Clinical trial results:
A double-blind, randomized, placebo-controlled multicenter study to investigate efficacy and safety of elinzanetant for the treatment of vasomotor symptoms over 26 weeks in postmenopausal women

Summary

EudraCT number	2020-004908-33
Trial protocol	AT IT HU NL GR
Global end of trial date	27 November 2023

Results information

Result version number	v1 (current)
This version publication date	07 December 2024
First version publication date	07 December 2024

Trial information

Trial identification

Sponsor protocol code	BAY3427080/21651

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT05042362
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Bayer AG
Sponsor organisation address	Kaiser Wilhelm Allee, Leverkusen, Germany, D-51368
Public contact	Therapeutic Area Head, Bayer AG, +49 30 300139003, clinical-trials-contact@bayer.com
Scientific contact	Therapeutic Area Head, Bayer AG, +49 30 300139003, clinical-trials-contact@bayer.com

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	20 December 2023
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	27 November 2023
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 elinzanetant for the treatment of Vasomotor symptoms (VMS) associated with the menopause.

Protection of trial subjects:

The conduct of this clinical study met all local legal and regulatory requirements. The study was conducted in accordance with ethical principles that have their origin in the Declaration of Helsinki and the International Council for Harmonization guideline E6: Good Clinical Practice. Before entering the study, the informed consent was read by and explained to all the subjects. Participating subjects signed informed consent form and could withdraw from the study at any time without any disadvantage and without having to provide a reason for this decision. Only investigators qualified by training and experience were selected as appropriate experts to investigate the study drug.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	27 August 2021
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Austria: 27
Country: Number of subjects enrolled	Czechia: 67
Country: Number of subjects enrolled	Greece: 6
Country: Number of subjects enrolled	Hungary: 21
Country: Number of subjects enrolled	Israel: 2
Country: Number of subjects enrolled	Italy: 23
Country: Number of subjects enrolled	Netherlands: 15
Country: Number of subjects enrolled	United States: 235
Worldwide total number of subjects	396
EEA total number of subjects	159

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37	0

wk	
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)	390
From 65 to 84 years	6
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Study was conducted at 89 study centers in 8 countries, between 27-Aug-2021 (first subject first visit) and 27-Nov-2023 (last subject last visit).

Pre-assignment

Screening details:

A total of 1535 subjects were screened; 1139 subjects were not randomized. Most common reason for not being randomized was not meeting the eligibility criteria (1087 subjects). 396 subjects were randomized to treatment. A total of 197 subjects were randomized to placebo-elinzanetant 120 mg arm and 199 subjects to elinzanetant 120 mg arm.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Elinzanetant 120 mg

Arm description:

Subjects received elinzanetant 120 mg orally once daily for 26 weeks.

Arm type	Experimental
Investigational medicinal product name	Elinzanetant
Investigational medicinal product code	BAY3427080
Other name	NT-814
Pharmaceutical forms	Capsule, soft
Routes of administration	Oral use

Dosage and administration details:

Two capsules of 60 mg elinzanetant once daily in the evening before bedtime for 26 weeks.

Arm title	Placebo - Elinzanetant 120 mg

Arm description:

Subjects received placebo for 12 weeks, followed by elinzanetant 120 mg orally once daily for 14 weeks

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

Dosage and administration details:

Two capsules once daily in the evening before bedtime from week 1 to week 12.

Investigational medicinal product name	Elinzanetant
Investigational medicinal product code	BAY3427080
Other name	NT-814
Pharmaceutical forms	Capsule, soft
Routes of administration	Oral use

Dosage and administration details:

Two capsules of 60 mg elinzanetant once daily in the evening before bedtime from week 13 to week 26.

Number of subjects in period 1	Elinzanetant 120 mg	Placebo - Elinzanetant 120 mg
Started	199	197
Completed	154	155
Not completed	45	42
Consent withdrawn by subject	5	9
Physician decision	3	-
Randomized by Mistake	1	2
Non-Compliance with Study Drug	2	3
Adverse event, non-fatal	7	9
Other	-	1
Did not complete study treatment but completed FU	16	10
Lost to follow-up	7	4
Missing	4	2
Lack of efficacy	-	2

Baseline characteristics

Reporting groups	
Reporting group title	Elinzanetant 120 mg
Reporting group description:	
Subjects received elinzanetant 120 mg orally once daily for 26 weeks.	
Reporting group title	Placebo - Elinzanetant 120 mg
Reporting group description:	
Subjects received placebo for 12 weeks, followed by elinzanetant 120 mg orally once daily for 14 weeks	

Reporting group values	Elinzanetant 120 mg	Placebo - Elinzanetant 120 mg	Total
Number of subjects	199	197	396
Age Categorical Units: Subjects			
Age Continuous Units: years			
arithmetic mean	54.6	54.5	
standard deviation	± 4.9	± 4.9	-
Gender Categorical Units: Subjects			
Female	199	197	396
Male	0	0	0
Race Units: Subjects			
White	151	154	305
Black or African American	38	38	76
Asian	2	1	3
American Indian or Alaska Native	1	1	2
Multiple	3	0	3
Other	4	3	7
Ethnicity Units: Subjects			
Not Hispanic or Latino	180	179	359
Hispanic or Latino	17	14	31
Other	2	4	6
Mean frequency of moderate to severe hot flash (HF) at baseline			
Subjects' assessments of HF were recorded electronically twice daily using the sponsor developed Hot Flash Daily Diary (HFDD). The HFDD items assessed the number of mild, moderate, and severe HF experienced during the day and night. Mild HF was defined as a "sensation of heat without sweating", moderate HF was defined as a "sensation of heat with sweating, but able to continue activity", severe HF was defined as a "sensation of heat with sweating, causing cessation (stopping) of activity". The number of analyzed subjects was 199 for elinzanetant 120 mg, 197 for placebo - elinzanetant 120 mg.			
Units: Hot Flashes per day			
arithmetic mean	13.38	14.26	
standard deviation	± 6.57	± 13.94	-
Mean severity of moderate to severe HF at baseline			
The HFDD items assessed the number of mild, moderate, and severe HF experienced during the day and during the night. Mild HF are defined as a "sensation of heat without sweating", moderate HF are			

defined as a "sensation of heat with sweating, but able to continue activity", and severe HF are defined as a "sensation of heat with sweating, causing cessation (stopping) of activity". The number of analyzed subjects was 199 for elinzanetant 120 mg and 197 for placebo - elinzanetant 120 mg.			
Units: Severity scale			
arithmetic mean	2.56	2.53	
standard deviation	± 0.22	± 0.23	-
PROMIS SD SF 8b total T-score at baseline			
The PROMIS SD SF 8b included 8 items assessing sleep disturbance over the past 7 days. Items assessed sleep quality, sleep depth and restoration associated with sleep, perceived difficulties with getting to sleep or staying asleep and perceptions of the adequacy of and satisfaction with sleep. The number of analyzed subjects was 184 for elinzanetant 120 mg and 179 for placebo - elinzanetant 120 mg.			
Units: Scores on scale			
arithmetic mean	61.0	60.2	
standard deviation	± 7.7	± 7.2	-
Menopause-specific quality of life scale (MENQOL) total score at baseline			
The MENQOL questionnaire was comprised of 29 items assessing the presence of menopausal symptoms and the impact of menopause on health-related quality of life over the past week. The items assessed four domains of symptoms and functioning: VMS, psychosocial functioning, physical functioning, and sexual functioning. The number of analyzed subjects was 179 for elinzanetant 120 mg and 173 for placebo - elinzanetant 120 mg.			
Units: Scores on scale			
arithmetic mean	4.56	4.49	
standard deviation	± 1.27	± 1.31	-
Beck depression inventory (BDI-II) total score at baseline			
The BDI-II was a 21-item questionnaire assessing the intensity of depressive symptoms over the past 2 weeks. Items used a 4-point verbal response scale ranging from 0 (not at all) to 3 (extreme form of each symptom). A total score ranging from 0 to 63 was calculated with scores of 0-13 indicating mild minimal range, 14 – 19 mild depression, 20 – 28 indicating moderate and 29 – 63 severe depression (higher score = greater depression). The number of analyzed subjects was 199 for elinzanetant 120 mg and 197 for placebo - elinzanetant 120 mg.			
Units: Scores on scale			
arithmetic mean	6.8	6.2	
standard deviation	± 6.5	± 6.7	-

End points

End points reporting groups

Reporting group title	Elinzanetant 120 mg
Reporting group description:	
Subjects received elinzanetant 120 mg orally once daily for 26 weeks.	
Reporting group title	Placebo - Elinzanetant 120 mg
Reporting group description:	
Subjects received placebo for 12 weeks, followed by elinzanetant 120 mg orally once daily for 14 weeks	
Subject analysis set title	Safety Analysis Set (SAF)
Subject analysis set type	Safety analysis
Subject analysis set description:	
All subjects who received at least one dose of study intervention were analyzed according to the intervention they received.	
Subject analysis set title	Full Analysis Set (FAS)
Subject analysis set type	Full analysis
Subject analysis set description:	
All randomized subjects were included. Subjects in the full analysis set were analyzed according to the randomized intervention (intention-to-treat).	

Primary: Mean change in frequency of moderate to severe HF from baseline to Week 4 (assessed by hot flash daily diary [HFDD]).

End point title	Mean change in frequency of moderate to severe HF from baseline to Week 4 (assessed by hot flash daily diary [HFDD]).
End point description:	
Subjects recorded electronically twice daily using the sponsor developed Hot Flash Daily Diary (HFDD). The HFDD was completed in the morning after waking up (morning diary) and each evening at bedtime (evening diary) on the hand-held device. The HFDD items assessed the number of mild, moderate, and severe HF experienced during the day and during the night. Mild HF were defined as a "sensation of heat without sweating", moderate HF were defined as a "sensation of heat with sweating, but able to continue activity", and severe HF were defined as a "sensation of heat with sweating, causing cessation (stopping) of activity". The frequency of moderate to severe HF for each week during the treatment period was calculated using the available data during that particular week. Specifically, for Week 4 Days 22-28 were used (Day 1 corresponds to start of treatment).	
End point type	Primary
End point timeframe:	
From baseline to Week 4	

End point values	Elinzanetant 120 mg	Placebo - Elinzanetant 120 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	191[1]	185[2]		
Units: Hot Flashes per day				
arithmetic mean (standard deviation)				
Week 4: Change from baseline	-7.48 (± 5.80)	-4.37 (± 6.73)		

Notes:

[1] - FAS

[2] - FAS

Statistical analyses

Statistical analysis title	Elinzanetant 120 mg versus placebo

Statistical analysis description:

The total number of subjects with observed value for this timepoint, who were considered in the analysis model, was 383. This included subjects who prematurely discontinued study drug, and continued in a post-treatment period who were not considered under "number of subjects included in analysis" given below.

Comparison groups	Elinzanetant 120 mg v Placebo - Elinzanetant 120 mg
Number of subjects included in analysis	376
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [3]
Method	Mixed model repeated measures (MMRM)
Parameter estimate	Difference in LS-means
Point estimate	-3.29
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.47
upper limit	-2.1

Notes:

[3] - one-sided

Primary: Mean change in frequency of moderate to severe HF from baseline to Week 12 (assessed by HFDD).

End point title	Mean change in frequency of moderate to severe HF from baseline to Week 12 (assessed by HFDD).

End point description:

The frequency of moderate to severe HF for each week during the treatment period was calculated using the available data during that particular week. Specifically, for Week 12 Days 78-84 were used (Day 1 corresponds to start of treatment).

End point type	Primary

End point timeframe:

From baseline to Week 12

End point values	Elinzanetant 120 mg	Placebo - Elinzanetant 120 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	175[4]	169[5]		
Units: Hot Flashes per day				
arithmetic mean (standard deviation)				
Week 12: Change from baseline	-8.74 (± 6.70)	-5.53 (± 10.16)		

Notes:

[4] - FAS

[5] - FAS

Statistical analyses

Statistical analysis title	Elinzanetant 120 mg versus placebo

Statistical analysis description:

The total number of subjects with observed value for this timepoint, who were considered in the analysis model, was 353. This included subjects who prematurely discontinued study drug, and continued in a post-treatment period who were not considered under "number of subjects included in analysis" given below.

Comparison groups	Elinzanetant 120 mg v Placebo - Elinzanetant 120 mg
Number of subjects included in analysis	344
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [6]
Method	MMRM
Parameter estimate	Difference in LS-means
Point estimate	-3.22
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.81
upper limit	-1.63

Notes:

[6] - one-sided

Secondary: Mean change in severity of moderate to severe HF from baseline to Week 4 (assessed by HFDD).

End point title	Mean change in severity of moderate to severe HF from baseline to Week 4 (assessed by HFDD).

End point description:

In the HFDD, the severity of HFs was categorized as: 1 = mild, 2 = moderate, and 3 = severe; therefore, a decrease in severity indicates an improvement. The HFDD items assessed the number of mild, moderate, and severe HF experienced during the day and during the night. Mild HF were defined as a "sensation of heat without sweating", moderate HF were defined as a "sensation of heat with sweating, but able to continue activity", and severe HF were defined as a "sensation of heat with sweating, causing cessation (stopping) of activity".

End point type	Secondary

End point timeframe:

From baseline to Week 4

End point values	Elinzanetant 120 mg	Placebo - Elinzanetant 120 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	191[7]	185[8]		
Units: Severity scale				
arithmetic mean (standard deviation)				
Week 4: Change from baseline	-0.73 (± 0.64)	-0.39 (± 0.43)		

Notes:

[7] - FAS

[8] - FAS

Statistical analyses

Statistical analysis title	Elinzanetant 120 mg versus placebo

Statistical analysis description:

The total number of subjects with observed value for this timepoint, who were considered in the analysis model, was 383. This included subjects who prematurely discontinued study drug, and continued in a post-treatment period who were not considered under "number of subjects included in analysis" given below.

Comparison groups	Elinzanetant 120 mg v Placebo - Elinzanetant 120 mg
Number of subjects included in analysis	376
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [9]
Method	MMRM
Parameter estimate	Difference in LS-means
Point estimate	-0.33
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.44
upper limit	-0.23

Notes:

[9] - one-sided

Secondary: Mean change in severity of moderate to severe HF from baseline to Week 12 (assessed by HFDD).

End point title	Mean change in severity of moderate to severe HF from baseline to Week 12 (assessed by HFDD).

End point description:

In the HFDD, the severity of HFs was categorized as: 1 = mild, 2 = moderate, and 3 = severe; therefore, a decrease in the HF severity score indicates an improvement. The HFDD items assessed the number of mild, moderate, and severe HF experienced during the day and during the night. Mild HF are defined as a "sensation of heat without sweating", moderate HF are defined as a "sensation of heat with sweating, but able to continue activity", and severe HF are defined as a "sensation of heat with sweating, causing cessation (stopping) of activity".

End point type	Secondary

End point timeframe:

From baseline to Week 12

End point values	Elinzanetant 120 mg	Placebo - Elinzanetant 120 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	175[10]	169[11]		
Units: Severity scale				
arithmetic mean (standard deviation)				
Week 12: Change from baseline	-0.95 (± 0.78)	-0.55 (± 0.60)		

Notes:

[10] - FAS

[11] - FAS

Statistical analyses

Statistical analysis title	Elinzanetant 120 mg versus placebo

Statistical analysis description:

The total number of subjects with observed value for this timepoint, who were considered in the analysis model, was 353. This included subjects who prematurely discontinued study drug, and continued in a post-treatment period who were not considered under "number of subjects included in analysis" given below.

Comparison groups	Elinzanetant 120 mg v Placebo - Elinzanetant 120 mg
Number of subjects included in analysis	344
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [12]
Method	MMRM
Parameter estimate	Difference in LS-means
Point estimate	-0.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.54
upper limit	-0.25

Notes:

[12] - one-sided

Secondary: Mean change in frequency of moderate to severe HF from baseline to Week 1 (assessed by HFDD).

End point title	Mean change in frequency of moderate to severe HF from baseline to Week 1 (assessed by HFDD).

End point description:

Subjects' assessments of HF were recorded electronically twice daily using the sponsor developed HFDD. The HFDD was completed in the morning after waking up (morning diary) and each evening at bedtime (evening diary) on the hand-held device.

End point type	Secondary

End point timeframe:

From baseline to Week 1

End point values	Elinzanetant 120 mg	Placebo - Elinzanetant 120 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	196[13]	189[14]		
Units: Hot Flashes per day				
arithmetic mean (standard deviation)				
Week 1: Change from baseline	-5.00 (± 5.05)	-2.72 (± 4.99)		

Notes:

[13] - FAS

[14] - FAS

Statistical analyses

Statistical analysis title	Elinzanetant 120 mg versus placebo

Statistical analysis description:

The total number of subjects with observed value for this timepoint, who were considered in the analysis

model, was 385. This included subjects who prematurely discontinued study drug, and continued in a post-treatment period who were not considered under "number of subjects included in analysis" given below.

Comparison groups	Elinzanetant 120 mg v Placebo - Elinzanetant 120 mg
Number of subjects included in analysis	385
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [15]
Method	MMRM
Parameter estimate	Difference in LS-means
Point estimate	-2.45
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.36
upper limit	-1.55

Notes:

[15] - one-sided

Secondary: Mean change in frequency of moderate to severe HF from baseline over time.

End point title	Mean change in frequency of moderate to severe HF from baseline over time.

End point description:

The frequency of moderate to severe HF for each week during the treatment period was calculated using the available data during that particular week. Specifically, for Week 1 Days 2-8 were used instead of 1-7, because the intake started on Day 1 only before going to bed, for Week 4 Days 22-28 were used and for Week 12 Days 78-84 were used (Day 1 corresponds to start of treatment). These data were aggregated to a mean daily frequency as (total number of moderate to severe HF during that week) / (total number of available days with data during that week). In case data was not available for more than 2 days within a week, the value for that particular week was set to missing.

End point type	Secondary

End point timeframe:

From baseline to Week 30

End point values	Elinzanetant 120 mg	Placebo - Elinzanetant 120 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	199[16]	197[17]		
Units: Hot Flashes per day				
arithmetic mean (standard deviation)				
Week 1 (N=196, 189)	-5.00 (± 5.05)	-2.72 (± 4.99)		
Week 4 (N=191, 185)	-7.48 (± 5.8)	-4.37 (± 6.73)		
Week 8 (N=180, 175)	-8.42 (± 6.5)	-5.24 (± 8.08)		
Week 12 (N=175, 169)	-8.74 (± 6.7)	-5.53 (± 10.16)		
Week 16 (N=170, 160)	-9.19 (± 6.21)	-8.08 (± 8.87)		
Week 20 (N=161, 160)	-9.87 (± 6.40)	-8.88 (± 8.30)		
Week 26 (N=114, 110)	-10.11 (± 6.41)	-10.10 (± 8.75)		

Week 30 (N=141, 129)	-6.70 (± 5.99)	-6.15 (± 10.52)		

Notes:

[16] - FAS

[17] - FAS

Statistical analyses

No statistical analyses for this end point

Secondary: Mean change in Patient-reported outcomes measurement information system sleep disturbance short form 8b (PROMIS SD SF 8b) total T-score from baseline to Week 12.

End point title	Mean change in Patient-reported outcomes measurement information system sleep disturbance short form 8b (PROMIS SD SF 8b) total T-score from baseline to Week 12.

End point description:

The PROMIS SD SF 8b included 8 items assessing sleep disturbance over the past 7 days. Items assessed sleep quality, sleep depth and restoration associated with sleep, perceived difficulties with getting to sleep or staying asleep and perceptions of the adequacy of and satisfaction with sleep. Subjects responded to the items on a 5-point scale from not at all, never or very poor to very much, always or very good. Four of the items were scored reversely. Total scores ranged from 8 to 40, with higher scores indicating greater severity of sleep disturbance. The total scores were converted to total T-scores used for the analysis.

End point type	Secondary

End point timeframe:

From baseline to Week 12

End point values	Elinzanetant 120 mg	Placebo - Elinzanetant 120 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	166[18]	156[19]		
Units: Scores on scale				
arithmetic mean (standard deviation)				
Week 12: Change from baseline	-10.8 (± 9.6)	-5.0 (± 6.9)		

Notes:

[18] - FAS

[19] - FAS

Statistical analyses

Statistical analysis title	Elinzanetant 120 mg versus placebo

Statistical analysis description:

The total number of subjects with observed value for this timepoint, who were considered in the analysis model, was 354. This included subjects who prematurely discontinued study drug, and continued in a post-treatment period who were not considered under "number of subjects included in analysis" given below.

Comparison groups	Elinzanetant 120 mg v Placebo - Elinzanetant 120 mg

Number of subjects included in analysis	322
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [20]
Method	MMRM
Parameter estimate	Difference in LS-means
Point estimate	-5.58
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.18
upper limit	-3.98

Notes:

[20] - one-sided

Secondary: Mean change in MENQOL total score from baseline to Week 12.

End point title	Mean change in MENQOL total score from baseline to Week 12.

End point description:

The MENQOL questionnaire is comprised of 29 items assessing the presence of menopausal symptoms and the impact of menopause on health-related quality of life over the past week. The items assess four domains of symptoms and functioning: VMS, psychosocial functioning, physical functioning, and sexual functioning. For each item, the subject indicates if they have experienced the symptom (yes/no). If subjects select yes, subjects rate how bothered they were by the symptom using a six-point verbal descriptor scale, with response options ranging from 0 'not at all bothered' to 6 'extremely bothered'. Based on the individual responses, item scores, domain scores, and a total MENQOL score are calculated. Each score ranges from 1-8, higher scores indicate greater bother.

End point type	Secondary

End point timeframe:

From baseline to Week 12

End point values	Elinzanetant 120 mg	Placebo - Elinzanetant 120 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	160[21]	152[22]		
Units: Scores on scale				
arithmetic mean (standard deviation)				
Week 12: Change from baseline	-1.41 (± 1.30)	-0.96 (± 1.11)		

Notes:

[21] - FAS

[22] - FAS

Statistical analyses

Statistical analysis title	Elinzanetant 120 mg versus placebo

Statistical analysis description:

The total number of subjects with observed value for this timepoint, who were considered in the analysis model, was 351. This included subjects who prematurely discontinued study drug, and continued in a post-treatment period who were not considered under "number of subjects included in analysis" given below.

Comparison groups	Elinzanetant 120 mg v Placebo - Elinzanetant 120 mg

Number of subjects included in analysis	312
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [23]
Method	MMRM
Parameter estimate	Difference in LS-means
Point estimate	-0.42
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.64
upper limit	-0.2

Notes:

[23] - one-sided

Secondary: Mean change in BDI-II total score from baseline to Week 12.

End point title	Mean change in BDI-II total score from baseline to Week 12.

End point description:

The BDI-II is a 21-item questionnaire assessing the intensity of depressive symptoms over the past 2 weeks. Each item is a list of four statements arranged in increasing levels of severity about a particular symptom of depression. Items use a 4-point verbal response scale ranging from 0 (not at all) to 3 (extreme form of each symptom); specific response options are tailored to the aspect of depression being measured in each item. A total score ranging from 0 to 63 is calculated with scores of 0-13 indicating mild minimal range, 14 – 19 mild depression, 20 – 28 indicating moderate and 29 – 63 severe depression (higher score = greater depression).

End point type	Secondary

End point timeframe:

From baseline to Week 12

End point values	Elinzanetant 120 mg	Placebo - Elinzanetant 120 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	175[24]	168[25]		
Units: Scores on scale				
arithmetic mean (standard deviation)				
Week 12: Change from baseline	-0.5 (± 7.2)	0.9 (± 6.5)		

Notes:

[24] - FAS

[25] - FAS

Statistical analyses

No statistical analyses for this end point

Secondary: Mean change in BDI-II total score from baseline to Week 26.

End point title	Mean change in BDI-II total score from baseline to Week 26.

End point description:

End point type	Secondary

End point timeframe:
From baseline to Week 26

End point values	Elinzanetant 120 mg	Placebo - Elinzanetant 120 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	108[26]	104[27]		
Units: Scores on scale				
arithmetic mean (standard deviation)				
Week 26: Change from baseline	-0.9 (± 6.7)	-0.6 (± 5.5)		

Notes:
[26] - FAS
[27] - FAS

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From the start of study medication up to 14 days after the last dose of medication, approximately 28 weeks.

Adverse event reporting additional description:

Adverse event reporting for the deaths (all causes) considers all deaths that occurred at any time during the study before the last contact, approximately 30 weeks.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	26.0

Reporting groups

Reporting group title	Elinzanetant 120 mg Week 1-12

Reporting group description:

Subjects who received elinzanetant 120 mg during Weeks 1-12. Reported AEs for the exposure period Weeks 1-12 to elinzanetant.

Reporting group title	Placebo Week 1-12

Reporting group description:

Subjects who received placebo during Weeks 1-12. Reported AEs for the exposure period to placebo.

Reporting group title	Elinzanetant 120 mg Week 1-26

Reporting group description:

Subjects who received elinzanetant 120 mg at any time during the study (including those who switched from placebo to elinzanetant 120 mg at Week 13). Reported AEs for the exposure period to elinzanetant for both treatment groups.

Reporting group title	Placebo - Elinzanetant 120 mg Week 13-26

Reporting group description:

Subjects who received placebo during Weeks 1-12 and switched to elinzanetant 120 mg after Week 12. Reported AEs for the exposure period to elinzanetant.

Reporting group title	Elinzanetant 120 mg Week 13-26

Reporting group description:

Subjects who received elinzanetant 120 mg during Weeks 1-12 and continued with elinzanetant 120 mg after Week 12. Reported AEs for the exposure period Weeks 13 - 26 to elinzanetant.

Serious adverse events	Elinzanetant 120 mg Week 1-12	Placebo Week 1-12	Elinzanetant 120 mg Week 1-26
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 199 (2.01%)	2 / 194 (1.03%)	13 / 367 (3.54%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Injury, poisoning and procedural complications			
Accident			
subjects affected / exposed	0 / 199 (0.00%)	0 / 194 (0.00%)	1 / 367 (0.27%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Tibia fracture			
subjects affected / exposed	0 / 199 (0.00%)	0 / 194 (0.00%)	1 / 367 (0.27%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Surgical and medical procedures			
Arthrodesis			
subjects affected / exposed	1 / 199 (0.50%)	0 / 194 (0.00%)	1 / 367 (0.27%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bunion operation			
subjects affected / exposed	0 / 199 (0.00%)	0 / 194 (0.00%)	1 / 367 (0.27%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mammoplasty			
subjects affected / exposed	0 / 199 (0.00%)	0 / 194 (0.00%)	1 / 367 (0.27%)
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			
Syncope			
subjects affected / exposed	1 / 199 (0.50%)	0 / 194 (0.00%)	1 / 367 (0.27%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 199 (0.00%)	0 / 194 (0.00%)	1 / 367 (0.27%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Cholecystitis acute			
subjects affected / exposed	0 / 199 (0.00%)	1 / 194 (0.52%)	0 / 367 (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
Cholelithiasis			

subjects affected / exposed	0 / 199 (0.00%)	1 / 194 (0.52%)	2 / 367 (0.54%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Pulmonary embolism			
subjects affected / exposed	1 / 199 (0.50%)	0 / 194 (0.00%)	1 / 367 (0.27%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Diverticulitis			
subjects affected / exposed	1 / 199 (0.50%)	0 / 194 (0.00%)	1 / 367 (0.27%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Otitis externa			
subjects affected / exposed	0 / 199 (0.00%)	0 / 194 (0.00%)	1 / 367 (0.27%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	1 / 199 (0.50%)	0 / 194 (0.00%)	1 / 367 (0.27%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyelonephritis			
subjects affected / exposed	0 / 199 (0.00%)	0 / 194 (0.00%)	1 / 367 (0.27%)
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	Placebo - Elinzanetant 120 mg Week 13-26	Elinzanetant 120 mg Week 13-26	
Total subjects affected by serious adverse events			
subjects affected / exposed	9 / 168 (5.36%)	0 / 171 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Injury, poisoning and procedural complications			
Accident			

subjects affected / exposed	1 / 168 (0.60%)	0 / 171 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tibia fracture			
subjects affected / exposed	1 / 168 (0.60%)	0 / 171 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Arthrodesis			
subjects affected / exposed	0 / 168 (0.00%)	0 / 171 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bunion operation			
subjects affected / exposed	1 / 168 (0.60%)	0 / 171 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mammoplasty			
subjects affected / exposed	1 / 168 (0.60%)	0 / 171 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Syncope			
subjects affected / exposed	0 / 168 (0.00%)	0 / 171 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 168 (0.60%)	0 / 171 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholecystitis acute			

subjects affected / exposed	0 / 168 (0.00%)	0 / 171 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholelithiasis			
subjects affected / exposed	2 / 168 (1.19%)	0 / 171 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Pulmonary embolism			
subjects affected / exposed	0 / 168 (0.00%)	0 / 171 (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			
Diverticulitis			
subjects affected / exposed	0 / 168 (0.00%)	0 / 171 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Otitis externa			
subjects affected / exposed	1 / 168 (0.60%)	0 / 171 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	0 / 168 (0.00%)	0 / 171 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis			
subjects affected / exposed	1 / 168 (0.60%)	0 / 171 (0.00%)	
occurrences causally related to treatment / all	0 / 1	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	Elinzanetant 120 mg Week 1-12	Placebo Week 1-12	Elinzanetant 120 mg Week 1-26
Total subjects affected by non-serious adverse events			
subjects affected / exposed	38 / 199 (19.10%)	28 / 194 (14.43%)	51 / 367 (13.90%)
Investigations			
Depression rating scale score increased			
subjects affected / exposed	12 / 199 (6.03%)	11 / 194 (5.67%)	14 / 367 (3.81%)
occurrences (all)	13	12	16
Nervous system disorders			
Headache			
subjects affected / exposed	14 / 199 (7.04%)	5 / 194 (2.58%)	24 / 367 (6.54%)
occurrences (all)	14	5	25
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	14 / 199 (7.04%)	3 / 194 (1.55%)	15 / 367 (4.09%)
occurrences (all)	14	3	15
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	10 / 199 (5.03%)	10 / 194 (5.15%)	12 / 367 (3.27%)
occurrences (all)	10	11	12

Non-serious adverse events	Placebo - Elinzanetant 120 mg Week 13-26	Elinzanetant 120 mg Week 13-26	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	9 / 168 (5.36%)	6 / 171 (3.51%)	
Investigations			
Depression rating scale score increased			
subjects affected / exposed	2 / 168 (1.19%)	1 / 171 (0.58%)	
occurrences (all)	2	1	
Nervous system disorders			
Headache			
subjects affected / exposed	6 / 168 (3.57%)	4 / 171 (2.34%)	
occurrences (all)	7	4	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	1 / 168 (0.60%)	0 / 171 (0.00%)	
occurrences (all)	1	0	
Musculoskeletal and connective tissue			

disorders Arthralgia subjects affected / exposed occurrences (all)	1 / 168 (0.60%) 1	1 / 171 (0.58%) 1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
10 February 2022	Changes consist of three types, (i) they addressed comments from authorities (FDA and Portuguese Health Authority) during the initial CTA review process, (ii) helped to clarify certain aspects of the protocol or (iii) they were minor corrections.
22 June 2022	Changes consist of three types, (i) they addressed comments from FDA, (ii) helped to clarify certain aspects of the protocol or (iii) they were minor corrections.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported