Clinical trial results:
An Open-Label Study to Evaluate the Long-Term Safety of Arbaclofen Extended-Release Tablets in Multiple Sclerosis Patients with Spasticity (Study OS440-3005).

Summary

EudraCT number	2017-004101-40
Trial protocol	BG PL HR
Global end of trial date	27 January 2020

Results information

Result version number	v1 (current)
This version publication date	29 July 2021
First version publication date	29 July 2021

Trial information

Trial identification

Sponsor protocol code	OS440-3005

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03319732
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Osmotica Pharmaceutical US LLC
Sponsor organisation address	400 Crossing Boulevard, Bridgewater/NJ, United States, 08807
Public contact	Meredith Velasco, Osmotica Pharmaceutical US LLC, +1 908809 1423, mvelasco@osmotica.com
Scientific contact	Meredith Velasco, Osmotica Pharmaceutical US LLC, +1 908809 1423, mvelasco@osmotica.com

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	11 June 2020
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	27 January 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study is to evaluate the long-term safety and tolerability of AERT in patients with spasticity due to MS.

Protection of trial subjects:

This study was performed in accordance with Good Clinical Practice standards.

Before undertaking any study-related procedures with subjects, the purpose and nature of the study, as well as possible adverse effects, were explained to them in understandable terms and written informed consent was obtained from each individual.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	30 January 2018
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Poland: 25
Country: Number of subjects enrolled	Croatia: 13
Country: Number of subjects enrolled	Bulgaria: 48
Country: Number of subjects enrolled	Belarus: 14
Country: Number of subjects enrolled	Bosnia and Herzegovina: 14
Country: Number of subjects enrolled	Moldova, Republic of: 5
Country: Number of subjects enrolled	Russian Federation: 62
Country: Number of subjects enrolled	Serbia: 18
Country: Number of subjects enrolled	Ukraine: 99
Country: Number of subjects enrolled	United States: 25
Worldwide total number of subjects	323
EEA total number of subjects	86

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)	318
From 65 to 84 years	5
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

First subject enrolled on 20 Mar 2018; last subject completed on 27 Jan 2020. A total of 323 subjects were enrolled at 67 sites in Poland, Croatia, Bulgaria, Belarus, Bosnia and Herzegovina, Moldova, Russia, Serbia, Ukraine, and the United States.

Pre-assignment

Screening details:

Subjects from Study OS440-3004 could rollover into this open-label extension study plus de novo subjects, provided. Eligible de novo subjects underwent a 21-day washout
period, withdrawing all medications used for anti-spasticity and/or muscle relaxation. 328 subjects screened, 323 enrolled.

Period 1

Period 1 title	overall period
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Blinding implementation details:

This was an open-label study

Arms

Arm title	open-label long-term follow-up

Arm description: -

Arm type	Experimental
Investigational medicinal product name	arbaclofen extended-release tablets
Investigational medicinal product code	
Other name	AERT, arbaclofen ER tablets
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

AERT was supplied as blue, round biconvex tablets in HDPE white bottles with 60 active 20-mg tablets

Number of subjects in period 1	open-label long-term follow-up
Started	323
Completed	218
Not completed	105
Physician decision	1
Adverse event, non-fatal	40
medical condition	1
subject request	50
unspecified	3
relapse	10

Baseline characteristics

Reporting groups	
Reporting group title	open-label long-term follow-up

Reporting group description: -

Reporting group values	open-label long-term follow-up	Total	
Number of subjects	323	323	
Age categorical			
Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	318	318	
From 65-84 years	5	5	
85 years and over	0	0	
Age continuous			
Units: years			
arithmetic mean	47.2		
full range (min-max)	22 to 66	-	
Gender categorical			
For the Safety population, the majority of subjects were female (58.8%).			
Units: Subjects			
Female	190	190	
Male	133	133	
Race			
For the Safety population, the majority of subjects were white (96.6%). The results for race were generally balanced across treatment groups.			
Units: Subjects			
Black or African American	6	6	
White	312	312	
More than one race	1	1	
Not collected	4	4	
Height			
Units: cm			
arithmetic mean	169.6		
full range (min-max)	148 to 198	-	
weight			
Study subjects' weight was collected at baseline			
Units: kg			
arithmetic mean	71.67		
full range (min-max)	42.0 to 124.4	-	
Body Mass Index			
Body Mass Index was collected for study subjects at baseline			

Units: kg/m2			
arithmetic mean	24.825		
full range (min-max)	16.41 to 43.23	-	

Subject analysis sets	
Subject analysis set title	AERT 40 mg
Subject analysis set type	Safety analysis
Subject analysis set description:	
Screened population received 20 mg AERT bid	
Subject analysis set title	AERT 60 mg
Subject analysis set type	Safety analysis
Subject analysis set description:	
screened population received 20 mg in the morning and 40 mg in the evening	
Subject analysis set title	AERT 80 mg
Subject analysis set type	Safety analysis
Subject analysis set description:	
screened population 2 20-mg tablets bid	

Reporting group values	AERT 40 mg	AERT 60 mg	AERT 80 mg
Number of subjects	44	39	239
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 continuous			
Units: years			
arithmetic mean	48.4	48.4	46.7
full range (min-max)	26 to 65	27 to 65	22 to 66
Gender categorical			
For the Safety population, the majority of subjects were female (58.8%).			
Units: Subjects			
Female	30	24	136
Male	14	15	103
Race			
For the Safety population, the majority of subjects were white (96.6%). The results for race were generally balanced across treatment groups.			
Units: Subjects			
Black or African American	1	3	2
White	43	35	233
More than one race	0	0	1
Not collected	0	1	3

Height Units: cm arithmetic mean full range (min-max)	 168.0 155 to 189	 169.0 150 to 196	 170.0 148 to 198
weight			
Study subjects' weight was collected at baseline			
Units: kg arithmetic mean full range (min-max)	 72.23 48.0 to 97.0	 68.10 45.0 to 96.0	 72.16 42.0 to 124.4
Body Mass Index			
Body Mass Index was collected for study subjects at baseline			
Units: kg/m2 arithmetic mean full range (min-max)	 25.547 18.37 to 38.86	 23.811 16.94 to 37.08	 24.860 16.41 to 43.23

End points

End points reporting groups

Reporting group title	open-label long-term follow-up
Reporting group description: -	
Subject analysis set title	AERT 40 mg
Subject analysis set type	Safety analysis
Subject analysis set description: Screened population received 20 mg AERT bid	
Subject analysis set title	AERT 60 mg
Subject analysis set type	Safety analysis
Subject analysis set description: screened population received 20 mg in the morning and 40 mg in the evening	
Subject analysis set title	AERT 80 mg
Subject analysis set type	Safety analysis
Subject analysis set description: screened population 2 20-mg tablets bid	

Primary: Co-primary Efficacy Endpoint: Patient Global Impression of Change (PGIC) in the Safety population

End point title	Co-primary Efficacy Endpoint: Patient Global Impression of Change (PGIC) in the Safety population

End point description:

The PGIC is a standard instrument that is a well-validated outcome measure. The 7-point PGIC measures the change in the subject's overall status. PGIC Scores of 2.0 corresponded to "almost the same," scores of 3.0 corresponded to "a little better," and scores of 4.0 corresponded to "somewhat better."

Note: In the AERT <40 mg group, there is only 1 patient. At baseline and at Visit 8, no confidence intervals are provided with the mean values.

End point type	Primary

End point timeframe:

The PGIC was recorded at Baseline and at Visit 8 (Week 60).

End point values	open-label long-term follow-up	AERT 40 mg	AERT 60 mg	AERT 80 mg
Subject group type	Reporting group	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	323	44	39	232
Units: score				
least squares mean (confidence interval 95%)				
Baseline	3.3 (3.1 to 3.5)	2.7 (2.2 to 3.2)	3.3 (2.6 to 3.9)	3.3 (3.1 to 3.5)
Viait 8 (Week 60)	2.7 (2.5 to 2.9)	2.0 (1.5 to 2.4)	2.4 (1.9 to 3.0)	2.7 (2.5 to 2.9)

Statistical analyses

Statistical analysis title	PGIC

Statistical analysis description:

The PGIC categories were summarized by frequencies and percentages by study visit.
The PGIC values were also summarized by study visit using descriptive statistics.

Comparison groups	AERT 40 mg v AERT 60 mg v AERT 80 mg
Number of subjects included in analysis	315
Analysis specification	Pre-specified
Analysis type	other[1]
Parameter estimate	Mean difference (final values)
Point estimate	2.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.5
upper limit	2.9
Variability estimate	Standard deviation
Dispersion value	2

Notes:

[1] - descriptive statistics

Primary: Co-primary endpoint: TNmAS-MAL in the Safety population

End point title	Co-primary endpoint: TNmAS-MAL in the Safety population

End point description:

The TNmAS is considered the primary clinical measure of muscle spasticity in subjects with neurological conditions. It is a useful 6-point rating scale to measure abnormality in tone or the resistance to passive movements, since there is no clinically direct method for measuring spasticity. Although there are no standardized guidelines for its use, it can be applied to muscles of
both the upper or lower body. The TNmAS assessment was performed by the Investigator who had been appropriately trained to perform and assess the TNmAS. When possible, all TNmAS assessments were to be performed for a particular subject by the same person throughout the study and always prior to any scheduled laboratory sample draw. The most affected limb was determined by the Investigator.
Note: in the AERT <40 mg group, there is only 1 patient. Confidence intervals are not provided with the mean values at baseline and Visit 4. There is no mean value provided at Visit 8.

End point type	Primary

End point timeframe:

From baseline to Week 60

End point values	open-label long-term follow-up	AERT 40 mg	AERT 60 mg	AERT 80 mg
Subject group type	Reporting group	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	323	44	39	239
Units: score				
least squares mean (confidence interval 95%)				
Baseline	6.3 (5.9 to 6.6)	5.6 (4.5 to 6.6)	5.9 (4.9 to 7.0)	6.5 (6.1 to 6.9)
Visit 4 (Week 28)	5.6 (5.2 to 5.9)	4.9 (3.8 to 5.9)	5.6 (4.4 to 6.7)	5.7 (5.3 to 6.1)
Visit 4 (Week 28) change from Baseline	-0.7 (-0.9 to -0.5)	-0.6 (-1.2 to 0)	-0.4 (-0.9 to 0.1)	-0.7 (-1.0 to -0.5)
Visit 8 (Week 60)	6.0 (5.6 to 6.5)	5.1 (3.9 to 6.3)	5.5 (3.8 to 7.1)	6.3 (5.8 to 6.7)

Visit 8 (Week 60) change from Baseline	-0.1 (-0.3 to 0.1)	0 (-0.7 to 0.7)	-0.2 (-0.9 to 0.6)	-0.1 (-0.3 to 0.1)

Statistical analyses

Statistical analysis title	TNmAS-MAL

Statistical analysis description:

Results from TNmAS-MAL were summarized descriptively by study visit in terms of actual values and change from baseline values.

Comparison groups	AERT 40 mg v AERT 80 mg v AERT 60 mg
Number of subjects included in analysis	322
Analysis specification	Pre-specified
Analysis type	other[2]
Parameter estimate	Mean difference (final values)
Point estimate	-0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.3
upper limit	0.1
Variability estimate	Standard deviation
Dispersion value	1.7

Notes:

[2] - Descriptive statistics

Primary: Co-primary Endpoint: Expanded Disability Status Scale (EDSS) in the Safety population

End point title	Co-primary Endpoint: Expanded Disability Status Scale (EDSS) in the Safety population

End point description:

The EDSS is a method of quantifying disability in MS and monitoring changes in the level of disability over time. It is widely used in clinical studies and in the assessment of people with MS. The EDSS scale ranges from 0 to 10 in 0.5-unit increments that represent higher levels of disability. EDSS steps 1.0 to 4.5 refer to people with MS who are able to walk without any aid and is based on measures of impairment in 8 functional systems (FS): pyramidal (weakness or difficulty moving limbs), cerebellar (ataxia, loss of coordination, or tremor), brainstem (problems with speech, swallowing, and nystagmus), sensory (numbness or loss of sensations), bowel and bladder function, visual function, cerebral (or mental) functions, and other. Each FS is scored on a scale of 0 (no disability) to 5 or 6 (more severe disability). EDSS steps 5.0 to 9.5 are defined by the impairment to walking.

Note: in the AERT <40 mg group, there is only 1 patient, causing lack of confidence intervals.

End point type	Primary

End point timeframe:

Baseline to Visit 8 (Week 60)

End point values	open-label long-term follow-up	AERT 40 mg	AERT 60 mg	AERT 80 mg
Subject group type	Reporting group	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	323	44	39	323
Units: score				
least squares mean (confidence interval 95%)				
Baseline	4.98 (4.84 to 5.12)	4.90 (4.45 to 5.34)	5.21 (4.79 to 5.62)	4.98 (4.84 to 5.12)
Visit 4 (Week 28)	4.98 (4.82 to 5.15)	4.77 (4.22 to 5.31)	5.03 (4.42 to 5.63)	4.98 (4.82 to 5.15)
Visit 4 (Week 28) change from baseline	0.06 (0.02 to 0.11)	0.03 (-0.08 to 0.14)	0.15 (-0.15 to 0.45)	0.06 (0.02 to 0.11)
Visit 8 (Week 60)	5.01 (4.87 to 5.16)	4.83 (4.39 to 5.27)	5.47 (5.06 to 5.89)	5.01 (4.87 to 5.16)
Visit 8 (Week 60) change from baseline	0.08 (0.04 to 0.12)	0.07 (-0.02 to 0.17)	0.32 (0.10 to 0.54)	0.08 (0.04 to 0.12)

Statistical analyses

Statistical analysis title	EDSS

Statistical analysis description:

Results from EDSS were summarized descriptively by study visit in terms of actual values and change from baseline values.

Comparison groups	AERT 40 mg v AERT 60 mg v AERT 80 mg
Number of subjects included in analysis	406
Analysis specification	Pre-specified
Analysis type	other[3]
Parameter estimate	Mean difference (final values)
Point estimate	0.08
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.04
upper limit	0.12
Variability estimate	Standard deviation
Dispersion value	0.351

Notes:

[3] - Descriptive statistics

Primary: Co-primary Endpoint: TNmAS-TL in the Safety population

End point title	Co-primary Endpoint: TNmAS-TL in the Safety population

End point description:

The TNmAS is considered the primary clinical measure of muscle spasticity in subjects with neurological conditions. It is a useful 6-point rating scale to measure abnormality in
tone or the resistance to passive movements, since there is no clinically direct method for measuring spasticity. The TNmAS-TL score is the sum of the 3 main joint muscular group scores for all 4 limbs. The TNmAS assessment was performed by the Investigator who had been appropriately trained to perform and assess the TNmAS. When possible, all TNmAS assessments were to be performed for a particular subject by the same person throughout the study and always prior to any scheduled laboratory sample draw.

Note: in the AERT <40 mg group, there is only 1 patient. Confidence intervals are not provided with the

mean values at baseline and Visit 4. There is no mean value provided at Visit 8.

End point type	Primary

End point timeframe:

From baseline to Week 60

End point values	open-label long-term follow-up	AERT 40 mg	AERT 60 mg	AERT 80 mg
Subject group type	Reporting group	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	323	44	39	239
Units: score				
least squares mean (confidence interval 95%)				
Baseline	13.0 (12.2 to 13.9)	11.1 (8.3 to 13.9)	11.3 (8.6 to 14.0)	13.7 (12.7 to 14.6)
Visit 4 (Week 28)	11.5 (10.7 to 12.4)	9.5 (6.8 to 12.1)	11.0 (8.1 to 13.9)	12.0 (11.1 to 13.0)
Visit 4 (Week 28) change from baseline	-1.3 (-1.7 to -0.9)	-1.4 (-2.9 to 0.1)	-0.4 (-1.3 to 0.5)	-1.4 (-1.9 to -1.0)
Visit 8 (Week 60)	12.8 (11.7 to 13.9)	11.0 (7.1 to 14.8)	10.2 (6.6 to 13.7)	13.4 (12.2 to 14.6)
Visit 8 (Week 60) change from baseline	0.3 (-0.2 to 0.9)	0.3 (-1.9 to 2.5)	0.4 (-0.9 to 1.7)	0.3 (-0.2 to 0.9)

Statistical analyses

Statistical analysis title	TNm-AS-TL

Statistical analysis description:

Results from TNmAS-TL were summarized descriptively by study visit in terms of actual values and change from baseline values.

Comparison groups	AERT 40 mg v AERT 60 mg v AERT 80 mg
Number of subjects included in analysis	322
Analysis specification	Pre-specified
Analysis type	other[4]
Parameter estimate	Mean difference (final values)
Point estimate	0.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.2
upper limit	0.9
Variability estimate	Standard deviation
Dispersion value	4.18

Notes:

[4] - Descriptive statistics

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were recorded from time of informed consent through completion of the last study visit. A treatment-emergent AE was any AE with onset or worsening on or after the first dose of study drug up until 30 days after the last dose of study drug

Adverse event reporting additional description:

Adverse events could have been reported spontaneously by the subject or observed by the Investigator. Within each preferred term, subjects were counted only once if they had more than 1 event reported during the treatment period.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	20.1

Reporting groups

Reporting group title	AERT <40 mg

Reporting group description:

Adverse event results are presented for the Safety population, which includes all subjects who received at least 1 dose of open-label study treatment and had at least 1 postdose visit.
All serious TEAEs that occurred are reported. Non-serious TEAEs that occurred in 5% or more of subjects in any treatment group are reported.
No deaths occurred during the study.

Reporting group title	AERT 40 mg

Reporting group description:

The safety population included all subjects who received at least 1 dose of open-label study treatment and had at least 1 postdose visit.
All serious TEAEs that occurred are reported. Non-serious TEAEs that occurred in 5% or more of subjects in any treatment group are reported.
No deaths occurred during the study.

Reporting group title	AERT 60 mg

Reporting group description:

The safety population included all subjects who received at least 1 dose of open-label study treatment and had at least 1 postdose visit.
All serious TEAEs that occurred are reported. Non-serious TEAEs that occurred in 5% or more of subjects in any treatment group are reported.
No deaths occurred during the study.

Reporting group title	AERT 80 mg

Reporting group description:

The safety population included all subjects who received at least 1 dose of open-label study treatment and had at least 1 postdose visit.
All serious TEAEs that occurred are reported. Non-serious TEAEs that occurred in 5% or more of subjects in any treatment group are reported.
One death occurred during the study.

Serious adverse events	AERT <40 mg	AERT 40 mg	AERT 60 mg
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 1 (0.00%)	2 / 44 (4.55%)	6 / 39 (15.38%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0

Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Adenocarcinoma of colon			
subjects affected / exposed	0 / 1 (0.00%)	0 / 44 (0.00%)	0 / 39 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Myocardial infarction			
subjects affected / exposed	0 / 1 (0.00%)	0 / 44 (0.00%)	0 / 39 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute myocardial infarction			
subjects affected / exposed	0 / 1 (0.00%)	0 / 44 (0.00%)	0 / 39 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Death			
subjects affected / exposed	0 / 1 (0.00%)	0 / 44 (0.00%)	0 / 39 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Surgical and medical procedures			
Hypertension			
subjects affected / exposed	0 / 1 (0.00%)	0 / 44 (0.00%)	0 / 39 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Multiple sclerosis relapse			
subjects affected / exposed	0 / 1 (0.00%)	1 / 44 (2.27%)	4 / 39 (10.26%)
occurrences causally related to treatment / all	0 / 0	0 / 1	1 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Restless legs syndrome			
subjects affected / exposed	0 / 1 (0.00%)	0 / 44 (0.00%)	0 / 39 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Paraparesis			

subjects affected / exposed	0 / 1 (0.00%)	0 / 44 (0.00%)	0 / 39 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Meningioma			
subjects affected / exposed	0 / 1 (0.00%)	0 / 44 (0.00%)	0 / 39 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Somnolence			
subjects affected / exposed	0 / 1 (0.00%)	0 / 44 (0.00%)	1 / 39 (2.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Withdrawal syndrome			
subjects affected / exposed	0 / 1 (0.00%)	0 / 44 (0.00%)	1 / 39 (2.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Toxicity to various agents			
subjects affected / exposed	0 / 1 (0.00%)	0 / 44 (0.00%)	0 / 39 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Drug withdrawal syndrome			
subjects affected / exposed	0 / 1 (0.00%)	0 / 44 (0.00%)	0 / 39 (0.00%)
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			
Nausea			
subjects affected / exposed	0 / 1 (0.00%)	0 / 44 (0.00%)	1 / 39 (2.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis chronic			
subjects affected / exposed	0 / 1 (0.00%)	0 / 44 (0.00%)	0 / 39 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Constipation			
subjects affected / exposed	0 / 1 (0.00%)	0 / 44 (0.00%)	0 / 39 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholecystitis			
subjects affected / exposed	0 / 1 (0.00%)	0 / 44 (0.00%)	0 / 39 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Dermatitis allergic			
subjects affected / exposed	0 / 1 (0.00%)	1 / 44 (2.27%)	0 / 39 (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
Decubitus ulcer			
subjects affected / exposed	0 / 1 (0.00%)	0 / 44 (0.00%)	0 / 39 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Atonic urinary bladder			
subjects affected / exposed	0 / 1 (0.00%)	0 / 44 (0.00%)	0 / 39 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Osteomyelitis			
subjects affected / exposed	0 / 1 (0.00%)	0 / 44 (0.00%)	0 / 39 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	AERT 80 mg		
Total subjects affected by serious adverse events			
subjects affected / exposed	18 / 239 (7.53%)		
number of deaths (all causes)	1		
number of deaths resulting from adverse events	1		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Adenocarcinoma of colon			

subjects affected / exposed	1 / 239 (0.42%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Myocardial infarction			
subjects affected / exposed	1 / 239 (0.42%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Acute myocardial infarction			
subjects affected / exposed	1 / 239 (0.42%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Death			
subjects affected / exposed	1 / 239 (0.42%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Surgical and medical procedures			
Hypertension			
subjects affected / exposed	1 / 239 (0.42%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Multiple sclerosis relapse			
subjects affected / exposed	5 / 239 (2.09%)		
occurrences causally related to treatment / all	0 / 5		
deaths causally related to treatment / all	0 / 0		
Restless legs syndrome			
subjects affected / exposed	1 / 239 (0.42%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Paraparesis			
subjects affected / exposed	1 / 239 (0.42%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Meningioma				
subjects affected / exposed	1 / 239 (0.42%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
General disorders and administration site conditions				
Somnolence				
subjects affected / exposed	0 / 239 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Withdrawal syndrome				
subjects affected / exposed	0 / 239 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Toxicity to various agents				
subjects affected / exposed	1 / 239 (0.42%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Drug withdrawal syndrome				
subjects affected / exposed	1 / 239 (0.42%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal disorders				
Nausea				
subjects affected / exposed	0 / 239 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pancreatitis chronic				
subjects affected / exposed	1 / 239 (0.42%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Constipation				
subjects affected / exposed	1 / 239 (0.42%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			

Cholecystitis			
subjects affected / exposed	1 / 239 (0.42%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			
Dermatitis allergic			
subjects affected / exposed	0 / 239 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Decubitus ulcer			
subjects affected / exposed	1 / 239 (0.42%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Atonic urinary bladder			
subjects affected / exposed	1 / 239 (0.42%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Osteomyelitis			
subjects affected / exposed	1 / 239 (0.42%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	AERT <40 mg	AERT 40 mg	AERT 60 mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	1 / 1 (100.00%)	42 / 44 (95.45%)	36 / 39 (92.31%)
Nervous system disorders			
Dizziness			
subjects affected / exposed	0 / 1 (0.00%)	4 / 44 (9.09%)	7 / 39 (17.95%)
occurrences (all)	0	4	7
Somnolence			

subjects affected / exposed	1 / 1 (100.00%)	7 / 44 (15.91%)	4 / 39 (10.26%)
occurrences (all)	1	7	4
Headache			
subjects affected / exposed	0 / 1 (0.00%)	7 / 44 (15.91%)	1 / 39 (2.56%)
occurrences (all)	0	7	1
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 1 (0.00%)	4 / 44 (9.09%)	11 / 39 (28.21%)
occurrences (all)	0	4	11
Gait disturbance			
subjects affected / exposed	0 / 1 (0.00%)	4 / 44 (9.09%)	4 / 39 (10.26%)
occurrences (all)	0	4	4
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	1 / 1 (100.00%)	25 / 44 (56.82%)	11 / 39 (28.21%)
occurrences (all)	1	25	11
Vomiting			
subjects affected / exposed	0 / 1 (0.00%)	10 / 44 (22.73%)	7 / 39 (17.95%)
occurrences (all)	0	10	7
Renal and urinary disorders			
Urinary tract disorder			
subjects affected / exposed	0 / 1 (0.00%)	16 / 44 (36.36%)	13 / 39 (33.33%)
occurrences (all)	0	16	13
Musculoskeletal and connective tissue disorders			
Muscular weakness			
subjects affected / exposed	0 / 1 (0.00%)	28 / 44 (63.64%)	14 / 39 (35.90%)
occurrences (all)	0	28	14

Non-serious adverse events	AERT 80 mg		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	197 / 239 (82.43%)		
Nervous system disorders			
Dizziness			
subjects affected / exposed	40 / 239 (16.74%)		
occurrences (all)	40		
Somnolence			

subjects affected / exposed	28 / 239 (11.72%)		
occurrences (all)	28		
Headache			
subjects affected / exposed	16 / 239 (6.69%)		
occurrences (all)	16		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	46 / 239 (19.25%)		
occurrences (all)	46		
Gait disturbance			
subjects affected / exposed	12 / 239 (5.02%)		
occurrences (all)	12		
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	29 / 239 (12.13%)		
occurrences (all)	29		
Vomiting			
subjects affected / exposed	10 / 239 (4.18%)		
occurrences (all)	10		
Renal and urinary disorders			
Urinary tract disorder			
subjects affected / exposed	82 / 239 (34.31%)		
occurrences (all)	82		
Musculoskeletal and connective tissue disorders			
Muscular weakness			
subjects affected / exposed	35 / 239 (14.64%)		
occurrences (all)	35		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
06 November 2017	Entire protocol: editorial corrections and clarifications, added revised protocol number, added hyperlinks. Title page: added protocol version history. Section 9.6.2: Corrected the mistake in the original protocol regarding a 4-point change in total USP score by replacing "A reduction of 4 points…" with "An increase of 4 points…." Appendix 8: Added new Appendix 8 Summary of Changes to summarize the changes made to the original protocol with Amendment 1.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

None reported

Notes: