Clinical trial results:
A Randomized, Double-Blind, Placebo-Controlled Parallel Group Study to Investigate the Safety and Efficacy of Arbaclofen Extended-Release Tablets for the Treatment of Spasticity in Patients with Multiple Sclerosis (Study OS440-3004)

Summary

EudraCT number	2017-004100-22
Trial protocol	BG PL HR
Global end of trial date	03 December 2018

Results information

Result version number	v1 (current)
This version publication date	30 November 2020
First version publication date	30 November 2020
Summary attachment (see zip file)	OS440-3004 CSR Synopsis (OS440-3004_Clinical Study Report Synopsis [05-JUN-2020].pdf)

Trial information

Trial identification

Sponsor protocol code	OS440-3004

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03290131
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Osmotica Pharmaceutical US LLC
Sponsor organisation address	400 Crossing Boulevard, Bridgewater, United States, NJ 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	03 December 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	03 December 2018
Global end of trial reached?	Yes
Global end of trial date	03 December 2018
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 demonstrate the safety and efficacy of Arbaclofen Extended-Release Tablets (AERT) for treatment of spasticity in patients with Multiple Sclerosis (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.

An independent, chartered Data Safety Monitoring Board (DSMB) reviewed all safety data on 4 occasions during the study.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	31 January 2018
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	Poland: 54
Country: Number of subjects enrolled	Croatia: 20
Country: Number of subjects enrolled	Bulgaria: 57
Country: Number of subjects enrolled	Belarus: 33
Country: Number of subjects enrolled	Bosnia and Herzegovina: 21
Country: Number of subjects enrolled	Moldova, Republic of: 12
Country: Number of subjects enrolled	Russian Federation: 149
Country: Number of subjects enrolled	Serbia: 30
Country: Number of subjects enrolled	Ukraine: 135
Country: Number of subjects enrolled	United States: 25
Worldwide total number of subjects	536
EEA total number of subjects	131

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)	531
From 65 to 84 years	5
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

First subject enrolled on 13 Feb 2018; last subject completed on 03 Dec 2018. Total of 536 subjects were enrolled at 82 sites in the United States and Central and Eastern Europe (Russia, Belarus, Serbia, Bosnia and Herzegovina, Croatia, Bulgaria, Moldova, Poland, and Ukraine).

Pre-assignment

Screening details:

Eligible subjects underwent up to a 21-day washout period for withdrawal of anti-spasticity and/or muscle relaxation medications before randomization. Eligibility was confirmed before randomization (Visit 2). 594 subjects were screened; 58 subjects were screen failures (39 due to inclusion/exclusion criteria not met); 536 subjects were randomized.

Period 1

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

Blinding implementation details:

Every effort was made to retain the integrity of the blind. The study medication was identical in appearance for all subjects, regardless of treatment assignment.

No premature unblinding occurred during the study. The study blind was broken at study completion once the following were met: 1) Database was locked and 2) the statistical analysis plan (SAP) was finalized.

Arms

Are arms mutually exclusive?	Yes
Arm title	AERT 40 mg

Arm description:

Experimental therapy arm: arbaclofen extended-release tablets (AERT) 40 mg (20 mg twice daily).

Results are presented for the Intent-to-Treat (ITT) population, which includes all 179 subjects who were randomized to the AERT 40 mg arm.

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 blister card wallets with matching placebo tablets. IMP was administered as follows:
- Days 1 to 6: AERT 20 mg/day given as two placebo tablets in the morning and one placebo tablet and one 20-mg AERT in the evening
- Days 7 to 84: AERT 40 mg/day given as one placebo tablet and one 20-mg AERT in both the morning and the evening
- Days 85 to 88: AERT 20 mg/day given as two placebo tablets in the morning and one placebo tablet and one 20-mg AERT in the evening
- Days 89 to 91: AERT 0 mg/day given as two placebo tablets both in the morning and the evening.

Arm title	AERT 80 mg

Arm description:

Experimental therapy arm: arbaclofen extended-release tablets (AERT) 80 mg (40 mg twice daily).

Results are presented for the Intent-to-Treat (ITT) population, which includes all 179 subjects who were

randomized to the AERT 80 mg arm.

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 blister card wallets with matching placebo tablets. IMP was administered as follows:
- Days 1 to 3: AERT 20 mg/day given as two placebo tablets in the morning and one placebo tablet and one 20-mg AERT in the evening
- Days 4 to 6: AERT 40 mg/day given as one placebo tablet and one 20-mg AERT both in the morning and the evening
- Days 7 to 9: AERT 60 mg/day was given as one placebo tablet and one 20-mg AERT in the morning and two 20-mg AERT in the evening
- Days 10 to 84: AERT 80 mg/day was given as two 20-mg AERT both in the morning and the evening
- Days 85 to 88: AERT 40 mg/day was given as one placebo tablet and one 20-mg AERT both in the morning and the evening
- Days 89 to 91: AERT 20 mg/day was given as two placebo tablets in the morning and one placebo tablet and one 20-mg AERT in the evening

Arm title	Placebo

Arm description:

Placebo arm: placebo tablets administered twice daily.

Results are presented for the Intent-to-Treat (ITT) population, which includes all 178 subjects who were randomized to the placebo arm.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Placebo tablets were supplied as blue, round biconvex tablets that matched the AERT tablets and were packaged in blister card wallets. From Days 1 to 91, two placebo tablets were administered both in the morning and the evening.

Number of subjects in period 1	AERT 40 mg	AERT 80 mg	Placebo
Started	179	179	178
Completed	137	107	159
Not completed	42	72	19
Adverse event, non-fatal	22	57	11
Subject moved to another city	-	1	-
Subject request	18	13	8
MS relapse	2	1	-

Baseline characteristics

Reporting groups	
Reporting group title	AERT 40 mg
Reporting group description:	
Experimental therapy arm: arbaclofen extended-release tablets (AERT) 40 mg (20 mg twice daily). Results are presented for the Intent-to-Treat (ITT) population, which includes all 179 subjects who were randomized to the AERT 40 mg arm.	
Reporting group title	AERT 80 mg
Reporting group description:	
Experimental therapy arm: arbaclofen extended-release tablets (AERT) 80 mg (40 mg twice daily). Results are presented for the Intent-to-Treat (ITT) population, which includes all 179 subjects who were randomized to the AERT 80 mg arm.	
Reporting group title	Placebo
Reporting group description:	
Placebo arm: placebo tablets administered twice daily. Results are presented for the Intent-to-Treat (ITT) population, which includes all 178 subjects who were randomized to the placebo arm.	

Reporting group values	AERT 40 mg	AERT 80 mg	Placebo
Number of subjects	179	179	178
Age categorical			
For the ITT population, the overall mean (SD) age at baseline was 46.5 (9.60) years (range, 21 to 65 years). The results for age were generally balanced across the treatment groups.			
Units: Subjects			
Adults (18-65 years)	179	179	178
Age continuous			
Units: years			
arithmetic mean	46.0	46.0	47.5
standard deviation	± 9.50	± 9.71	± 9.55
Gender categorical			
For the ITT population, the majority of subjects were female (59.5%). The results for gender were generally balanced across treatment groups.			
Units: Subjects			
Female	108	101	110
Male	71	78	68
Race			
For the ITT population, the majority of subjects were white (97.4%). The results for race were generally balanced across treatment groups.			
Units: Subjects			
Asian	0	0	1
Black or African American	4	0	2
White	171	177	174
More than one race	1	0	1
Missing	3	2	0
MS Subtype			
For the ITT population, the MS subtype at baseline was relapsing-remitting (RR) for the majority of subjects (323 subjects; 60.3%); 186 subjects (34.7%) had secondary progressive (SP) MS and 27 subjects (5.0%) had primary progressive (PP) MS. The results for MS subtype were generally balanced across treatment groups.			

Units: Subjects			
Relapsing remitting	117	100	106
Primary progressive	9	8	10
Secondary progressive	53	71	62
Weight			
For the ITT population, the overall mean (SD) weight at baseline was 70.85 (15.182) kg (range, 36.5 to 126.0 kg). The results for weight were generally balanced across treatment groups.			
Units: kg			
arithmetic mean	70.38	71.45	70.71
standard deviation	± 15.371	± 15.405	± 14.825
Body Mass Index			
For the ITT population, the overall mean (SD) BMI at baseline was 24.648 (4.6036) kg/m2 (range, 16.23 to 42.52 kg/m2). Results for BMI were generally balanced across treatment groups.			
Units: kg/m2			
arithmetic mean	24.661	24.660	24.623
standard deviation	± 5.1229	± 4.2615	± 4.4048

Reporting group values	Total		
Number of subjects	536		
Age categorical			
For the ITT population, the overall mean (SD) age at baseline was 46.5 (9.60) years (range, 21 to 65 years). The results for age were generally balanced across the treatment groups.			
Units: Subjects			
Adults (18-65 years)	536		
Age continuous			
Units: years			
arithmetic mean			
standard deviation	-		
Gender categorical			
For the ITT population, the majority of subjects were female (59.5%). The results for gender were generally balanced across treatment groups.			
Units: Subjects			
Female	319		
Male	217		
Race			
For the ITT population, the majority of subjects were white (97.4%). The results for race were generally balanced across treatment groups.			
Units: Subjects			
Asian	1		
Black or African American	6		
White	522		
More than one race	2		
Missing	5		
MS Subtype			
For the ITT population, the MS subtype at baseline was relapsing-remitting (RR) for the majority of subjects (323 subjects; 60.3%); 186 subjects (34.7%) had secondary progressive (SP) MS and 27 subjects (5.0%) had primary progressive (PP) MS. The results for MS subtype were generally balanced across treatment groups.			
Units: Subjects			
Relapsing remitting	323		
Primary progressive	27		
Secondary progressive	186		

Weight			
For the ITT population, the overall mean (SD) weight at baseline was 70.85 (15.182) kg (range, 36.5 to 126.0 kg). The results for weight were generally balanced across treatment groups.			
Units: kg arithmetic mean standard deviation	- 		
Body Mass Index			
For the ITT population, the overall mean (SD) BMI at baseline was 24.648 (4.6036) kg/m2 (range, 16.23 to 42.52 kg/m2). Results for BMI were generally balanced across treatment groups.			
Units: kg/m2 arithmetic mean standard deviation	- 		

End points

End points reporting groups

Reporting group title	AERT 40 mg

Reporting group description:

Experimental therapy arm: arbaclofen extended-release tablets (AERT) 40 mg (20 mg twice daily).

Results are presented for the Intent-to-Treat (ITT) population, which includes all 179 subjects who were randomized to the AERT 40 mg arm.

Reporting group title	AERT 80 mg

Reporting group description:

Experimental therapy arm: arbaclofen extended-release tablets (AERT) 80 mg (40 mg twice daily).

Results are presented for the Intent-to-Treat (ITT) population, which includes all 179 subjects who were randomized to the AERT 80 mg arm.

Reporting group title	Placebo

Reporting group description:

Placebo arm: placebo tablets administered twice daily.

Results are presented for the Intent-to-Treat (ITT) population, which includes all 178 subjects who were randomized to the placebo arm.

Primary: Co-primary Efficacy Endpoint: TNmAS-MAL in the ITT Population

End point title	Co-primary Efficacy Endpoint: TNmAS-MAL in the ITT Population

End point description:

The Total Numeric-transformed modified Ashworth Scale (TNmAS) is considered the primary clinical measure of muscle spasticity in subjects with neurological conditions. It consists of a 6-point rating scale to measure abnormality in tone or the resistance to passive movements.

The TNmAS assessment was to be performed by the study evaluator (someone other than the Investigator) who had been appropriately trained to perform and assess the TNmAS, and when possible all TNmAS assessments were performed for a particular subject by the same study evaluator throughout the study.

The outcome variable for TNmAS-MAL was least-squares (LS) mean change from baseline (and 95% confidence interval [CI]) to Day 84 in the ITT population by treatment group. AERT 40 mg was compared with placebo first (for both co-primary endpoints, TNmAS-MAL and CGIC). Both co-primary endpoints had to meet the 0.05 level for AERT 40 mg vs placebo for the study to be considered a success.

End point type	Primary

End point timeframe:

TNmAS score of the most affected limb (TNmAS-MAL) was recorded at screening (Visit 1), baseline (Visit 2), Day 42 (Visit 4), Day 84 (Visit 5), and Day 92 (final visit or early termination).

End point values	AERT 40 mg	AERT 80 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	139	115	164	
Units: Change from baseline to Day 84				
least squares mean (confidence interval 95%)	-1.67 (-1.97 to -1.36)	-1.79 (-2.12 to -1.46)	-1.28 (-1.57 to -0.99)	

Statistical analyses

Statistical analysis title	LS mean difference for AERT 40 mg vs placebo

Statistical analysis description:

Least-squares mean were used to compare AERT 40 mg vs placebo. The TNmAS-MAL was analyzed using a restricted maximum likelihood (REML)-based mixed model for repeated measures (MMRM) with fixed effects for treatment, visit, country, and the treatment-by-visit interaction; and with baseline score as a covariate.

There was statistically significant greater improvement from baseline to Day 84 in TNmAS-MAL scores in the AERT 40 mg group compared to the placebo group.

Comparison groups	AERT 40 mg v Placebo
Number of subjects included in analysis	303
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0482 [1]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.39
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.77
upper limit	0
Variability estimate	Standard error of the mean
Dispersion value	0.196

Notes:

[1] - p-value calculated for AERT 40 mg LS mean - placebo LS mean.

Statistical analysis title	LS mean difference for AERT 80 mg vs placebo

Statistical analysis description:

Least-squares mean were used to compare AERT 80 mg versus placebo. The TNmAS-MAL was analyzed using a restricted maximum likelihood (REML)-based mixed model for repeated measures (MMRM) with fixed effects for treatment, visit, country, and the treatment-by-visit interaction; and with baseline score as a covariate.

There was statistically significant greater improvement from baseline to Day 84 in TNmAS-MAL scores in the AERT 80 mg group compared to the placebo group.

Comparison groups	AERT 80 mg v Placebo
Number of subjects included in analysis	279
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0118 [2]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.51

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.91
upper limit	-0.11
Variability estimate	Standard error of the mean
Dispersion value	0.203

Notes:

[2] - p-value calculated for AERT 80 mg LS mean - placebo LS mean.

Primary: Co-primary Efficacy Endpoint: CGIC in the ITT Population

End point title	Co-primary Efficacy Endpoint: CGIC in the ITT Population

End point description:

For the CGIC, the Investigator rated the change in overall global functional performance (not limited to spasticity) the subject was experiencing (based on assessment of the subject since Visit 2). The Investigator evaluated the subject's status on a -3 to +3 scale judging whether there had been a change from significantly worse (-3) to significantly improved (+3) relative to baseline (Visit 2) and had to have access to the TNmAS.

The outcome variable was LS mean CGIC score (and 95% CI) at Day 84 in the ITT population by treatment group. AERT 40 mg was compared with placebo first (for both co-primary endpoints, TNmAS-MAL and CGIC). Both co-primary endpoints had to meet the 0.05 level for AERT 40 mg vs placebo for the study to be considered a success.

End point type	Primary

End point timeframe:

The CGIC was recorded at Day 42 (Visit 4), Day 84 (Visit 5), and Day 92 (final visit or early termination).

End point values	AERT 40 mg	AERT 80 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	140	115	164	
Units: Score				
least squares mean (confidence interval 95%)	0.36 (0.17 to 0.54)	0.01 (-0.19 to 0.22)	0.45 (0.27 to 0.63)	

Statistical analyses

Statistical analysis title	LS mean difference for AERT 40 mg vs placebo

Statistical analysis description:

Least-squares mean were used to compare AERT 40 mg versus placebo. The CGIC was analyzed using a REML-based MMRM with fixed effects for treatment, visit, country, and the treatment-by-visit interaction. Because the CGIC is a change score, no value was measured at baseline.

No statistically significant difference in the mean CGIC score was observed between the placebo group and the AERT 40 mg group.

Comparison groups	AERT 40 mg v Placebo

Number of subjects included in analysis	304
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4272 [3]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.33
upper limit	0.14
Variability estimate	Standard error of the mean
Dispersion value	0.121

Notes:

[3] - p-value calculated for AERT 40 mg LS mean - placebo LS mean.

Statistical analysis title	LS mean difference for AERT 80 mg vs placebo

Statistical analysis description:

Least-squares mean were used to compare AERT 80 mg versus placebo. The CGIC was analyzed using a REML-based MMRM with fixed effects for treatment, visit, country, and the treatment-by-visit interaction. Because the CGIC is a change score, no value was measured at baseline.

A statistically significant difference in the mean CGIC score was observed between the placebo group and the AERT 80 mg group.

Comparison groups	AERT 80 mg v Placebo
Number of subjects included in analysis	279
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0005 [4]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.44
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.69
upper limit	-0.19
Variability estimate	Standard error of the mean
Dispersion value	0.126

Notes:

[4] - p-value calculated for AERT 80 mg LS mean - placebo LS mean.

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 one AE 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 double-blind study treatment and had at least 1 postdose visit. The Safety population includes all 179 subjects who were randomized to the AERT 40 mg arm.

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:

Adverse event results are presented for the Safety population, which includes all subjects who received at least 1 dose of double-blind study treatment and had at least 1 postdose visit. The Safety population includes all 179 subjects who were randomized to the AERT 80 mg arm.

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	Placebo

Reporting group description:

Adverse event results are presented for the Safety population, which includes all subjects who received at least 1 dose of double-blind study treatment and had at least 1 postdose visit. The Safety population includes all 178 subjects who were randomized to the placebo arm.

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.

Serious adverse events	AERT 40 mg	AERT 80 mg	Placebo
Total subjects affected by serious adverse events			
subjects affected / exposed	6 / 179 (3.35%)	6 / 179 (3.35%)	6 / 178 (3.37%)
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)			
Schwannoma			
subjects affected / exposed	0 / 179 (0.00%)	0 / 179 (0.00%)	1 / 178 (0.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	1 / 179 (0.56%)	0 / 179 (0.00%)	0 / 178 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hip fracture			
subjects affected / exposed	1 / 179 (0.56%)	0 / 179 (0.00%)	0 / 178 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Joint injury			
subjects affected / exposed	0 / 179 (0.00%)	1 / 179 (0.56%)	0 / 178 (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
Nervous system disorders			
Multiple sclerosis relapse			
subjects affected / exposed	2 / 179 (1.12%)	3 / 179 (1.68%)	0 / 178 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Restless legs syndrome			
subjects affected / exposed	1 / 179 (0.56%)	0 / 179 (0.00%)	0 / 178 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Somnolence			
subjects affected / exposed	0 / 179 (0.00%)	0 / 179 (0.00%)	1 / 178 (0.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Trigeminal neuralgia			

subjects affected / exposed	0 / 179 (0.00%)	0 / 179 (0.00%)	1 / 178 (0.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Status epilepticus			
subjects affected / exposed	1 / 179 (0.56%)	0 / 179 (0.00%)	0 / 178 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Withdrawal syndrome			
subjects affected / exposed	0 / 179 (0.00%)	0 / 179 (0.00%)	1 / 178 (0.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	0 / 179 (0.00%)	1 / 179 (0.56%)	0 / 178 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Vomiting			
subjects affected / exposed	0 / 179 (0.00%)	1 / 179 (0.56%)	0 / 178 (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
Respiratory, thoracic and mediastinal disorders			
Pulmonary embolism			
subjects affected / exposed	1 / 179 (0.56%)	0 / 179 (0.00%)	0 / 178 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Toxic skin eruption			
subjects affected / exposed	0 / 179 (0.00%)	0 / 179 (0.00%)	1 / 178 (0.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Delirium			

subjects affected / exposed	1 / 179 (0.56%)	0 / 179 (0.00%)	0 / 178 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Depression suicidal			
subjects affected / exposed	0 / 179 (0.00%)	1 / 179 (0.56%)	0 / 178 (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
Somatic symptom disorder			
subjects affected / exposed	0 / 179 (0.00%)	1 / 179 (0.56%)	0 / 178 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Urosepsis			
subjects affected / exposed	0 / 179 (0.00%)	0 / 179 (0.00%)	1 / 178 (0.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	AERT 40 mg	AERT 80 mg	Placebo
Total subjects affected by non-serious adverse events			
subjects affected / exposed	137 / 179 (76.54%)	146 / 179 (81.56%)	126 / 178 (70.79%)
Nervous system disorders			
Dizziness			
subjects affected / exposed	25 / 179 (13.97%)	33 / 179 (18.44%)	19 / 178 (10.67%)
occurrences (all)	25	33	19
Somnolence			
subjects affected / exposed	18 / 179 (10.06%)	26 / 179 (14.53%)	17 / 178 (9.55%)
occurrences (all)	18	26	17
Headache			
subjects affected / exposed	2 / 179 (1.12%)	6 / 179 (3.35%)	12 / 178 (6.74%)
occurrences (all)	2	6	12
General disorders and administration site conditions			

Asthenia			
subjects affected / exposed	23 / 179 (12.85%)	33 / 179 (18.44%)	27 / 178 (15.17%)
occurrences (all)	23	33	27
Gait disturbance			
subjects affected / exposed	2 / 179 (1.12%)	14 / 179 (7.82%)	6 / 178 (3.37%)
occurrences (all)	2	14	6
Fatigue			
subjects affected / exposed	4 / 179 (2.23%)	9 / 179 (5.03%)	6 / 178 (3.37%)
occurrences (all)	4	9	6
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	39 / 179 (21.79%)	27 / 179 (15.08%)	28 / 178 (15.73%)
occurrences (all)	39	27	28
Vomiting			
subjects affected / exposed	13 / 179 (7.26%)	18 / 179 (10.06%)	16 / 178 (8.99%)
occurrences (all)	13	18	16
Renal and urinary disorders			
Urinary tract disorder			
subjects affected / exposed	48 / 179 (26.82%)	54 / 179 (30.17%)	61 / 178 (34.27%)
occurrences (all)	48	54	61
Musculoskeletal and connective tissue disorders			
Muscular weakness			
subjects affected / exposed	39 / 179 (21.79%)	39 / 179 (21.79%)	27 / 178 (15.17%)
occurrences (all)	39	39	27

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
19 September 2017	The following changes were made to Protocol CLN.OS440-3004.PR.A01 as Amendment 1 dated 19 September 2017: - Clarified birth control requirements for subjects and partners of subjects. - Clarified that "high dose (120 mg daily)" oral or intravenous methylprednisolone or equivalent within 3 months before Visit 1 (Screening) would be exclusionary. - Added a criterion excluding subjects with clinically significant abnormal laboratory values at Screening. - Added taper and washout periods for specific anti-spasticity and/or muscle relaxation medications. - 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..." - In the sample size calculation, specified that the determination of sample size should be based on the AERT 40 mg/day dose, as the AERT 40 mg/day dose will be analyzed first versus placebo.
09 November 2017	The following changes were made to Protocol CLN.OS440-3004.PR.A02 as Amendment 2 dated 09 November 2017: - Disallowed subjects who experienced an acute MS exacerbation/relapse during study OS440-3004 from enrolling in study OS440-3005.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported