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	2020-004855-34
Trial protocol	DE NO PT SK PL CZ IT
Global end of trial date	10 October 2023

Results information

Result version number	v1 (current)
This version publication date	12 October 2024
First version publication date	12 October 2024

Trial information

Trial identification

Sponsor protocol code	21652

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT05099159
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 30300139 003, clinical-trials-contact@bayer.com
Scientific contact	Therapeutic Area Head, Bayer AG, +49 30300139 003, 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	03 November 2023
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	10 October 2023
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the efficacy of elinzanetant for the treatment of Vasomotor symptoms (VMS) associated with 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	29 October 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	Canada: 27
Country: Number of subjects enrolled	United States: 175
Country: Number of subjects enrolled	Czechia: 21
Country: Number of subjects enrolled	Germany: 43
Country: Number of subjects enrolled	Italy: 6
Country: Number of subjects enrolled	Norway: 23
Country: Number of subjects enrolled	Poland: 84
Country: Number of subjects enrolled	Portugal: 7
Country: Number of subjects enrolled	Slovakia: 13
Country: Number of subjects enrolled	Switzerland: 1
Worldwide total number of subjects	400
EEA total number of subjects	197

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)	397
From 65 to 84 years	3
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Study was conducted at 95 study centers in 10 countries worldwide, between 29-Oct-2021 (first subject first visit) and 10-Oct-2023 (last subject last visit).

Pre-assignment

Screening details:

A total of 1483 subjects were screened, of whom 1083 subjects were screen failures. Most common reason for screen failure was not meeting the eligibility criteria (1044 subjects). 400 of the screened subjects were randomized to treatment and 324 subjects completed the study.

Period 1

Period 1 title	Overall (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	
Pharmaceutical forms	Capsule, soft
Routes of administration	Oral use

Dosage and administration details:

Two capsules of 60 mg elinzanetant once daily before going to bed with or without food 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	Elinzanetant
Investigational medicinal product code	BAY3427080
Other name	
Pharmaceutical forms	Capsule, soft
Routes of administration	Oral use

Dosage and administration details:

Two capsules of 60 mg elinzanetant once daily before going to bed with or without food for week 13-26.

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 of Elinzanetant matching placebo once daily before going to bed with or without food for week 1-12.

Number of subjects in period 1	Elinzanetant 120 mg	Placebo - Elinzanetant 120 mg
Started	200	200
Completed	157	167
Not completed	43	33
Subject Decision	14	10
Adverse event, non-fatal	7	3
Non-compliance with study drug	1	4
Did not complete study treatment but completed FU	13	12
Unspecified	1	1
Lost to follow-up	6	1
Lack of efficacy	1	1
Protocol deviation	-	1

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	200	200	400
Age Categorical Units: Subjects			
Age Continuous Units: years			
standard deviation	54.8 ± 5.0	54.4 ± 4.5	-
Gender Categorical Units: Subjects			
Female	200	200	400
Male	0	0	0
Race Units: Subjects			
White	163	172	335
Black or African American	35	25	60
Asian	0	1	1
American Indian or Alaska Native	1	1	2
Multiple	0	1	1
Not reported	1	0	1
Ethnicity Units: Subjects			
Not Hispanic or Latino	186	175	361
Hispanic or Latino	13	24	37
Other	1	1	2
Mean frequency of moderate to severe hot flash (HF) at baseline			
Subjects' assessments of HF were recorded electronically using the sponsor developed Hot Flash Daily Diary (HFDD). HFDD items assessed the number of mild, moderate, and severe HF experienced during the day and during the 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", and 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 and 200 for placebo - elinzanetant 120 mg.			
Units: Hot flashes per day			
arithmetic mean	14.66	16.16	
standard deviation	± 11.08	± 11.15	-
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 200 for placebo - elinzanetant 120 mg.			
Units: Severity scale			
arithmetic mean	2.53	2.54	
standard deviation	± 0.24	± 0.24	-
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. A total raw scores (range 8–40), which were converted to total T-scores for analysis of this endpoint (range 28.9–76.5), with higher scores indicating greater severity of sleep disturbance. The number of analyzed subjects was 188 for elinzanetant 120 mg and and 193 for placebo - elinzanetant 120 mg.			
Units: Scores on a scale			
arithmetic mean	61.7	60.7	
standard deviation	± 6.2	± 7.2	-
Beck depression inventory (BDI-II) total score at baseline			
The BDI-II consisted of 21 items to assess the severity of depression over the past 2 weeks. Each item was a list of four statements arranged in increasing levels of severity about a particular symptom of depression. Items used a 4-point verbal response scale ranging from 0 (not at all) to 3 (extreme form of each symptom); specific response options were tailored to the aspect of depression being measured in each item.			
Units: Scores on a scale			
arithmetic mean	6.6	7.2	
standard deviation	± 6.5	± 6.8	-
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. Based on the individual responses, item scores, domain scores, and a total MENQOL score were calculated. Each score ranged from 1-8, higher scores indicated greater bother. The number of analyzed subjects was 186 for elinzanetant 120 mg and 189 for placebo - elinzanetant 120 mg.			
Units: Scores on a scale			
arithmetic mean	4.48	4.49	
standard deviation	± 1.14	± 1.17	-

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	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).	
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.	

Primary: Mean change in frequency of moderate to severe HF from baseline to Week 4 (assessed by HFDD)

End point title	Mean change in frequency of moderate to severe HF from baseline to Week 4 (assessed by HFDD)
End point description:	
Subjects' assessments of HF were 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 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", and severe HF was 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, Day 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	185[1]	192[2]		
Units: Hot Flashes per day				
arithmetic mean (standard deviation)	-8.58 (± 9.16)	-6.07 (± 8.91)		

Notes:

[1] - FAS

[2] - FAS

Statistical analyses

Statistical analysis title	Elinzanetant 120 mg vs placebo

Statistical analysis description:

The total number of subjects with observed value for this timepoint, who were considered in the analysis model, was 384. 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	377
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [3]
Method	Mixed model repeated measures (MMRM)
Parameter estimate	Least squares (LS)-means
Point estimate	-3.04
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.4
upper limit	-1.68

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:

Subjects' assessments of HF were 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 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", and severe HF was 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 12, Day 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	174[4]	180[5]		
Units: Hot flashes per day				
arithmetic mean (standard deviation)	-9.96 (± 10.25)	-7.24 (± 8.49)		

Notes:

[4] - FAS

[5] - FAS

Statistical analyses

Statistical analysis title	Elinzanetant 120 mg vs placebo

Statistical analysis description:

The total number of subjects with observed value for this timepoint, who were considered in the analysis model, was 364. 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	354
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [6]
Method	MMRM
Parameter estimate	LS-means
Point estimate	-3.24
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.6
upper limit	-1.88

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 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 4

End point values	Elinzanetant 120 mg	Placebo - Elinzanetant 120 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	185[7]	192[8]		
Units: Severity scale				
arithmetic mean (standard deviation)	-0.75 (± 0.68)	-0.53 (± 0.55)		

Notes:

[7] - FAS

[8] - FAS

Statistical analyses

Statistical analysis title	Elinzanetant 120 mg vs placebo

Statistical analysis description:

The total number of subjects with observed value for this timepoint, who were considered in the analysis model, was 384. 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	377
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0003 [9]
Method	MMRM
Parameter estimate	LS-means
Point estimate	-0.22
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.34
upper limit	-0.09

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	174[10]	180[11]		
Units: Severity scale				
arithmetic mean (standard deviation)	-0.97 (± 0.78)	-0.65 (± 0.67)		

Notes:

[10] - FAS

[11] - FAS

Statistical analyses

Statistical analysis title	Elinzanetant 120 mg vs placebo

Statistical analysis description:

The total number of subjects with observed value for this timepoint, who were considered in the analysis model, was 364. 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	354
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [12]
Method	MMRM
Parameter estimate	LS-means
Point estimate	-0.29
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.44
upper limit	-0.14

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	198[13]	197[14]		
Units: Hot flashes per day				
arithmetic mean (standard deviation)	-4.66 (± 6.70)	-3.57 (± 6.86)		

Notes:

[13] - FAS

[14] - FAS

Statistical analyses

Statistical analysis title	Elinzanetant 120 mg vs placebo

Statistical analysis description:

The total number of subjects with observed value for this timepoint, who were considered in the analysis model, was 395. 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	395
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0013 [15]
Method	Mixed model repeated measures (MMRM)
Parameter estimate	LS-means
Point estimate	-1.66
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.73
upper limit	-0.58

Notes:

[15] - One side

Secondary: Mean change in frequency of moderate to severe HF from baseline over time (assessed by HFDD)

End point title	Mean change in frequency of moderate to severe HF from baseline over time (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 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 is not available for more than 2 days within a week, the value for that particular week was be 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	200	200		
Units: Hot flashes per day				
arithmetic mean (standard deviation)				
Week 1 (n=198, 197)	-4.66 (± 6.70)	-3.57 (± 6.86)		
Week 4 (n=185, 192)	-8.58 (± 9.16)	-6.07 (± 8.91)		
Week 8 (n=178, 181)	-9.67 (± 10.02)	-6.91 (± 9.07)		
Week 12 (n=174, 180)	-9.96 (± 10.25)	-7.24 (± 8.49)		
Week 16 (n=166, 175)	-10.96 (± 11.55)	-10.89 (± 9.54)		
Week 20 (n=162, 169)	-11.60 (± 11.54)	-11.26 (± 9.31)		
Week 26 (n=108, 120)	-11.76 (± 11.38)	-12.76 (± 12.28)		

Week 30 (n=132, 134)	-7.90 (± 11.68)	-9.36 (± 11.71)		

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. A total raw scores (range 8–40), which were converted to total T-scores for analysis of this endpoint (range 28.9–76.5), with higher scores indicating greater severity of sleep disturbance.

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	161[16]	172[17]		
Units: Scores on a scale				
arithmetic mean (standard deviation)	-10.6 (± 7.7)	-5.5 (± 6.9)		

Notes:

[16] - FAS

[17] - FAS

Statistical analyses

Statistical analysis title	Elinzanetant 120 mg vs placebo

Statistical analysis description:

The total number of subjects with observed value for this timepoint, who were considered in the analysis model, was 361. 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	333
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [18]
Method	MMRM
Parameter estimate	LS-means
Point estimate	-4.32
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.77
upper limit	-2.86

Notes:

[18] - One-sided

Secondary: Mean change in menopause specific quality of life scale (MENQOL) total score from baseline to Week 12

End point title	Mean change in menopause specific quality of life scale (MENQOL) total score from baseline to Week 12

End point description:

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. For each item, the subjects indicated if they had experienced the symptom (yes/no). If subjects selected yes, subjects rated 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 were calculated. The four domain scores were calculated as a mean of converted single item scores (range 1–8), and the mean of the four domain scores yielded the MENQOL total score. Higher scores indicated 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	157[19]	167[20]		
Units: Scores on a scale				
arithmetic mean (standard deviation)	-1.34 (± 1.29)	-0.97 (± 1.16)		

Notes:

[19] - FAS

[20] - FAS

Statistical analyses

Statistical analysis title	Elinzanetant 120 mg vs placebo

Statistical analysis description:

The total number of subjects with observed value for this timepoint, who were considered in the analysis model, was 355. 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	324
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0059 [21]
Method	MMRM
Parameter estimate	LS-means
Point estimate	-0.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.53
upper limit	-0.07

Notes:

[21] - One-sided

Secondary: Mean change in Beck depression inventory (BDI-II) total score from baseline to Week 12

End point title	Mean change in Beck depression inventory (BDI-II) total score from baseline to Week 12

End point description:

The BDI-II consisted of 21 items to assess the severity of depression over the past 2 weeks. Each item was a list of four statements arranged in increasing levels of severity about a particular symptom of depression. Items used a 4-point verbal response scale ranging from 0 (not at all) to 3 (extreme form of each symptom); specific response options were tailored to the aspect of depression being measured in each item. A total score ranging from 0 to 63 was calculated with scores of 0-13 indicating mild minimal range, 14 – 19 indicating mild depression, 20 – 28 indicating moderate and 29 – 63 indicating 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	170[22]	174[23]		
Units: Scores on a scale				
arithmetic mean (standard deviation)	-0.2 (± 8.3)	0.8 (± 8.6)		

Notes:

[22] - FAS

[23] - 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:

The BDI-II consisted of 21 items to assess the severity of depression over the past 2 weeks. Each item

was a list of four statements arranged in increasing levels of severity about a particular symptom of depression. Items used a 4-point verbal response scale ranging from 0 (not at all) to 3 (extreme form of each symptom); specific response options were tailored to the aspect of depression being measured in each item. A total score ranging from 0 to 63 was calculated with scores of 0-13 indicating mild minimal range, 14 – 19 indicating mild depression, 20 – 28 indicating moderate and 29 – 63 indicating severe depression (higher score = greater depression).

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	111[24]	110[25]		
Units: Scores on a scale				
arithmetic mean (standard deviation)	-1.0 (± 6.9)	-1.1 (± 6.7)		

Notes:

[24] - FAS

[25] - 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 120mg Week 1-12

Reporting group description:

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

Reporting group description:

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

Serious adverse events	Elinzanetant 120mg Week 1-12	Placebo Week 1-12	Elinzanetant 120mg Week 1-26
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 201 (0.50%)	1 / 199 (0.50%)	5 / 381 (1.31%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	1 / 201 (0.50%)	0 / 199 (0.00%)	1 / 381 (0.26%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			

Generalised tonic-clonic seizure			
subjects affected / exposed	0 / 201 (0.00%)	0 / 199 (0.00%)	1 / 381 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Mechanical ileus			
subjects affected / exposed	0 / 201 (0.00%)	0 / 199 (0.00%)	1 / 381 (0.26%)
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			
Pulmonary embolism			
subjects affected / exposed	1 / 201 (0.50%)	0 / 199 (0.00%)	1 / 381 (0.26%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Joint range of motion decreased			
subjects affected / exposed	0 / 201 (0.00%)	0 / 199 (0.00%)	1 / 381 (0.26%)
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			
Pyelonephritis			
subjects affected / exposed	0 / 201 (0.00%)	1 / 199 (0.50%)	0 / 381 (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
Urinary tract infection			
subjects affected / exposed	0 / 201 (0.00%)	0 / 199 (0.00%)	1 / 381 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urosepsis			
subjects affected / exposed	0 / 201 (0.00%)	1 / 199 (0.50%)	0 / 381 (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
Product issues			
Device loosening			

subjects affected / exposed	0 / 201 (0.00%)	0 / 199 (0.00%)	1 / 381 (0.26%)
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 120mg Week 13-26	Elinzanetant 120mg Week 13-26	
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 180 (1.67%)	1 / 171 (0.58%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	0 / 180 (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	
Nervous system disorders			
Generalised tonic-clonic seizure			
subjects affected / exposed	1 / 180 (0.56%)	0 / 171 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Mechanical ileus			
subjects affected / exposed	1 / 180 (0.56%)	0 / 171 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Pulmonary embolism			
subjects affected / exposed	0 / 180 (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	
Musculoskeletal and connective tissue disorders			
Joint range of motion decreased			
subjects affected / exposed	1 / 180 (0.56%)	0 / 171 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Infections and infestations			
Pyelonephritis			
subjects affected / exposed	0 / 180 (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	
Urinary tract infection			
subjects affected / exposed	0 / 180 (0.00%)	1 / 171 (0.58%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urosepsis			
subjects affected / exposed	0 / 180 (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	
Product issues			
Device loosening			
subjects affected / exposed	1 / 180 (0.56%)	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 120mg Week 1-12	Placebo Week 1-12	Elinzanetant 120mg Week 1-26
Total subjects affected by non-serious adverse events			
subjects affected / exposed	34 / 201 (16.92%)	25 / 199 (12.56%)	45 / 381 (11.81%)
Investigations			
Depression rating scale score increased			
subjects affected / exposed	9 / 201 (4.48%)	17 / 199 (8.54%)	11 / 381 (2.89%)
occurrences (all)	10	19	12
Nervous system disorders			
Headache			
subjects affected / exposed	18 / 201 (8.96%)	5 / 199 (2.51%)	24 / 381 (6.30%)
occurrences (all)	21	5	30
General disorders and administration site conditions			
Fatigue			

subjects affected / exposed	11 / 201 (5.47%)	3 / 199 (1.51%)	15 / 381 (3.94%)
occurrences (all)	14	3	18

Non-serious adverse events	Placebo - Elinzanetant 120mg Week 13-26	Elinzanetant 120mg Week 13-26	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	8 / 180 (4.44%)	5 / 171 (2.92%)	
Investigations			
Depression rating scale score increased			
subjects affected / exposed	2 / 180 (1.11%)	0 / 171 (0.00%)	
occurrences (all)	2	0	
Nervous system disorders			
Headache			
subjects affected / exposed	4 / 180 (2.22%)	4 / 171 (2.34%)	
occurrences (all)	4	5	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	3 / 180 (1.67%)	1 / 171 (0.58%)	
occurrences (all)	3	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
10 February 2022	Changes in protocol amendment 1 consist of three types, (i) address comments from authorities (FDA and Portuguese Health Authority) during the initial CTA review process, (ii) help to clarify certain aspects of the protocol or (iii) minor corrections. In addition, the sleep quality tracking sub-study was removed due to technical difficulties.
22 June 2022	Changes in protocol amendment 2 consist of three types, (i) address comments from FDA, (ii) help to clarify certain aspects of the protocol or (iii) minor corrections.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported