Clinical trial results:
A Randomized, Placebo-Controlled, Double-Blind Phase 3 Clinical Study to Investigate the Long-Term Safety of Fezolinetant in Women Suffering From Vasomotor Symptoms (Hot Flashes) Associated with Menopause

Summary

EudraCT number	2019-000275-16
Trial protocol	GB PL LV ES CZ HU
Global end of trial date	04 January 2022

Results information

Result version number	v1 (current)
This version publication date	18 December 2022
First version publication date	18 December 2022

Trial information

Trial identification

Sponsor protocol code	2693-CL-0304

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04003389
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, +1 8008887704, astellas.resultsdisclosure@astellas.com
Scientific contact	Clinical Trial Disclosure, Astellas Pharma Global Development, Inc, +1 8008887704, astellas.resultsdisclosure@astellas.com

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	04 January 2022
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	04 January 2022
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 long-term safety and tolerability and endometrial health after long-term treatment of fezolinetant in female individuals
seeking treatment for relief of vasomotor symptoms (VMS) associated with menopause.

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: 169
Country: Number of subjects enrolled	Czechia: 15
Country: Number of subjects enrolled	Latvia: 11
Country: Number of subjects enrolled	Poland: 249
Country: Number of subjects enrolled	Spain: 19
Country: Number of subjects enrolled	Ukraine: 36
Country: Number of subjects enrolled	United Kingdom: 76
Country: Number of subjects enrolled	United States: 1256
Worldwide total number of subjects	1831
EEA total number of subjects	294

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)	1804
From 65 to 84 years	27
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Female participants aged ≥ 40 and ≤ 65 years seeking treatment for vasomotor symptoms (VMS) associated with menopause and who met the inclusion criteria and none of the exclusion criteria were enrolled in this study.

Pre-assignment

Screening details:

Prior to randomization, participants had a screening period during which participants had transvaginal ultrasound, endometrial biopsy, dual-energy X-ray absorptiometry scan.

Period 1

Period 1 title	Overall Period (overall period)
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	Placebo

Arm description:

Participants received fezolinetant matching placebo (two fezolinetant matching placebo tablets) orally, once daily (QD) for a of period of 52 Weeks.

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:

Placebo administered orally, QD for a period of 52 Weeks.

Arm title	Fezolinetant 30 mg

Arm description:

Participants received fezolinetant 30 milligrams (mg) (one 30 mg fezolinetant tablet and one placebo tablet) orally, QD for a period of 52 Weeks.

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:

Fezolinetant 30 mg administered orally, QD for a period of 52 Weeks.

Arm title	Fezolinetant 45 mg

Arm description:

Participants received fezolinetant 45 mg (one 30 mg tablet and one 15 mg tablet) orally, QD for a period of 52 Weeks.

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:

Fezolinetant 45 mg administered orally, QD for a period of 52 Weeks.

Number of subjects in period 1	Placebo	Fezolinetant 30 mg	Fezolinetant 45 mg
Started	611	611	609
Treated	610	611	609
Completed	410	451	444
Not completed	201	160	165
Consent withdrawn by subject	119	79	85
Adverse event, non-fatal	27	34	28
Miscellaneous	14	11	14
Participant did not receive study drug	1	-	-
Lost to follow-up	39	30	33
Protocol deviation	1	6	5

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Participants received fezolinetant matching placebo (two fezolinetant matching placebo tablets) orally, once daily (QD) for a of period of 52 Weeks.	
Reporting group title	Fezolinetant 30 mg
Reporting group description:	
Participants received fezolinetant 30 milligrams (mg) (one 30 mg fezolinetant tablet and one placebo tablet) orally, QD for a period of 52 Weeks.	
Reporting group title	Fezolinetant 45 mg
Reporting group description:	
Participants received fezolinetant 45 mg (one 30 mg tablet and one 15 mg tablet) orally, QD for a period of 52 Weeks.	

Reporting group values	Placebo	Fezolinetant 30 mg	Fezolinetant 45 mg
Number of subjects	611	611	609
Age categorical Units: Subjects			
In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over			
Age Units: years			
arithmetic mean	54.8	54.7	54.7
standard deviation	± 4.8	± 4.7	± 4.8
Sex Units: Subjects			
Female	611	611	609
Analysis Race Units: Subjects			
American Indian or Alaska Native	3	3	2
Black or African American	92	114	110
Missing	0	1	1
More Than One Race	6	6	4
Asian	8	8	13
White	502	479	479
Ethnicity Units: Subjects			
HISPANIC OR LATINO	133	118	116
Missing	0	0	2

NOT HISPANIC OR LATINO	478	493	491
Smoking Status			
Participants with smoking status as current or former/never were reported.			
Units: Subjects			
Current	117	116	116
Former/Never	494	495	493

Reporting group values	Total		
Number of subjects	1831		
Age categorical			
Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	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)	0		
From 65-84 years	0		
85 years and over	0		
Age			
Units: years			
arithmetic mean			
standard deviation	-		
Sex			
Units: Subjects			
Female	1831		
Analysis Race			
Units: Subjects			
American Indian or Alaska Native	8		
Black or African American	316		
Missing	2		
More Than One Race	16		
Asian	29		
White	1460		
Ethnicity			
Units: Subjects			
HISPANIC OR LATINO	367		
Missing	2		
NOT HISPANIC OR LATINO	1462		
Smoking Status			
Participants with smoking status as current or former/never were reported.			
Units: Subjects			
Current	349		
Former/Never	1482		

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description:	
Participants received fezolinetant matching placebo (two fezolinetant matching placebo tablets) orally, once daily (QD) for a of period of 52 Weeks.	
Reporting group title	Fezolinetant 30 mg
Reporting group description:	
Participants received fezolinetant 30 milligrams (mg) (one 30 mg fezolinetant tablet and one placebo tablet) orally, QD for a period of 52 Weeks.	
Reporting group title	Fezolinetant 45 mg
Reporting group description:	
Participants received fezolinetant 45 mg (one 30 mg tablet and one 15 mg tablet) orally, QD for a period of 52 Weeks.	

Primary: Number of Participants with Treatment Emergent Adverse Events (TEAEs)

End point title	Number of Participants with Treatment Emergent Adverse Events (TEAEs)[1]

End point description:

An AE is any untoward medical occurrence in a participant administered a study drug, & which does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable & unintended sign, symptom, or disease temporally associated with the use of medicinal product (MP) whether or not considered related to 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. A TEAE is defined as an AE observed after starting administration of study drug & 21 days after the last dose of study drug.

End point type	Primary

End point timeframe:

From first dose of study drug until 21 days after last dose of study drug (Up to 55 weeks)

Analysis population description (APD):Safety analysis set (SAF) consisted of all randomized participants who took at least 1 dose of study intervention.

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: There was no pre-specified statistical analysis for this endpoint

End point values	Placebo	Fezolinetant 30 mg	Fezolinetant 45 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	610	611	609	
Units: participants				
TEAE	391	415	389	
Drug-Related TEAE	106	94	110	
Serious TEAE	14	20	23	
Drug-Related Serious TEAE	1	0	0	
TEAE Leading to Death	0	1	0	
Drug-Related TEAE Leading to Death	0	0	0	
TEAE Leading to Withdrawal of Treatment (Trt)	26	34	28	

Drug-Related TEAE Leading to Withdrawal of Trt	16	16	17	
Death	0	1	0	

Statistical analyses

No statistical analyses for this end point

Primary: Number of Participants With Mild, Moderate and Severe TEAE

End point title	Number of Participants With Mild, Moderate and Severe TEAE[2]

End point description:

An adverse event (AE) is any untoward medical occurrence in a participant administered a study drug, and which does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product whether or not considered related to the medicinal product. A TEAE is defined as an AE observed after starting administration of the study drug and 21 days after the last dose of study drug. Severity of AE we were classified as Mild: No disruption of normal daily activities; Moderate: Affect normal daily activities; and Severe: Inability to perform daily activities.

End point type	Primary

End point timeframe:

From first dose of study drug until 21 days after last dose of study drug (Up to 55 weeks)

APD: SAF population

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: There was no pre-specified statistical analysis for this endpoint

End point values	Placebo	Fezolinetant 30 mg	Fezolinetant 45 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	610	611	609	
Units: participants				
Mild	180	215	195	
Moderate	191	185	171	
Severe	20	12	23	

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of Participants With Endometrial Hyperplasia

End point title	Percentage of Participants With Endometrial Hyperplasia[3]

End point description:

Endometrial hyperplasia was confirmed from the endometrial biopsy report.

APD: Endometrial health set (EHS):All randomized participants who received at least 1 dose of study drug, had postbaseline (PB) biopsy done within 30 days after last dose, & had an acceptable biopsy at baseline (at least 1 endometrial biopsy (EB) with satisfactory tissue & no read of hyperplasia, disordered proliferative pattern or malignant) & had a satisfactory EB result after or on day 326 or had a PB final

diagnosis of hyperplasia, disordered proliferative pattern or malignant prior to day 326.

End point type	Primary

End point timeframe:

Baseline Up to 52 weeks

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: There was no pre-specified statistical analysis for this endpoint

End point values	Placebo	Fezolinetant 30 mg	Fezolinetant 45 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	186	210	203	
Units: percentage of participants				
number (not applicable)	0	0	0.5	

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of Participants With Endometrial Cancer

End point title	Percentage of Participants With Endometrial Cancer[4]

End point description:

Endometrial cancer was confirmed from the endometrial biopsy report.

APD: Endometrial Health Set

End point type	Primary

End point timeframe:

Baseline Up to 52 weeks

Notes:

[4] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: There was no pre-specified statistical analysis for this endpoint

End point values	Placebo	Fezolinetant 30 mg	Fezolinetant 45 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	186	210	203	
Units: percentage of participants				
number (not applicable)	0	0.5	0	

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Endometrial Thickness at Week 52

End point title	Change From Baseline in Endometrial Thickness at Week 52

End point description:

Endometrial thicness was obtained from the transvaginal ultrasound. The endometrium was measured in the long axis or sagittal plane. The measurement was of the thickest echogenic area from 1 basal endometrial interface across the endometrial canal to the other basal surface.

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

End point type	Secondary

End point timeframe:

Baseline and week 52

End point values	Placebo	Fezolinetant 30 mg	Fezolinetant 45 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	316	334	346	
Units: millimeter (mm)				
arithmetic mean (standard deviation)	-0.17 (± 2.35)	-0.15 (± 1.97)	-0.28 (± 2.30)	

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

LSMeans (LSM), standard errors (SE), confidence intervals (CI)

Comparison groups	Placebo v Fezolinetant 30 mg
Number of subjects included in analysis	650
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0604 [5]
Method	ANCOVA
Parameter estimate	LSMean difference
Point estimate	-0.08
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.36
upper limit	0.21
Variability estimate	Standard error of the mean
Dispersion value	0.14

Notes:

[5] - LSM, SE, CI, & p-values come from an analysis of covariance (ANCOVA) model with change from baseline at Week 52 timepoint as response, treatment & smoking status (current vs former/never) as fixed effects with baseline weight & baseline as covariate.

Statistical analysis title	Statistical Analysis 2
Comparison groups	Placebo v Fezolinetant 45 mg

Number of subjects included in analysis	662
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.239 [6]
Method	ANCOVA
Parameter estimate	LSMean difference
Point estimate	-0.17
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.45
upper limit	0.11
Variability estimate	Standard error of the mean
Dispersion value	0.14

Notes:

[6] - The LSM, SE, CI, and p-values come from an ANCOVA model with change from baseline at the Week 52 timepoint as response, treatment and smoking status (current vs former/never) as fixed effects with baseline weight and baseline as covariates.

Secondary: Percentage of Participants With Disordered Proliferative Endometrium

End point title	Percentage of Participants With Disordered Proliferative Endometrium

End point description:

Disordered proliferative endometrium was confirmed from the endometrial biopsy report.

APD: Endometrial Health Set

End point type	Secondary

End point timeframe:

Baseline Up to 52 weeks

End point values	Placebo	Fezolinetant 30 mg	Fezolinetant 45 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	186	210	203	
Units: percentage of participants				
number (not applicable)	2.2	1.4	0	

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Bone Mineral Density (BMD) at Hip at Week 52

End point title	Change From Baseline in Bone Mineral Density (BMD) at Hip at Week 52

End point description:

Changes in BMD hip was assessed by dual-energy X-ray absorptiometry (DXA) scan.

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

End point type	Secondary

End point timeframe:

Baseline and week 52

End point values	Placebo	Fezolinetant 30 mg	Fezolinetant 45 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	246	221	234	
Units: gram per square centimeter (g/cm^2)				
arithmetic mean (standard deviation)				
Hip (Femoral Neck) (n = 246, 221, 234)	-0.010 (± 0.033)	-0.001 (± 0.044)	-0.009 (± 0.033)	
Hip (Femur) (n = 246, 221, 234)	-0.011 (± 0.022)	-0.003 (± 0.041)	-0.008 (± 0.024)	
Hip (Trochanter) (n = 246, 221, 234)	-0.008 (± 0.027)	-0.001 (± 0.042)	-0.004 (± 0.026)	

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Statistical analysis description: Hip (Femoral Neck)	
Comparison groups	Placebo v Fezolinetant 30 mg
Number of subjects included in analysis	467
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.029 [7]
Method	ANCOVA
Parameter estimate	LSMean difference
Point estimate	0.007
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.001
upper limit	0.014
Variability estimate	Standard error of the mean
Dispersion value	0.003

Notes:

[7] - The LSM, SE, CI, and p-values come from an ANCOVA model with change from baseline at the Week 52 timepoint as response, treatment and smoking status (current vs former/never) as fixed effects with baseline weight and baseline as covariates.

Statistical analysis title	Statistical Analysis 2
Statistical analysis description: Hip (Femoral Neck)	
Comparison groups	Placebo v Fezolinetant 45 mg

Number of subjects included in analysis	480
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.867 [8]
Method	ANCOVA
Parameter estimate	LSMean difference
Point estimate	0.001
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.006
upper limit	0.007
Variability estimate	Standard error of the mean
Dispersion value	0.003

Notes:

[8] - The LSM, SE, CI, and p-values come from an ANCOVA model with change from baseline at the Week 52 timepoint as response, treatment and smoking status (current vs former/never) as fixed effects with baseline weight and baseline as covariates.

Statistical analysis title	Statistical Analysis 3

Statistical analysis description:

Hip (Femur)

Comparison groups	Placebo v Fezolinetant 30 mg
Number of subjects included in analysis	467
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.027 [9]
Method	ANCOVA
Parameter estimate	LSMean difference
Point estimate	0.006
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.001
upper limit	0.012
Variability estimate	Standard error of the mean
Dispersion value	0.003

Notes:

[9] - The LSM, SE, CI, and p-values come from an ANCOVA model with change from baseline at the Week 52 timepoint as response, treatment and smoking status (current vs former/never) as fixed effects with baseline weight and baseline as covariates.

Statistical analysis title	Statistical Analysis 4

Statistical analysis description:

Hip (Femur)

Comparison groups	Placebo v Fezolinetant 45 mg
Number of subjects included in analysis	480
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.41 [10]
Method	ANCOVA
Parameter estimate	LSMean difference
Point estimate	0.002

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.003
upper limit	0.008
Variability estimate	Standard error of the mean
Dispersion value	0.003

Notes:

[10] - The LSM, SE, CI, and p-values come from an ANCOVA model with change from baseline at the Week 52 timepoint as response, treatment and smoking status (current vs former/never) as fixed effects with baseline weight and baseline as covariates.

Statistical analysis title	Statistical Analysis 5
Statistical analysis description:	
Hip (Trochanter)	
Comparison groups	Placebo v Fezolinetant 30 mg
Number of subjects included in analysis	467
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.087 [11]
Method	ANCOVA
Parameter estimate	LSMean difference
Point estimate	0.005
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.001
upper limit	0.011
Variability estimate	Standard error of the mean
Dispersion value	0.003

Notes:

[11] - The LSM, SE, CI, and p-values come from an ANCOVA model with change from baseline at the Week 52 timepoint as response, treatment and smoking status (current vs former/never) as fixed effects with baseline weight and baseline as covariates.

Statistical analysis title	Statistical Analysis 6
Statistical analysis description:	
Hip (Trochanter)	
Comparison groups	Placebo v Fezolinetant 45 mg
Number of subjects included in analysis	480
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.259 [12]
Method	ANCOVA
Parameter estimate	LSMean difference
Point estimate	0.003
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.002
upper limit	0.009
Variability estimate	Standard error of the mean
Dispersion value	0.003

Notes:

[12] - The LSM, SE, CI, and p-values come from an ANCOVA model with change from baseline at the Week 52 timepoint as response, treatment and smoking status (current vs former/never) as fixed effects with baseline weight and baseline as covariates.

Secondary: Change From Baseline in Trabecular Bone Score (TBS) at Hip at Week 52

End point title	Change From Baseline in Trabecular Bone Score (TBS) at Hip at Week 52

End point description:

TBS was a bone texture assessment that serves as a substitute for bone microarchitecture and predicts fracture risk independent of BMD and clinical risk factors. The DXA imaging was processed and analyzed as it would normally be and then evaluated using an automated algorithm to determine the TBS. T-score ≥1.350 was considered to be normal; T-score between 1.200 and 1.350 is considered to be consistent with partially degraded microarchitecture; and T-score ≤1.200 defines degraded microarchitecture.

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

End point type	Secondary

End point timeframe:

Baseline and week 52

End point values	Placebo	Fezolinetant 30 mg	Fezolinetant 45 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	246	221	234	
Units: T-Score (Index)				
arithmetic mean (standard deviation)				
Hip (Femoral Neck) (n = 246, 221, 234)	-0.078 (± 0.246)	-0.011 (± 0.372)	-0.073 (± 0.265)	
Hip (Femur) (n = 246, 221, 234)	-0.085 (± 0.192)	-0.024 (± 0.354)	-0.063 (± 0.192)	
Hip (Trochanter) (n = 246, 221, 234)	-0.071 (± 0.255)	-0.009 (± 0426)	-0.036 (± 0.246)	

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Hip (Femoral Neck)

Comparison groups	Placebo v Fezolinetant 30 mg
Number of subjects included in analysis	467
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.079 [13]
Method	ANCOVA
Parameter estimate	LSMean difference
Point estimate	0.048
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.006
upper limit	0.102

Variability estimate	Standard error of the mean
Dispersion value	0.027

Notes:

[13] - The LSM, SE, CI, and p-values come from an ANCOVA model with change from baseline at the Week 52 timepoint as response, treatment and smoking status (current vs former/never) as fixed effects with baseline weight and baseline as covariates.

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

Hip (Femoral Neck)

Comparison groups	Placebo v Fezolinetant 45 mg
Number of subjects included in analysis	480
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.98 [14]
Method	ANCOVA
Parameter estimate	LSMean difference
Point estimate	0.001
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.052
upper limit	0.053
Variability estimate	Standard error of the mean
Dispersion value	0.027

Notes:

[14] - The LSM, SE, CI, and p-values come from an ANCOVA model with change from baseline at the Week 52 timepoint as response, treatment and smoking status (current vs former/never) as fixed effects with baseline weight and baseline as covariates.

Statistical analysis title	Statistical Analysis 3

Statistical analysis description:

Hip (Femur)

Comparison groups	Placebo v Fezolinetant 30 mg
Number of subjects included in analysis	467
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.042 [15]
Method	ANCOVA
Parameter estimate	LSMean difference
Point estimate	0.048
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.002
upper limit	0.094
Variability estimate	Standard error of the mean
Dispersion value	0.023

Notes:

[15] - The LSM, SE, CI, and p-values come from an ANCOVA model with change from baseline at the Week 52 timepoint as response, treatment and smoking status (current vs former/never) as fixed effects with baseline weight and baseline as covariates.

Statistical analysis title	Statistical Analysis 4

Statistical analysis description:	
Hip (Femur)	
Comparison groups	Placebo v Fezolinetant 45 mg
Number of subjects included in analysis	480
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.386 [16]
Method	ANCOVA
Parameter estimate	LSMean difference
Point estimate	0.02
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.025
upper limit	0.065
Variability estimate	Standard error of the mean
Dispersion value	0.023

Notes:

[16] - The LSM, SE, CI, and p-values come from an ANCOVA model with change from baseline at the Week 52 timepoint as response, treatment and smoking status (current vs former/never) as fixed effects with baseline weight and baseline as covariates.

Statistical analysis title	Statistical Analysis 5
Statistical analysis description:	
Hip (Trochanter)	
Comparison groups	Placebo v Fezolinetant 30 mg
Number of subjects included in analysis	467
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.156 [17]
Method	ANCOVA
Parameter estimate	LSMean difference
Point estimate	0.041
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.016
upper limit	0.099
Variability estimate	Standard error of the mean
Dispersion value	0.029

Notes:

[17] - The LSM, SE, CI, and p-values come from an ANCOVA model with change from baseline at the Week 52 timepoint as response, treatment and smoking status (current vs former/never) as fixed effects with baseline weight and baseline as covariates.

Statistical analysis title	Statistical Analysis 6
Statistical analysis description:	
Hip (Trochanter)	
Comparison groups	Placebo v Fezolinetant 45 mg

Number of subjects included in analysis	480
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.328 [18]
Method	ANCOVA
Parameter estimate	LSMean difference
Point estimate	0.028
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.028
upper limit	0.084
Variability estimate	Standard error of the mean
Dispersion value	0.029

Notes:

[18] - The LSM, SE, CI, and p-values come from an ANCOVA model with change from baseline at the Week 52 timepoint as response, treatment and smoking status (current vs former/never) as fixed effects with baseline weight and baseline as covariates.

Secondary: Change From Baseline in BMD at Spine at Week 52

End point title	Change From Baseline in BMD at Spine at Week 52

End point description:

Changes in BMD spine was assessed by DXA scan.

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

End point type	Secondary

End point timeframe:

Baseline and week 52

End point values	Placebo	Fezolinetant 30 mg	Fezolinetant 45 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	253	225	242	
Units: g/cm^2				
arithmetic mean (standard deviation)	-0.013 (± 0.035)	-0.010 (± 0.049)	-0.014 (± 0.034)	

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Placebo v Fezolinetant 30 mg
Number of subjects included in analysis	478
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.497 [19]
Method	ANCOVA
Parameter estimate	LSMean difference
Point estimate	0.002

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.005
upper limit	0.009
Variability estimate	Standard error of the mean
Dispersion value	0.004

Notes:

[19] - The LSM, SE, CI, and p-values come from an ANCOVA model with change from baseline at the Week 52 timepoint as response, treatment and smoking status (current vs former/never) as fixed effects with baseline weight and baseline as covariates.

Statistical analysis title	Statistical Analysis 2
Comparison groups	Placebo v Fezolinetant 45 mg
Number of subjects included in analysis	495
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.878 [20]
Method	ANCOVA
Parameter estimate	LSMean difference
Point estimate	-0.001
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.007
upper limit	0.006
Variability estimate	Standard error of the mean
Dispersion value	0.004

Notes:

[20] - The LSM, SE, CI, and p-values come from an ANCOVA model with change from baseline at the Week 52 timepoint as response, treatment and smoking status (current vs former/never) as fixed effects with baseline weight and baseline as covariates.

Secondary: Change From Baseline in TBS at Spine at Week 52

End point title	Change From Baseline in TBS at Spine at Week 52

End point description:

TBS was a bone texture assessment that serves as a substitute for bone microarchitecture and predicts fracture risk independent of BMD and clinical risk factors. The DXA imaging was processed and analyzed as it would normally be and then evaluated using an automated algorithm to determine the TBS. T-score ≥1.350 was considered to be normal; T-score between 1.200 and 1.350 is considered to be consistent with partially degraded microarchitecture; and T-score ≤1.200 defines degraded microarchitecture.

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

End point type	Secondary

End point timeframe:

Baseline and week 52

End point values	Placebo	Fezolinetant 30 mg	Fezolinetant 45 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	253	225	242	
Units: T-Score (Index)				
arithmetic mean (standard deviation)	-0.117 (± 0.296)	-0.084 (± 0.025)	-0.119 (± 0.298)	

Statistical analyses

Statistical analysis title	Statistical Analysis 2
Comparison groups	Placebo v Fezolinetant 45 mg
Number of subjects included in analysis	495
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.872 [21]
Method	ANCOVA
Parameter estimate	LSMean difference
Point estimate	-0.005
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.066
upper limit	0.056
Variability estimate	Standard error of the mean
Dispersion value	0.031

Notes:

[21] - The LSM, SE, CI, and p-values come from an ANCOVA model with change from baseline at the Week 52 timepoint as response, treatment and smoking status (current vs former/never) as fixed effects with baseline weight and baseline as covariates.

Statistical analysis title	Statistical Analysis 1
Comparison groups	Placebo v Fezolinetant 30 mg
Number of subjects included in analysis	478
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.527 [22]
Method	ANCOVA
Parameter estimate	LSMean difference
Point estimate	0.02
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.042
upper limit	0.082
Variability estimate	Standard error of the mean
Dispersion value	0.031

Notes:

[22] - The LSM, SE, CI, and p-values come from an ANCOVA model with change from baseline at the Week 52 timepoint as response, treatment and smoking status (current vs former/never) as fixed effects with baseline weight and baseline as covariates.

Secondary: Number of Participants With Suicidal Ideation and/or Behaviour as Assessed by Columbia-Suicide Severity Rating Scale (C-SSRS)

End point title	Number of Participants With Suicidal Ideation and/or Behaviour as Assessed by Columbia-Suicide Severity Rating Scale (C-SSRS)

End point description:

The C-SSRS assessed the risk for suicidal behavior and suicide ideation. Participants responded as "Yes" or "No" 10 items. Suicidal ideation (1. Wish to be dead; 2. Non-specific active suicidal thoughts; 3. Active suicidal ideation with any methods (not plan) without intent to act; 4. Active suicidal ideation with some intent to act, without specific plan; 5. Active suicidal ideation with specific plan and intent;). Suicidal behaviour (1. Preparatory acts or behavior 2. Aborted attempt 3. Interrupted attempt 4. Actual attempt 5. Completed suicide). Participants with 'Yes' to any one of the above 10 questions for suicidal ideation and behavior were reported.

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

End point type	Secondary

End point timeframe:

Baseline, week 12, week 24, week 52 and follow-up (week 55)

End point values	Placebo	Fezolinetant 30 mg	Fezolinetant 45 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	610	611	609	
Units: participants				
Baseline (n = 610, 611, 609)	2	2	4	
Week 12 (n = 501, 531, 536)	0	0	1	
Week 24 (n= 451, 484, 489)	1	1	2	
Week 52 (n = 374, 394, 400)	1	0	0	
Follow-up (Week 55) (n = 470, 481, 484)	0	1	2	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Self-injurious Behavior Without Suicidal Intent as Assessed by C-SSRS

End point title	Number of Participants With Self-injurious Behavior Without Suicidal Intent as Assessed by C-SSRS

End point description:

The C-SSRS assessed the risk for Self-injurious Behavior without Suicidal Intent. Question was asked "Has participant engaged in Non-Suicidal Self-Injurious Behavior?". Participants with 'yes' to the question were reported.

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

End point type	Secondary

End point timeframe:

Baseline, week 12, week 24, week 52 and follow-up (week 55)

End point values	Placebo	Fezolinetant 30 mg	Fezolinetant 45 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	610	611	609	
Units: participants				
Baseline (n = 610, 611, 609)	0	1	0	
Week 12 (n = 501, 531, 536)	1	0	0	
Week 24 (n = 451, 484, 489)	0	0	0	
Week 52 (n = 374, 394, 400)	0	0	0	
Follow-up (Week 55) (n = 470, 481, 484)	1	0	0	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
From first dose of study drug until 21 days after last dose of study drug (Up to 55 weeks)	
Adverse event reporting additional description:	
SAF Population	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	v23.0

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Participants received fezolinetant matching placebo (two fezolinetant matching placebo tablets) orally, QD for a period of 52 Weeks.	
Reporting group title	Fezolinetant 45 mg
Reporting group description:	
Participants received fezolinetant 45 mg (one 30 mg tablet and one 15 mg tablet) orally, QD for a period of 52 Weeks.	
Reporting group title	Fezolinetant 30 mg
Reporting group description:	
Participants received fezolinetant matching placebo (two fezolinetant matching placebo tablets) orally, QD for a period of 52 Weeks.	

Serious adverse events	Placebo	Fezolinetant 45 mg	Fezolinetant 30 mg
Total subjects affected by serious adverse events			
subjects affected / exposed	14 / 610 (2.30%)	23 / 609 (3.78%)	20 / 611 (3.27%)
number of deaths (all causes)	0	0	1
number of deaths resulting from adverse events	0	0	1
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Basal cell carcinoma			
subjects affected / exposed	0 / 610 (0.00%)	0 / 609 (0.00%)	1 / 611 (0.16%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Benign breast neoplasm			
subjects affected / exposed	0 / 610 (0.00%)	0 / 609 (0.00%)	1 / 611 (0.16%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bone cancer			

subjects affected / exposed	0 / 610 (0.00%)	1 / 609 (0.16%)	0 / 611 (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
Chronic lymphocytic leukaemia			
subjects affected / exposed	0 / 610 (0.00%)	0 / 609 (0.00%)	1 / 611 (0.16%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colon cancer			
subjects affected / exposed	0 / 610 (0.00%)	2 / 609 (0.33%)	0 / 611 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endometrial adenocarcinoma			
subjects affected / exposed	0 / 610 (0.00%)	2 / 609 (0.33%)	1 / 611 (0.16%)
occurrences causally related to treatment / all	0 / 0	1 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic cancer			
subjects affected / exposed	0 / 610 (0.00%)	1 / 609 (0.16%)	0 / 611 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Malignant melanoma in situ			
subjects affected / exposed	0 / 610 (0.00%)	1 / 609 (0.16%)	0 / 611 (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
Neurilemmoma benign			
subjects affected / exposed	1 / 610 (0.16%)	0 / 609 (0.00%)	0 / 611 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Non-small cell lung cancer			
subjects affected / exposed	0 / 610 (0.00%)	1 / 609 (0.16%)	0 / 611 (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
Squamous cell carcinoma of skin			

subjects affected / exposed	1 / 610 (0.16%)	0 / 609 (0.00%)	1 / 611 (0.16%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Squamous cell carcinoma of the oral cavity			
subjects affected / exposed	0 / 610 (0.00%)	1 / 609 (0.16%)	0 / 611 (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
Surgical and medical procedures			
Fracture treatment			
subjects affected / exposed	0 / 610 (0.00%)	0 / 609 (0.00%)	1 / 611 (0.16%)
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 / 610 (0.00%)	1 / 609 (0.16%)	0 / 611 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Uterine polyp			
subjects affected / exposed	0 / 610 (0.00%)	0 / 609 (0.00%)	1 / 611 (0.16%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Acute respiratory failure			
subjects affected / exposed	1 / 610 (0.16%)	0 / 609 (0.00%)	1 / 611 (0.16%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoxia			
subjects affected / exposed	0 / 610 (0.00%)	0 / 609 (0.00%)	1 / 611 (0.16%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary embolism			

subjects affected / exposed	0 / 610 (0.00%)	1 / 609 (0.16%)	0 / 611 (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
Pulmonary oedema			
subjects affected / exposed	0 / 610 (0.00%)	0 / 609 (0.00%)	1 / 611 (0.16%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Alcohol abuse			
subjects affected / exposed	0 / 610 (0.00%)	0 / 609 (0.00%)	1 / 611 (0.16%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Depression			
subjects affected / exposed	1 / 610 (0.16%)	0 / 609 (0.00%)	0 / 611 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Suicidal ideation			
subjects affected / exposed	1 / 610 (0.16%)	0 / 609 (0.00%)	0 / 611 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 610 (0.00%)	1 / 609 (0.16%)	0 / 611 (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
Gamma-glutamyltransferase increased			
subjects affected / exposed	1 / 610 (0.16%)	0 / 609 (0.00%)	0 / 611 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Liver function test abnormal			
subjects affected / exposed	0 / 610 (0.00%)	1 / 609 (0.16%)	0 / 611 (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	1 / 610 (0.16%)	0 / 609 (0.00%)	0 / 611 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Animal bite			
subjects affected / exposed	1 / 610 (0.16%)	0 / 609 (0.00%)	0 / 611 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fibula fracture			
subjects affected / exposed	0 / 610 (0.00%)	1 / 609 (0.16%)	0 / 611 (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
Joint dislocation			
subjects affected / exposed	1 / 610 (0.16%)	0 / 609 (0.00%)	0 / 611 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lumbar vertebral fracture			
subjects affected / exposed	0 / 610 (0.00%)	1 / 609 (0.16%)	0 / 611 (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
Radius fracture			
subjects affected / exposed	0 / 610 (0.00%)	0 / 609 (0.00%)	1 / 611 (0.16%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Stab wound			
subjects affected / exposed	0 / 610 (0.00%)	1 / 609 (0.16%)	0 / 611 (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
Tendon rupture			
subjects affected / exposed	1 / 610 (0.16%)	0 / 609 (0.00%)	0 / 611 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Tibia fracture			
subjects affected / exposed	0 / 610 (0.00%)	1 / 609 (0.16%)	0 / 611 (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
Congenital, familial and genetic disorders			
Alpha-1 antitrypsin deficiency			
subjects affected / exposed	0 / 610 (0.00%)	0 / 609 (0.00%)	1 / 611 (0.16%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	0 / 610 (0.00%)	0 / 609 (0.00%)	1 / 611 (0.16%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial fibrillation			
subjects affected / exposed	1 / 610 (0.16%)	0 / 609 (0.00%)	0 / 611 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac arrest			
subjects affected / exposed	0 / 610 (0.00%)	0 / 609 (0.00%)	1 / 611 (0.16%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Cardiac failure			
subjects affected / exposed	0 / 610 (0.00%)	0 / 609 (0.00%)	1 / 611 (0.16%)
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			
Brain injury			
subjects affected / exposed	0 / 610 (0.00%)	0 / 609 (0.00%)	1 / 611 (0.16%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Headache			

subjects affected / exposed	0 / 610 (0.00%)	1 / 609 (0.16%)	0 / 611 (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
Hemiparesis			
subjects affected / exposed	0 / 610 (0.00%)	1 / 609 (0.16%)	0 / 611 (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
Transient ischaemic attack			
subjects affected / exposed	0 / 610 (0.00%)	1 / 609 (0.16%)	0 / 611 (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
Ear and labyrinth disorders			
Deafness bilateral			
subjects affected / exposed	0 / 610 (0.00%)	0 / 609 (0.00%)	1 / 611 (0.16%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 610 (0.00%)	2 / 609 (0.33%)	1 / 611 (0.16%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis			
subjects affected / exposed	0 / 610 (0.00%)	1 / 609 (0.16%)	0 / 611 (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
Small intestinal obstruction			
subjects affected / exposed	1 / 610 (0.16%)	0 / 609 (0.00%)	0 / 611 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	0 / 610 (0.00%)	1 / 609 (0.16%)	0 / 611 (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			

Cholecystitis			
subjects affected / exposed	1 / 610 (0.16%)	0 / 609 (0.00%)	0 / 611 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholecystitis acute			
subjects affected / exposed	1 / 610 (0.16%)	0 / 609 (0.00%)	0 / 611 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatitis			
subjects affected / exposed	0 / 610 (0.00%)	0 / 609 (0.00%)	1 / 611 (0.16%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 610 (0.00%)	1 / 609 (0.16%)	0 / 611 (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
Endocrine disorders			
Goitre			
subjects affected / exposed	0 / 610 (0.00%)	1 / 609 (0.16%)	1 / 611 (0.16%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Lumbar spinal stenosis			
subjects affected / exposed	0 / 610 (0.00%)	0 / 609 (0.00%)	1 / 611 (0.16%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
COVID-19			
subjects affected / exposed	1 / 610 (0.16%)	2 / 609 (0.33%)	0 / 611 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
COVID-19 pneumonia			

subjects affected / exposed	1 / 610 (0.16%)	0 / 609 (0.00%)	1 / 611 (0.16%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Influenza			
subjects affected / exposed	1 / 610 (0.16%)	1 / 609 (0.16%)	0 / 611 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Meningitis			
subjects affected / exposed	0 / 610 (0.00%)	1 / 609 (0.16%)	0 / 611 (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
Pneumonia			
subjects affected / exposed	1 / 610 (0.16%)	0 / 609 (0.00%)	1 / 611 (0.16%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection bacterial			
subjects affected / exposed	0 / 610 (0.00%)	0 / 609 (0.00%)	1 / 611 (0.16%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	0 / 610 (0.00%)	0 / 609 (0.00%)	1 / 611 (0.16%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diabetic ketoacidosis			
subjects affected / exposed	0 / 610 (0.00%)	1 / 609 (0.16%)	0 / 611 (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
Hypercholesterolaemia			
subjects affected / exposed	0 / 610 (0.00%)	0 / 609 (0.00%)	1 / 611 (0.16%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Placebo	Fezolinetant 45 mg	Fezolinetant 30 mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	90 / 610 (14.75%)	78 / 609 (12.81%)	86 / 611 (14.08%)
Nervous system disorders			
Headache			
subjects affected / exposed	56 / 610 (9.18%)	54 / 609 (8.87%)	52 / 611 (8.51%)
occurrences (all)	60	72	57
Infections and infestations			
COVID-19			
subjects affected / exposed	37 / 610 (6.07%)	30 / 609 (4.93%)	38 / 611 (6.22%)
occurrences (all)	37	30	38

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
17 May 2019	The changes included: A fezolinetant 45 mg treatment group was added for a total of 3 treatment groups. A fezolinetant 15 mg tablet was added for subjects in the 45 mg dose group. The randomization schema was updated to a 1:1:1 ratio (fezolinetant 45 mg: fezolinetant 30 mg: placebo). The number of subjects enrolled was updated to 1149 (383 subjects per treatment group). • 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. Further details were provided regarding the circumstances under which these procedures were performed. • The screening serology panel was updated to include testing for antibody against hepatitis B antigen and antibody to hepatitis B core antigen. • The schedule of assessments was updated to include an additional study visit (2b) at week 2. • The schedule of assessments and pharmacokinetics assessment sections were updated to include the addition of blood draws for pharmacokinetic analysis in subjects with a signal of elevated transaminases who were returning for a repeat hepatic abnormality testing blood draw. • The primary objective was reworded "to evaluate the long-term safety and tolerability of fezolinetant," rather than "the effect of fezolinetant on long-term safety and tolerability." • 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. • Details were added for the reporting of drug-induced liver damage and it was clarified that such events were to be characterized as SAEs.
15 June 2020	The changes included: The evaluation of the effect of fezolinetant on endometrial health was moved from the secondary objective of the study to the primary objective of the study. • The endometrial health analysis set was added to the protocol for analysis of endometrial health-related endpoints. This set was defined as having 1 year of evaluable biopsy results. • The planned number of subjects was increased to 1740, with approximately 580 subjects randomized to each treatment group. The sample size justification was updated and the table in Section 7.1, Sample Size, showing the probability of observing 1 or more events and 2 or more events for different background event rate was updated to include the probability of observing 3 or more events for different background event rate. • The percentages of subjects with endometrial hyperplasia and endometrial cancer were moved from secondary to primary endpoints. The percentage of subjects with disordered proliferative endometrium was added as a secondary endpoint. It was noted that the rates of endometrial hyperplasia, endometrial cancer and disordered proliferative endometrium were evaluated separately. • Inclusion criterion No. 4 was updated to remove with or without hysterectomy from the bilateral oophorectomy screening criteria. Inclusion criteria No. 8 and No. 10 were aligned to account for the exclusion of subjects who had had a hysterectomy. Inclusion criterion No. 9 was updated to specify that the endometrial biopsy obtained at screening had to be considered evaluable; this criterion was now required for all subjects.

15 June 2020	• Alternate measures that could be implemented due to site closures related to the COVID-19 pandemic were added to the protocol. These include telemedicine conferences (by telephone), home healthcare services, and laboratory assessments performed at local laboratories. It was noted that subjects who screen failed due to a COVID-19 pandemic study suspension and had an evaluable endometrial biopsy were not required to have a repeat biopsy if they rescreen. • Exclusion criteria No. 6 and No. 7 were updated so that they applied to all subjects, not just subjects with a uterus, and the exception for endometrial thickness less than 4 mm was removed from exclusion criterion No. 7. Exclusion criterion No. 20 was added to exclude subjects who had had partial or full hysterectomies. • Language was added to specify that the screening endometrial biopsy had to be evaluable. Retest biopsies could only be performed for insufficient material or unevaluable biopsies and a maximum of 1 retest biopsy during screening was allowed. It was noted that subjects were allowed into the study based on the primary endometrial result/diagnosis, but a second and tertiary diagnosis was also to be reported. • 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 subject discontinuation. • Other minor text adjustments were made.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported