



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	2018-003528-35
Trial protocol	GB ES CZ HU
Global end of trial date	11 August 2021

Results information

Result version number	v1 (current)
This version publication date	29 July 2022
First version publication date	29 July 2022

Trial information

Trial identification

Sponsor protocol code	2693-CL-0301
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04003155
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	11 August 2021
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	11 August 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study was 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: 27
Country: Number of subjects enrolled	Czechia: 9
Country: Number of subjects enrolled	Hungary: 30
Country: Number of subjects enrolled	Poland: 121
Country: Number of subjects enrolled	Spain: 5
Country: Number of subjects enrolled	United Kingdom: 11
Country: Number of subjects enrolled	United States: 324
Worldwide total number of subjects	527
EEA total number of subjects	165

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)	518
From 65 to 84 years	9
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 minimum average of 7 to 8 moderate to severe VMS per day within 10 days prior to randomization & who met inclusion & none of 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 (12 weeks)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Investigator, Subject

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
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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
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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
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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	175	176	176
Full Analysis Set	175	173	174
Safety Analysis Set	175	174	173
Treated	175	173	174
Completed	152	142	161
Not completed	23	34	15
Consent withdrawn by subject	9	12	4
Adverse event, non-fatal	9	8	5
Miscellaneous	1	7	3
Lost to follow-up	3	4	-
Protocol deviation	1	3	3

Period 2

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

Arms

Are arms mutually exclusive?	Yes
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
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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: Placebo/Extension Fezolinetant 30 mg
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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 Placebo/Extension: Fezolinetant 45 mg
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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^[1]	Double-blind: Fezolinetant 30 mg/Extension: Fezolinetant 30 mg	Double-blind: Fezolinetant 45 mg/Extension: Fezolinetant 45 mg	Double-blind: Placebo/Extension Fezolinetant 30 mg
Started	142	158	76
Completed	124	143	62
Not completed	18	15	14
Consent withdrawn by subject	12	7	9
Adverse event, non-fatal	5	4	2
Miscellaneous	-	1	2

Lost to follow-up	1	3	1
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Number of subjects in period 2^[1]	Double-blind Placebo/Extension: Fezolinetant 45 mg
Started	76
Completed	67
Not completed	9
Consent withdrawn by subject	5
Adverse event, non-fatal	2
Miscellaneous	1
Lost to follow-up	1

Notes:

[1] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.

Justification: Participants who received placebo in double-blind period were moved to fezolinetant 30/45 mg arms in extension treatment period

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	175	176	176
Age categorical Units: Subjects			
Age Continuous Units: Years arithmetic mean standard deviation	54.7 ± 4.8	54.1 ± 4.9	54.3 ± 5.2
Sex: Female, Male Units:			
Female	175	176	176
Male	0	0	0
Race/Ethnicity, Customized Units: Subjects			
Race: White	142	150	143
Race: Black or African American	28	21	27
Race: American Indian or Alaska Native	2	0	1
Race: Asian	3	3	3
Race: Pacific Islander	0	0	1
Race: More Than One Race	0	1	1
Race: Unknown	0	1	0
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	46	43	48
Not Hispanic or Latino	128	133	128
Unknown or Not Reported	1	0	0
Frequency of Moderate and Severe Vasomotor Symptoms 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.			
Analysis population description (APD): FAS Population			

Units: VMS per day			
arithmetic mean	10.51	10.65	10.44
standard deviation	± 3.79	± 4.73	± 3.92
Severity of Moderate and Severe Vasomotor Symptoms 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.			
APD: FAS Population			
Units: Score on a scale			
arithmetic mean	2.43	2.39	2.40
standard deviation	± 0.35	± 0.34	± 0.35

Reporting group values	Total		
Number of subjects	527		
Age categorical			
Units: Subjects			

Age Continuous			
Units: Years			
arithmetic mean			
standard deviation	-		
Sex: Female, Male			
Units:			
Female	527		
Male	0		
Race/Ethnicity, Customized			
Units: Subjects			
Race: White	435		
Race: Black or African American	76		
Race: American Indian or Alaska Native	3		
Race: Asian	9		
Race: Pacific Islander	1		
Race: More Than One Race	2		
Race: Unknown	1		
Ethnicity (NIH/OMB)			
Units: Subjects			
Hispanic or Latino	137		
Not Hispanic or Latino	389		
Unknown or Not Reported	1		
Frequency of Moderate and Severe Vasomotor Symptoms 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.			
Analysis population description (APD): FAS Population			
Units: VMS per day			
arithmetic mean			
standard deviation	-		
Severity of Moderate and Severe Vasomotor Symptoms per 24 hours			

Severity of moderate to severe VMS per day was calculated as follows: $[(\text{number of moderate VMS} \times 2) + (\text{number of severe VMS} \times 3)] / \text{number of daily moderate/severe VMS}$. 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.

APD: FAS Population

Units: Score on a scale			
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: 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.	
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.	
Subject analysis set title	Full Analysis Set (FAS)
Subject analysis set type	Full analysis
Subject analysis set description: Full analysis set (FAS) consisted of all participants who were randomized and received at least 1 dose of study intervention. The randomized treatment for each participant was used for summaries by treatment group based on the FAS, even if a participant erroneously received a different treatment.	
Subject analysis set title	Safety Analysis Set

Subject analysis set type	Safety analysis
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Subject analysis set description:

Safety population included all randomized participants who took at least 1 dose of study intervention. A participant erroneously receiving a treatment different from their randomized treatment was assigned to the treatment group that the participant received as first dose.

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
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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 participant 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.

APD: FAS Population with available data at specified time point.

End point type	Primary
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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	166	157	164	
Units: VMS per day				
least squares mean (standard error)	-3.32 (± 0.29)	-5.19 (± 0.30)	-5.39 (± 0.30)	

Statistical analyses

Statistical analysis title	Statistical Analysis 1
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Statistical analysis description:

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)

Comparison groups	Double-blind Period: Placebo v Double-blind Period: Fezolinetant 30 mg
Number of subjects included in analysis	323
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.001 ^[1]
Method	MMRM
Parameter estimate	LSMean Difference
Point estimate	-1.87

Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.69
upper limit	-1.05
Variability estimate	Standard error of the mean
Dispersion value	0.42

Notes:

[1] - 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	330
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 ^[2]
Method	MMRM
Parameter estimate	LSMean Difference
Point estimate	-2.07
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.89
upper limit	-1.25
Variability estimate	Standard error of the mean
Dispersion value	0.42

Notes:

[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	323
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.012
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	330
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.007
Method	Hochberg

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
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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 participant 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.

APD: FAS population with available data at specified time point.

End point type	Primary
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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	139	131	146	
Units: VMS per day				
least squares mean (standard error)	-3.90 (± 0.31)	-6.28 (± 0.32)	-6.44 (± 0.31)	

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	270
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 ^[3]
Method	MMRM
Parameter estimate	LSMean difference
Point estimate	-2.39

Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.25
upper limit	-1.52
Variability estimate	Standard error of the mean
Dispersion value	0.44

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.

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 ^[4]
Method	MMRM
Parameter estimate	LSMean Difference
Point estimate	-2.55
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.4
upper limit	-1.7
Variability estimate	Standard error of the mean
Dispersion value	0.43

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	270
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.012
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	= 0.007
Method	Hochberg

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
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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 participant 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.

APD: FAS population with available data at specified time point.

End point type	Primary
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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	166	157	164	
Units: Score on a scale				
least squares mean (standard error)	-0.27 (± 0.04)	-0.42 (± 0.04)	-0.46 (± 0.04)	

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	323
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.012 ^[5]
Method	MMRM
Parameter estimate	LSMean Difference
Point estimate	-0.15

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.27
upper limit	-0.03
Variability estimate	Standard error of the mean
Dispersion value	0.06

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.

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	330
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.002 ^[6]
Method	MMRM
Parameter estimate	LSMean Difference
Point estimate	-0.19
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.3
upper limit	-0.07
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 45 mg
Number of subjects included in analysis	330
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.012
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	330
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.007
Method	Hochberg

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
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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 participant 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.

APD: FAS population with available data at specified time point.

End point type	Primary
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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	139	131	146	
Units: Score on a scale				
least squares mean (standard error)	-0.37 (± 0.05)	-0.60 (± 0.05)	-0.57 (± 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	270
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.002 ^[7]
Method	MMRM
Parameter estimate	LSMean Difference
Point estimate	-0.24

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.39
upper limit	-0.09
Variability estimate	Standard error of the mean
Dispersion value	0.08

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.

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	= 0.007 ^[8]
Method	MMRM
Parameter estimate	LSMean Difference
Point estimate	-0.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.35
upper limit	-0.06
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 3
Comparison groups	Double-blind Period: Placebo v Double-blind Period: Fezolinetant 30 mg
Number of subjects included in analysis	270
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.012
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	= 0.007
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
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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.

APD: 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	148	133	156	
Units: Score on a scale				
least squares mean (standard error)	-3.2 (± 0.5)	-3.7 (± 0.6)	-4.2 (± 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	281
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.489 ^[9]
Method	MMRM
Parameter estimate	LSMean Difference
Point estimate	-0.5

Confidence interval	
level	95 %
sides	2-sided
lower limit	-2
upper limit	1
Variability estimate	Standard error of the mean
Dispersion value	0.8

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 2
Comparison groups	Double-blind Period: Placebo v Double-blind Period: Fezolinetant 45 mg
Number of subjects included in analysis	304
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.155 ^[10]
Method	MMRM
Parameter estimate	LSMean Difference
Point estimate	-1.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.5
upper limit	0.4
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.

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
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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 participant 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.

APD: FAS population with available data at specified time point.

End point type	Secondary
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End point timeframe:

Baseline and weeks 1, 2, 3, 5, 6, 7, 8, 9, 10 and 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	174	169	166	
Units: VMS per day				
least squares mean (standard error)				
Week 1	-1.82 (± 0.26)	-3.63 (± 0.26)	-3.07 (± 0.26)	
Week 2	-2.76 (± 0.28)	-4.73 (± 0.28)	-4.58 (± 0.28)	
Week 3	-3.15 (± 0.28)	-5.14 (± 0.29)	-5.25 (± 0.29)	
Week 5	-3.49 (± 0.28)	-5.56 (± 0.29)	-5.67 (± 0.29)	
Week 6	-3.58 (± 0.29)	-5.70 (± 0.30)	-5.97 (± 0.29)	
Week 7	-3.71 (± 0.30)	-5.80 (± 0.31)	-5.97 (± 0.30)	
Week 8	-3.71 (± 0.30)	-6.10 (± 0.31)	-6.10 (± 0.30)	
Week 9	-4.09 (± 0.30)	-6.16 (± 0.31)	-6.24 (± 0.30)	
Week 10	-4.09 (± 0.30)	-6.30 (± 0.31)	-6.25 (± 0.30)	
Week 11	-3.89 (± 0.31)	-6.37 (± 0.31)	-6.34 (± 0.30)	

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	343
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 ^[11]
Method	MMRM
Parameter estimate	LSMean difference
Point estimate	-1.81
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.53
upper limit	-1.09
Variability estimate	Standard error of the mean
Dispersion value	0.37

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.

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	340
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 ^[12]
Method	MMRM
Parameter estimate	LSMean Difference
Point estimate	-1.25
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.97
upper limit	-0.53
Variability estimate	Standard error of the mean
Dispersion value	0.37

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 3
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Statistical analysis description:

Week 2

Comparison groups	Double-blind Period: Placebo v Double-blind Period: Fezolinetant 30 mg
Number of subjects included in analysis	343
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 ^[13]
Method	MMRM
Parameter estimate	LSMean Difference
Point estimate	-1.97
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.75
upper limit	-1.19
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 4
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Statistical analysis description:

Week 2

Comparison groups	Double-blind Period: Placebo v Double-blind Period: Fezolinetant 45 mg
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Number of subjects included in analysis	340
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 ^[14]
Method	MMRM
Parameter estimate	LSMean Difference
Point estimate	-1.83
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.6
upper limit	-1.05
Variability estimate	Standard error of the mean
Dispersion value	0.39

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 5
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Statistical analysis description:

Week 3

Comparison groups	Double-blind Period: Placebo v Double-blind Period: Fezolinetant 30 mg
Number of subjects included in analysis	343
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 ^[15]
Method	MMRM
Parameter estimate	LSMean Difference
Point estimate	-1.99
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.79
upper limit	-1.19
Variability estimate	Standard error of the mean
Dispersion value	0.41

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 6
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Statistical analysis description:

Week 3

Comparison groups	Double-blind Period: Placebo v Double-blind Period: Fezolinetant 45 mg
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Number of subjects included in analysis	340
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 ^[16]
Method	MMRM
Parameter estimate	LSMean Difference
Point estimate	-2.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.9
upper limit	-1.31
Variability estimate	Standard error of the mean
Dispersion value	0.4

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 7
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Statistical analysis description:

Week 5

Comparison groups	Double-blind Period: Placebo v Double-blind Period: Fezolinetant 30 mg
Number of subjects included in analysis	343
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 ^[17]
Method	MMRM
Parameter estimate	LSMean Difference
Point estimate	-2.07
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.87
upper limit	-1.27
Variability estimate	Standard error of the mean
Dispersion value	0.41

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 8
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Statistical analysis description:

Week 5

Comparison groups	Double-blind Period: Placebo v Double-blind Period: Fezolinetant 45 mg
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Number of subjects included in analysis	340
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 ^[18]
Method	MMRM
Parameter estimate	LSMean Difference
Point estimate	-2.18
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.98
upper limit	-1.39
Variability estimate	Standard error of the mean
Dispersion value	0.4

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 9
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Statistical analysis description:

Week 6

Comparison groups	Double-blind Period: Placebo v Double-blind Period: Fezolinetant 30 mg
Number of subjects included in analysis	343
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 ^[19]
Method	MMRM
Parameter estimate	LSMean Difference
Point estimate	-2.11
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.92
upper limit	-1.3
Variability estimate	Standard error of the mean
Dispersion value	0.41

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 10
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Statistical analysis description:

Week 6

Comparison groups	Double-blind Period: Placebo v Double-blind Period: Fezolinetant 45 mg
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Number of subjects included in analysis	340
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 ^[20]
Method	MMRM
Parameter estimate	LSMean Difference
Point estimate	-2.39
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.19
upper limit	-1.59
Variability estimate	Standard error of the mean
Dispersion value	0.41

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
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Statistical analysis description:

Week 7

Comparison groups	Double-blind Period: Placebo v Double-blind Period: Fezolinetant 30 mg
Number of subjects included in analysis	343
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 ^[21]
Method	MMRM
Parameter estimate	LSMean Difference
Point estimate	-2.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.95
upper limit	-1.25
Variability estimate	Standard error of the mean
Dispersion value	0.43

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 12
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Statistical analysis description:

Week 7

Comparison groups	Double-blind Period: Placebo v Double-blind Period: Fezolinetant 45 mg
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Number of subjects included in analysis	340
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 ^[22]
Method	MMRM
Parameter estimate	LSMean Difference
Point estimate	-2.27
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.11
upper limit	-1.42
Variability estimate	Standard error of the mean
Dispersion value	0.43

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 13
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Statistical analysis description:

Week 8

Comparison groups	Double-blind Period: Placebo v Double-blind Period: Fezolinetant 30 mg
Number of subjects included in analysis	343
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 ^[23]
Method	MMRM
Parameter estimate	LSMean Difference
Point estimate	-2.39
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.25
upper limit	-1.54
Variability estimate	Standard error of the mean
Dispersion value	0.43

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 14
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Statistical analysis description:

Week 8

Comparison groups	Double-blind Period: Placebo v Double-blind Period: Fezolinetant 45 mg
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Number of subjects included in analysis	340
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 ^[24]
Method	MMRM
Parameter estimate	LSMean Difference
Point estimate	-2.39
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.23
upper limit	-1.55
Variability estimate	Standard error of the mean
Dispersion value	0.43

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 15
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Statistical analysis description:

Week 9

Comparison groups	Double-blind Period: Placebo v Double-blind Period: Fezolinetant 30 mg
Number of subjects included in analysis	343
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 ^[25]
Method	MMRM
Parameter estimate	LSMean Difference
Point estimate	-2.08
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.93
upper limit	-1.22
Variability estimate	Standard error of the mean
Dispersion value	0.43

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 16
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Statistical analysis description:

Week 9

Comparison groups	Double-blind Period: Placebo v Double-blind Period: Fezolinetant 45 mg
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Number of subjects included in analysis	340
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 ^[26]
Method	MMRM
Parameter estimate	LSMean Difference
Point estimate	-2.16
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3
upper limit	-1.31
Variability estimate	Standard error of the mean
Dispersion value	0.43

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 18
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Statistical analysis description:

Week 10

Comparison groups	Double-blind Period: Placebo v Double-blind Period: Fezolinetant 45 mg
Number of subjects included in analysis	340
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 ^[27]
Method	MMRM
Parameter estimate	LSMean Difference
Point estimate	-2.16
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.98
upper limit	-1.33
Variability estimate	Standard error of the mean
Dispersion value	0.42

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
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Statistical analysis description:

Week 10

Comparison groups	Double-blind Period: Placebo v Double-blind Period: Fezolinetant 30 mg
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Number of subjects included in analysis	343
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 ^[28]
Method	MMRM
Parameter estimate	LSMean Difference
Point estimate	-2.21
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.05
upper limit	-1.37
Variability estimate	Standard error of the mean
Dispersion value	0.43

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 19
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Statistical analysis description:

Week 11

Comparison groups	Double-blind Period: Placebo v Double-blind Period: Fezolinetant 30 mg
Number of subjects included in analysis	343
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 ^[29]
Method	MMRM
Parameter estimate	LSMean Difference
Point estimate	-2.48
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.34
upper limit	-1.62
Variability estimate	Standard error of the mean
Dispersion value	0.44

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 20
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Statistical analysis description:

Week 11

Comparison groups	Double-blind Period: Placebo v Double-blind Period: Fezolinetant 45 mg
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Number of subjects included in analysis	340
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 ^[30]
Method	MMRM
Parameter estimate	LSMean Difference
Point estimate	-2.45
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.3
upper limit	-1.6
Variability estimate	Standard error of the mean
Dispersion value	0.43

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.

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
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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 participant 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.

APD: FAS population with available data at specified time point.

End point type	Secondary
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End point timeframe:

Baseline and weeks 1, 2, 3, 5, 6, 7, 8, 9, 10 and 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	175	173	174	
Units: Score on a scale				
least squares mean (standard error)				
Week 1	-0.15 (± 0.03)	-0.25 (± 0.03)	-0.25 (± 0.03)	
Week 2	-0.21 (± 0.03)	-0.35 (± 0.04)	-0.36 (± 0.03)	
Week 3	-0.27 (± 0.04)	-0.43 (± 0.04)	-0.43 (± 0.04)	
Week 5	-0.29 (± 0.04)	-0.46 (± 0.04)	-0.46 (± 0.04)	
Week 6	-0.30 (± 0.05)	-0.50 (± 0.05)	-0.55 (± 0.05)	
Week 7	-0.28 (± 0.05)	-0.52 (± 0.05)	-0.54 (± 0.05)	

Week 8	-0.29 (± 0.05)	-0.57 (± 0.05)	-0.53 (± 0.05)	
Week 9	-0.35 (± 0.05)	-0.62 (± 0.05)	-0.56 (± 0.05)	
Week 10	-0.34 (± 0.05)	-0.62 (± 0.05)	-0.57 (± 0.05)	
Week 11	-0.37 (± 0.06)	-0.64 (± 0.06)	-0.61 (± 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	348
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.006 ^[31]
Method	MMRM
Parameter estimate	LSMean Difference
Point estimate	-0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.17
upper limit	-0.03
Variability estimate	Standard error of the mean
Dispersion value	0.04

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.

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	349
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.006 ^[32]
Method	MMRM
Parameter estimate	LSMean Difference
Point estimate	-0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.17
upper limit	-0.03
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 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	348
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.003 ^[33]
Method	MMRM
Parameter estimate	LSMean Difference
Point estimate	-0.15
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.24
upper limit	-0.05
Variability estimate	Standard error of the mean
Dispersion value	0.05

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 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	349
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.002 ^[34]
Method	MMRM
Parameter estimate	LSMean Difference
Point estimate	-0.15
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.25
upper limit	-0.06
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 5
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Statistical analysis description:

Week 3

Comparison groups	Double-blind Period: Placebo v Double-blind Period: Fezolinetant 30 mg
Number of subjects included in analysis	348
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.004 ^[35]
Method	MMRM
Parameter estimate	LSMean Difference
Point estimate	-0.16
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.27
upper limit	-0.05
Variability estimate	Standard error of the mean
Dispersion value	0.06

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 6
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Statistical analysis description:

Week 3

Comparison groups	Double-blind Period: Placebo v Double-blind Period: Fezolinetant 45 mg
Number of subjects included in analysis	349
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.003 ^[36]
Method	MMRM
Parameter estimate	LSMean Difference
Point estimate	-0.17
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.28
upper limit	-0.06
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 7
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Statistical analysis description:

Week 5

Comparison groups	Double-blind Period: Placebo v Double-blind Period: Fezolinetant 30 mg
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Number of subjects included in analysis	348
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.006 ^[37]
Method	MMRM
Parameter estimate	LSMean Difference
Point estimate	-0.17
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.29
upper limit	-0.05
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 8
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Statistical analysis description:

Week 5

Comparison groups	Double-blind Period: Placebo v Double-blind Period: Fezolinetant 45 mg
Number of subjects included in analysis	349
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.004 ^[38]
Method	MMRM
Parameter estimate	LSMean Difference
Point estimate	-0.17
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.29
upper limit	-0.06
Variability estimate	Standard error of the mean
Dispersion value	0.06

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 9
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Statistical analysis description:

Week 6

Comparison groups	Double-blind Period: Placebo v Double-blind Period: Fezolinetant 30 mg
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Number of subjects included in analysis	348
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.003 ^[39]
Method	MMRM
Parameter estimate	LSMean Difference
Point estimate	-0.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.33
upper limit	-0.07
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 10
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Statistical analysis description:

Week 6

Comparison groups	Double-blind Period: Placebo v Double-blind Period: Fezolinetant 45 mg
Number of subjects included in analysis	349
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 ^[40]
Method	MMRM
Parameter estimate	LSMean Difference
Point estimate	-0.25
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.38
upper limit	-0.13
Variability estimate	Standard error of the mean
Dispersion value	0.06

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 11
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Statistical analysis description:

Week 7

Comparison groups	Double-blind Period: Placebo v Double-blind Period: Fezolinetant 30 mg
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Number of subjects included in analysis	348
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 ^[41]
Method	MMRM
Parameter estimate	LSMean Difference
Point estimate	-0.24
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.37
upper limit	-0.11
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 12
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Statistical analysis description:

Week 7

Comparison groups	Double-blind Period: Placebo v Double-blind Period: Fezolinetant 45 mg
Number of subjects included in analysis	349
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 ^[42]
Method	MMRM
Parameter estimate	LSMean Difference
Point estimate	-0.26
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.39
upper limit	-0.13
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 13
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Statistical analysis description:

Week 8

Comparison groups	Double-blind Period: Placebo v Double-blind Period: Fezolinetant 30 mg
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Number of subjects included in analysis	348
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	-0.41
upper limit	-0.15
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 14
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Statistical analysis description:

Week 8

Comparison groups	Double-blind Period: Placebo v Double-blind Period: Fezolinetant 45 mg
Number of subjects included in analysis	349
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 ^[44]
Method	MMRM
Parameter estimate	LSMean Difference
Point estimate	-0.24
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.37
upper limit	-0.11
Variability estimate	Standard error of the mean
Dispersion value	0.07

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 15
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Statistical analysis description:

Week 9

Comparison groups	Double-blind Period: Placebo v Double-blind Period: Fezolinetant 30 mg
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Number of subjects included in analysis	348
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 ^[45]
Method	MMRM
Parameter estimate	MMRM
Point estimate	-0.26
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.41
upper limit	-0.12
Variability estimate	Standard error of the mean
Dispersion value	0.07

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 16
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Statistical analysis description:

Week 9

Comparison groups	Double-blind Period: Placebo v Double-blind Period: Fezolinetant 45 mg
Number of subjects included in analysis	349
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.004 ^[46]
Method	MMRM
Parameter estimate	LSMean Difference
Point estimate	-0.21
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.35
upper limit	-0.06
Variability estimate	Standard error of the mean
Dispersion value	0.07

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 17
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Statistical analysis description:

Week 10

Comparison groups	Double-blind Period: Placebo v Double-blind Period: Fezolinetant 30 mg
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Number of subjects included in analysis	348
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	-0.13
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 18
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Statistical analysis description:

Week 10

Comparison groups	Double-blind Period: Placebo v Double-blind Period: Fezolinetant 45 mg
Number of subjects included in analysis	349
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.002 ^[48]
Method	MMRM
Parameter estimate	LSMean Difference
Point estimate	-0.23
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.37
upper limit	-0.08
Variability estimate	Standard error of the mean
Dispersion value	0.07

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 19
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Statistical analysis description:

Week 11

Comparison groups	Double-blind Period: Placebo v Double-blind Period: Fezolinetant 30 mg
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Number of subjects included in analysis	348
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 ^[49]
Method	MMRM
Parameter estimate	LSMean Difference
Point estimate	-0.27
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:

[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 20
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Statistical analysis description:

Week 11

Comparison groups	Double-blind Period: Placebo v Double-blind Period: Fezolinetant 45 mg
Number of subjects included in analysis	349
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.002 ^[50]
Method	MMRM
Parameter estimate	LSMean Difference
Point estimate	-0.24
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.4
upper limit	-0.09
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.

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
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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 participant 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.

APD: 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	175	173	174	
Units: Percent change				
least squares mean (standard error)				
Week 1	-16.63 (± 2.31)	-32.15 (± 2.34)	-28.84 (± 2.35)	
Week 2	-25.08 (± 2.50)	-42.37 (± 2.55)	-43.37 (± 2.54)	
Week 3	-28.81 (± 2.54)	-46.94 (± 2.59)	-50.00 (± 2.57)	
Week 4	-30.59 (± 2.67)	-47.34 (± 2.72)	-51.65 (± 2.69)	
Week 5	-32.55 (± 2.65)	-50.12 (± 2.71)	-54.33 (± 2.67)	
Week 6	-33.35 (± 2.72)	-51.74 (± 2.78)	-57.18 (± 2.73)	
Week 7	-34.85 (± 2.86)	-53.14 (± 2.93)	-56.26 (± 2.85)	
Week 8	-35.71 (± 2.83)	-55.88 (± 2.90)	-56.89 (± 2.83)	
Week 9	-39.64 (± 2.87)	-56.31 (± 2.93)	-58.54 (± 2.85)	
Week 10	-39.51 (± 2.81)	-57.39 (± 2.87)	-59.01 (± 2.79)	
Week 11	-38.05 (± 2.84)	-58.37 (± 2.90)	-60.18 (± 2.82)	
Week 12	-37.06 (± 2.89)	-57.13 (± 2.95)	-61.24 (± 2.86)	

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	348
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 ^[51]
Method	MMRM
Parameter estimate	LSMean Difference
Point estimate	-15.52
Confidence interval	
level	95 %
sides	2-sided
lower limit	-21.99
upper limit	-9.06
Variability estimate	Standard error of the mean
Dispersion value	3.29

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.

Statistical analysis title	Statistical Analysis 2
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Statistical analysis description:

Week 1

Comparison groups	Double-blind Period: Placebo v Double-blind Period: Fezolinetant 45 mg
Number of subjects included in analysis	349
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 ^[52]
Method	MMRM
Parameter estimate	LSMean Difference
Point estimate	-12.22
Confidence interval	
level	95 %
sides	2-sided
lower limit	-18.69
upper limit	-5.74
Variability estimate	Standard error of the mean
Dispersion value	3.3

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
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Statistical analysis description:

Week 2

Comparison groups	Double-blind Period: Placebo v Double-blind Period: Fezolinetant 30 mg
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Number of subjects included in analysis	348
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 ^[53]
Method	MMRM
Parameter estimate	LSMean Difference
Point estimate	-17.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-24.32
upper limit	-10.27
Variability estimate	Standard error of the mean
Dispersion value	3.57

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 4
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Statistical analysis description:

Week 2

Comparison groups	Double-blind Period: Placebo v Double-blind Period: Fezolinetant 45 mg
Number of subjects included in analysis	349
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 ^[54]
Method	MMRM
Parameter estimate	LSMean Difference
Point estimate	-18.29
Confidence interval	
level	95 %
sides	2-sided
lower limit	-25.3
upper limit	-11.29
Variability estimate	Standard error of the mean
Dispersion value	3.57

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
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Statistical analysis description:

Week 3

Comparison groups	Double-blind Period: Placebo v Double-blind Period: Fezolinetant 30 mg
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Number of subjects included in analysis	348
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 ^[55]
Method	MMRM
Parameter estimate	LSMean Difference
Point estimate	-18.13
Confidence interval	
level	95 %
sides	2-sided
lower limit	-25.25
upper limit	-11
Variability estimate	Standard error of the mean
Dispersion value	3.63

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 6
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Statistical analysis description:

Week 3

Comparison groups	Double-blind Period: Placebo v Double-blind Period: Fezolinetant 45 mg
Number of subjects included in analysis	349
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 ^[56]
Method	MMRM
Parameter estimate	LSMean Difference
Point estimate	-21.19
Confidence interval	
level	95 %
sides	2-sided
lower limit	-28.29
upper limit	-14.09
Variability estimate	Standard error of the mean
Dispersion value	3.61

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
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Statistical analysis description:

Week 4

Comparison groups	Double-blind Period: Placebo v Double-blind Period: Fezolinetant 30 mg
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Number of subjects included in analysis	348
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 ^[57]
Method	MMRM
Parameter estimate	LSMean Difference
Point estimate	-16.75
Confidence interval	
level	95 %
sides	2-sided
lower limit	-24.24
upper limit	-9.26
Variability estimate	Standard error of the mean
Dispersion value	3.81

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 8
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Statistical analysis description:

Week 4

Comparison groups	Double-blind Period: Placebo v Double-blind Period: Fezolinetant 45 mg
Number of subjects included in analysis	349
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 ^[58]
Method	MMRM
Parameter estimate	LSMean Difference
Point estimate	-21.05
Confidence interval	
level	95 %
sides	2-sided
lower limit	-28.5
upper limit	-13.61
Variability estimate	Standard error of the mean
Dispersion value	3.79

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 9
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Statistical analysis description:

Week 5

Comparison groups	Double-blind Period: Placebo v Double-blind Period: Fezolinetant 30 mg
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Number of subjects included in analysis	348
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 ^[59]
Method	MMRM
Parameter estimate	LSMean Difference
Point estimate	-17.57
Confidence interval	
level	95 %
sides	2-sided
lower limit	-25.02
upper limit	-10.12
Variability estimate	Standard error of the mean
Dispersion value	3.79

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 10
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Statistical analysis description:

Week 5

Comparison groups	Double-blind Period: Placebo v Double-blind Period: Fezolinetant 45 mg
Number of subjects included in analysis	349
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 ^[60]
Method	MMRM
Parameter estimate	LSMean Difference
Point estimate	-21.78
Confidence interval	
level	95 %
sides	2-sided
lower limit	-29.18
upper limit	-14.39
Variability estimate	Standard error of the mean
Dispersion value	3.76

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 11
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Statistical analysis description:

Week 6

Comparison groups	Double-blind Period: Placebo v Double-blind Period: Fezolinetant 30 mg
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Number of subjects included in analysis	348
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 ^[61]
Method	MMRM
Parameter estimate	LSMean Difference
Point estimate	-18.39
Confidence interval	
level	95 %
sides	2-sided
lower limit	-26.03
upper limit	-10.75
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 12
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Statistical analysis description:

Week 6

Comparison groups	Double-blind Period: Placebo v Double-blind Period: Fezolinetant 45 mg
Number of subjects included in analysis	349
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 ^[62]
Method	MMRM
Parameter estimate	LSMean Difference
Point estimate	-23.83
Confidence interval	
level	95 %
sides	2-sided
lower limit	-31.39
upper limit	-16.27
Variability estimate	Standard error of the mean
Dispersion value	3.85

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 13
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Statistical analysis description:

Week 7

Comparison groups	Double-blind Period: Placebo v Double-blind Period: Fezolinetant 30 mg
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Number of subjects included in analysis	348
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 ^[63]
Method	MMRM
Parameter estimate	LSMean Difference
Point estimate	-18.29
Confidence interval	
level	95 %
sides	2-sided
lower limit	-26.33
upper limit	-10.25
Variability estimate	Standard error of the mean
Dispersion value	4.09

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 14
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Statistical analysis description:

Week 7

Comparison groups	Double-blind Period: Placebo v Double-blind Period: Fezolinetant 45 mg
Number of subjects included in analysis	349
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 ^[64]
Method	MMRM
Parameter estimate	LSMean Difference
Point estimate	-21.41
Confidence interval	
level	95 %
sides	2-sided
lower limit	-29.35
upper limit	-13.48
Variability estimate	Standard error of the mean
Dispersion value	4.04

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
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Statistical analysis description:

Week 8

Comparison groups	Double-blind Period: Placebo v Double-blind Period: Fezolinetant 30 mg
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Number of subjects included in analysis	348
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 ^[65]
Method	MMRM
Parameter estimate	LSMean Difference
Point estimate	-20.16
Confidence interval	
level	95 %
sides	2-sided
lower limit	-28.14
upper limit	-12.19
Variability estimate	Standard error of the mean
Dispersion value	4.06

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 16
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Statistical analysis description:

Week 8

Comparison groups	Double-blind Period: Placebo v Double-blind Period: Fezolinetant 45 mg
Number of subjects included in analysis	349
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.001 ^[66]
Method	MMRM
Parameter estimate	LSMean Difference
Point estimate	-21.17
Confidence interval	
level	95 %
sides	2-sided
lower limit	-29.04
upper limit	-13.3
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 17
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Statistical analysis description:

Week 9

Comparison groups	Double-blind Period: Placebo v Double-blind Period: Fezolinetant 30 mg
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Number of subjects included in analysis	348
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.001 ^[67]
Method	MMRM
Parameter estimate	LSMean Difference
Point estimate	-16.67
Confidence interval	
level	95 %
sides	2-sided
lower limit	-24.73
upper limit	-8.61
Variability estimate	Standard error of the mean
Dispersion value	4.1

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 18
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Statistical analysis description:

Week 9

Comparison groups	Double-blind Period: Placebo v Double-blind Period: Fezolinetant 45 mg
Number of subjects included in analysis	349
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 ^[68]
Method	MMRM
Parameter estimate	LSMean Difference
Point estimate	-18.89
Confidence interval	
level	95 %
sides	2-sided
lower limit	-26.84
upper limit	-10.94
Variability estimate	Standard error of the mean
Dispersion value	4.05

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
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Statistical analysis description:

Week 10

Comparison groups	Double-blind Period: Placebo v Double-blind Period: Fezolinetant 30 mg
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Number of subjects included in analysis	348
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 ^[69]
Method	MMRM
Parameter estimate	LSMean Difference
Point estimate	-17.88
Confidence interval	
level	95 %
sides	2-sided
lower limit	-25.77
upper limit	-9.99
Variability estimate	Standard error of the mean
Dispersion value	4.01

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 20
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Statistical analysis description:

Week 10

Comparison groups	Double-blind Period: Placebo v Double-blind Period: Fezolinetant 45 mg
Number of subjects included in analysis	349
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 ^[70]
Method	MMRM
Parameter estimate	LSMean Difference
Point estimate	-19.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-27.28
upper limit	-11.72
Variability estimate	Standard error of the mean
Dispersion value	3.96

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 21
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Statistical analysis description:

Week 11

Comparison groups	Double-blind Period: Placebo v Double-blind Period: Fezolinetant 30 mg
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Number of subjects included in analysis	348
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 ^[71]
Method	MMRM
Parameter estimate	LSMean Difference
Point estimate	-20.32
Confidence interval	
level	95 %
sides	2-sided
lower limit	-28.3
upper limit	-12.35
Variability estimate	Standard error of the mean
Dispersion value	4.06

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
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Statistical analysis description:

Week 11

Comparison groups	Double-blind Period: Placebo v Double-blind Period: Fezolinetant 45 mg
Number of subjects included in analysis	349
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 ^[72]
Method	MMRM
Parameter estimate	LSMean Difference
Point estimate	-22.14
Confidence interval	
level	95 %
sides	2-sided
lower limit	-30
upper limit	-14.28
Variability estimate	Standard error of the mean
Dispersion value	4

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 23
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Statistical analysis description:

Week 12

Comparison groups	Double-blind Period: Placebo v Double-blind Period: Fezolinetant 30 mg
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Number of subjects included in analysis	348
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 ^[73]
Method	MMRM
Parameter estimate	LSMean Difference
Point estimate	-20.08
Confidence interval	
level	95 %
sides	2-sided
lower limit	-28.19
upper limit	-11.96
Variability estimate	Standard error of the mean
Dispersion value	4.13

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 24
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Statistical analysis description:

Week 12

Comparison groups	Double-blind Period: Placebo v Double-blind Period: Fezolinetant 45 mg
Number of subjects included in analysis	349
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 ^[74]
Method	MMRM
Parameter estimate	LSMean Difference
Point estimate	-24.18
Confidence interval	
level	95 %
sides	2-sided
lower limit	-32.16
upper limit	-16.2
Variability estimate	Standard error of the mean
Dispersion value	4.06

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.

Secondary: Number of Participants With Percent Reduction of $\geq 50\%$ 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 $\geq 50\%$ in the Mean Frequency of Moderate and Severe VMS From Baseline to Each Study Week Up to Week 12
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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 participant 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 $\geq 50\%$ reduction from baseline to each post baseline week for the frequency of moderate to severe VMS.

APD: FAS Population

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	175	173	174	
Units: Participants				
Week 1	18	47	44	
Week 2	37	64	75	
Week 3	42	69	89	
Week 4	49	77	94	
Week 5	47	76	94	
Week 6	50	78	96	
Week 7	52	79	98	
Week 8	52	93	87	
Week 9	56	85	97	
Week 10	45	84	100	
Week 11	55	85	100	
Week 12	52	77	99	

Statistical analyses

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	348
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.001 ^[75]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	2.187
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.363
upper limit	3.549

Notes:

[75] - 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 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	348
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 ^[76]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	3.245
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.823
upper limit	5.999

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	349
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 ^[77]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	2.964
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.658
upper limit	5.497

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 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	348
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.002 ^[78]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	2.096
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.326
upper limit	3.345

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	349
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 ^[79]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	2.847
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.786
upper limit	4.601

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 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	349
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 ^[80]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	3.025

Confidence interval	
level	95 %
sides	2-sided
lower limit	1.947
upper limit	4.746

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 7
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Statistical analysis description:

Week 4

Comparison groups	Double-blind Period: Placebo v Double-blind Period: Fezolinetant 30 mg
Number of subjects included in analysis	348
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.001 ^[81]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	2.061

Confidence interval

level	95 %
sides	2-sided
lower limit	1.323
upper limit	3.233

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 6
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Statistical analysis description:

Week 3

Comparison groups	Double-blind Period: Placebo v Double-blind Period: Fezolinetant 45 mg
Number of subjects included in analysis	349
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 ^[82]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	3.333

Confidence interval

level	95 %
sides	2-sided
lower limit	2.121
upper limit	5.302

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 11
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Statistical analysis description:

Week 6

Comparison groups	Double-blind Period: Placebo v Double-blind Period: Fezolinetant 30 mg
Number of subjects included in analysis	348
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.002 ^[83]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	2.049
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.317
upper limit	3.21

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 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	348
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.001 ^[84]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	2.13
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.363
upper limit	3.357

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 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	349
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 ^[85]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	3.223

Confidence interval	
level	95 %
sides	2-sided
lower limit	2.067
upper limit	5.08

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 13
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Statistical analysis description:

Week 7

Comparison groups	Double-blind Period: Placebo v Double-blind Period: Fezolinetant 30 mg
Number of subjects included in analysis	348
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.002 ^[86]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.984

Confidence interval

level	95 %
sides	2-sided
lower limit	1.28
upper limit	3.097

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
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Statistical analysis description:

Week 6

Comparison groups	Double-blind Period: Placebo v Double-blind Period: Fezolinetant 45 mg
Number of subjects included in analysis	349
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 ^[87]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	3.097

Confidence interval

level	95 %
sides	2-sided
lower limit	1.994
upper limit	4.858

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 14
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Statistical analysis description:

Week 7

Comparison groups	Double-blind Period: Placebo v Double-blind Period: Fezolinetant 45 mg
Number of subjects included in analysis	349
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 ^[88]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	3.062
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.977
upper limit	4.788

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 15
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Statistical analysis description:

Week 8

Comparison groups	Double-blind Period: Placebo v Double-blind Period: Fezolinetant 30 mg
Number of subjects included in analysis	348
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 ^[89]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	2.748
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.774
upper limit	4.294

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 16
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Statistical analysis description:

Week 8

Comparison groups	Double-blind Period: Placebo v Double-blind Period: Fezolinetant 45 mg
Number of subjects included in analysis	349
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.001 ^[90]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	2.379

Confidence interval	
level	95 %
sides	2-sided
lower limit	1.536
upper limit	3.712

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 19
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Statistical analysis description:

Week 10

Comparison groups	Double-blind Period: Placebo v Double-blind Period: Fezolinetant 30 mg
Number of subjects included in analysis	348
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 ^[91]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	2.725

Confidence interval

level	95 %
sides	2-sided
lower limit	1.742
upper limit	4.306

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
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Statistical analysis description:

Week 9

Comparison groups	Double-blind Period: Placebo v Double-blind Period: Fezolinetant 30 mg
Number of subjects included in analysis	348
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.001 ^[92]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	2.051

Confidence interval

level	95 %
sides	2-sided
lower limit	1.329
upper limit	3.186

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
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Statistical analysis description:

Week 9

Comparison groups	Double-blind Period: Placebo v Double-blind Period: Fezolinetant 45 mg
Number of subjects included in analysis	349
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 ^[93]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	2.701
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.75
upper limit	4.204

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 21
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Statistical analysis description:

Week 11

Comparison groups	Double-blind Period: Placebo v Double-blind Period: Fezolinetant 30 mg
Number of subjects included in analysis	348
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 ^[94]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	2.104
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.363
upper limit	3.27

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
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Statistical analysis description:

Week 10

Comparison groups	Double-blind Period: Placebo v Double-blind Period: Fezolinetant 45 mg
Number of subjects included in analysis	349
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.001 ^[95]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	3.921

Confidence interval	
level	95 %
sides	2-sided
lower limit	2.505
upper limit	6.214

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 22
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Statistical analysis description:

Week 11

Comparison groups	Double-blind Period: Placebo v Double-blind Period: Fezolinetant 45 mg
Number of subjects included in analysis	349
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 ^[96]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	2.953

Confidence interval

level	95 %
sides	2-sided
lower limit	1.912
upper limit	4.602

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 23
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Statistical analysis description:

Week 12

Comparison groups	Double-blind Period: Placebo v Double-blind Period: Fezolinetant 30 mg
Number of subjects included in analysis	348
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.005 ^[97]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.894

Confidence interval

level	95 %
sides	2-sided
lower limit	1.22
upper limit	2.961

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 24
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Statistical analysis description:

Week 12

Comparison groups	Double-blind Period: Placebo v Double-blind Period: Fezolinetant 45 mg
Number of subjects included in analysis	349
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 ^[98]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	3.156
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.035
upper limit	4.944

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.

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
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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 participant 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.

APD: FAS Population

End point type	Secondary
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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	175	173	174	
Units: Participants				
Week 1	0	0	0	
Week 2	1	3	4	
Week 3	1	6	5	
Week 4	5	6	8	

Week 5	2	10	6	
Week 6	2	8	10	
Week 7	2	13	13	
Week 8	2	10	14	
Week 9	5	15	16	
Week 10	7	17	18	
Week 11	10	16	19	
Week 12	6	12	18	

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Statistical analysis description: Week 2	
Comparison groups	Double-blind Period: Placebo v Double-blind Period: Fezolinetant 30 mg
Number of subjects included in analysis	348
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.322 ^[99]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	3.158
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.398
upper limit	64.304

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.

Statistical analysis title	Statistical Analysis 2
Statistical analysis description: Week 2	
Comparison groups	Double-blind Period: Placebo v Double-blind Period: Fezolinetant 45 mg
Number of subjects included in analysis	349
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.225 ^[100]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	3.925
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.569
upper limit	77.353

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 3
Statistical analysis description: Week 3	
Comparison groups	Double-blind Period: Placebo v Double-blind Period: Fezolinetant 30 mg
Number of subjects included in analysis	348
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.089 ^[101]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	6.334
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.064
upper limit	120.422

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 4
Statistical analysis description: Week 3	
Comparison groups	Double-blind Period: Placebo v Double-blind Period: Fezolinetant 45 mg
Number of subjects included in analysis	349
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.143 ^[102]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	5.026
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.797
upper limit	96.916

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 5
Statistical analysis description: Week 4	
Comparison groups	Double-blind Period: Placebo v Double-blind Period: Fezolinetant 30 mg

Number of subjects included in analysis	348
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.711 ^[103]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.257
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.37
upper limit	4.468

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 6
Statistical analysis description:	
Week 4	
Comparison groups	Double-blind Period: Placebo v Double-blind Period: Fezolinetant 45 mg
Number of subjects included in analysis	349
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.441 ^[104]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.57
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.508
upper limit	5.328

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 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	348
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.032 ^[105]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	5.351

Confidence interval	
level	95 %
sides	2-sided
lower limit	1.383
upper limit	35.172

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 8
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Statistical analysis description:

Week 5

Comparison groups	Double-blind Period: Placebo v Double-blind Period: Fezolinetant 45 mg
Number of subjects included in analysis	349
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.175 ^[106]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	3.059

Confidence interval

level	95 %
sides	2-sided
lower limit	0.693
upper limit	21.086

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 9
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Statistical analysis description:

Week 6

Comparison groups	Double-blind Period: Placebo v Double-blind Period: Fezolinetant 30 mg
Number of subjects included in analysis	348
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.071 ^[107]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	4.225

Confidence interval

level	95 %
sides	2-sided
lower limit	1.039
upper limit	28.29

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 10
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Statistical analysis description:

Week 6

Comparison groups	Double-blind Period: Placebo v Double-blind Period: Fezolinetant 45 mg
Number of subjects included in analysis	349
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.035 ^[108]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	5.22
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.348
upper limit	34.323

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 11
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Statistical analysis description:

Week 7

Comparison groups	Double-blind Period: Placebo v Double-blind Period: Fezolinetant 30 mg
Number of subjects included in analysis	348
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.011 ^[109]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	7.064
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.912
upper limit	45.64

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 12
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Statistical analysis description:

Week 7

Comparison groups	Double-blind Period: Placebo v Double-blind Period: Fezolinetant 45 mg
Number of subjects included in analysis	349
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.012 ^[110]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	6.949

Confidence interval	
level	95 %
sides	2-sided
lower limit	1.881
upper limit	44.892

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 13
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Statistical analysis description:

Week 8

Comparison groups	Double-blind Period: Placebo v Double-blind Period: Fezolinetant 30 mg
Number of subjects included in analysis	348
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.032 ^[111]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	5.344

Confidence interval

level	95 %
sides	2-sided
lower limit	1.381
upper limit	35.134

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 14
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Statistical analysis description:

Week 8

Comparison groups	Double-blind Period: Placebo v Double-blind Period: Fezolinetant 45 mg
Number of subjects included in analysis	349
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.008 ^[112]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	7.514

Confidence interval

level	95 %
sides	2-sided
lower limit	2.055
upper limit	48.354

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 15
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Statistical analysis description:

Week 9

Comparison groups	Double-blind Period: Placebo v Double-blind Period: Fezolinetant 30 mg
Number of subjects included in analysis	348
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.026 ^[113]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	3.238
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.222
upper limit	10.148

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 16
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Statistical analysis description:

Week 9

Comparison groups	Double-blind Period: Placebo v Double-blind Period: Fezolinetant 45 mg
Number of subjects included in analysis	349
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.019 ^[114]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	3.438
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.311
upper limit	10.714

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 17
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Statistical analysis description:

Week 10

Comparison groups	Double-blind Period: Placebo v Double-blind Period: Fezolinetant 30 mg
Number of subjects included in analysis	348
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.037 ^[115]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	2.626

Confidence interval	
level	95 %
sides	2-sided
lower limit	1.101
upper limit	6.951

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 18
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Statistical analysis description:

Week 10

Comparison groups	Double-blind Period: Placebo v Double-blind Period: Fezolinetant 45 mg
Number of subjects included in analysis	349
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.027 ^[116]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	2.758

Confidence interval

level	95 %
sides	2-sided
lower limit	1.167
upper limit	7.263

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 19
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Statistical analysis description:

Week 11

Comparison groups	Double-blind Period: Placebo v Double-blind Period: Fezolinetant 30 mg
Number of subjects included in analysis	348
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.21 ^[117]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.69

Confidence interval

level	95 %
sides	2-sided
lower limit	0.753
upper limit	3.968

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 20
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Statistical analysis description:

Week 11

Comparison groups	Double-blind Period: Placebo v Double-blind Period: Fezolinetant 45 mg
Number of subjects included in analysis	349
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.087 ^[118]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	2.01
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.923
upper limit	4.634

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 21
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Statistical analysis description:

Week 12

Comparison groups	Double-blind Period: Placebo v Double-blind Period: Fezolinetant 30 mg
Number of subjects included in analysis	348
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.148 ^[119]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	2.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.795
upper limit	6.157

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 22
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Statistical analysis description:

Week 12

Comparison groups	Double-blind Period: Fezolinetant 45 mg v Double-blind Period: Placebo
Number of subjects included in analysis	349
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.015 ^[120]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	3.262

Confidence interval	
level	95 %
sides	2-sided
lower limit	1.329
upper limit	9.194

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.

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 ^[121]
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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.

99999 denotes "NA".

APD: FAS population with available data at specified time point.

End point type	Secondary
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End point timeframe:

Weeks 4, 12, 16, 20, 24, 28, 32, 36, 40, 48, 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:

[121] - 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: Placebo/Extension Fezolinetant 30 mg	Double-blind: Placebo/Extension: Fezolinetant 45 mg	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	160	68	70	150
Units: Participants				
Week 4: Much better (N=160,0,1,150,160)	32	0	1	50
Week 4: Moderately better (N=160,0,1,150,160)	21	0	0	33
Week 4: A little better (N=160,0,1,150,160)	44	0	0	42
Week 4: No change (N=160,0,1,150,160)	55	0	0	23
Week 4: A little worse (N=160,0,1,150,160)	1	0	0	1
Week 4: Moderately worse (N=160,0,1,150,160)	1	0	0	1
Week 4: Much worse (N=160,0,1,150,160)	6	0	0	0
Week 12: Much better (N=149,68,70,136,157)	35	31	44	50

Week 12: Moderately better (N=149,68,70,136,157)	24	14	16	24
Week 12: A little better (N=149,68,70,136,157)	40	16	8	41
Week 12: No change (N=149,68,70,136,157)	37	4	2	19
Week 12: A little worse (N=149,68,70,136,157)	6	1	0	1
Week 12: Moderately worse (N=149,68,70,136,157)	4	2	0	1
Week 12: Much worse (N=149,68,70,149,136)	3	0	0	0
Week 16: Much better (N=0,1,0,5,4)	99999	0	99999	1
Week 16: Moderately better (N=0,1,0,5,4)	99999	0	99999	2
Week 16: A little better (N=0,1,0,5,4)	99999	1	99999	1
Week 16: No change (N=0,1,0,5,4)	99999	0	99999	1
Week 16: A little worse (N=0,1,0,5,4)	99999	0	99999	0
Week 16: Moderately worse (N=0,1,0,5,4)	99999	0	99999	0
Week 16: Much worse (N=0,1,0,5,4)	99999	0	99999	0
Week 20: Much better (N=0,0,0,3,4)	99999	99999	99999	1
Week 20: Moderately better (N=0,0,0,3,4)	99999	99999	99999	1
Week 20: A little better (N=0,0,0,3,4)	99999	99999	99999	0
Week 20: No change (N=0,0,0,3,4)	99999	99999	99999	1
Week 20: A little worse (N=0,0,0,3,4)	99999	99999	99999	0
Week 20: Moderately worse (N=0,0,0,3,4)	99999	99999	99999	0
Week 20: Much worse (N=0,0,0,3,4)	99999	99999	99999	0
Week 24: Much better (N=0,0,0,127,148)	99999	99999	99999	55
Week 24: Moderately better (N=0,0,0,127,148)	99999	99999	99999	27
Week 24: A little better (N=0,0,0,127,148)	99999	99999	99999	34
Week 24: No change (N=0,0,0,127,148)	99999	99999	99999	10
Week 24: A little worse (N=0,0,0,127,148)	99999	99999	99999	0
Week 24: Moderately worse (N=0,0,0,127,148)	99999	99999	99999	1
Week 24: Much worse (N=0,0,0,127,148)	99999	99999	99999	0
Week 28: Much better (N=0,0,0,1,1)	99999	99999	99999	0
Week 28: Moderately better (N=0,0,0,1,1)	99999	99999	99999	0
Week 28: A little better (N=0,0,0,1,1)	99999	99999	99999	0
Week 28: No change (N=0,0,0,1,1)	99999	99999	99999	0
Week 28: A little worse (N=0,0,0,1,1)	99999	99999	99999	0
Week 28: Moderately worse (N=0,0,0,1,1)	99999	99999	99999	0
Week 28: Much worse (N=0,0,0,1,1)	99999	99999	99999	0
Week 32: Much better (N=0,0,0,0,1)	99999	99999	99999	99999
Week 32: Moderately better (N=0,0,0,0,1)	99999	99999	99999	99999
Week 32: A little better (N=0,0,0,0,1)	99999	99999	99999	99999
Week 32: No change (N=0,0,0,0,1)	99999	99999	99999	99999
Week 32: A little worse (N=0,0,0,0,1)	99999	99999	99999	99999

Week 32: Moderately worse (N=0,0,0,0,1)	99999	99999	99999	99999
Week 32: Much worse (N=0,0,0,0,1)	99999	99999	99999	99999
Week 36: Much better (N=0,1,0,0,1)	99999	0	99999	0
Week 36: Moderately better (N=0,1,0,0,1)	99999	1	99999	99999
Week 36: A little better (N=0,1,0,0,1)	99999	0	99999	99999
Week 36: No change (N=0,1,0,0,1)	99999	0	99999	99999
Week 36: A little worse (N=0,1,0,0,1)	99999	0	99999	99999
Week 36: Moderately worse (N=0,1,0,0,1)	99999	0	99999	99999
Week 36: Much worse (N=0,1,0,0,1)	99999	0	99999	99999
Week 40: Much better (N=0,55,63,2,0)	99999	33	39	0
Week 40: Moderately better (N=0,55,63,2,0)	99999	8	12	2
Week 40: A little better (N=0,55,63,2,0)	99999	6	10	0
Week 40: No change (N=0,55,63,2,0)	99999	6	1	0
Week 40: A little worse (N=0,55,63,2,0)	99999	2	1	0
Week 40: Moderately worse (N=0,55,63,2,0)	99999	0	0	0
Week 40: Much worse (N=0,55,63,2,0)	99999	0	0	0
Week 48: Much better (N=0,0,0,2,0)	99999	99999	99999	0
Week 48: Moderately better (N=0,0,0,2,0)	99999	99999	99999	1
Week 48: A little better (N=0,0,0,2,0)	99999	99999	99999	1
Week 48: No change (N=0,0,0,2,0)	99999	99999	99999	0
Week 48: A little worse (N=0,0,0,2,0)	99999	99999	99999	0
Week 48: Moderately worse (N=0,0,0,2,0)	99999	99999	99999	0
Week 48: Much worse (N=0,0,0,2,0)	99999	99999	99999	0
Week 52: Much better (N=0,0,0,111,127)	99999	99999	99999	56
Week 52: Moderately better (N=0,0,0,111,127)	99999	99999	99999	26
Week 52: A little better (N=0,0,0,111,127)	99999	99999	99999	23
Week 52: No change (N=0,0,0,111,127)	99999	99999	99999	6
Week 52: A little worse (N=0,0,0,111,127)	99999	99999	99999	0
Week 52: Moderately worse (N=0,0,0,111,127)	99999	99999	99999	0
Week 52: Much worse (N=0,0,0,111,127)	99999	99999	99999	0

End point values	Double-blind: Fezolinetant 45 mg/Extension: Fezolinetant 45 mg			
Subject group type	Subject analysis set			
Number of subjects analysed	160			
Units: Participants				
Week 4: Much better (N=160,0,1,150,160)	72			

Week 4: Moderately better (N=160,0,1,150,160)	24			
Week 4: A little better (N=160,0,1,150,160)	35			
Week 4: No change (N=160,0,1,150,160)	28			
Week 4: A little worse (N=160,0,1,150,160)	0			
Week 4: Moderately worse (N=160,0,1,150,160)	1			
Week 4: Much worse (N=160,0,1,150,160)	0			
Week 12: Much better (N=149,68,70,136,157)	74			
Week 12: Moderately better (N=149,68,70,136,157)	30			
Week 12: A little better (N=149,68,70,136,157)	35			
Week 12: No change (N=149,68,70,136,157)	11			
Week 12: A little worse (N=149,68,70,136,157)	2			
Week 12: Moderately worse (N=149,68,70,136,157)	4			
Week 12: Much worse (N=149,68,70,149,136)	1			
Week 16: Much better (N=0,1,0,5,4)	2			
Week 16: Moderately better (N=0,1,0,5,4)	1			
Week 16: A little better (N=0,1,0,5,4)	1			
Week 16: No change (N=0,1,0,5,4)	0			
Week 16: A little worse (N=0,1,0,5,4)	0			
Week 16: Moderately worse (N=0,1,0,5,4)	0			
Week 16: Much worse (N=0,1,0,5,4)	0			
Week 20: Much better (N=0,0,0,3,4)	1			
Week 20: Moderately better (N=0,0,0,3,4)	0			
Week 20: A little better (N=0,0,0,3,4)	2			
Week 20: No change (N=0,0,0,3,4)	1			
Week 20: A little worse (N=0,0,0,3,4)	0			
Week 20: Moderately worse (N=0,0,0,3,4)	0			
Week 20: Much worse (N=0,0,0,3,4)	0			
Week 24: Much better (N=0,0,0,127,148)	81			
Week 24: Moderately better (N=0,0,0,127,148)	30			
Week 24: A little better (N=0,0,0,127,148)	27			
Week 24: No change (N=0,0,0,127,148)	6			
Week 24: A little worse (N=0,0,0,127,148)	1			
Week 24: Moderately worse (N=0,0,0,127,148)	2			
Week 24: Much worse (N=0,0,0,127,148)	1			
Week 28: Much better (N=0,0,0,1,1)	1			
Week 28: Moderately better (N=0,0,0,1,1)	0			

Week 28: A little better (N=0,0,0,1,1)	0			
Week 28: No change (N=0,0,0,1,1)	0			
Week 28: A little worse (N=0,0,0,1,1)	0			
Week 28: Moderately worse (N=0,0,0,1,1)	0			
Week 28: Much worse (N=0,0,0,1,1)	0			
Week 32: Much better (N=0,0,0,0,1)	0			
Week 32: Moderately better (N=0,0,0,0,1)	1			
Week 32: A little better (N=0,0,0,0,1)	0			
Week 32: No change (N=0,0,0,0,1)	0			
Week 32: A little worse (N=0,0,0,0,1)	0			
Week 32: Moderately worse (N=0,0,0,0,1)	0			
Week 32: Much worse (N=0,0,0,0,1)	0			
Week 36: Much better (N=0,1,0,0,1)	0			
Week 36: Moderately better (N=0,1,0,0,1)	1			
Week 36: A little better (N=0,1,0,0,1)	0			
Week 36: No change (N=0,1,0,0,1)	0			
Week 36: A little worse (N=0,1,0,0,1)	0			
Week 36: Moderately worse (N=0,1,0,0,1)	0			
Week 36: Much worse (N=0,1,0,0,1)	0			
Week 40: Much better (N=0,55,63,2,0)	99999			
Week 40: Moderately better (N=0,55,63,2,0)	99999			
Week 40: A little better (N=0,55,63,2,0)	99999			
Week 40: No change (N=0,55,63,2,0)	99999			
Week 40: A little worse (N=0,55,63,2,0)	99999			
Week 40: Moderately worse (N=0,55,63,2,0)	99999			
Week 40: Much worse (N=0,55,63,2,0)	99999			
Week 48: Much better (N=0,0,0,2,0)	99999			
Week 48: Moderately better (N=0,0,0,2,0)	99999			
Week 48: A little better (N=0,0,0,2,0)	99999			
Week 48: No change (N=0,0,0,2,0)	99999			
Week 48: A little worse (N=0,0,0,2,0)	99999			
Week 48: Moderately worse (N=0,0,0,2,0)	99999			
Week 48: Much worse (N=0,0,0,2,0)	99999			
Week 52: Much better (N=0,0,0,111,127)	71			
Week 52: Moderately better (N=0,0,0,111,127)	30			
Week 52: A little better (N=0,0,0,111,127)	15			
Week 52: No change (N=0,0,0,111,127)	8			
Week 52: A little worse (N=0,0,0,111,127)	1			
Week 52: Moderately worse (N=0,0,0,111,127)	1			
Week 52: Much worse (N=0,0,0,111,127)	1			

Statistical analyses

No statistical analyses for this end point

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
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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 participant 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.

APD: FAS population with available data at specified time point.

End point type	Secondary
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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: Placebo/Extension Fezolinetant 30 mg	Double-blind: Placebo/Extension: Fezolinetant 45 mg	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	60	62	121	138
Units: VMS per day				
arithmetic mean (standard deviation)	-6.89 (± 3.67)	-7.32 (± 4.53)	-7.15 (± 6.02)	-7.32 (± 4.58)

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
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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 participant 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.

APD: 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: Placebo/Extension Fezolinetant 30 mg	Double-blind: Placebo/Extension Fezolinetant 45 mg	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	60	62	121	138
Units: Score on a scale				
arithmetic mean (standard deviation)	-0.78 (± 0.80)	-0.76 (± 0.89)	-0.75 (± 0.82)	-0.77 (± 0.90)

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 ^[122]
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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
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End point timeframe:

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

Notes:

[122] - 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: Placebo/Extension Fezolinetant 30 mg	Double-blind Placebo/Extension: Fezolinetant 45 mg	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	175	76	76	174
Units: Participants				
TEAE	78	48	37	108
Drug-Related TEAE	22	6	2	20
Serious TEAE	1	3	2	7
Drug-Related Serious TEAE	0	0	0	2
TEAE Leading to Death	0	0	0	0
Drug-Related TEAE Leading to Death	0	0	0	0
TEAE Leading to Withdrawal of treatment (trt)	9	2	1	13
Drug-Related TEAE Leading to Withdrawal of trt	7	0	1	7
Death	0	0	0	0

End point values	Double-blind: Fezolinetant 45 mg/Extension: Fezolinetant 45 mg			
Subject group type	Subject analysis set			
Number of subjects analysed	173			
Units: Participants				
TEAE	115			
Drug-Related TEAE	21			
Serious TEAE	8			
Drug-Related Serious TEAE	0			
TEAE Leading to Death	0			
Drug-Related TEAE Leading to Death	0			
TEAE Leading to Withdrawal of treatment (trt)	8			
Drug-Related TEAE Leading to Withdrawal of trt	5			
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 (up to 55 weeks)

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	v23.0
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Reporting groups

Reporting group title	Double-blind Period: Placebo
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Reporting group description:

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

Reporting group title	Double-blind: Fezolinetant 30 mg/Extension: Fezolinetant 30 mg
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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
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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: Fezolinetant 45 mg/Extension: Fezolinetant 45 mg
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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	Placebo/Fezolinetant 45 mg
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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	1 / 175 (0.57%)	7 / 174 (4.02%)	8 / 173 (4.62%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Investigations			
Blood pressure increased			

subjects affected / exposed	0 / 175 (0.00%)	0 / 174 (0.00%)	1 / 173 (0.58%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Liver function test increased			
subjects affected / exposed	0 / 175 (0.00%)	1 / 174 (0.57%)	0 / 173 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transaminases increased			
subjects affected / exposed	0 / 175 (0.00%)	1 / 174 (0.57%)	0 / 173 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Apocrine breast carcinoma			
subjects affected / exposed	0 / 175 (0.00%)	0 / 174 (0.00%)	0 / 173 (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
Benign lung neoplasm			
subjects affected / exposed	0 / 175 (0.00%)	0 / 174 (0.00%)	1 / 173 (0.58%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemangioma of liver			
subjects affected / exposed	0 / 175 (0.00%)	0 / 174 (0.00%)	1 / 173 (0.58%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung neoplasm			
subjects affected / exposed	0 / 175 (0.00%)	0 / 174 (0.00%)	1 / 173 (0.58%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Squamous cell carcinoma of skin			
subjects affected / exposed	0 / 175 (0.00%)	0 / 174 (0.00%)	0 / 173 (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			

Ankle fracture			
subjects affected / exposed	0 / 175 (0.00%)	1 / 174 (0.57%)	0 / 173 (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
Foot fracture			
subjects affected / exposed	0 / 175 (0.00%)	0 / 174 (0.00%)	0 / 173 (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
Vascular disorders			
Varicose vein			
subjects affected / exposed	0 / 175 (0.00%)	0 / 174 (0.00%)	1 / 173 (0.58%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Paraesthesia			
subjects affected / exposed	0 / 175 (0.00%)	0 / 174 (0.00%)	1 / 173 (0.58%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	0 / 175 (0.00%)	0 / 174 (0.00%)	1 / 173 (0.58%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Pelvic pain			
subjects affected / exposed	0 / 175 (0.00%)	0 / 174 (0.00%)	0 / 173 (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
Uterine haemorrhage			
subjects affected / exposed	0 / 175 (0.00%)	1 / 174 (0.57%)	0 / 173 (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
Hepatobiliary disorders			
Cholelithiasis			

subjects affected / exposed	1 / 175 (0.57%)	0 / 174 (0.00%)	1 / 173 (0.58%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Anxiety			
subjects affected / exposed	0 / 175 (0.00%)	1 / 174 (0.57%)	0 / 173 (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
Renal and urinary disorders			
Renal colic			
subjects affected / exposed	0 / 175 (0.00%)	0 / 174 (0.00%)	1 / 173 (0.58%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ureteric stenosis			
subjects affected / exposed	0 / 175 (0.00%)	0 / 174 (0.00%)	1 / 173 (0.58%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Intervertebral disc protrusion			
subjects affected / exposed	0 / 175 (0.00%)	1 / 174 (0.57%)	0 / 173 (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
Rhabdomyolysis			
subjects affected / exposed	0 / 175 (0.00%)	1 / 174 (0.57%)	0 / 173 (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
Infections and infestations			
COVID-19 pneumonia			
subjects affected / exposed	0 / 175 (0.00%)	0 / 174 (0.00%)	1 / 173 (0.58%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Serious adverse events			
	Double-blind: Fezolinetant 45 mg/Extension: Fezolinetant 45 mg	Placebo/Fezolinetant 45 mg	

Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 76 (3.95%)	2 / 76 (2.63%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Investigations			
Blood pressure increased			
subjects affected / exposed	0 / 76 (0.00%)	0 / 76 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Liver function test increased			
subjects affected / exposed	1 / 76 (1.32%)	0 / 76 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transaminases increased			
subjects affected / exposed	0 / 76 (0.00%)	0 / 76 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Apocrine breast carcinoma			
subjects affected / exposed	0 / 76 (0.00%)	1 / 76 (1.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Benign lung neoplasm			
subjects affected / exposed	0 / 76 (0.00%)	0 / 76 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemangioma of liver			
subjects affected / exposed	0 / 76 (0.00%)	0 / 76 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung neoplasm			
subjects affected / exposed	0 / 76 (0.00%)	0 / 76 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Squamous cell carcinoma of skin subjects affected / exposed	1 / 76 (1.32%)	0 / 76 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Ankle fracture			
subjects affected / exposed	0 / 76 (0.00%)	0 / 76 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Foot fracture			
subjects affected / exposed	1 / 76 (1.32%)	0 / 76 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Varicose vein			
subjects affected / exposed	0 / 76 (0.00%)	0 / 76 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Paraesthesia			
subjects affected / exposed	0 / 76 (0.00%)	0 / 76 (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 / 76 (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			
Pelvic pain			
subjects affected / exposed	0 / 76 (0.00%)	1 / 76 (1.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Uterine haemorrhage			

subjects affected / exposed	0 / 76 (0.00%)	0 / 76 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	0 / 76 (0.00%)	0 / 76 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	0 / 76 (0.00%)	0 / 76 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Renal colic			
subjects affected / exposed	0 / 76 (0.00%)	0 / 76 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ureteric stenosis			
subjects affected / exposed	0 / 76 (0.00%)	0 / 76 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Intervertebral disc protrusion			
subjects affected / exposed	0 / 76 (0.00%)	0 / 76 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rhabdomyolysis			
subjects affected / exposed	0 / 76 (0.00%)	0 / 76 (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 pneumonia			

subjects affected / exposed	0 / 76 (0.00%)	0 / 76 (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	24 / 175 (13.71%)	38 / 174 (21.84%)	45 / 173 (26.01%)
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	4 / 175 (2.29%)	8 / 174 (4.60%)	10 / 173 (5.78%)
occurrences (all)	4	9	13
Blood alkaline phosphatase increased			
subjects affected / exposed	6 / 175 (3.43%)	6 / 174 (3.45%)	5 / 173 (2.89%)
occurrences (all)	6	6	8
Blood glucose increased			
subjects affected / exposed	0 / 175 (0.00%)	10 / 174 (5.75%)	8 / 173 (4.62%)
occurrences (all)	0	15	14
Gamma-glutamyltransferase increased			
subjects affected / exposed	4 / 175 (2.29%)	6 / 174 (3.45%)	7 / 173 (4.05%)
occurrences (all)	4	8	12
Nervous system disorders			
Headache			
subjects affected / exposed	13 / 175 (7.43%)	11 / 174 (6.32%)	14 / 173 (8.09%)
occurrences (all)	14	17	15
Infections and infestations			
COVID-19			
subjects affected / exposed	0 / 175 (0.00%)	9 / 174 (5.17%)	11 / 173 (6.36%)
occurrences (all)	0	9	11
Urinary tract infection			
subjects affected / exposed	3 / 175 (1.71%)	3 / 174 (1.72%)	9 / 173 (5.20%)
occurrences (all)	3	6	9

Non-serious adverse events	Double-blind:	Placebo/Fezolinetant	
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	Fezolinetant 45 mg/Extension: Fezolinetant 45 mg	45 mg	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	18 / 76 (23.68%)	14 / 76 (18.42%)	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	2 / 76 (2.63%)	2 / 76 (2.63%)	
occurrences (all)	2	2	
Blood alkaline phosphatase increased			
subjects affected / exposed	5 / 76 (6.58%)	1 / 76 (1.32%)	
occurrences (all)	11	1	
Blood glucose increased			
subjects affected / exposed	2 / 76 (2.63%)	0 / 76 (0.00%)	
occurrences (all)	4	0	
Gamma-glutamyltransferase increased			
subjects affected / exposed	4 / 76 (5.26%)	0 / 76 (0.00%)	
occurrences (all)	4	0	
Nervous system disorders			
Headache			
subjects affected / exposed	3 / 76 (3.95%)	5 / 76 (6.58%)	
occurrences (all)	5	11	
Infections and infestations			
COVID-19			
subjects affected / exposed	4 / 76 (5.26%)	6 / 76 (7.89%)	
occurrences (all)	4	6	
Urinary tract infection			
subjects affected / exposed	2 / 76 (2.63%)	1 / 76 (1.32%)	
occurrences (all)	2	2	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
17 May 2019	The study title was updated to convey that the second phase of the study was a non-controlled extension period. The number of participants to be enrolled was increased from 300 to 450, and the sample size justification parameters were updated to reflect a possible 20% discontinuation rate instead of a 32% rate. An additional treatment arm was added to include a 45 mg dose of fezolinetant. The schedule of assessments was updated to include a mammogram at week 52/end of treatment/early discontinuation and an endometrial biopsy following study discontinuation. The screening serology panel was updated to include testing for antibody against hepatitis B antigen and antibody to hepatitis B core antigen. The dose rationale was 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 was increased to within 12 months of trial enrollment. The schedule of assessments was updated to include 2 additional study visits (2b and 5b). The schedule of assessments and pharmacokinetics assessment sections were updated to include the addition of blood draws for pharmacokinetic analysis in participants with a signal of elevated transaminases who were returning for a repeat hepatic abnormality testing blood draw. Details were added for the reporting of drug-induced liver damage and it was clarified that such events were to be characterized as serious adverse events. The statistical analysis was updated to accommodate inclusion of a second dosing cohort.
01 July 2020	Inclusion criterion 4 was updated to remove with or without hysterectomy from the bilateral oophorectomy screening criteria. Inclusion criteria 8 and 10 were aligned to account for the exclusion of participants who had a hysterectomy. Inclusion criterion 9 was updated to specify that the endometrial biopsy obtained at screening must have been considered evaluable; this criterion was now required for all participants. Alternate measures that may be implemented due to site closures related to the COVID-19 pandemic were added to the protocol. These included telemedicine conferences (by telephone), home healthcare services and laboratory assessments performed at local laboratories. It was noted that participants who screen failed due to a COVID-19 pandemic study suspension and have had an evaluable endometrial biopsy would not require a repeat biopsy if they rescreened. Exclusion criteria 6 and 7 were updated so that they applied to all participants, not just participants with a uterus, and the exception for endometrial thickness less than 4 mm was removed from exclusion criterion 7. Exclusion criterion 20 was added to exclude participants who had partial or full hysterectomies. Language was added to specify that the screening endometrial biopsy must have been evaluable. Retest biopsies were only to be performed for insufficient material or unevaluable biopsies, and a maximum of 1 retest biopsy during screening was allowed. It was noted that participants would be allowed into the study based on the primary endometrial result/diagnosis, but a second and tertiary diagnosis would also be reported.
01 July 2020	Adverse events (AEs) of abuse liability, depression, wakefulness and effect on memory were added to the protocol as AEs of special interest. AEs of liver test elevation were clarified. Category 2 results of secondary or tertiary screening endometrial biopsy diagnosis were added to the list of reasons for participant discontinuation. The exploratory endpoint of "Mean score on the Patient Global Impression of Change (PGI-C) in VMS from baseline to each visit" was re-categorized as a secondary endpoint. Sections 7.4.2.2 Secondary Endpoints and 7.4.3 Exploratory Endpoints were updated to move the PGI-C analysis to Section 7.4.2.2. Language was 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