168	166	167
Male	0	0	0
Race Units: Subjects			
American Indian or Alaska Native	0	0	1
Asian	1	0	0
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	31	35	33
White	135	131	132
More than one race	1	0	1
Unknown or Not Reported	0	0	0
Ethnicity Units: Subjects			
Hispanic or Latino	33	34	41
Not Hispanic or Latino	134	132	126
Unknown or Not Reported	1	0	0
Severity of Moderate and Severe VMS per 24 hours			
Severity of moderate to severe VMS per day was calculated as follows: [(number of moderate VMS × 2) + (number of severe VMS × 3)]/number of daily moderate/severe VMS. Higher score indicates greater severity. Baseline was the weighted average of moderate to severe VMS per 24 hours based on the non-missing values in the 10 days immediately prior to randomization			
Units: Score on a scale			

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

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

standard deviation	-		

End points

End points reporting groups

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

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

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

End point description:

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

End point type	Primary

End point timeframe:

Baseline and week 4

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

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

Statistical analyses

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

Notes:

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

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

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

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

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

Notes:

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

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

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

End point description:

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

End point type	Primary

End point timeframe:

Baseline and week 12

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

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Double-blind Period: Placebo v Double-blind Period: Fezolinetant 30 mg
Number of subjects included in analysis	273
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [4]
Method	MMRM
Parameter estimate	LSMean Difference
Point estimate	-1.86
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.94
upper limit	-0.78
Variability estimate	Standard error of the mean
Dispersion value	0.55

Notes:

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

Statistical analysis title	Statistical Analysis 3

Comparison groups	Double-blind Period: Placebo v Double-blind Period: Fezolinetant 30 mg
Number of subjects included in analysis	273
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.049
Method	Hochberg

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

Statistical analysis title	Statistical Analysis 2
Comparison groups	Double-blind Period: Placebo v Double-blind Period: Fezolinetant 45 mg
Number of subjects included in analysis	285
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [5]
Method	MMRM
Parameter estimate	LSMean difference
Point estimate	-2.53
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.6
upper limit	-1.46
Variability estimate	Standard error of the mean
Dispersion value	0.55

Notes:

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

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

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

End point description:

Severity of moderate to severe VMS per day at post baseline visit was calculated as follows: [(number of mild hot flashes per day x 1) + (number of moderate hot flashes per day x 2) + (number of severe hot flashes per day x 3)]/Total number of daily mild/moderate/severe hot flashes
Moderate VMS was defined as sensation of heat with sweating/dampness, but was able to continue activity. If at night, participant woke up because she was feeling hot and/or was sweating, but no action was necessary other than rearranging the bed sheets. Severe VMS was defined as sensation of intense

heat with sweating, caused disruption of activity. If at night, participant woke up hot and was sweating and needed to take action (e.g., remove layers of clothes, open the window, or get out of bed). Severity was zero for participants that had no mild or moderate or severe VMS. Higher scores indicates greater severity.

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

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

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

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Double-blind Period: Placebo v Double-blind Period: Fezolinetant 30 mg
Number of subjects included in analysis	306
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.021 [6]
Method	MMRM
Parameter estimate	LSMean difference
Point estimate	-0.15
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.27
upper limit	-0.02
Variability estimate	Standard error of the mean
Dispersion value	0.06

Notes:

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

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

Number of subjects included in analysis	306
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.049
Method	Hochberg

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

Statistical analysis title	Statistical Analysis 2
Comparison groups	Double-blind Period: Placebo v Double-blind Period: Fezolinetant 45 mg
Number of subjects included in analysis	306
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [7]
Method	MMRM
Parameter estimate	LSMean difference
Point estimate	-0.29
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.41
upper limit	-0.16
Variability estimate	Standard error of the mean
Dispersion value	0.06

Notes:

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

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

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

End point description:

Severity of moderate to severe VMS per day at post baseline visit was calculated as follows: [(number of mild hot flashes per day x 1) + (number of moderate hot flashes per day x 2) + (number of severe hot flashes per day x 3)]/Total number of daily mild/moderate/severe hot flashes
Moderate VMS was defined as sensation of heat with sweating/dampness, but was able to continue activity. If at night, participant woke up because she was feeling hot and/or was sweating, but no action was necessary other than rearranging the bed sheets. Severe VMS was defined as sensation of intense heat with sweating, caused disruption of activity. If at night, participant woke up hot and was sweating and needed to take action (e.g., remove layers of clothes, open the window, or get out of bed).

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

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

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

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

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Double-blind Period: Placebo v Double-blind Period: Fezolinetant 30 mg
Number of subjects included in analysis	273
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.049 [8]
Method	MMRM
Parameter estimate	LSMean difference
Point estimate	-0.16
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.33
upper limit	0
Variability estimate	Standard error of the mean
Dispersion value	0.08

Notes:

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

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

Number of subjects included in analysis	285
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [9]
Method	MMRM
Parameter estimate	LSMean difference
Point estimate	-0.29
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.45
upper limit	-0.13
Variability estimate	Standard error of the mean
Dispersion value	0.08

Notes:

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

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

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

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

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

End point description:

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

sleep) to 5 (disturbed sleep), and the range of possible summed raw scores is 8 to 40. Higher scores on the PROMIS SD SF 8b indicate more of the disturbed sleep.
Analysis Population: FAS population with available data at specified time point.

End point type	Secondary
End point timeframe:	
Baseline and week 12	

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

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Double-blind Period: Placebo v Double-blind Period: Fezolinetant 30 mg
Number of subjects included in analysis	282
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.381 [10]
Method	MMRM
Parameter estimate	LSMean difference
Point estimate	-0.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.1
upper limit	0.8
Variability estimate	Standard error of the mean
Dispersion value	0.7

Notes:

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

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

Number of subjects included in analysis	288
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.007 [11]
Method	MMRM
Parameter estimate	LSMean difference
Point estimate	-2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.5
upper limit	-0.6
Variability estimate	Standard error of the mean
Dispersion value	0.7

Notes:

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

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

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

End point description:

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

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

End point type	Secondary

End point timeframe:

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

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

Week 9 (n = 145, 140, 148)	-4.88 (± 0.38)	-6.54 (± 0.38)	-7.39 (± 0.38)	
Week 10 (n = 139, 138, 149)	-4.83 (± 0.38)	-6.74 (± 0.38)	-7.47 (± 0.38)	
Week 11 (n = 138, 142, 149)	-4.90 (± 0.38)	-6.76 (± 0.38)	-7.46 (± 0.37)	

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Statistical analysis description:	
Week 1	
Comparison groups	Double-blind Period: Placebo v Double-blind Period: Fezolinetant 30 mg
Number of subjects included in analysis	330
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.001 [12]
Method	MMRM
Parameter estimate	LSMean difference
Point estimate	-1.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.09
upper limit	-0.51
Variability estimate	Standard error of the mean
Dispersion value	0.4

Notes:

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

Statistical analysis title	Statistical Analysis 2
Statistical analysis description:	
Week 1	
Comparison groups	Double-blind Period: Placebo v Double-blind Period: Fezolinetant 45 mg
Number of subjects included in analysis	324
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [13]
Method	MMRM
Parameter estimate	LSMean difference
Point estimate	-1.71
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.51
upper limit	-0.91
Variability estimate	Standard error of the mean
Dispersion value	0.4

Notes:

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

Statistical analysis title	Statistical Analysis 3
Statistical analysis description:	
Week 2	
Comparison groups	Double-blind Period: Placebo v Double-blind Period: Fezolinetant 30 mg
Number of subjects included in analysis	330
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [14]
Method	MMRM
Parameter estimate	LSMean difference
Point estimate	-1.76
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.65
upper limit	-0.87
Variability estimate	Standard error of the mean
Dispersion value	0.45

Notes:

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

Statistical analysis title	Statistical Analysis 4
Statistical analysis description:	
Week 2	
Comparison groups	Double-blind Period: Placebo v Double-blind Period: Fezolinetant 45 mg
Number of subjects included in analysis	324
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [15]
Method	MMRM
Parameter estimate	LSMean difference
Point estimate	-1.97
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.86
upper limit	-1.08
Variability estimate	Standard error of the mean
Dispersion value	0.45

Notes:

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

Statistical analysis title	Statistical Analysis 5

Statistical analysis description:	
Week 3	
Comparison groups	Double-blind Period: Placebo v Double-blind Period: Fezolinetant 30 mg
Number of subjects included in analysis	330
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [16]
Method	MMRM
Parameter estimate	LSMean difference
Point estimate	-1.74
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.63
upper limit	-0.84
Variability estimate	Standard error of the mean
Dispersion value	0.46

Notes:

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

Statistical analysis title	Statistical Analysis 6
Statistical analysis description:	
Week 3	
Comparison groups	Double-blind Period: Placebo v Double-blind Period: Fezolinetant 45 mg
Number of subjects included in analysis	324
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [17]
Method	MMRM
Parameter estimate	LSMean difference
Point estimate	-2.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.29
upper limit	-1.5
Variability estimate	Standard error of the mean
Dispersion value	0.46

Notes:

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

Statistical analysis title	Statistical Analysis 7
Statistical analysis description:	
Week 5	
Comparison groups	Double-blind Period: Placebo v Double-blind Period: Fezolinetant 30 mg

Number of subjects included in analysis	330
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [18]
Method	MMRM
Parameter estimate	LSMean difference
Point estimate	-1.84
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.79
upper limit	-0.9
Variability estimate	Standard error of the mean
Dispersion value	0.48

Notes:

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

Statistical analysis title	Statistical Analysis 8

Statistical analysis description:

Week 5

Comparison groups	Double-blind Period: Placebo v Double-blind Period: Fezolinetant 45 mg
Number of subjects included in analysis	324
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [19]
Method	MMRM
Parameter estimate	LSMean difference
Point estimate	-2.66
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.61
upper limit	-1.72
Variability estimate	Standard error of the mean
Dispersion value	0.48

Notes:

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

Statistical analysis title	Statistical Analysis 9

Statistical analysis description:

Week 6

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

Number of subjects included in analysis	330
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [20]
Method	MMRM
Parameter estimate	LSMean difference
Point estimate	-1.78
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.71
upper limit	-0.85
Variability estimate	Standard error of the mean
Dispersion value	0.47

Notes:

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

Statistical analysis title	Statistical Analysis 11

Statistical analysis description:

Week 7

Comparison groups	Double-blind Period: Placebo v Double-blind Period: Fezolinetant 30 mg
Number of subjects included in analysis	330
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [21]
Method	MMRM
Parameter estimate	LSMean difference
Point estimate	-1.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.77
upper limit	-0.83
Variability estimate	Standard error of the mean
Dispersion value	0.49

Notes:

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

Statistical analysis title	Statistical Analysis 10

Statistical analysis description:

Week 6

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

Number of subjects included in analysis	324
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [22]
Method	MMRM
Parameter estimate	LSMean difference
Point estimate	-2.66
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.59
upper limit	-1.73
Variability estimate	Standard error of the mean
Dispersion value	0.47

Notes:

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

Statistical analysis title	Statistical Analysis 12

Statistical analysis description:

Week 7

Comparison groups	Double-blind Period: Placebo v Double-blind Period: Fezolinetant 45 mg
Number of subjects included in analysis	324
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [23]
Method	MMRM
Parameter estimate	LSMean difference
Point estimate	-2.34
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.3
upper limit	-1.37
Variability estimate	Standard error of the mean
Dispersion value	0.49

Notes:

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

Statistical analysis title	Statistical Analysis 13

Statistical analysis description:

Week 8

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

Number of subjects included in analysis	330
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [24]
Method	MMRM
Parameter estimate	LSMean difference
Point estimate	-1.76
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.79
upper limit	-0.74
Variability estimate	Standard error of the mean
Dispersion value	0.52

Notes:

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

Statistical analysis title	Statistical Analysis 14

Statistical analysis description:

Week 8

Comparison groups	Double-blind Period: Placebo v Double-blind Period: Fezolinetant 45 mg
Number of subjects included in analysis	324
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [25]
Method	MMRM
Parameter estimate	LSMean difference
Point estimate	-2.38
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.4
upper limit	-1.35
Variability estimate	Standard error of the mean
Dispersion value	0.52

Notes:

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

Statistical analysis title	Statistical Analysis 15

Statistical analysis description:

Week 9

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

Number of subjects included in analysis	330
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.002 [26]
Method	MMRM
Parameter estimate	LSMean difference
Point estimate	-1.65
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.71
upper limit	-0.59
Variability estimate	Standard error of the mean
Dispersion value	0.54

Notes:

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

Statistical analysis title	Statistical Analysis 16

Statistical analysis description:

Week 9

Comparison groups	Double-blind Period: Placebo v Double-blind Period: Fezolinetant 45 mg
Number of subjects included in analysis	324
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [27]
Method	MMRM
Parameter estimate	LSMean difference
Point estimate	-2.51
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.57
upper limit	-1.45
Variability estimate	Standard error of the mean
Dispersion value	0.54

Notes:

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

Statistical analysis title	Statistical Analysis 17

Statistical analysis description:

Week 10

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

Number of subjects included in analysis	330
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [28]
Method	MMRM
Parameter estimate	LSMean difference
Point estimate	-1.91
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.96
upper limit	-0.86
Variability estimate	Standard error of the mean
Dispersion value	0.54

Notes:

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

Statistical analysis title	Statistical Analysis 18

Statistical analysis description:

Week 10

Comparison groups	Double-blind Period: Placebo v Double-blind Period: Fezolinetant 45 mg
Number of subjects included in analysis	324
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [29]
Method	MMRM
Parameter estimate	LSMean difference
Point estimate	-2.65
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.69
upper limit	-1.6
Variability estimate	Standard error of the mean
Dispersion value	0.53

Notes:

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

Statistical analysis title	Statistical Analysis 19

Statistical analysis description:

Week 11

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

Number of subjects included in analysis	330
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [30]
Method	MMRM
Parameter estimate	LSMean difference
Point estimate	-1.86
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.91
upper limit	-0.81
Variability estimate	Standard error of the mean
Dispersion value	0.53

Notes:

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

Statistical analysis title	Statistical Analysis 20

Statistical analysis description:

Week 11

Comparison groups	Double-blind Period: Placebo v Double-blind Period: Fezolinetant 45 mg
Number of subjects included in analysis	324
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [31]
Method	MMRM
Parameter estimate	LSMean difference
Point estimate	-2.56
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.61
upper limit	-1.52
Variability estimate	Standard error of the mean
Dispersion value	0.53

Notes:

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

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

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

End point description:

Severity of moderate to severe VMS per day at post baseline visit was calculated as follows: [(number of mild hot flashes per day x 1) + (number of moderate hot flashes per day x 2) + (number of severe hot flashes per day x 3)]/Total number of daily mild/moderate/severe hot flashes
Moderate VMS was defined as sensation of heat with sweating/dampness, but was able to continue activity. If at night, participant woke up because she was feeling hot and/or was sweating, but no action was necessary other than rearranging the bed sheets. Severe VMS was defined as sensation of intense heat with sweating, caused disruption of activity. If at night, participant woke up hot and was sweating and needed to take action (e.g., remove layers of clothes, open the window, or get out of bed).

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

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

End point type	Secondary

End point timeframe:

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

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

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Week 1

Comparison groups	Double-blind Period: Placebo v Double-blind Period: Fezolinetant 30 mg
Number of subjects included in analysis	330
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.001 [32]
Method	MMRM
Parameter estimate	LSMean difference
Point estimate	-0.13
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.21
upper limit	-0.05
Variability estimate	Standard error of the mean
Dispersion value	0.04

Notes:

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

Statistical analysis title	Statistical Analysis 2
Statistical analysis description:	
Week 1	
Comparison groups	Double-blind Period: Placebo v Double-blind Period: Fezolinetant 45 mg
Number of subjects included in analysis	324
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [33]
Method	MMRM
Parameter estimate	LSMean difference
Point estimate	-0.16
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.24
upper limit	-0.08
Variability estimate	Standard error of the mean
Dispersion value	0.04

Notes:

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

Statistical analysis title	Statistical Analysis 3
Statistical analysis description:	
Week 2	
Comparison groups	Double-blind Period: Placebo v Double-blind Period: Fezolinetant 30 mg
Number of subjects included in analysis	330
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.001 [34]
Method	MMRM
Parameter estimate	LSMean difference
Point estimate	-0.17
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.28
upper limit	-0.07
Variability estimate	Standard error of the mean
Dispersion value	0.05

Notes:

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

Statistical analysis title	Statistical Analysis 4

Statistical analysis description:	
Week 2	
Comparison groups	Double-blind Period: Placebo v Double-blind Period: Fezolinetant 45 mg
Number of subjects included in analysis	324
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.001 [35]
Method	MMRM
Parameter estimate	LSMean difference
Point estimate	-0.18
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.28
upper limit	-0.07
Variability estimate	Standard error of the mean
Dispersion value	0.05

Notes:

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

Statistical analysis title	Statistical Analysis 5
Statistical analysis description:	
Week 3	
Comparison groups	Double-blind Period: Placebo v Double-blind Period: Fezolinetant 30 mg
Number of subjects included in analysis	330
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.067 [36]
Method	MMRM
Parameter estimate	LSMean difference
Point estimate	-0.11
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.23
upper limit	0.01
Variability estimate	Standard error of the mean
Dispersion value	0.06

Notes:

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

Statistical analysis title	Statistical Analysis 6
Statistical analysis description:	
Week 3	
Comparison groups	Double-blind Period: Fezolinetant 45 mg v Double-blind Period: Placebo

Number of subjects included in analysis	324
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [37]
Method	MMRM
Parameter estimate	LSMean difference
Point estimate	-0.23
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.35
upper limit	-0.11
Variability estimate	Standard error of the mean
Dispersion value	0.06

Notes:

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

Statistical analysis title	Statistical Analysis 7

Statistical analysis description:

Week 5

Comparison groups	Double-blind Period: Placebo v Double-blind Period: Fezolinetant 30 mg
Number of subjects included in analysis	330
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.02 [38]
Method	MMRM
Parameter estimate	LSMean difference
Point estimate	-0.16
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.3
upper limit	-0.03
Variability estimate	Standard error of the mean
Dispersion value	0.07

Notes:

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

Statistical analysis title	Statistical Analysis 8

Statistical analysis description:

Week 5

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

Number of subjects included in analysis	324
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [39]
Method	MMRM
Parameter estimate	LSMean difference
Point estimate	-0.29
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.43
upper limit	-0.16
Variability estimate	Standard error of the mean
Dispersion value	0.07

Notes:

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

Statistical analysis title	Statistical Analysis 9

Statistical analysis description:

Week 6

Comparison groups	Double-blind Period: Placebo v Double-blind Period: Fezolinetant 30 mg
Number of subjects included in analysis	330
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.012 [40]
Method	MMRM
Parameter estimate	LSMean difference
Point estimate	-0.18
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.32
upper limit	-0.04
Variability estimate	Standard error of the mean
Dispersion value	0.07

Notes:

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

Statistical analysis title	Statistical Analysis 10

Statistical analysis description:

Week 6

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

Number of subjects included in analysis	324
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [41]
Method	MMRM
Parameter estimate	LSMean difference
Point estimate	-0.28
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.42
upper limit	-0.14
Variability estimate	Standard error of the mean
Dispersion value	0.07

Notes:

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

Statistical analysis title	Statistical Analysis 11

Statistical analysis description:

Week 7

Comparison groups	Double-blind Period: Placebo v Double-blind Period: Fezolinetant 30 mg
Number of subjects included in analysis	330
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.03 [42]
Method	MMRM
Parameter estimate	LSMean difference
Point estimate	-0.16
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.31
upper limit	-0.02
Variability estimate	Standard error of the mean
Dispersion value	0.07

Notes:

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

Statistical analysis title	Statistical Analysis 12

Statistical analysis description:

Week 7

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

Number of subjects included in analysis	324
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [43]
Method	MMRM
Parameter estimate	LSMean difference
Point estimate	-0.28
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.43
upper limit	-0.14
Variability estimate	Standard error of the mean
Dispersion value	0.07

Notes:

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

Statistical analysis title	Statistical Analysis 13

Statistical analysis description:

Week 8

Comparison groups	Double-blind Period: Placebo v Double-blind Period: Fezolinetant 30 mg
Number of subjects included in analysis	330
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.095 [44]
Method	MMRM
Parameter estimate	LSMean difference
Point estimate	-0.13
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.28
upper limit	0.02
Variability estimate	Standard error of the mean
Dispersion value	0.08

Notes:

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

Statistical analysis title	Statistical Analysis 14

Statistical analysis description:

Week 8

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

Number of subjects included in analysis	324
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [45]
Method	MMRM
Parameter estimate	LSMean difference
Point estimate	-0.26
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.41
upper limit	-0.11
Variability estimate	Standard error of the mean
Dispersion value	0.08

Notes:

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

Statistical analysis title	Statistical Analysis 15

Statistical analysis description:

Week 9

Comparison groups	Double-blind Period: Placebo v Double-blind Period: Fezolinetant 30 mg
Number of subjects included in analysis	330
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.109 [46]
Method	MMRM
Parameter estimate	LSMean difference
Point estimate	-0.13
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.28
upper limit	0.03
Variability estimate	Standard error of the mean
Dispersion value	0.08

Notes:

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

Statistical analysis title	Statistical Analysis 16

Statistical analysis description:

Week 9

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

Number of subjects included in analysis	324
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [47]
Method	MMRM
Parameter estimate	LSMean difference
Point estimate	-0.28
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.43
upper limit	-0.12
Variability estimate	Standard error of the mean
Dispersion value	0.08

Notes:

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

Statistical analysis title	Statistical Analysis 17

Statistical analysis description:

Week 10

Comparison groups	Double-blind Period: Placebo v Double-blind Period: Fezolinetant 30 mg
Number of subjects included in analysis	330
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.02 [48]
Method	MMRM
Parameter estimate	LSMean difference
Point estimate	-0.19
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.35
upper limit	-0.03
Variability estimate	Standard error of the mean
Dispersion value	0.08

Notes:

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

Statistical analysis title	Statistical Analysis 18

Statistical analysis description:

Week 10

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

Number of subjects included in analysis	324
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [49]
Method	MMRM
Parameter estimate	LSMean difference
Point estimate	-0.31
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.47
upper limit	-0.15
Variability estimate	Standard error of the mean
Dispersion value	0.08

Notes:

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

Statistical analysis title	Statistical Analysis 19

Statistical analysis description:

Week 11

Comparison groups	Double-blind Period: Placebo v Double-blind Period: Fezolinetant 30 mg
Number of subjects included in analysis	330
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.012 [50]
Method	MMRM
Parameter estimate	LSMean diferrence
Point estimate	-0.21
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.37
upper limit	-0.05
Variability estimate	Standard error of the mean
Dispersion value	0.08

Notes:

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

Statistical analysis title	Statistical Analysis 20

Statistical analysis description:

Week 11

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

Number of subjects included in analysis	324
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [51]
Method	MMRM
Parameter estimate	LSMean difference
Point estimate	-0.31
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.47
upper limit	-0.15
Variability estimate	Standard error of the mean
Dispersion value	0.08

Notes:

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

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

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

End point description:

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

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

End point type	Secondary

End point timeframe:

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

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

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

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Statistical analysis description:	
Week 1	
Comparison groups	Double-blind Period: Placebo v Double-blind Period: Fezolinetant 30 mg
Number of subjects included in analysis	330
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [52]
Method	MMRM
Parameter estimate	LSMean difference
Point estimate	-12.16
Confidence interval	
level	95 %
sides	2-sided
lower limit	-18.9
upper limit	-5.43
Variability estimate	Standard error of the mean
Dispersion value	3.43

Notes:

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

Statistical analysis title	Statistical Analysis 3
Statistical analysis description:	
Week 2	
Comparison groups	Double-blind Period: Placebo v Double-blind Period: Fezolinetant 30 mg

Number of subjects included in analysis	330
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [53]
Method	MMRM
Parameter estimate	LSMean difference
Point estimate	-14.61
Confidence interval	
level	95 %
sides	2-sided
lower limit	-22.09
upper limit	-7.13
Variability estimate	Standard error of the mean
Dispersion value	3.81

Notes:

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

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

Week 1

Comparison groups	Double-blind Period: Placebo v Double-blind Period: Fezolinetant 45 mg
Number of subjects included in analysis	324
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [54]
Method	MMRM
Parameter estimate	LSMean difference
Point estimate	-15.68
Confidence interval	
level	95 %
sides	2-sided
lower limit	-22.44
upper limit	-8.91
Variability estimate	Standard error of the mean
Dispersion value	3.44

Notes:

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

Statistical analysis title	Statistical Analysis 5

Statistical analysis description:

Week 3

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

Number of subjects included in analysis	330
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [55]
Method	MMRM
Parameter estimate	LSMean difference
Point estimate	-15.51
Confidence interval	
level	95 %
sides	2-sided
lower limit	-23.16
upper limit	-7.86
Variability estimate	Standard error of the mean
Dispersion value	3.89

Notes:

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

Statistical analysis title	Statistical Analysis 4

Statistical analysis description:

Week 2

Comparison groups	Double-blind Period: Placebo v Double-blind Period: Fezolinetant 45 mg
Number of subjects included in analysis	324
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [56]
Method	MMRM
Parameter estimate	LSMean difference
Point estimate	-15.95
Confidence interval	
level	95 %
sides	2-sided
lower limit	-23.45
upper limit	-8.45
Variability estimate	Standard error of the mean
Dispersion value	3.82

Notes:

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

Statistical analysis title	Statistical Analysis 7

Statistical analysis description:

Week 4

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

Number of subjects included in analysis	330
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [57]
Method	MMRM
Parameter estimate	LSMean difference
Point estimate	-16.34
Confidence interval	
level	95 %
sides	2-sided
lower limit	-24.04
upper limit	-8.63
Variability estimate	Standard error of the mean
Dispersion value	3.92

Notes:

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

Statistical analysis title	Statistical Analysis 6

Statistical analysis description:

Week 3

Comparison groups	Double-blind Period: Placebo v Double-blind Period: Fezolinetant 45 mg
Number of subjects included in analysis	324
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [58]
Method	MMRM
Parameter estimate	LSMean difference
Point estimate	-20.25
Confidence interval	
level	95 %
sides	2-sided
lower limit	-27.91
upper limit	-12.59
Variability estimate	Standard error of the mean
Dispersion value	3.9

Notes:

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

Statistical analysis title	Statistical Analysis 8

Statistical analysis description:

Week 4

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

Number of subjects included in analysis	324
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [59]
Method	MMRM
Parameter estimate	LSMean difference
Point estimate	-21.65
Confidence interval	
level	95 %
sides	2-sided
lower limit	-29.36
upper limit	-13.94
Variability estimate	Standard error of the mean
Dispersion value	3.92

Notes:

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

Statistical analysis title	Statistical Analysis 9

Statistical analysis description:

Week 5

Comparison groups	Double-blind Period: Placebo v Double-blind Period: Fezolinetant 30 mg
Number of subjects included in analysis	330
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [60]
Method	MMRM
Parameter estimate	LSMean difference
Point estimate	-15.62
Confidence interval	
level	95 %
sides	2-sided
lower limit	-23.27
upper limit	-7.98
Variability estimate	Standard error of the mean
Dispersion value	3.89

Notes:

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

Statistical analysis title	Statistical Analysis 10

Statistical analysis description:

Week 5

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

Number of subjects included in analysis	324
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [61]
Method	MMRM
Parameter estimate	LSMean difference
Point estimate	-22.88
Confidence interval	
level	95 %
sides	2-sided
lower limit	-30.52
upper limit	-15.24
Variability estimate	Standard error of the mean
Dispersion value	3.89

Notes:

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

Statistical analysis title	Statistical Analysis 11

Statistical analysis description:

Week 6

Comparison groups	Double-blind Period: Placebo v Double-blind Period: Fezolinetant 30 mg
Number of subjects included in analysis	330
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [62]
Method	MMRM
Parameter estimate	LSMean difference
Point estimate	-14.78
Confidence interval	
level	95 %
sides	2-sided
lower limit	-22.38
upper limit	-7.19
Variability estimate	Standard error of the mean
Dispersion value	3.87

Notes:

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

Statistical analysis title	Statistical Analysis 12

Statistical analysis description:

Week 6

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

Number of subjects included in analysis	324
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [63]
Method	MMRM
Parameter estimate	LSMean difference
Point estimate	-22.66
Confidence interval	
level	95 %
sides	2-sided
lower limit	-30.25
upper limit	-15.07
Variability estimate	Standard error of the mean
Dispersion value	3.86

Notes:

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

Statistical analysis title	Statistical Analysis 13

Statistical analysis description:

Week 7

Comparison groups	Double-blind Period: Placebo v Double-blind Period: Fezolinetant 30 mg
Number of subjects included in analysis	330
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [64]
Method	MMRM
Parameter estimate	LSMean difference
Point estimate	-14.97
Confidence interval	
level	95 %
sides	2-sided
lower limit	-22.86
upper limit	-7.09
Variability estimate	Standard error of the mean
Dispersion value	4.01

Notes:

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

Statistical analysis title	Statistical Analysis 15

Statistical analysis description:

Week 8

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

Number of subjects included in analysis	330
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [65]
Method	MMRM
Parameter estimate	LSMean difference
Point estimate	-14.38
Confidence interval	
level	95 %
sides	2-sided
lower limit	-22.33
upper limit	-6.43
Variability estimate	Standard error of the mean
Dispersion value	4.05

Notes:

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

Statistical analysis title	Statistical Analysis 14

Statistical analysis description:

Week 7

Comparison groups	Double-blind Period: Placebo v Double-blind Period: Fezolinetant 45 mg
Number of subjects included in analysis	324
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [66]
Method	MMRM
Parameter estimate	LSMean difference
Point estimate	-21.47
Confidence interval	
level	95 %
sides	2-sided
lower limit	-29.34
upper limit	-13.6
Variability estimate	Standard error of the mean
Dispersion value	4.01

Notes:

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

Statistical analysis title	Statistical Analysis 16

Statistical analysis description:

Week 8

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

Number of subjects included in analysis	324
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [67]
Method	MMRM
Parameter estimate	LSMean difference
Point estimate	-20.57
Confidence interval	
level	95 %
sides	2-sided
lower limit	-28.5
upper limit	-12.65
Variability estimate	Standard error of the mean
Dispersion value	4.03

Notes:

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

Statistical analysis title	Statistical Analysis 17

Statistical analysis description:

Week 9

Comparison groups	Double-blind Period: Placebo v Double-blind Period: Fezolinetant 30 mg
Number of subjects included in analysis	330
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.003 [68]
Method	MMRM
Parameter estimate	LSMean difference
Point estimate	-12.14
Confidence interval	
level	95 %
sides	2-sided
lower limit	-20.14
upper limit	-4.14
Variability estimate	Standard error of the mean
Dispersion value	4.07

Notes:

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

Statistical analysis title	Statistical Analysis 19

Statistical analysis description:

Week 10

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

Number of subjects included in analysis	330
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [69]
Method	MMRM
Parameter estimate	LSMean difference
Point estimate	-14.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-22.25
upper limit	-6.54
Variability estimate	Standard error of the mean
Dispersion value	4

Notes:

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

Statistical analysis title	Statistical Analysis 18

Statistical analysis description:

Week 9

Comparison groups	Double-blind Period: Placebo v Double-blind Period: Fezolinetant 45 mg
Number of subjects included in analysis	324
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [70]
Method	MMRM
Parameter estimate	LSMean difference
Point estimate	-19.73
Confidence interval	
level	95 %
sides	2-sided
lower limit	-27.71
upper limit	-11.755
Variability estimate	Standard error of the mean
Dispersion value	4.06

Notes:

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

Statistical analysis title	Statistical Analysis 20

Statistical analysis description:

Week 10

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

Number of subjects included in analysis	324
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [71]
Method	MMRM
Parameter estimate	LSMean difference
Point estimate	-20.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-27.93
upper limit	-12.27
Variability estimate	Standard error of the mean
Dispersion value	3.98

Notes:

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

Statistical analysis title	Statistical Analysis 22

Statistical analysis description:

Week 11

Comparison groups	Double-blind Period: Placebo v Double-blind Period: Fezolinetant 45 mg
Number of subjects included in analysis	324
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [72]
Method	MMRM
Parameter estimate	LSMean difference
Point estimate	-20.15
Confidence interval	
level	95 %
sides	2-sided
lower limit	-28.13
upper limit	-12.18
Variability estimate	Standard error of the mean
Dispersion value	4.06

Notes:

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

Statistical analysis title	Statistical Analysis 21

Statistical analysis description:

Week 11

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

Number of subjects included in analysis	330
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [73]
Method	MMRM
Parameter estimate	LSMean difference
Point estimate	-14.96
Confidence interval	
level	95 %
sides	2-sided
lower limit	-22.96
upper limit	-6.96
Variability estimate	Standard error of the mean
Dispersion value	4.07

Notes:

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

Statistical analysis title	Statistical Analysis 23

Statistical analysis description:

Week 12

Comparison groups	Double-blind Period: Placebo v Double-blind Period: Fezolinetant 30 mg
Number of subjects included in analysis	330
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [74]
Method	MMRM
Parameter estimate	LSMean difference
Point estimate	-13.64
Confidence interval	
level	95 %
sides	2-sided
lower limit	-21.62
upper limit	-5.65
Variability estimate	Standard error of the mean
Dispersion value	4.07

Notes:

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

Statistical analysis title	Statistical Analysis 24

Statistical analysis description:

Week 12

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

Number of subjects included in analysis	324
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [75]
Method	MMRM
Parameter estimate	LSMean difference
Point estimate	-18.94
Confidence interval	
level	95 %
sides	2-sided
lower limit	-26.89
upper limit	-10.98
Variability estimate	Standard error of the mean
Dispersion value	4.05

Notes:

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

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

End point title	Number of Participants With Percent Reduction of >=50% in the Mean Frequency of Moderate and Severe VMS From Baseline to Each Study Week Up to Week 12

End point description:

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

End point type	Secondary

End point timeframe:

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

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

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

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

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Statistical analysis description:	
Week 1	
Comparison groups	Double-blind Period: Placebo v Double-blind Period: Fezolinetant 30 mg
Number of subjects included in analysis	333
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.02 [76]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.881
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.11
upper limit	3.233

Notes:

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

Statistical analysis title	Statistical Analysis 2
Statistical analysis description:	
Week 1	
Comparison groups	Double-blind Period: Placebo v Double-blind Period: Fezolinetant 45 mg
Number of subjects included in analysis	334
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [77]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	2.645
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.585
upper limit	4.498

Notes:

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

Statistical analysis title	Statistical Analysis 3
Statistical analysis description:	
Week 2	
Comparison groups	Double-blind Period: Placebo v Double-blind Period: Fezolinetant 30 mg
Number of subjects included in analysis	333
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [78]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	2.464
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.535
upper limit	4.001

Notes:

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

Statistical analysis title	Statistical Analysis 4
Statistical analysis description:	
Week 2	
Comparison groups	Double-blind Period: Placebo v Double-blind Period: Fezolinetant 45 mg
Number of subjects included in analysis	334
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [79]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	2.464
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.534
upper limit	4.004

Notes:

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

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

Number of subjects included in analysis	333
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [80]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	2.367
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.502
upper limit	3.762

Notes:

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

Statistical analysis title	Statistical Analysis 6

Statistical analysis description:

Week 3

Comparison groups	Double-blind Period: Placebo v Double-blind Period: Fezolinetant 45 mg
Number of subjects included in analysis	334
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [81]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	2.894
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.835
upper limit	4.609

Notes:

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

Statistical analysis title	Statistical Analysis 8

Statistical analysis description:

Week 4

Comparison groups	Double-blind Period: Placebo v Double-blind Period: Fezolinetant 45 mg
Number of subjects included in analysis	334
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [82]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	3.218

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

Notes:

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

Statistical analysis title	Statistical Analysis 7

Statistical analysis description:

Week 4

Comparison groups	Double-blind Period: Placebo v Double-blind Period: Fezolinetant 30 mg
Number of subjects included in analysis	333
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [83]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	2.902
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.829
upper limit	4.657

Notes:

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

Statistical analysis title	Statistical Analysis 10

Statistical analysis description:

Week 5

Comparison groups	Double-blind Period: Placebo v Double-blind Period: Fezolinetant 45 mg
Number of subjects included in analysis	334
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [84]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	3.074
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.957
upper limit	4.878

Notes:

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

Statistical analysis title	Statistical Analysis 9

Statistical analysis description:	
Week 5	
Comparison groups	Double-blind Period: Placebo v Double-blind Period: Fezolinetant 30 mg
Number of subjects included in analysis	333
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [85]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	2.153
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.375
upper limit	3.394

Notes:

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

Statistical analysis title	Statistical Analysis 11
Statistical analysis description:	
Week 6	
Comparison groups	Double-blind Period: Placebo v Double-blind Period: Fezolinetant 30 mg
Number of subjects included in analysis	333
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.002 [86]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	2.05
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.31
upper limit	3.228

Notes:

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

Statistical analysis title	Statistical Analysis 12
Statistical analysis description:	
Week 6	
Comparison groups	Double-blind Period: Placebo v Double-blind Period: Fezolinetant 45 mg
Number of subjects included in analysis	334
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [87]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	2.908

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

Notes:

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

Statistical analysis title	Statistical Analysis 13

Statistical analysis description:

Week 7

Comparison groups	Double-blind Period: Placebo v Double-blind Period: Fezolinetant 30 mg
Number of subjects included in analysis	333
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.001 [88]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	2.113
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.349
upper limit	3.332

Notes:

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

Statistical analysis title	Statistical Analysis 14

Statistical analysis description:

Week 7

Comparison groups	Double-blind Period: Placebo v Double-blind Period: Fezolinetant 45 mg
Number of subjects included in analysis	334
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [89]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	2.594
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.653
upper limit	4.104

Notes:

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

Statistical analysis title	Statistical Analysis 15

Statistical analysis description:	
Week 8	
Comparison groups	Double-blind Period: Placebo v Double-blind Period: Fezolinetant 30 mg
Number of subjects included in analysis	333
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.005 [90]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.891
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.21
upper limit	2.973

Notes:

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

Statistical analysis title	Statistical Analysis 16
Statistical analysis description:	
Week 8	
Comparison groups	Double-blind Period: Placebo v Double-blind Period: Fezolinetant 45 mg
Number of subjects included in analysis	334
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [91]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	3.314
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.108
upper limit	5.265

Notes:

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

Statistical analysis title	Statistical Analysis 17
Statistical analysis description:	
Week 9	
Comparison groups	Double-blind Period: Placebo v Double-blind Period: Fezolinetant 30 mg
Number of subjects included in analysis	333
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.027 [92]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.646

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

Notes:

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

Statistical analysis title	Statistical Analysis 18

Statistical analysis description:

Week 9

Comparison groups	Double-blind Period: Placebo v Double-blind Period: Fezolinetant 45 mg
Number of subjects included in analysis	334
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [93]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	2.347
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.507
upper limit	3.683

Notes:

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

Statistical analysis title	Statistical Analysis 19

Statistical analysis description:

Week 10

Comparison groups	Double-blind Period: Placebo v Double-blind Period: Fezolinetant 30 mg
Number of subjects included in analysis	333
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.01 [94]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.792
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.153
upper limit	2.799

Notes:

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

Statistical analysis title	Statistical Analysis 20

Statistical analysis description:	
Week 10	
Comparison groups	Double-blind Period: Placebo v Double-blind Period: Fezolinetant 45 mg
Number of subjects included in analysis	334
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [95]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	2.819
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.805
upper limit	4.441

Notes:

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

Statistical analysis title	Statistical Analysis 21
Statistical analysis description:	
Week 11	
Comparison groups	Double-blind Period: Placebo v Double-blind Period: Fezolinetant 30 mg
Number of subjects included in analysis	333
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [96]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	2.357
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.513
upper limit	3.699

Notes:

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

Statistical analysis title	Statistical Analysis 22
Statistical analysis description:	
Week 11	
Comparison groups	Double-blind Period: Placebo v Double-blind Period: Fezolinetant 45 mg
Number of subjects included in analysis	334
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [97]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	3.131

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

Notes:

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

Statistical analysis title	Statistical Analysis 23

Statistical analysis description:

Week 12

Comparison groups	Double-blind Period: Placebo v Double-blind Period: Fezolinetant 30 mg
Number of subjects included in analysis	333
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.152 [98]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.373
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.891
upper limit	2.122

Notes:

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

Statistical analysis title	Statistical Analysis 24

Statistical analysis description:

Week 12

Comparison groups	Double-blind Period: Placebo v Double-blind Period: Fezolinetant 45 mg
Number of subjects included in analysis	334
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [99]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	2.09
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.351
upper limit	3.252

Notes:

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

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

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

End point description:

The frequency of moderate to severe VMS was the number of moderate to severe VMS per 24 hours. A daily frequency per week was derived by taking the mean of the data over 7 days. Moderate VMS was defined as sensation of heat with sweating/dampness, but was able to continue activity. If at night, participant woke up because she was feeling hot and/or was sweating, but no action was necessary other than rearranging the bed sheets. Severe VMS was defined as sensation of intense heat with sweating, caused disruption of activity. If at night, participant woke up hot and was sweating and needed to take action (e.g., remove layers of clothes, open the window, or get out of bed). Baseline was the average number of moderate to severe VMS per 24 hours based on the non-missing values in the 10 days immediately prior to randomization. Participant has 100% reduction from baseline to each post baseline week for the frequency of moderate to severe VMS.

End point type	Secondary

End point timeframe:

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

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

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

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Week 1

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

Number of subjects included in analysis	333
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.951 [100]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.915
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.036
upper limit	23.464

Notes:

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

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

Week 1

Comparison groups	Double-blind Period: Placebo v Double-blind Period: Fezolinetant 45 mg
Number of subjects included in analysis	334
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.362 [101]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	2.889
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.364
upper limit	58.864

Notes:

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

Statistical analysis title	Statistical Analysis 3

Statistical analysis description:

Week 2

Comparison groups	Double-blind Period: Placebo v Double-blind Period: Fezolinetant 30 mg
Number of subjects included in analysis	333
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.138 [102]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	2.775

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

Notes:

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

Statistical analysis title	Statistical Analysis 4

Statistical analysis description:

Week 2

Comparison groups	Double-blind Period: Placebo v Double-blind Period: Fezolinetant 45 mg
Number of subjects included in analysis	334
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.704 [103]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.342
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.291
upper limit	6.914

Notes:

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

Statistical analysis title	Statistical Analysis 5

Statistical analysis description:

Week 3

Comparison groups	Double-blind Period: Placebo v Double-blind Period: Fezolinetant 30 mg
Number of subjects included in analysis	333
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.741 [104]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.798
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.194
upper limit	3.079

Notes:

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

Statistical analysis title	Statistical Analysis 6

Statistical analysis description:	
Week 3	
Comparison groups	Double-blind Period: Placebo v Double-blind Period: Fezolinetant 45 mg
Number of subjects included in analysis	334
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.134 [105]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	2.292
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.809
upper limit	7.443

Notes:

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

Statistical analysis title	Statistical Analysis 7
Statistical analysis description:	
Week 4	
Comparison groups	Double-blind Period: Placebo v Double-blind Period: Fezolinetant 30 mg
Number of subjects included in analysis	333
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.062 [106]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	3.474
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.039
upper limit	15.712

Notes:

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

Statistical analysis title	Statistical Analysis 8
Statistical analysis description:	
Week 4	
Comparison groups	Double-blind Period: Placebo v Double-blind Period: Fezolinetant 45 mg
Number of subjects included in analysis	334
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.004 [107]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	6.184

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

Notes:

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

Statistical analysis title	Statistical Analysis 9

Statistical analysis description:

Week 5

Comparison groups	Double-blind Period: Placebo v Double-blind Period: Fezolinetant 30 mg
Number of subjects included in analysis	333
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.028 [108]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	4.217
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.305
upper limit	18.806

Notes:

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

Statistical analysis title	Statistical Analysis 10

Statistical analysis description:

Week 5

Comparison groups	Double-blind Period: Placebo v Double-blind Period: Fezolinetant 45 mg
Number of subjects included in analysis	334
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.044 [109]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	3.802
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.157
upper limit	17.075

Notes:

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

Statistical analysis title	Statistical Analysis 11

Statistical analysis description:	
Week 6	
Comparison groups	Double-blind Period: Placebo v Double-blind Period: Fezolinetant 30 mg
Number of subjects included in analysis	333
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.519 [110]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.342
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.551
upper limit	3.382

Notes:

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

Statistical analysis title	Statistical Analysis 12
Statistical analysis description:	
Week 6	
Comparison groups	Double-blind Period: Placebo v Double-blind Period: Fezolinetant 45 mg
Number of subjects included in analysis	334
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.117 [111]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.961
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.863
upper limit	4.741

Notes:

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

Statistical analysis title	Statistical Analysis 13
Statistical analysis description:	
Week 7	
Comparison groups	Double-blind Period: Placebo v Double-blind Period: Fezolinetant 30 mg
Number of subjects included in analysis	333
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.393 [112]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.471

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

Notes:

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

Statistical analysis title	Statistical Analysis 14

Statistical analysis description:

Week 7

Comparison groups	Double-blind Period: Placebo v Double-blind Period: Fezolinetant 45 mg
Number of subjects included in analysis	334
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.086 [113]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	2.087
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.923
upper limit	5.043

Notes:

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

Statistical analysis title	Statistical Analysis 15

Statistical analysis description:

Week 8

Comparison groups	Double-blind Period: Placebo v Double-blind Period: Fezolinetant 30 mg
Number of subjects included in analysis	333
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.168 [114]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.774
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.798
upper limit	4.143

Notes:

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

Statistical analysis title	Statistical Analysis 16

Statistical analysis description:	
Week 8	
Comparison groups	Double-blind Period: Placebo v Double-blind Period: Fezolinetant 45 mg
Number of subjects included in analysis	334
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.03 [115]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	2.374
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.112
upper limit	5.41

Notes:

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

Statistical analysis title	Statistical Analysis 17
Statistical analysis description:	
Week 9	
Comparison groups	Double-blind Period: Placebo v Double-blind Period: Fezolinetant 30 mg
Number of subjects included in analysis	333
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.287 [116]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.605
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.681
upper limit	3.971

Notes:

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

Statistical analysis title	Statistical Analysis 18
Statistical analysis description:	
Week 9	
Comparison groups	Double-blind Period: Placebo v Double-blind Period: Fezolinetant 45 mg
Number of subjects included in analysis	334
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.08 [117]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	2.108

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

Notes:

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

Statistical analysis title	Statistical Analysis 19

Statistical analysis description:

Week 10

Comparison groups	Double-blind Period: Placebo v Double-blind Period: Fezolinetant 30 mg
Number of subjects included in analysis	333
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.247 [118]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.599
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.73
upper limit	3.636

Notes:

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

Statistical analysis title	Statistical Analysis 20

Statistical analysis description:

Week 10

Comparison groups	Double-blind Period: Placebo v Double-blind Period: Fezolinetant 45 mg
Number of subjects included in analysis	334
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.017 [119]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	2.481
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.201
upper limit	5.441

Notes:

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

Statistical analysis title	Statistical Analysis 21

Statistical analysis description:	
Week 11	
Comparison groups	Double-blind Period: Placebo v Double-blind Period: Fezolinetant 30 mg
Number of subjects included in analysis	333
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.212 [120]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.728
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.744
upper limit	4.236

Notes:

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

Statistical analysis title	Statistical Analysis 22
Statistical analysis description:	
Week 11	
Comparison groups	Double-blind Period: Placebo v Double-blind Period: Fezolinetant 45 mg
Number of subjects included in analysis	334
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.002 [121]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	3.536
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.666
upper limit	8.207

Notes:

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

Statistical analysis title	Statistical Analysis 23
Statistical analysis description:	
Week 12	
Comparison groups	Double-blind Period: Placebo v Double-blind Period: Fezolinetant 30 mg
Number of subjects included in analysis	333
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.225 [122]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.701

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

Notes:

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

Statistical analysis title	Statistical Analysis 24

Statistical analysis description:

Week 12

Comparison groups	Double-blind Period: Placebo v Double-blind Period: Fezolinetant 45 mg
Number of subjects included in analysis	334
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.006 [123]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	3.049
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.42
upper limit	7.125

Notes:

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

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

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

End point description:

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

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

End point type	Secondary

End point timeframe:

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

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

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

Severity of moderate to severe VMS per day at post baseline visit was calculated as follows: [(number of mild hot flashes per day x 1) + (number of moderate hot flashes per day x 2) + (number of severe hot flashes per day x 3)]/Total number of daily mild/moderate/severe hot flashes
Moderate VMS was defined as sensation of heat with sweating/dampness, but was able to continue activity. If at night, participant woke up because she was feeling hot and/or was sweating, but no action was necessary other than rearranging the bed sheets. Severe VMS was defined as sensation of intense heat with sweating, caused disruption of activity. If at night, participant woke up hot and was sweating and needed to take action (e.g., remove layers of clothes, open the window, or get out of bed).
Severity was zero for participants that had no mild or moderate or severe VMS. Higher scores indicates greater severity.

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

End point type	Secondary

End point timeframe:

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

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

Statistical analyses

No statistical analyses for this end point

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

End point title	Number of Participants in Each Category of Patient's Global Impression of Change (PGIC) in VMS at Each Visit[124]

End point description:

The PGI is comprised of 2 companion 1-item PRO measures analogous to the Clinical Global Impression (CGI) scales. These measures provide brief, stand-alone global assessments prior to and after initiating a study medication. Patient-perceived change from the initiation of treatment (PGI-C)-VMS is used to evaluate meaningful within-person changes over time in VMS. This measure provides patient-perceived change from the initiation of treatment.
The PGI-C VMS asks: "Compared to the beginning of this study, how would you rate your HFs/night sweats now?" Subject ratings range from (1) much better to (7) much worse. Participant ratings range from 1=much better, 2= moderately better, 3= a little better, 4= no change, 5= a little worse, 6= moderately worse, 7= much worse.

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

End point type	Secondary

End point timeframe:

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

Notes:

[124] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: There was no pre-specified statistical analysis for this endpoint.

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

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

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

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

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

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

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Adverse Events

End point title	Number of Participants With Adverse Events[125]

End point description:

An AE is any untoward medical occurrence in a participant administered a study drug, & which does not necessarily have to have a causal relationship with treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with use of a medicinal product (mp) whether or not considered related to the mp. An AE is considered "serious" if it results in death, is life-threatening, results in persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions, Results in congenital anomaly or birth defect, requires inpatient hospitalization or leads to prolongation of hospitalization, hospitalization for treatment/observation/examination caused by AE is to be considered as serious, discontinuation due to increases in liver enzymes, other medically important events. TEAE was defined as an AE observed from first dose date up to 21 days after last dose.

End point type	Secondary

End point timeframe:

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

Analysis Population: Safety analysis set consisted of all randomized participants who took at least 1 dose of study intervention.

Notes:

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

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

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

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

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
From first dose date up to 21 days after last dose (to 55 weeks)	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	v23.0

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

Serious adverse events	Double-blind Period: Placebo	Double-blind: Fezolinetant 30 mg/Extension: Fezolinetant 30 mg	Double-blind: Fezolinetant 45 mg/Extension: Fezolinetant 45 mg
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 167 (0.00%)	9 / 166 (5.42%)	8 / 167 (4.79%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Invasive breast carcinoma			

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

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

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

Serious adverse events	Double-blind : Placebo/Extension : Fezolinetant 30 mg	Double-blind : Placebo/Extension : Fezolinetant 45 mg	
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 76 (2.63%)	4 / 75 (5.33%)	

number of deaths (all causes)	0	1	
number of deaths resulting from adverse events	0	1	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Invasive breast carcinoma			
subjects affected / exposed	1 / 76 (1.32%)	0 / 75 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Squamous cell carcinoma of skin			
subjects affected / exposed	0 / 76 (0.00%)	0 / 75 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Keratoacanthoma			
subjects affected / exposed	0 / 76 (0.00%)	0 / 75 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Uterine leiomyoma			
subjects affected / exposed	0 / 76 (0.00%)	1 / 75 (1.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Foot fracture			
subjects affected / exposed	0 / 76 (0.00%)	1 / 75 (1.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Limb injury			
subjects affected / exposed	0 / 76 (0.00%)	0 / 75 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multiple injuries			
subjects affected / exposed	0 / 76 (0.00%)	1 / 75 (1.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Limb traumatic amputation			

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

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

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

Non-serious adverse events	Double-blind Period: Placebo	Double-blind: Fezolinetant 30 mg/Extension: Fezolinetant 30 mg	Double-blind: Fezolinetant 45 mg/Extension: Fezolinetant 45 mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	6 / 167 (3.59%)	20 / 166 (12.05%)	34 / 167 (20.36%)
Investigations			
Blood creatine phosphokinase increased			
subjects affected / exposed	0 / 167 (0.00%)	2 / 166 (1.20%)	3 / 167 (1.80%)
occurrences (all)	0	2	3
Vascular disorders			
Hot flush			
subjects affected / exposed	1 / 167 (0.60%)	3 / 166 (1.81%)	7 / 167 (4.19%)
occurrences (all)	1	3	7
Nervous system disorders			
Headache			
subjects affected / exposed	4 / 167 (2.40%)	8 / 166 (4.82%)	12 / 167 (7.19%)
occurrences (all)	4	9	14
Infections and infestations			
COVID-19			
subjects affected / exposed	1 / 167 (0.60%)	8 / 166 (4.82%)	15 / 167 (8.98%)
occurrences (all)	1	8	15

Non-serious adverse events	Double-blind : Placebo/Extension : Fezolinetant 30 mg	Double-blind : Placebo/Extension : Fezolinetant 45 mg	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	10 / 76 (13.16%)	12 / 75 (16.00%)	
Investigations			
Blood creatine phosphokinase increased			
subjects affected / exposed	1 / 76 (1.32%)	5 / 75 (6.67%)	
occurrences (all)	1	6	
Vascular disorders			

Hot flush subjects affected / exposed occurrences (all)	4 / 76 (5.26%) 4	0 / 75 (0.00%) 0	
Nervous system disorders Headache subjects affected / exposed occurrences (all)	1 / 76 (1.32%) 1	4 / 75 (5.33%) 5	
Infections and infestations COVID-19 subjects affected / exposed occurrences (all)	4 / 76 (5.26%) 4	3 / 75 (4.00%) 3	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

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

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

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported