Clinical trial results:
A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, DOSE FINDING STUDY TO EVALUATE THE EFFICACY AND SAFETY OF PADSEVONIL AS ADJUNCTIVE TREATMENT OF FOCAL-ONSET SEIZURES IN ADULT SUBJECTS WITH DRUG-RESISTANT EPILEPSY

Summary

EudraCT number	2017-003200-48
Trial protocol	GB DE HU CZ BE ES FR BG LT SK PT IT
Global end of trial date	30 January 2020

Results information

Result version number	v1
This version publication date	14 February 2021
First version publication date	14 February 2021

Trial information

Trial identification

Sponsor protocol code	EP0091

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03373383
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	UCB Biopharma SRL
Sponsor organisation address	Allée de la Recherche 60, Brussels, Belgium, 1070
Public contact	Clin Trial Reg & Results Disclosure, UCB BIOSCIENCES GmbH, clinicaltrials@ucb.com
Scientific contact	Clin Trial Reg & Results Disclosure, UCB BIOSCIENCES GmbH, clinicaltrials@ucb.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	18 February 2020
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	30 January 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objectives of this study are to characterize the dose-response relationship with respect to efficacy of Padsevonil (PSL) administered concomitantly with up to 3 anti-epileptic drugs (AEDs) for treatment of observable focal-onset seizures in subjects with drug-resistant epilepsy and to evaluate the efficacy of the 4 selected dose regimens of PSL compared with placebo.

Protection of trial subjects:

During the conduct of the study all participants were closely monitored.

Background therapy:

Background therapy as permitted in the protocol.

Evidence for comparator:

Not applicable

Actual start date of recruitment	12 February 2018
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	27 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Australia: 13
Country: Number of subjects enrolled	Belgium: 11
Country: Number of subjects enrolled	Bulgaria: 42
Country: Number of subjects enrolled	Canada: 8
Country: Number of subjects enrolled	Czechia: 27
Country: Number of subjects enrolled	France: 27
Country: Number of subjects enrolled	Germany: 46
Country: Number of subjects enrolled	Hungary: 14
Country: Number of subjects enrolled	Italy: 25
Country: Number of subjects enrolled	Japan: 27
Country: Number of subjects enrolled	Lithuania: 11
Country: Number of subjects enrolled	Mexico: 5
Country: Number of subjects enrolled	Poland: 28
Country: Number of subjects enrolled	Slovakia: 6
Country: Number of subjects enrolled	Spain: 62
Country: Number of subjects enrolled	Turkey: 5

Country: Number of subjects enrolled	United Kingdom: 9
Country: Number of subjects enrolled	United States: 45
Worldwide total number of subjects	411
EEA total number of subjects	299

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)	401
From 65 to 84 years	10
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study started to enroll patients in February 2018 and concluded in January 2020.

Pre-assignment

Screening details:

The study included: a 4-week Baseline Period, a 16-week Treatment Period, a 4-week Taper Period (for participants who discontinued or choose not to enroll in the open-label extension study) and a Safety Follow-up Period. Participants continuing to the OLE study had a 3-week Conversion Period. Participant Flow refers to the Randomized Set.

Period 1

Period 1 title	Treatment period: Wk0-16
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Carer, Subject, Investigator, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Participants randomized to the placebo group received a combination of several Placebo tablets to maintain the blinding.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	PBO
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Placebo was provided as tablets of matching size and aspect to Padsevonil tablets allowing a double-blind packaging. All study participants were instructed to take 5 or 6 tablets containing either PSL or placebo bid, approximately 12 hours apart. The IMP was to be dosed within 30 minutes after food when practically feasible.

Arm title	Padsevonil dosing regimen 1

Arm description:

Participants were randomized to receive a combination of tablets of Padsevonil dose 1 and Placebo (as appropriate) to maintain the blinding.

Arm type	Experimental
Investigational medicinal product name	Padsevonil
Investigational medicinal product code	PSL
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Padsevonil was administered as film-coated tablets of different doses, sizes and appearance. All study participants were instructed to take 5 or 6 tablets containing either PSL or placebo bid, approximately 12 hours apart. The IMP was to be dosed within 30 minutes after food when practically feasible.

Arm title	Padsevonil dosing regimen 2

Arm description:

Participants were randomized to receive a combination of tablets of Padsevonil dose 2 and Placebo (as

appropriate) to maintain the blinding.

Arm type	Experimental
Investigational medicinal product name	Padsevonil
Investigational medicinal product code	PSL
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Padsevonil was administered as film-coated tablets of different doses, sizes and appearance. All study participants were instructed to take 5 or 6 tablets containing either PSL or placebo bid, approximately 12 hours apart. The IMP was to be dosed within 30 minutes after food when practically feasible.

Arm title	Padsevonil dosing regimen 3

Arm description:

Participants were randomized to receive a combination of tablets of Padsevonil dose 3 and Placebo (as appropriate) to maintain the blinding.

Arm type	Experimental
Investigational medicinal product name	Padsevonil
Investigational medicinal product code	PSL
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Padsevonil was administered as film-coated tablets of different doses, sizes and appearance. All study participants were instructed to take 5 or 6 tablets containing either PSL or placebo bid, approximately 12 hours apart. The IMP was to be dosed within 30 minutes after food when practically feasible.

Arm title	Padsevonil dosing regimen 4

Arm description:

Participants were randomized to receive a combination of tablets of Padsevonil dose 4 and Placebo (as appropriate) to maintain the blinding.

Arm type	Experimental
Investigational medicinal product name	Padsevonil
Investigational medicinal product code	PSL
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Padsevonil was administered as film-coated tablets of different doses, sizes and appearance. All study participants were instructed to take 5 or 6 tablets containing either PSL or placebo bid, approximately 12 hours apart. The IMP was to be dosed within 30 minutes after food when practically feasible.

Number of subjects in period 1	Placebo	Padsevonil dosing regimen 1	Padsevonil dosing regimen 2
Started	83	81	83
Completed Titration and Stabilization	78	72	71
Completed Maintenance Period	70	66	68
Had Taper and Safety Follow-up	6 [1]	11 [2]	8 [3]
Completed	70	66	68
Not completed	13	15	15
Consent withdrawn by subject	2	3	2

Adverse event, non-fatal	7	6	11
By opinion of investigator	-	-	-
Lost to follow-up	2	-	-
Sponsor decision	-	-	-
As advised by the sponsor	-	1	-
Lack of efficacy	2	1	-
Protocol deviation	-	4	2

Number of subjects in period 1	Padsevonil dosing regimen 3	Padsevonil dosing regimen 4
Started	82	82
Completed Titration and Stabilization	68	65
Completed Maintenance Period	61	58
Had Taper and Safety Follow-up	18 [4]	21 [5]
Completed	61	58
Not completed	21	24
Consent withdrawn by subject	3	3
Adverse event, non-fatal	15	21
By opinion of investigator	1	-
Lost to follow-up	-	-
Sponsor decision	1	-
As advised by the sponsor	-	-
Lack of efficacy	-	-
Protocol deviation	1	-

Notes:

[1] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: Number of participants at this milestone reflect those who were randomized to Placebo and entered to conversion period, completed conversion period, had taper and safety follow-up or enrolled in EP0093. Participants could enter taper and safety follow-up after period 1.

[2] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: Number of participants at this milestone reflect those who were randomized to Padsevonil dosing regimen 1 and entered to conversion period, completed conversion period, had taper and safety follow-up or enrolled in EP0093. Participants could enter taper and safety follow-up after period 1.

[3] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: Number of participants at this milestone reflect those who were randomized to Padsevonil dosing regimen 2 and entered to conversion period, completed conversion period, had taper and safety follow-up or enrolled in EP0093. Participants could enter taper and safety follow-up after period 1.

[4] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: Number of participants at this milestone reflect those who were randomized to Padsevonil dosing regimen 3 and entered to conversion period, completed conversion period, had taper and safety follow-up or enrolled in EP0093. Participants could enter taper and safety follow-up after period 1.

[5] - The number of subjects at this milestone seems inconsistent with the number of subjects in the

arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: Number of participants at this milestone reflect those who were randomized to Padsevonil dosing regimen 4 and entered to conversion period, completed conversion period, had taper and safety follow-up or enrolled in EP0093. Participants could enter taper and safety follow-up after period 1.

Period 2

Period 2 title	Post-Treatment period: Wk16-23
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Carer, Investigator, Assessor, Subject

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Participants randomized to the placebo group received a combination of several Placebo tablets to maintain the blinding.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	PBO
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Placebo was provided as tablets of matching size and aspect to Padsevonil tablets allowing a double-blind packaging. All study participants were instructed to take 5 or 6 tablets containing either PSL or placebo bid, approximately 12 hours apart. The IMP was to be dosed within 30 minutes after food when practically feasible.

Arm title	Padsevonil dosing regimen 1

Arm description:

Participants were randomized to receive a combination of tablets of Padsevonil dose 1 and Placebo (as appropriate) to maintain the blinding.

Arm type	Experimental
Investigational medicinal product name	Padsevonil
Investigational medicinal product code	PSL
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Padsevonil was administered as film-coated tablets of different doses, sizes and appearance. All study participants were instructed to take 5 or 6 tablets containing either PSL or placebo bid, approximately 12 hours apart. The IMP was to be dosed within 30 minutes after food when practically feasible.

Arm title	Padsevonil dosing regimen 2

Arm description:

Participants were randomized to receive a combination of tablets of Padsevonil dose 2 and Placebo (as appropriate) to maintain the blinding.

Arm type	Experimental
Investigational medicinal product name	Padsevonil
Investigational medicinal product code	PSL
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Padsevonil was administered as film-coated tablets of different doses, sizes and appearance. All study participants were instructed to take 5 or 6 tablets containing either PSL or placebo bid, approximately 12 hours apart. The IMP was to be dosed within 30 minutes after food when practically feasible.

Arm title	Padsevonil dosing regimen 3

Arm description:

Participants were randomized to receive a combination of tablets of Padsevonil dose 3 and Placebo (as appropriate) to maintain the blinding.

Arm type	Experimental
Investigational medicinal product name	Padsevonil
Investigational medicinal product code	PSL
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Padsevonil was administered as film-coated tablets of different doses, sizes and appearance. All study participants were instructed to take 5 or 6 tablets containing either PSL or placebo bid, approximately 12 hours apart. The IMP was to be dosed within 30 minutes after food when practically feasible.

Arm title	Padsevonil dosing regimen 4

Arm description:

Participants were randomized to receive a combination of tablets of Padsevonil dose 4 and Placebo (as appropriate) to maintain the blinding.

Arm type	Experimental
Investigational medicinal product name	Padsevonil
Investigational medicinal product code	PSL
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Padsevonil was administered as film-coated tablets of different doses, sizes and appearance. All study participants were instructed to take 5 or 6 tablets containing either PSL or placebo bid, approximately 12 hours apart. The IMP was to be dosed within 30 minutes after food when practically feasible.

Number of subjects in period 2	Placebo	Padsevonil dosing regimen 1	Padsevonil dosing regimen 2
Started	70	66	68
Started Conversion Period	69	64 [6]	66 [7]
Completed Conversion Period	68 [8]	64 [9]	66 [10]
Had Taper and Safety Follow-up	3 [11]	3 [12]	3 [13]
Enrolled in EP0093	67 [14]	63 [15]	65 [16]
Completed	69	66	68
Not completed	1	0	0
Participant decided not to roll over	1	-	-

Number of subjects in period 2	Padsevonil dosing regimen 3	Padsevonil dosing regimen 4
Started	61	58

Started Conversion Period	55 [17]	57 [18]
Completed Conversion Period	55 [19]	57 [20]
Had Taper and Safety Follow-up	6 [21]	1 [22]
Enrolled in EP0093	55 [23]	57 [24]
Completed	61	58
Not completed	0	0
Participant decided not to roll over	-	-

Notes:

[6] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: Number of participants at this milestone reflect those who were randomized to Padsevonil dosing regimen 1 and entered to conversion period, completed conversion period, had taper and safety follow-up or enrolled in EP0093. Participants could enter taper and safety follow-up after period 1.

[7] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: Number of participants at this milestone reflect those who were randomized to Padsevonil dosing regimen 2 and entered to conversion period, completed conversion period, had taper and safety follow-up or enrolled in EP0093. Participants could enter taper and safety follow-up after period 1.

[8] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: Number of participants at this milestone reflect those who were randomized to Placebo and entered to conversion period, completed conversion period, had taper and safety follow-up or enrolled in EP0093. Participants could enter taper and safety follow-up after period 1.

[9] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: Number of participants at this milestone reflect those who were randomized to Padsevonil dosing regimen 1 and entered to conversion period, completed conversion period, had taper and safety follow-up or enrolled in EP0093. Participants could enter taper and safety follow-up after period 1.

[10] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: Number of participants at this milestone reflect those who were randomized to Padsevonil dosing regimen 2 and entered to conversion period, completed conversion period, had taper and safety follow-up or enrolled in EP0093. Participants could enter taper and safety follow-up after period 1.

[11] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: Number of participants at this milestone reflect those who were randomized to Placebo and entered to conversion period, completed conversion period, had taper and safety follow-up or enrolled in EP0093. Participants could enter taper and safety follow-up after period 1.

[12] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: Number of participants at this milestone reflect those who were randomized to Padsevonil dosing regimen 1 and entered to conversion period, completed conversion period, had taper and safety follow-up or enrolled in EP0093. Participants could enter taper and safety follow-up after period 1.

[13] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: Number of participants at this milestone reflect those who were randomized to Padsevonil dosing regimen 2 and entered to conversion period, completed conversion period, had taper and safety follow-up or enrolled in EP0093. Participants could enter taper and safety follow-up after period 1.

[14] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: Number of participants at this milestone reflect those who were randomized to Placebo and entered to conversion period, completed conversion period, had taper and safety follow-up or enrolled in EP0093. Participants could enter taper and safety follow-up after period 1.

[15] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: Number of participants at this milestone reflect those who were randomized to Padsevonil dosing regimen 1 and entered to conversion period, completed conversion period, had taper and safety follow-up or enrolled in EP0093. Participants could enter taper and safety follow-up after period 1.
[16] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: Number of participants at this milestone reflect those who were randomized to Padsevonil dosing regimen 2 and entered to conversion period, completed conversion period, had taper and safety follow-up or enrolled in EP0093. Participants could enter taper and safety follow-up after period 1.
[17] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: Number of participants at this milestone reflect those who were randomized to Padsevonil dosing regimen 3 and entered to conversion period, completed conversion period, had taper and safety follow-up or enrolled in EP0093. Participants could enter taper and safety follow-up after period 1.
[18] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: Number of participants at this milestone reflect those who were randomized to Padsevonil dosing regimen 4 and entered to conversion period, completed conversion period, had taper and safety follow-up or enrolled in EP0093. Participants could enter taper and safety follow-up after period 1.

[19] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: Number of participants at this milestone reflect those who were randomized to Padsevonil dosing regimen 3 and entered to conversion period, completed conversion period, had taper and safety follow-up or enrolled in EP0093. Participants could enter taper and safety follow-up after period 1.
[20] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: Number of participants at this milestone reflect those who were randomized to Padsevonil dosing regimen 4 and entered to conversion period, completed conversion period, had taper and safety follow-up or enrolled in EP0093. Participants could enter taper and safety follow-up after period 1.

[21] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: Number of participants at this milestone reflect those who were randomized to Padsevonil dosing regimen 3 and entered to conversion period, completed conversion period, had taper and safety follow-up or enrolled in EP0093. Participants could enter taper and safety follow-up after period 1.
[22] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: Number of participants at this milestone reflect those who were randomized to Padsevonil dosing regimen 4 and entered to conversion period, completed conversion period, had taper and safety follow-up or enrolled in EP0093. Participants could enter taper and safety follow-up after period 1.

[23] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: Number of participants at this milestone reflect those who were randomized to Padsevonil dosing regimen 3 and entered to conversion period, completed conversion period, had taper and safety follow-up or enrolled in EP0093. Participants could enter taper and safety follow-up after period 1.
[24] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: Number of participants at this milestone reflect those who were randomized to Padsevonil dosing regimen 4 and entered to conversion period, completed conversion period, had taper and safety follow-up or enrolled in EP0093. Participants could enter taper and safety follow-up after period 1.

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Participants randomized to the placebo group received a combination of several Placebo tablets to maintain the blinding.	
Reporting group title	Padsevonil dosing regimen 1
Reporting group description:	
Participants were randomized to receive a combination of tablets of Padsevonil dose 1 and Placebo (as appropriate) to maintain the blinding.	
Reporting group title	Padsevonil dosing regimen 2
Reporting group description:	
Participants were randomized to receive a combination of tablets of Padsevonil dose 2 and Placebo (as appropriate) to maintain the blinding.	
Reporting group title	Padsevonil dosing regimen 3
Reporting group description:	
Participants were randomized to receive a combination of tablets of Padsevonil dose 3 and Placebo (as appropriate) to maintain the blinding.	
Reporting group title	Padsevonil dosing regimen 4
Reporting group description:	
Participants were randomized to receive a combination of tablets of Padsevonil dose 4 and Placebo (as appropriate) to maintain the blinding.	

Reporting group values	Placebo	Padsevonil dosing regimen 1	Padsevonil dosing regimen 2
Number of subjects	83	81	83
Age categorical Units: Subjects			
<=18 years	0	0	2
Between 18 and 65 years	82	76	80
>=65 years	1	5	1
Age continuous Units: years			
arithmetic mean	40.0	42.5	36.9
standard deviation	± 12.9	± 11.6	± 13.1
Gender categorical Units: Subjects			
Female	48	46	47
Male	35	35	36

Reporting group values	Padsevonil dosing regimen 3	Padsevonil dosing regimen 4	Total
Number of subjects	82	82	411
Age categorical Units: Subjects			
<=18 years	1	1	4
Between 18 and 65 years	79	80	397
>=65 years	2	1	10

Age continuous Units: years			
arithmetic mean	40.9	38.8	
standard deviation	± 12.0	± 12.1	-
Gender categorical Units: Subjects			
Female	51	43	235
Male	31	39	176

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description:	
Participants randomized to the placebo group received a combination of several Placebo tablets to maintain the blinding.	
Reporting group title	Padsevonil dosing regimen 1
Reporting group description:	
Participants were randomized to receive a combination of tablets of Padsevonil dose 1 and Placebo (as appropriate) to maintain the blinding.	
Reporting group title	Padsevonil dosing regimen 2
Reporting group description:	
Participants were randomized to receive a combination of tablets of Padsevonil dose 2 and Placebo (as appropriate) to maintain the blinding.	
Reporting group title	Padsevonil dosing regimen 3
Reporting group description:	
Participants were randomized to receive a combination of tablets of Padsevonil dose 3 and Placebo (as appropriate) to maintain the blinding.	
Reporting group title	Padsevonil dosing regimen 4
Reporting group description:	
Participants were randomized to receive a combination of tablets of Padsevonil dose 4 and Placebo (as appropriate) to maintain the blinding.	
Reporting group title	Placebo
Reporting group description:	
Participants randomized to the placebo group received a combination of several Placebo tablets to maintain the blinding.	
Reporting group title	Padsevonil dosing regimen 1
Reporting group description:	
Participants were randomized to receive a combination of tablets of Padsevonil dose 1 and Placebo (as appropriate) to maintain the blinding.	
Reporting group title	Padsevonil dosing regimen 2
Reporting group description:	
Participants were randomized to receive a combination of tablets of Padsevonil dose 2 and Placebo (as appropriate) to maintain the blinding.	
Reporting group title	Padsevonil dosing regimen 3
Reporting group description:	
Participants were randomized to receive a combination of tablets of Padsevonil dose 3 and Placebo (as appropriate) to maintain the blinding.	
Reporting group title	Padsevonil dosing regimen 4
Reporting group description:	
Participants were randomized to receive a combination of tablets of Padsevonil dose 4 and Placebo (as appropriate) to maintain the blinding.	
Subject analysis set title	Placebo (FAS)
Subject analysis set type	Full analysis
Subject analysis set description:	
Participants randomized to the placebo group received a combination of several Placebo tablets to maintain the blinding. Participants formed the Full Analysis Set (FAS).	
Subject analysis set title	Padsevonil dosing regimen 1 (FAS)
Subject analysis set type	Full analysis
Subject analysis set description:	
Participants were randomized to receive a combination of tablets of Padsevonil dose 1 and Placebo (as appropriate) to maintain the blinding. Participants formed the FAS.	
Subject analysis set title	Padsevonil dosing regimen 2 (FAS)

Subject analysis set type	Full analysis

Subject analysis set description:

Participants were randomized to receive a combination of tablets of Padsevonil dose 2 and Placebo (as appropriate) to maintain the blinding. Participants formed the FAS.

Subject analysis set title	Padsevonil dosing regimen 3 (FAS)
Subject analysis set type	Full analysis

Subject analysis set description:

Participants were randomized to receive a combination of tablets of Padsevonil dose 3 and Placebo (as appropriate) to maintain the blinding. Participants formed the FAS.

Subject analysis set title	Padsevonil dosing regimen 4 (FAS)
Subject analysis set type	Full analysis

Subject analysis set description:

Participants were randomized to receive a combination of tablets of Padsevonil dose 4 and Placebo (as appropriate) to maintain the blinding. Participants formed the FAS.

Subject analysis set title	Placebo Treatment period (SS)
Subject analysis set type	Safety analysis

Subject analysis set description:

During the Treatment period, participants randomized to the placebo group received a combination of several Placebo tablets to maintain the blinding. Participants formed the Safety Set (SS).

Subject analysis set title	Padsevonil dosing regimen 1 Treatment period (SS)
Subject analysis set type	Safety analysis

Subject analysis set description:

During the Treatment period, participants were randomized to receive a combination of tablets of Padsevonil dose 1 and Placebo (as appropriate) to maintain the blinding. Participants formed the SS.

Subject analysis set title	Padsevonil dosing regimen 2 Treatment period (SS)
Subject analysis set type	Safety analysis

Subject analysis set description:

During the Treatment period, participants were randomized to receive a combination of tablets of Padsevonil dose 2 and Placebo (as appropriate) to maintain the blinding. Participants formed the SS.

Subject analysis set title	Padsevonil dosing regimen 3 Treatment period (SS)
Subject analysis set type	Safety analysis

Subject analysis set description:

During the Treatment period, participants were randomized to receive a combination of tablets of Padsevonil dose 3 and Placebo (as appropriate) to maintain the blinding. Participants formed the SS.

Subject analysis set title	Padsevonil dosing regimen 4 Treatment period (SS)
Subject analysis set type	Safety analysis

Subject analysis set description:

During the Treatment period, participants were randomized to receive a combination of tablets of Padsevonil dose 4 and Placebo (as appropriate) to maintain the blinding. Participants formed the SS.

Subject analysis set title	Placebo Conversion period (SS)
Subject analysis set type	Safety analysis

Subject analysis set description:

A 3-week Conversion Period was required for study participants who chose to enroll in the OLE study at the end of the 12-week Maintenance Period. Participants initially randomized to Placebo progressively received Padsevonil in a blinded way to reach the entry dose for the OLE. Participants formed the Safety Set (SS).

Subject analysis set title	Padsevonil dosing regimen 1 Conversion period (SS)
Subject analysis set type	Safety analysis

Subject analysis set description:

A 3-week Conversion Period was required for study participants who chose to enroll in the OLE study at the end of the 12-week Maintenance Period. The dose for participants initially randomized to Padsevonil dose 1 was gradually adapted (increased or decreased) in a blinded way to reach the entry dose for the OLE. Participants formed the SS.

Subject analysis set title	Padsevonil dosing regimen 2 Conversion period (SS)
Subject analysis set type	Safety analysis

Subject analysis set description:

A 3-week Conversion Period was required for study participants who chose to enroll in the OLE study at the end of the 12-week Maintenance Period. The dose for participants initially randomized to Padsevonil dose 2 was gradually adapted (increased or decreased) in a blinded way to reach the entry dose for the OLE. Participants formed the SS.

Subject analysis set title	Padsevonil dosing regimen 3 Conversion period (SS)
Subject analysis set type	Safety analysis

Subject analysis set description:

A 3-week Conversion Period was required for study participants who chose to enroll in the OLE study at the end of the 12-week Maintenance Period. The dose for participants initially randomized to Padsevonil dose 3 was gradually adapted (increased or decreased) in a blinded way to reach the entry dose for the OLE. Participants formed the SS.

Subject analysis set title	Padsevonil dosing regimen 4 Conversion period (SS)
Subject analysis set type	Safety analysis

Subject analysis set description:

A 3-week Conversion Period was required for study participants who chose to enroll in the OLE study at the end of the 12-week Maintenance Period. The dose for participants initially randomized to Padsevonil dose 4 was gradually adapted (increased or decreased) in a blinded way to reach the entry dose for the OLE. Participants formed the SS.

Subject analysis set title	Placebo Taper and SFU period (SS)
Subject analysis set type	Safety analysis

Subject analysis set description:

A 4-week Taper Period was required for participants who chose not to enroll in the OLE study or who discontinued prior to the end of the 12-week Maintenance Period. Participants initially randomized to Placebo have been gradually tapered off the IMP over a 3-week period followed by 1-week drug-free period.
Afterwards, participants had a Safety Follow-Up visit 30 days after the last IMP intake. Participants formed the Safety Set (SS).

Subject analysis set title	Padsevonil dosing regimen 1 Taper and SFU period (SS)
Subject analysis set type	Safety analysis

Subject analysis set description:

A 4-week Taper Period was required for participants who chose not to enroll in the OLE study or who discontinued prior to the end of the 12-week Maintenance Period. Participants initially randomized to Padsevonil dose 1 have been gradually tapered off the IMP over a 3-week period followed by 1-week drug-free period.
Afterwards, participants had a Safety Follow-Up visit 30 days after the last IMP intake. Participants formed the SS.

Subject analysis set title	Padsevonil dosing regimen 2 Taper and SFU period (SS)
Subject analysis set type	Safety analysis

Subject analysis set description:

A 4-week Taper Period was required for participants who chose not to enroll in the OLE study or who discontinued prior to the end of the 12-week Maintenance Period. Participants initially randomized to Padsevonil dose 2 have been gradually tapered off the IMP over a 3-week period followed by 1-week drug-free period.
Afterwards, participants had a Safety Follow-Up visit 30 days after the last IMP intake. Participants formed the SS.

Subject analysis set title	Padsevonil dosing regimen 3 Taper and SFU period (SS)
Subject analysis set type	Safety analysis

Subject analysis set description:

A 4-week Taper Period was required for participants who chose not to enroll in the OLE study or who discontinued prior to the end of the 12-week Maintenance Period. Participants initially randomized to Padsevonil dose 3 have been gradually tapered off the IMP over a 3-week period followed by 1-week drug-free period.
Afterwards, participants had a Safety Follow-Up visit 30 days after the last IMP intake. Participants formed the SS.

Subject analysis set title	Padsevonil dosing regimen 4 Taper and SFU period (SS)
Subject analysis set type	Safety analysis

Subject analysis set description:

A 4-week Taper Period was required for participants who chose not to enroll in the OLE study or who discontinued prior to the end of the 12-week Maintenance Period. Participants initially randomized to

Padsevonil dose 4 have been gradually tapered off the IMP over a 3-week period followed by 1-week drug-free period.
Afterwards, participants had a Safety Follow-Up visit 30 days after the last IMP intake. Participants formed the SS.

Subject analysis set title	Placebo (SS)
Subject analysis set type	Safety analysis

Subject analysis set description:

Participants randomized to the placebo group received a combination of several Placebo tablets to maintain the blinding. Participants formed the Safety Set (SS).

Subject analysis set title	Padsevonil dosing regimen 1 (SS)
Subject analysis set type	Safety analysis

Subject analysis set description:

Participants were randomized to receive a combination of tablets of Padsevonil dose 1 and Placebo (as appropriate) to maintain the blinding. Participants formed the SS.

Subject analysis set title	Padsevonil dosing regimen 2 (SS)
Subject analysis set type	Safety analysis

Subject analysis set description:

Participants were randomized to receive a combination of tablets of Padsevonil dose 2 and Placebo (as appropriate) to maintain the blinding. Participants formed the SS.

Subject analysis set title	Padsevonil dosing regimen 3 (SS)
Subject analysis set type	Safety analysis

Subject analysis set description:

Participants were randomized to receive a combination of tablets of Padsevonil dose 3 and Placebo (as appropriate) to maintain the blinding. Participants formed the SS.

Subject analysis set title	Padsevonil dosing regimen 4 (SS)
Subject analysis set type	Safety analysis

Subject analysis set description:

Participants were randomized to receive a combination of tablets of Padsevonil dose 4 and Placebo (as appropriate) to maintain the blinding. Participants formed the SS.

Primary: 75 % responder rate over the 12 Week Maintenance Period

End point title	75 % responder rate over the 12 Week Maintenance Period

End point description:

The 75% responder rate, where a responder is a participant experiencing a ≥75% reduction in observable focal-onset seizure frequency from Baseline, over the 12-Week Maintenance Period.
The Full Analysis Set (FAS) consisted of all study participants in the RS who were administered at least 1 dose or a partial dose of IMP and had Baseline and at least 1 post-Baseline seizure frequency data during the 16-week Treatment Period.

End point type	Primary

End point timeframe:

End of Maintenance Period (Week 16) following 3 Weeks of titration and 1 Week stabilization

End point values	Placebo (FAS)	Padsevonil dosing regimen 1 (FAS)	Padsevonil dosing regimen 2 (FAS)	Padsevonil dosing regimen 3 (FAS)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	81	80	82	81
Units: percentage of participants				
number (not applicable)	6.2	13.8	12.2	11.1

End point values	Padsevonil dosing regimen 4 (FAS)			
Subject group type	Subject analysis set			
Number of subjects analysed	81			
Units: percentage of participants				
number (not applicable)	16.0			

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

PSL dose/Placebo was calculated using logistic regression with categorical factors for treatment group, Region (Europe, Non-Europe), Baseline SV2A use (0, 1) and log-transformed Baseline seizure frequency as a continuous covariate.

Comparison groups	Padsevonil dosing regimen 1 (FAS) v Placebo (FAS)
Number of subjects included in analysis	161
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.081 [1]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	2.72
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.88
upper limit	8.39

Notes:

[1] - Nominal p-values were not adjusted for multiplicity.

Statistical analysis title	Statistical analysis 2

Statistical analysis description:

PSL dose/Placebo was calculated using logistic regression with categorical factors for treatment group, Region (Europe, Non-Europe), Baseline SV2A use (0, 1) and log-transformed Baseline seizure frequency as a continuous covariate.

Comparison groups	Padsevonil dosing regimen 2 (FAS) v Placebo (FAS)
Number of subjects included in analysis	163
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.137 [2]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	2.37
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.76
upper limit	7.41

Notes:

[2] - Nominal p-values were not adjusted for multiplicity.

Statistical analysis title	Statistical analysis 3

Statistical analysis description:

PSL dose/Placebo was calculated using logistic regression with categorical factors for treatment group, Region (Europe, Non-Europe), Baseline SV2A use (0, 1) and log-transformed Baseline seizure frequency as a continuous covariate.

Comparison groups	Padsevonil dosing regimen 3 (FAS) v Placebo (FAS)
Number of subjects included in analysis	162
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.192 [3]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	2.16
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.68
upper limit	6.89

Notes:

[3] - Nominal p-values were not adjusted for multiplicity.

Statistical analysis title	Statistical analysis 4

Statistical analysis description:

PSL dose/Placebo was calculated using logistic regression with categorical factors for treatment group, Region (Europe, Non-Europe), Baseline SV2A use (0, 1) and log-transformed Baseline seizure frequency as a continuous covariate.

Comparison groups	Padsevonil dosing regimen 4 (FAS) v Placebo (FAS)
Number of subjects included in analysis	162
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.041 [4]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	3.14
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.05
upper limit	9.42

Notes:

[4] - Nominal p-values were not adjusted for multiplicity.

Primary: Incidence of Treatment-Emergent Adverse Events (TEAEs) reported by the subject and/or caregiver or observed by the investigator during the entire study

End point title	Incidence of Treatment-Emergent Adverse Events (TEAEs) reported by the subject and/or caregiver or observed by the investigator during the entire study[5]

End point description:

An Adverse Event is any untoward medical occurrence in a patient or clinical investigation subject

administered a pharmaceutical product that does not necessarily have a causal relationship with this treatment.
The Safety Set consisted of all study participants who were administered at least 1 dose or a partial dose of IMP.

End point type	Primary

End point timeframe:

From Baseline until Safety Follow-Up (up to Week 23)

Notes:

[5] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No formal statistical hypothesis testing was planned for this endpoint. Results were summarized as descriptive statistics only.

End point values	Placebo (SS)	Padsevonil dosing regimen 1 (SS)	Padsevonil dosing regimen 2 (SS)	Padsevonil dosing regimen 3 (SS)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	83	81	83	82
Units: percentage of participants				
number (not applicable)	78.3	84.0	80.7	75.6

End point values	Padsevonil dosing regimen 4 (SS)			
Subject group type	Subject analysis set			
Number of subjects analysed	81			
Units: percentage of participants				
number (not applicable)	92.6			

Statistical analyses

No statistical analyses for this end point

Primary: Incidence of Treatment-Emergent Adverse Events (TEAEs) leading to study withdrawal

End point title	Incidence of Treatment-Emergent Adverse Events (TEAEs) leading to study withdrawal[6]

End point description:

An Adverse Event is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product that does not necessarily have a causal relationship with this treatment.
The Safety Set consisted of all study participants who were administered at least 1 dose or a partial dose of IMP.

End point type	Primary

End point timeframe:

From Baseline until Safety Follow-Up (up to Week 23)

Notes:

[6] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No formal statistical hypothesis testing was planned for this endpoint. Results were summarized as descriptive statistics only.

End point values	Placebo (SS)	Padsevonil dosing regimen 1 (SS)	Padsevonil dosing regimen 2 (SS)	Padsevonil dosing regimen 3 (SS)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	83	81	83	82
Units: percentage of participants				
number (not applicable)	8.4	7.4	12.0	18.3

End point values	Padsevonil dosing regimen 4 (SS)			
Subject group type	Subject analysis set			
Number of subjects analysed	81			
Units: percentage of participants				
number (not applicable)	25.9			

Statistical analyses

No statistical analyses for this end point

Primary: Incidence of Treatment-Emergent Serious Adverse Events (SAEs) during the entire study

End point title	Incidence of Treatment-Emergent Serious Adverse Events (SAEs) during the entire study[7]

End point description:

A Serious Adverse Event (SAE) is any untoward medical occurrence that at any dose:
- Results in death
- Is life-threatening
- Requires in patient hospitalization or prolongation of existing hospitalization
- Is a congenital anomaly or birth defect
- Is an infection that requires treatment parenteral antibiotics
- Other important medical events which based on medical or scientific judgement may jeopardize the patients, or may require medical or surgical intervention to prevent any of the above.

The Safety Set consisted of all study participants who were administered at least 1 dose or a partial dose of IMP.

End point type	Primary

End point timeframe:

From Baseline until Safety Follow-Up (up to Week 23)

Notes:

[7] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No formal statistical hypothesis testing was planned for this endpoint. Results were summarized as descriptive statistics only.

End point values	Placebo (SS)	Padsevonil dosing regimen 1 (SS)	Padsevonil dosing regimen 2 (SS)	Padsevonil dosing regimen 3 (SS)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	83	81	83	82
Units: percentage of participants				
number (not applicable)	4.8	7.4	4.8	6.1

End point values	Padsevonil dosing regimen 4 (SS)			
Subject group type	Subject analysis set			
Number of subjects analysed	81			
Units: percentage of participants				
number (not applicable)	6.2			

Statistical analyses

No statistical analyses for this end point

Secondary: Change in log-transformed observable focal onset seizure frequency from Baseline over the 12 week Maintenance Period

End point title	Change in log-transformed observable focal onset seizure frequency from Baseline over the 12 week Maintenance Period

End point description:

During the study, participants kept diaries to record daily seizure activity. Seizure frequency refers to 28-day adjusted frequency. Seizure frequency was based on investigator assessment of participants' reports of daily seizure type and frequency. Observable focal-onset seizures refer to Type IA1, IB, and IC (ILAE Classification of Epileptic Seizures, 1981). Based on ANCOVA on change in log-transformed, 28-day adjusted seizure frequency from Baseline with treatment group as the main factor, Baseline log-transformed seizure frequency as a continuous covariate, Baseline SV2A use (yes or no) and Region (Europe, Non-Europe) as categorical factors.
The Full Analysis Set (FAS) consisted of all study participants in the RS who were administered at least 1 dose or a partial dose of IMP and had Baseline and at least 1 post-Baseline seizure frequency data during the 16-week Treatment Period.

End point type	Secondary

End point timeframe:

From Baseline over the 12 week Maintenance Period

End point values	Placebo (FAS)	Padsevonil dosing regimen 1 (FAS)	Padsevonil dosing regimen 2 (FAS)	Padsevonil dosing regimen 3 (FAS)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	81	80	82	81
Units: seizures per 28 days				
least squares mean (confidence interval 95%)	-0.27585 (-0.44311 to -0.10858)	-0.46424 (-0.63276 to -0.29573)	-0.48804 (-0.65436 to -0.32172)	-0.48960 (-0.65734 to -0.32187)

End point values	Padsevonil dosing regimen 4 (FAS)			

Subject group type	Subject analysis set			
Number of subjects analysed	81			
Units: seizures per 28 days				
least squares mean (confidence interval 95%)	-0.40831 (-0.57485 to -0.24177)			

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

Percent reduction over placebo was calculated as 100*(1-exp[diff]), where diff was the model estimate of the log ratio between each PSL group and placebo group.

Comparison groups	Padsevonil dosing regimen 1 (FAS) v Placebo (FAS)
Number of subjects included in analysis	161
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.102 [8]
Method	ANCOVA
Parameter estimate	Percent reduction
Point estimate	17.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.8
upper limit	33.9

Notes:

[8] - Adjusted p-values were from the Hochberg step-up procedure within SAS® Proc Multtest to control Type I error.

Statistical analysis title	Statistical analysis 2

Statistical analysis description:

Percent reduction over placebo was calculated as 100*(1-exp[diff]), where diff was the model estimate of the log ratio between each PSL group and placebo group.

Comparison groups	Padsevonil dosing regimen 2 (FAS) v Placebo (FAS)
Number of subjects included in analysis	163
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.064 [9]
Method	ANCOVA
Parameter estimate	Percent reduction
Point estimate	19.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.2
upper limit	35.4

Notes:

[9] - Adjusted p-values were from the Hochberg step-up procedure within SAS® Proc Multtest to control Type I error.

Statistical analysis title	Statistical analysis 3

Statistical analysis description:

Percent reduction over placebo was calculated as 100*(1-exp[diff]), where diff was the model estimate of the log ratio between each PSL group and placebo group.

Comparison groups	Padsevonil dosing regimen 3 (FAS) v Placebo (FAS)
Number of subjects included in analysis	162
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.063 [10]
Method	ANCOVA
Parameter estimate	Percent reduction
Point estimate	19.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.2
upper limit	35.5

Notes:

[10] - Adjusted p-values were from the Hochberg step-up procedure within SAS® Proc Multtest to control Type I error.

Statistical analysis title	Statistical analysis 4

Statistical analysis description:

Percent reduction over placebo was calculated as 100*(1-exp[diff]), where diff was the model estimate of the log ratio between each PSL group and placebo group.

Comparison groups	Padsevonil dosing regimen 4 (FAS) v Placebo (FAS)
Number of subjects included in analysis	162
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.248 [11]
Method	ANCOVA
Parameter estimate	Percent reduction
Point estimate	12.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-9.7
upper limit	30.1

Notes:

[11] - Adjusted p-values were from the Hochberg step-up procedure within SAS® Proc Multtest to control Type I error.

Secondary: 50 % responder rate over the 12 Week Maintenance Period

End point title	50 % responder rate over the 12 Week Maintenance Period

End point description:

The 50% responder rate, where a responder was a participant experiencing a ≥50% reduction in observable focal-onset seizure frequency from Baseline, over the 12-Week Maintenance Period.
The Full Analysis Set (FAS) consisted of all study participants in the RS who were administered at least 1 dose or a partial dose of IMP and had Baseline and at least 1 post-Baseline seizure frequency data during the 16-week Treatment Period.

End point type	Secondary

End point timeframe:

End of Maintenance Period (Week 16) following 3 Weeks of titration and 1 Week stabilization

End point values	Placebo (FAS)	Padsevonil dosing regimen 1 (FAS)	Padsevonil dosing regimen 2 (FAS)	Padsevonil dosing regimen 3 (FAS)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	81	80	82	81
Units: percentage of participants				
number (not applicable)	21.0	33.8	31.7	25.9

End point values	Padsevonil dosing regimen 4 (FAS)			
Subject group type	Subject analysis set			
Number of subjects analysed	81			
Units: percentage of participants				
number (not applicable)	32.1			

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

PSL dose/placebo calculated using logistic regression with categorical factors for treatment group (each PSL dose group referenced to the placebo group), region (Europe, Non-Europe), Baseline SV2A use (0, 1) and log-transformed Baseline seizure frequency as a continuous covariate.

Comparison groups	Padsevonil dosing regimen 1 (FAS) v Placebo (FAS)
Number of subjects included in analysis	161
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.045 [12]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	2.09
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.02
upper limit	4.3

Notes:

[12] - Nominal p-values were not adjusted for multiplicity.

Statistical analysis title	Statistical analysis 2

Statistical analysis description:

PSL dose/placebo calculated using logistic regression with categorical factors for treatment group (each PSL dose group referenced to the placebo group), region (Europe, Non-Europe), Baseline SV2A use (0, 1) and log-transformed Baseline seizure frequency as a continuous covariate.

Comparison groups	Padsevonil dosing regimen 2 (FAS) v Placebo (FAS)

Number of subjects included in analysis	163
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.079 [13]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.91
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.93
upper limit	3.93

Notes:

[13] - Nominal p-values were not adjusted for multiplicity.

Statistical analysis title	Statistical analysis 3

Statistical analysis description:

PSL dose/placebo calculated using logistic regression with categorical factors for treatment group (each PSL dose group referenced to the placebo group), region (Europe, Non-Europe), Baseline SV2A use (0, 1) and log-transformed Baseline seizure frequency as a continuous covariate.

Comparison groups	Padsevonil dosing regimen 3 (FAS) v Placebo (FAS)
Number of subjects included in analysis	162
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.338 [14]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.44
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.68
upper limit	3.02

Notes:

[14] - Nominal p-values were not adjusted for multiplicity.

Statistical analysis title	Statistical analysis 4

Statistical analysis description:

PSL dose/Placebo calculated using logistic regression with categorical factors for treatment group, Region (Europe, Non-Europe), Baseline SV2A use (0, 1) and log-transformed Baseline seizure frequency as a continuous covariate.

Comparison groups	Padsevonil dosing regimen 4 (FAS) v Placebo (FAS)
Number of subjects included in analysis	162
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.087 [15]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.88

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.91
upper limit	3.87

Notes:

[15] - Nominal p-values were not adjusted for multiplicity.

Secondary: Percent change in observable focal-onset seizure frequency from Baseline over the 12 Week Maintenance Period

End point title	Percent change in observable focal-onset seizure frequency from Baseline over the 12 Week Maintenance Period

End point description:

During the study, participants kept diaries to record daily seizure activity. The percentage of participants who experienced a 50 % or greater reduction in seizure frequency per 28 days relative to Baseline (responders) was assessed.
The Full Analysis Set (FAS) consisted of all study participants in the RS who were administered at least 1 dose or a partial dose of IMP and had Baseline and at least 1 post-Baseline seizure frequency data during the 16-week Treatment Period.

End point type	Secondary

End point timeframe:

End of Maintenance Period (Week 16) following 3 Weeks of titration and 1 Week stabilization

End point values	Placebo (FAS)	Padsevonil dosing regimen 1 (FAS)	Padsevonil dosing regimen 2 (FAS)	Padsevonil dosing regimen 3 (FAS)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	81	80	82	81
Units: percent change				
arithmetic mean (standard deviation)	12.49 (± 58.26)	24.70 (± 46.62)	25.25 (± 51.73)	20.79 (± 66.54)

End point values	Padsevonil dosing regimen 4 (FAS)			
Subject group type	Subject analysis set			
Number of subjects analysed	81			
Units: percent change				
arithmetic mean (standard deviation)	15.79 (± 67.55)			

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

Dose group comparisons to Placebo p-value were based on the Wilcoxon-Mann-Whitney test. The Hodges-Lehmann nonparametric estimator was used to estimate the median difference between each PSL dose group versus placebo, along with the corresponding 95% CI of the estimate.

Comparison groups	Padsevonil dosing regimen 1 (FAS) v Placebo (FAS)
Number of subjects included in analysis	161
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.316 [16]
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Median difference (net)
Point estimate	7.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.59
upper limit	21.89

Notes:

[16] - Nominal p-values were not adjusted for multiplicity.

Statistical analysis title	Statistical analysis 2

Statistical analysis description:

Dose group comparisons to Placebo p-value were based on the Wilcoxon-Mann-Whitney test. The Hodges-Lehmann nonparametric estimator was used to estimate the median difference between each PSL dose group versus placebo, along with the corresponding 95% CI of the estimate.

Comparison groups	Padsevonil dosing regimen 2 (FAS) v Placebo (FAS)
Number of subjects included in analysis	163
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.133 [17]
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Median difference (net)
Point estimate	9.99
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.15
upper limit	23.26

Notes:

[17] - Nominal p-values were not adjusted for multiplicity.

Statistical analysis title	Statistical analysis 3

Statistical analysis description:

Dose group comparisons to Placebo p-value were based on the Wilcoxon-Mann-Whitney test. The Hodges-Lehmann nonparametric estimator was used to estimate the median difference between each PSL dose group versus placebo, along with the corresponding 95% CI of the estimate.

Comparison groups	Padsevonil dosing regimen 3 (FAS) v Placebo (FAS)
Number of subjects included in analysis	162
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.203 [18]
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Median difference (net)
Point estimate	8.19

Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.95
upper limit	21.37

Notes:

[18] - Nominal p-values were not adjusted for multiplicity.

Statistical analysis title	Statistical analysis 4

Statistical analysis description:

Dose group comparisons to Placebo p-value were based on the Wilcoxon-Mann-Whitney test. The Hodges-Lehmann nonparametric estimator was used to estimate the median difference between each PSL dose group versus placebo, along with the corresponding 95% CI of the estimate.

Comparison groups	Padsevonil dosing regimen 4 (FAS) v Placebo (FAS)
Number of subjects included in analysis	162
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.784 [19]
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Median difference (net)
Point estimate	2.39
Confidence interval	
level	95 %
sides	2-sided
lower limit	-13.65
upper limit	17.79

Notes:

[19] - Nominal p-values were not adjusted for multiplicity.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Treatment-emergent AEs were collected from Baseline to Safety Follow-Up (up to Week 23)

Adverse event reporting additional description:

Adverse events refer to the SS which consisted of all participants who were administered at least 1 dose or a partial dose of IMP.
TEAEs counts are for each study period: Treatment Period, Conversion Period for participants who entered the OLE study and Taper Period followed by SFU for participants not entering OLE study.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	22.1

Reporting groups

Reporting group title	Placebo Treatment period (SS)

Reporting group description:

During the Treatment period, participants randomized to the placebo group received a combination of several Placebo tablets to maintain the blinding. Participants formed the Safety Set (SS).

Reporting group title	Padsevonil dosing regimen 1 Treatment period (SS)

Reporting group description:

During the Treatment period, participants were randomized to receive a combination of tablets of Padsevonil dose 1 and Placebo (as appropriate) to maintain the blinding. Participants formed the SS.

Reporting group title	Padsevonil dosing regimen 2 Treatment period (SS)

Reporting group description:

During the Treatment period, participants were randomized to receive a combination of tablets of Padsevonil dose 2 and Placebo (as appropriate) to maintain the blinding. Participants formed the SS.

Reporting group title	Padsevonil dosing regimen 3 Treatment period (SS)

Reporting group description:

During the Treatment period, participants were randomized to receive a combination of tablets of Padsevonil dose 3 and Placebo (as appropriate) to maintain the blinding. Participants formed the SS.

Reporting group title	Padsevonil dosing regimen 4 Treatment period (SS)

Reporting group description:

During the Treatment period, participants were randomized to receive a combination of tablets of Padsevonil dose 4 and Placebo (as appropriate) to maintain the blinding. Participants formed the SS.

Reporting group title	Padsevonil dosing regimen 1 Conversion period (SS)

Reporting group description:

A 3-week Conversion Period was required for study participants who chose to enroll in the OLE study at the end of the 12-week Maintenance Period. The dose for participants initially randomized to Padsevonil dose 1 was gradually adapted (increased or decreased) in a blinded way to reach the entry dose for the OLE. Participants formed the SS.

Reporting group title	Placebo Conversion period (SS)

Reporting group description:

A 3-week Conversion Period was required for study participants who chose to enroll in the OLE study at the end of the 12-week Maintenance Period. Participants initially randomized to Placebo progressively received Padsevonil in a blinded way to reach the entry dose for the OLE. Participants formed the Safety Set (SS).

Reporting group title	Padsevonil dosing regimen 2 Conversion period (SS)

Reporting group description:

A 3-week Conversion Period was required for study participants who chose to enroll in the OLE study at the end of the 12-week Maintenance Period. The dose for participants initially randomized to Padsevonil dose 2 was gradually adapted (increased or decreased) in a blinded way to reach the entry dose for the OLE. Participants formed the SS.

Reporting group title	Padsevonil dosing regimen 3 Conversion period (SS)

Reporting group description:

A 3-week Conversion Period was required for study participants who chose to enroll in the OLE study at the end of the 12-week Maintenance Period. The dose for participants initially randomized to Padsevonil dose 3 was gradually adapted (increased or decreased) in a blinded way to reach the entry dose for the OLE. Participants formed the SS.

Reporting group title	Padsevonil dosing regimen 4 Conversion period (SS)

Reporting group description:

A 3-week Conversion Period was required for study participants who chose to enroll in the OLE study at the end of the 12-week Maintenance Period. The dose for participants initially randomized to Padsevonil dose 4 was gradually adapted (increased or decreased) in a blinded way to reach the entry dose for the OLE. Participants formed the SS.

Reporting group title	Placebo Taper and SFU period (SS)

Reporting group description:

A 4-week Taper Period was required for participants who chose not to enroll in the OLE study or who discontinued prior to the end of the 12-week Maintenance Period. Participants initially randomized to Placebo have been gradually tapered off the IMP over a 3-week period followed by 1-week drug-free period.
Afterwards, participants had a Safety Follow-Up visit 30 days after the last IMP intake. Participants formed the Safety Set (SS).

Reporting group title	Padsevonil dosing regimen 1 Taper and SFU period (SS)

Reporting group description:

A 4-week Taper Period was required for participants who chose not to enroll in the OLE study or who discontinued prior to the end of the 12-week Maintenance Period. Participants initially randomized to Padsevonil dose 1 have been gradually tapered off the IMP over a 3-week period followed by 1-week drug-free period.
Afterwards, participants had a Safety Follow-Up visit 30 days after the last IMP intake. Participants formed the SS.

Reporting group title	Padsevonil dosing regimen 2 Taper and SFU period (SS)

Reporting group description:

A 4-week Taper Period was required for participants who chose not to enroll in the OLE study or who discontinued prior to the end of the 12-week Maintenance Period. Participants initially randomized to Padsevonil dose 2 have been gradually tapered off the IMP over a 3-week period followed by 1-week drug-free period.
Afterwards, participants had a Safety Follow-Up visit 30 days after the last IMP intake. Participants formed the SS.

Reporting group title	Padsevonil dosing regimen 3 Taper and SFU period (SS)

Reporting group description:

A 4-week Taper Period was required for participants who chose not to enroll in the OLE study or who discontinued prior to the end of the 12-week Maintenance Period. Participants initially randomized to Padsevonil dose 3 have been gradually tapered off the IMP over a 3-week period followed by 1-week drug-free period.
Afterwards, participants had a Safety Follow-Up visit 30 days after the last IMP intake. Participants formed the SS.

Reporting group title	Padsevonil dosing regimen 4 Taper and SFU period (SS)

Reporting group description:

A 4-week Taper Period was required for participants who chose not to enroll in the OLE study or who discontinued prior to the end of the 12-week Maintenance Period. Participants initially randomized to Padsevonil dose 4 have been gradually tapered off the IMP over a 3-week period followed by 1-week drug-free period.
Afterwards, participants had a Safety Follow-Up visit 30 days after the last IMP intake. Participants formed the SS.

Serious adverse events	Placebo Treatment period (SS)	Padsevonil dosing regimen 1 Treatment period (SS)	Padsevonil dosing regimen 2 Treatment period (SS)
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 83 (3.61%)	5 / 81 (6.17%)	4 / 83 (4.82%)

number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Injury, poisoning and procedural complications			
Concussion			
subjects affected / exposed	0 / 83 (0.00%)	0 / 81 (0.00%)	1 / 83 (1.20%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fall			
subjects affected / exposed	0 / 83 (0.00%)	0 / 81 (0.00%)	0 / 83 (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
Head injury			
subjects affected / exposed	0 / 83 (0.00%)	0 / 81 (0.00%)	1 / 83 (1.20%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Toxicity to various agents			
subjects affected / exposed	0 / 83 (0.00%)	0 / 81 (0.00%)	0 / 83 (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
Traumatic haemothorax			
subjects affected / exposed	1 / 83 (1.20%)	0 / 81 (0.00%)	0 / 83 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Atrial flutter			
subjects affected / exposed	0 / 83 (0.00%)	1 / 81 (1.23%)	0 / 83 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Surgical and medical procedures			
Medical device battery replacement			
subjects affected / exposed	0 / 83 (0.00%)	0 / 81 (0.00%)	1 / 83 (1.20%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			

Altered state of consciousness			
subjects affected / exposed	0 / 83 (0.00%)	0 / 81 (0.00%)	0 / 83 (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
Encephalopathy			
subjects affected / exposed	0 / 83 (0.00%)	0 / 81 (0.00%)	0 / 83 (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
Focal dyscognitive seizures			
subjects affected / exposed	0 / 83 (0.00%)	1 / 81 (1.23%)	0 / 83 (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
Partial seizures			
subjects affected / exposed	0 / 83 (0.00%)	1 / 81 (1.23%)	0 / 83 (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
Seizure cluster			
subjects affected / exposed	1 / 83 (1.20%)	0 / 81 (0.00%)	0 / 83 (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
Status epilepticus			
subjects affected / exposed	1 / 83 (1.20%)	1 / 81 (1.23%)	1 / 83 (1.20%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Syncope			
subjects affected / exposed	0 / 83 (0.00%)	0 / 81 (0.00%)	0 / 83 (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
Respiratory, thoracic and mediastinal disorders			
Pneumonia aspiration			
subjects affected / exposed	0 / 83 (0.00%)	0 / 81 (0.00%)	1 / 83 (1.20%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Renal and urinary disorders			
Renal disorder			
subjects affected / exposed	0 / 83 (0.00%)	0 / 81 (0.00%)	1 / 83 (1.20%)
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			
Depression			
subjects affected / exposed	0 / 83 (0.00%)	0 / 81 (0.00%)	0 / 83 (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 psychosis			
subjects affected / exposed	0 / 83 (0.00%)	0 / 81 (0.00%)	0 / 83 (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
Infections and infestations			
Diverticulitis			
subjects affected / exposed	0 / 83 (0.00%)	1 / 81 (1.23%)	0 / 83 (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
Metabolism and nutrition disorders			
Hyperkalaemia			
subjects affected / exposed	0 / 83 (0.00%)	0 / 81 (0.00%)	1 / 83 (1.20%)
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	Padsevonil dosing regimen 3 Treatment period (SS)	Padsevonil dosing regimen 4 Treatment period (SS)	Padsevonil dosing regimen 1 Conversion period (SS)
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 82 (3.66%)	5 / 81 (6.17%)	0 / 64 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Injury, poisoning and procedural complications			
Concussion			
subjects affected / exposed	0 / 82 (0.00%)	0 / 81 (0.00%)	0 / 64 (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

Fall			
subjects affected / exposed	1 / 82 (1.22%)	0 / 81 (0.00%)	0 / 64 (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
Head injury			
subjects affected / exposed	0 / 82 (0.00%)	1 / 81 (1.23%)	0 / 64 (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
Toxicity to various agents			
subjects affected / exposed	1 / 82 (1.22%)	0 / 81 (0.00%)	0 / 64 (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
Traumatic haemothorax			
subjects affected / exposed	0 / 82 (0.00%)	0 / 81 (0.00%)	0 / 64 (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			
Atrial flutter			
subjects affected / exposed	0 / 82 (0.00%)	0 / 81 (0.00%)	0 / 64 (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			
Medical device battery replacement			
subjects affected / exposed	0 / 82 (0.00%)	1 / 81 (1.23%)	0 / 64 (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			
Altered state of consciousness			
subjects affected / exposed	0 / 82 (0.00%)	1 / 81 (1.23%)	0 / 64 (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
Encephalopathy			

subjects affected / exposed	0 / 82 (0.00%)	1 / 81 (1.23%)	0 / 64 (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
Focal dyscognitive seizures			
subjects affected / exposed	0 / 82 (0.00%)	0 / 81 (0.00%)	0 / 64 (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
Partial seizures			
subjects affected / exposed	0 / 82 (0.00%)	0 / 81 (0.00%)	0 / 64 (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
Seizure cluster			
subjects affected / exposed	0 / 82 (0.00%)	0 / 81 (0.00%)	0 / 64 (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
Status epilepticus			
subjects affected / exposed	1 / 82 (1.22%)	1 / 81 (1.23%)	0 / 64 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Syncope			
subjects affected / exposed	0 / 82 (0.00%)	1 / 81 (1.23%)	0 / 64 (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
Respiratory, thoracic and mediastinal disorders			
Pneumonia aspiration			
subjects affected / exposed	0 / 82 (0.00%)	0 / 81 (0.00%)	0 / 64 (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			
Renal disorder			
subjects affected / exposed	0 / 82 (0.00%)	0 / 81 (0.00%)	0 / 64 (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

Psychiatric disorders			
Depression			
subjects affected / exposed	0 / 82 (0.00%)	0 / 81 (0.00%)	0 / 64 (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 psychosis			
subjects affected / exposed	0 / 82 (0.00%)	0 / 81 (0.00%)	0 / 64 (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
Infections and infestations			
Diverticulitis			
subjects affected / exposed	0 / 82 (0.00%)	0 / 81 (0.00%)	0 / 64 (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
Metabolism and nutrition disorders			
Hyperkalaemia			
subjects affected / exposed	0 / 82 (0.00%)	0 / 81 (0.00%)	0 / 64 (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	Placebo Conversion period (SS)	Padsevonil dosing regimen 2 Conversion period (SS)	Padsevonil dosing regimen 3 Conversion period (SS)
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 69 (0.00%)	0 / 66 (0.00%)	2 / 55 (3.64%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Injury, poisoning and procedural complications			
Concussion			
subjects affected / exposed	0 / 69 (0.00%)	0 / 66 (0.00%)	0 / 55 (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
Fall			
subjects affected / exposed	0 / 69 (0.00%)	0 / 66 (0.00%)	0 / 55 (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

Head injury			
subjects affected / exposed	0 / 69 (0.00%)	0 / 66 (0.00%)	0 / 55 (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
Toxicity to various agents			
subjects affected / exposed	0 / 69 (0.00%)	0 / 66 (0.00%)	0 / 55 (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
Traumatic haemothorax			
subjects affected / exposed	0 / 69 (0.00%)	0 / 66 (0.00%)	0 / 55 (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			
Atrial flutter			
subjects affected / exposed	0 / 69 (0.00%)	0 / 66 (0.00%)	0 / 55 (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			
Medical device battery replacement			
subjects affected / exposed	0 / 69 (0.00%)	0 / 66 (0.00%)	0 / 55 (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			
Altered state of consciousness			
subjects affected / exposed	0 / 69 (0.00%)	0 / 66 (0.00%)	0 / 55 (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
Encephalopathy			
subjects affected / exposed	0 / 69 (0.00%)	0 / 66 (0.00%)	0 / 55 (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
Focal dyscognitive seizures			

subjects affected / exposed	0 / 69 (0.00%)	0 / 66 (0.00%)	0 / 55 (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
Partial seizures			
subjects affected / exposed	0 / 69 (0.00%)	0 / 66 (0.00%)	0 / 55 (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
Seizure cluster			
subjects affected / exposed	0 / 69 (0.00%)	0 / 66 (0.00%)	0 / 55 (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
Status epilepticus			
subjects affected / exposed	0 / 69 (0.00%)	0 / 66 (0.00%)	1 / 55 (1.82%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Syncope			
subjects affected / exposed	0 / 69 (0.00%)	0 / 66 (0.00%)	0 / 55 (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
Respiratory, thoracic and mediastinal disorders			
Pneumonia aspiration			
subjects affected / exposed	0 / 69 (0.00%)	0 / 66 (0.00%)	0 / 55 (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			
Renal disorder			
subjects affected / exposed	0 / 69 (0.00%)	0 / 66 (0.00%)	0 / 55 (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
Psychiatric disorders			
Depression			
subjects affected / exposed	0 / 69 (0.00%)	0 / 66 (0.00%)	1 / 55 (1.82%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Acute psychosis			
subjects affected / exposed	0 / 69 (0.00%)	0 / 66 (0.00%)	0 / 55 (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
Infections and infestations			
Diverticulitis			
subjects affected / exposed	0 / 69 (0.00%)	0 / 66 (0.00%)	0 / 55 (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
Metabolism and nutrition disorders			
Hyperkalaemia			
subjects affected / exposed	0 / 69 (0.00%)	0 / 66 (0.00%)	0 / 55 (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	Padsevonil dosing regimen 4 Conversion period (SS)	Placebo Taper and SFU period (SS)	Padsevonil dosing regimen 1 Taper and SFU period (SS)
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 57 (0.00%)	1 / 9 (11.11%)	1 / 14 (7.14%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Injury, poisoning and procedural complications			
Concussion			
subjects affected / exposed	0 / 57 (0.00%)	0 / 9 (0.00%)	0 / 14 (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
Fall			
subjects affected / exposed	0 / 57 (0.00%)	0 / 9 (0.00%)	0 / 14 (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
Head injury			
subjects affected / exposed	0 / 57 (0.00%)	0 / 9 (0.00%)	1 / 14 (7.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Toxicity to various agents			

subjects affected / exposed	0 / 57 (0.00%)	0 / 9 (0.00%)	0 / 14 (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
Traumatic haemothorax			
subjects affected / exposed	0 / 57 (0.00%)	0 / 9 (0.00%)	0 / 14 (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			
Atrial flutter			
subjects affected / exposed	0 / 57 (0.00%)	0 / 9 (0.00%)	0 / 14 (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			
Medical device battery replacement			
subjects affected / exposed	0 / 57 (0.00%)	0 / 9 (0.00%)	0 / 14 (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			
Altered state of consciousness			
subjects affected / exposed	0 / 57 (0.00%)	0 / 9 (0.00%)	0 / 14 (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
Encephalopathy			
subjects affected / exposed	0 / 57 (0.00%)	0 / 9 (0.00%)	0 / 14 (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
Focal dyscognitive seizures			
subjects affected / exposed	0 / 57 (0.00%)	0 / 9 (0.00%)	0 / 14 (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
Partial seizures			
subjects affected / exposed	0 / 57 (0.00%)	0 / 9 (0.00%)	0 / 14 (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

Seizure cluster			
subjects affected / exposed	0 / 57 (0.00%)	0 / 9 (0.00%)	0 / 14 (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
Status epilepticus			
subjects affected / exposed	0 / 57 (0.00%)	0 / 9 (0.00%)	0 / 14 (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
Syncope			
subjects affected / exposed	0 / 57 (0.00%)	0 / 9 (0.00%)	0 / 14 (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
Respiratory, thoracic and mediastinal disorders			
Pneumonia aspiration			
subjects affected / exposed	0 / 57 (0.00%)	0 / 9 (0.00%)	0 / 14 (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			
Renal disorder			
subjects affected / exposed	0 / 57 (0.00%)	0 / 9 (0.00%)	0 / 14 (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
Psychiatric disorders			
Depression			
subjects affected / exposed	0 / 57 (0.00%)	0 / 9 (0.00%)	0 / 14 (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 psychosis			
subjects affected / exposed	0 / 57 (0.00%)	1 / 9 (11.11%)	0 / 14 (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			
Diverticulitis			

subjects affected / exposed	0 / 57 (0.00%)	0 / 9 (0.00%)	0 / 14 (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
Metabolism and nutrition disorders			
Hyperkalaemia			
subjects affected / exposed	0 / 57 (0.00%)	0 / 9 (0.00%)	0 / 14 (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	Padsevonil dosing regimen 2 Taper and SFU period (SS)	Padsevonil dosing regimen 3 Taper and SFU period (SS)	Padsevonil dosing regimen 4 Taper and SFU period (SS)
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 11 (0.00%)	0 / 24 (0.00%)	0 / 22 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Injury, poisoning and procedural complications			
Concussion			
subjects affected / exposed	0 / 11 (0.00%)	0 / 24 (0.00%)	0 / 22 (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
Fall			
subjects affected / exposed	0 / 11 (0.00%)	0 / 24 (0.00%)	0 / 22 (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
Head injury			
subjects affected / exposed	0 / 11 (0.00%)	0 / 24 (0.00%)	0 / 22 (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
Toxicity to various agents			
subjects affected / exposed	0 / 11 (0.00%)	0 / 24 (0.00%)	0 / 22 (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
Traumatic haemothorax			

subjects affected / exposed	0 / 11 (0.00%)	0 / 24 (0.00%)	0 / 22 (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			
Atrial flutter			
subjects affected / exposed	0 / 11 (0.00%)	0 / 24 (0.00%)	0 / 22 (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			
Medical device battery replacement			
subjects affected / exposed	0 / 11 (0.00%)	0 / 24 (0.00%)	0 / 22 (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			
Altered state of consciousness			
subjects affected / exposed	0 / 11 (0.00%)	0 / 24 (0.00%)	0 / 22 (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
Encephalopathy			
subjects affected / exposed	0 / 11 (0.00%)	0 / 24 (0.00%)	0 / 22 (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
Focal dyscognitive seizures			
subjects affected / exposed	0 / 11 (0.00%)	0 / 24 (0.00%)	0 / 22 (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
Partial seizures			
subjects affected / exposed	0 / 11 (0.00%)	0 / 24 (0.00%)	0 / 22 (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
Seizure cluster			
subjects affected / exposed	0 / 11 (0.00%)	0 / 24 (0.00%)	0 / 22 (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

Status epilepticus			
subjects affected / exposed	0 / 11 (0.00%)	0 / 24 (0.00%)	0 / 22 (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
Syncope			
subjects affected / exposed	0 / 11 (0.00%)	0 / 24 (0.00%)	0 / 22 (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
Respiratory, thoracic and mediastinal disorders			
Pneumonia aspiration			
subjects affected / exposed	0 / 11 (0.00%)	0 / 24 (0.00%)	0 / 22 (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			
Renal disorder			
subjects affected / exposed	0 / 11 (0.00%)	0 / 24 (0.00%)	0 / 22 (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
Psychiatric disorders			
Depression			
subjects affected / exposed	0 / 11 (0.00%)	0 / 24 (0.00%)	0 / 22 (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 psychosis			
subjects affected / exposed	0 / 11 (0.00%)	0 / 24 (0.00%)	0 / 22 (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
Infections and infestations			
Diverticulitis			
subjects affected / exposed	0 / 11 (0.00%)	0 / 24 (0.00%)	0 / 22 (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
Metabolism and nutrition disorders			
Hyperkalaemia			

subjects affected / exposed	0 / 11 (0.00%)	0 / 24 (0.00%)	0 / 22 (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

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

Non-serious adverse events	Placebo Treatment period (SS)	Padsevonil dosing regimen 1 Treatment period (SS)	Padsevonil dosing regimen 2 Treatment period (SS)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	45 / 83 (54.22%)	54 / 81 (66.67%)	60 / 83 (72.29%)
Investigations			
Platelet count decreased			
subjects affected / exposed	0 / 83 (0.00%)	0 / 81 (0.00%)	1 / 83 (1.20%)
occurrences (all)	0	0	1
Anticonvulsant drug level increased			
subjects affected / exposed	0 / 83 (0.00%)	0 / 81 (0.00%)	0 / 83 (0.00%)
occurrences (all)	0	0	0
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	4 / 83 (4.82%)	2 / 81 (2.47%)	1 / 83 (1.20%)
occurrences (all)	4	2	1
Ligament sprain			
subjects affected / exposed	0 / 83 (0.00%)	2 / 81 (2.47%)	0 / 83 (0.00%)
occurrences (all)	0	2	0
Burns second degree			
subjects affected / exposed	0 / 83 (0.00%)	0 / 81 (0.00%)	0 / 83 (0.00%)
occurrences (all)	0	0	0
Nervous system disorders			
Dizziness			
subjects affected / exposed	9 / 83 (10.84%)	18 / 81 (22.22%)	23 / 83 (27.71%)
occurrences (all)	9	19	31
Somnolence			
subjects affected / exposed	10 / 83 (12.05%)	19 / 81 (23.46%)	24 / 83 (28.92%)
occurrences (all)	11	24	29
Headache			

subjects affected / exposed	10 / 83 (12.05%)	17 / 81 (20.99%)	9 / 83 (10.84%)
occurrences (all)	14	29	16
Memory impairment			
subjects affected / exposed	1 / 83 (1.20%)	3 / 81 (3.70%)	1 / 83 (1.20%)
occurrences (all)	1	3	1
Tremor			
subjects affected / exposed	0 / 83 (0.00%)	5 / 81 (6.17%)	2 / 83 (2.41%)
occurrences (all)	0	5	2
Balance disorder			
subjects affected / exposed	1 / 83 (1.20%)	3 / 81 (3.70%)	3 / 83 (3.61%)
occurrences (all)	2	3	3
Nystagmus			
subjects affected / exposed	0 / 83 (0.00%)	0 / 81 (0.00%)	0 / 83 (0.00%)
occurrences (all)	0	0	0
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	10 / 83 (12.05%)	20 / 81 (24.69%)	12 / 83 (14.46%)
occurrences (all)	10	27	17
Gait disturbance			
subjects affected / exposed	1 / 83 (1.20%)	2 / 81 (2.47%)	0 / 83 (0.00%)
occurrences (all)	1	2	0
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	7 / 83 (8.43%)	3 / 81 (3.70%)	2 / 83 (2.41%)
occurrences (all)	7	3	2
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	7 / 83 (8.43%)	4 / 81 (4.94%)	7 / 83 (8.43%)
occurrences (all)	7	4	7
Diarrhoea			
subjects affected / exposed	3 / 83 (3.61%)	6 / 81 (7.41%)	3 / 83 (3.61%)
occurrences (all)	3	8	4
Psychiatric disorders			
Irritability			
subjects affected / exposed	8 / 83 (9.64%)	4 / 81 (4.94%)	7 / 83 (8.43%)
occurrences (all)	8	4	7

Anxiety			
subjects affected / exposed	3 / 83 (3.61%)	1 / 81 (1.23%)	1 / 83 (1.20%)
occurrences (all)	3	1	2
Paranoia			
subjects affected / exposed	0 / 83 (0.00%)	0 / 81 (0.00%)	0 / 83 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 83 (0.00%)	1 / 81 (1.23%)	2 / 83 (2.41%)
occurrences (all)	0	1	2
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	5 / 83 (6.02%)	5 / 81 (6.17%)	9 / 83 (10.84%)
occurrences (all)	5	5	13
Upper respiratory tract infection			
subjects affected / exposed	1 / 83 (1.20%)	5 / 81 (6.17%)	0 / 83 (0.00%)
occurrences (all)	3	5	0
Urinary tract infection			
subjects affected / exposed	2 / 83 (2.41%)	1 / 81 (1.23%)	1 / 83 (1.20%)
occurrences (all)	2	1	1

Non-serious adverse events	Padsevonil dosing regimen 3 Treatment period (SS)	Padsevonil dosing regimen 4 Treatment period (SS)	Padsevonil dosing regimen 1 Conversion period (SS)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	53 / 82 (64.63%)	65 / 81 (80.25%)	18 / 64 (28.13%)
Investigations			
Platelet count decreased			
subjects affected / exposed	0 / 82 (0.00%)	0 / 81 (0.00%)	0 / 64 (0.00%)
occurrences (all)	0	0	0
Anticonvulsant drug level increased			
subjects affected / exposed	0 / 82 (0.00%)	0 / 81 (0.00%)	0 / 64 (0.00%)
occurrences (all)	0	0	0
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	1 / 82 (1.22%)	7 / 81 (8.64%)	0 / 64 (0.00%)
occurrences (all)	2	7	0
Ligament sprain			

subjects affected / exposed	0 / 82 (0.00%)	0 / 81 (0.00%)	2 / 64 (3.13%)
occurrences (all)	0	0	2
Burns second degree			
subjects affected / exposed	0 / 82 (0.00%)	0 / 81 (0.00%)	0 / 64 (0.00%)
occurrences (all)	0	0	0
Nervous system disorders			
Dizziness			
subjects affected / exposed	19 / 82 (23.17%)	28 / 81 (34.57%)	2 / 64 (3.13%)
occurrences (all)	25	55	2
Somnolence			
subjects affected / exposed	25 / 82 (30.49%)	30 / 81 (37.04%)	4 / 64 (6.25%)
occurrences (all)	26	35	5
Headache			
subjects affected / exposed	15 / 82 (18.29%)	9 / 81 (11.11%)	3 / 64 (4.69%)
occurrences (all)	21	31	3
Memory impairment			
subjects affected / exposed	8 / 82 (9.76%)	14 / 81 (17.28%)	0 / 64 (0.00%)
occurrences (all)	9	14	0
Tremor			
subjects affected / exposed	6 / 82 (7.32%)	5 / 81 (6.17%)	0 / 64 (0.00%)
occurrences (all)	6	5	0
Balance disorder			
subjects affected / exposed	5 / 82 (6.10%)	3 / 81 (3.70%)	0 / 64 (0.00%)
occurrences (all)	5	3	0
Nystagmus			
subjects affected / exposed	0 / 82 (0.00%)	0 / 81 (0.00%)	0 / 64 (0.00%)
occurrences (all)	0	0	0
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	14 / 82 (17.07%)	20 / 81 (24.69%)	5 / 64 (7.81%)
occurrences (all)	22	21	5
Gait disturbance			
subjects affected / exposed	1 / 82 (1.22%)	5 / 81 (6.17%)	0 / 64 (0.00%)
occurrences (all)	1	5	0
Ear and labyrinth disorders			

Vertigo			
subjects affected / exposed	3 / 82 (3.66%)	4 / 81 (4.94%)	0 / 64 (0.00%)
occurrences (all)	3	5	0
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	2 / 82 (2.44%)	7 / 81 (8.64%)	0 / 64 (0.00%)
occurrences (all)	3	13	0
Diarrhoea			
subjects affected / exposed	5 / 82 (6.10%)	4 / 81 (4.94%)	1 / 64 (1.56%)
occurrences (all)	7	5	1
Psychiatric disorders			
Irritability			
subjects affected / exposed	1 / 82 (1.22%)	5 / 81 (6.17%)	1 / 64 (1.56%)
occurrences (all)	1	6	1
Anxiety			
subjects affected / exposed	7 / 82 (8.54%)	0 / 81 (0.00%)	0 / 64 (0.00%)
occurrences (all)	9	0	0
Paranoia			
subjects affected / exposed	0 / 82 (0.00%)	0 / 81 (0.00%)	0 / 64 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	2 / 82 (2.44%)	5 / 81 (6.17%)	0 / 64 (0.00%)
occurrences (all)	2	5	0
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	7 / 82 (8.54%)	5 / 81 (6.17%)	1 / 64 (1.56%)
occurrences (all)	11	5	1
Upper respiratory tract infection			
subjects affected / exposed	0 / 82 (0.00%)	2 / 81 (2.47%)	1 / 64 (1.56%)
occurrences (all)	0	3	1
Urinary tract infection			
subjects affected / exposed	0 / 82 (0.00%)	2 / 81 (2.47%)	0 / 64 (0.00%)
occurrences (all)	0	2	0

Non-serious adverse events	Placebo Conversion period (SS)	Padsevonil dosing regimen 2 Conversion period (SS)	Padsevonil dosing regimen 3 Conversion period (SS)

Total subjects affected by non-serious adverse events subjects affected / exposed	11 / 69 (15.94%)	10 / 66 (15.15%)	5 / 55 (9.09%)
Investigations			
Platelet count decreased subjects affected / exposed	0 / 69 (0.00%)	0 / 66 (0.00%)	0 / 55 (0.00%)
occurrences (all)	0	0	0
Anticonvulsant drug level increased subjects affected / exposed	0 / 69 (0.00%)	0 / 66 (0.00%)	0 / 55 (0.00%)
occurrences (all)	0	0	0
Injury, poisoning and procedural complications			
Fall subjects affected / exposed	0 / 69 (0.00%)	1 / 66 (1.52%)	1 / 55 (1.82%)
occurrences (all)	0	2	1
Ligament sprain subjects affected / exposed	0 / 69 (0.00%)	0 / 66 (0.00%)	0 / 55 (0.00%)
occurrences (all)	0	0	0
Burns second degree subjects affected / exposed	0 / 69 (0.00%)	0 / 66 (0.00%)	0 / 55 (0.00%)
occurrences (all)	0	0	0
Nervous system disorders			
Dizziness subjects affected / exposed	3 / 69 (4.35%)	1 / 66 (1.52%)	2 / 55 (3.64%)
occurrences (all)	3	1	2
Somnolence subjects affected / exposed	1 / 69 (1.45%)	1 / 66 (1.52%)	1 / 55 (1.82%)
occurrences (all)	1	1	1
Headache subjects affected / exposed	0 / 69 (0.00%)	2 / 66 (3.03%)	0 / 55 (0.00%)
occurrences (all)	0	3	0
Memory impairment subjects affected / exposed	1 / 69 (1.45%)	1 / 66 (1.52%)	0 / 55 (0.00%)
occurrences (all)	1	1	0
Tremor subjects affected / exposed	1 / 69 (1.45%)	0 / 66 (0.00%)	0 / 55 (0.00%)
occurrences (all)	1	0	0
Balance disorder			

subjects affected / exposed	0 / 69 (0.00%)	0 / 66 (0.00%)	0 / 55 (0.00%)
occurrences (all)	0	0	0
Nystagmus			
subjects affected / exposed	1 / 69 (1.45%)	0 / 66 (0.00%)	0 / 55 (0.00%)
occurrences (all)	1	0	0
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	3 / 69 (4.35%)	2 / 66 (3.03%)	1 / 55 (1.82%)
occurrences (all)	3	2	1
Gait disturbance			
subjects affected / exposed	0 / 69 (0.00%)	0 / 66 (0.00%)	0 / 55 (0.00%)
occurrences (all)	0	0	0
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	1 / 69 (1.45%)	0 / 66 (0.00%)	0 / 55 (0.00%)
occurrences (all)	1	0	0
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	1 / 69 (1.45%)	1 / 66 (1.52%)	0 / 55 (0.00%)
occurrences (all)	1	1	0
Diarrhoea			
subjects affected / exposed	1 / 69 (1.45%)	1 / 66 (1.52%)	0 / 55 (0.00%)
occurrences (all)	1	1	0
Psychiatric disorders			
Irritability			
subjects affected / exposed	0 / 69 (0.00%)	1 / 66 (1.52%)	0 / 55 (0.00%)
occurrences (all)	0	1	0
Anxiety			
subjects affected / exposed	1 / 69 (1.45%)	0 / 66 (0.00%)	0 / 55 (0.00%)
occurrences (all)	1	0	0
Paranoia			
subjects affected / exposed	0 / 69 (0.00%)	0 / 66 (0.00%)	0 / 55 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal and connective tissue disorders			
Back pain			

subjects affected / exposed	0 / 69 (0.00%)	0 / 66 (0.00%)	0 / 55 (0.00%)
occurrences (all)	0	0	0
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	1 / 69 (1.45%)	0 / 66 (0.00%)	1 / 55 (1.82%)
occurrences (all)	1	0	1
Upper respiratory tract infection			
subjects affected / exposed	0 / 69 (0.00%)	0 / 66 (0.00%)	0 / 55 (0.00%)
occurrences (all)	0	0	0
Urinary tract infection			
subjects affected / exposed	1 / 69 (1.45%)	1 / 66 (1.52%)	0 / 55 (0.00%)
occurrences (all)	1	1	0

Non-serious adverse events	Padsevonil dosing regimen 4 Conversion period (SS)	Placebo Taper and SFU period (SS)	Padsevonil dosing regimen 1 Taper and SFU period (SS)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	5 / 57 (8.77%)	3 / 9 (33.33%)	3 / 14 (21.43%)
Investigations			
Platelet count decreased			
subjects affected / exposed	0 / 57 (0.00%)	1 / 9 (11.11%)	0 / 14 (0.00%)
occurrences (all)	0	1	0
Anticonvulsant drug level increased			
subjects affected / exposed	0 / 57 (0.00%)	1 / 9 (11.11%)	0 / 14 (0.00%)
occurrences (all)	0	1	0
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	0 / 57 (0.00%)	0 / 9 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Ligament sprain			
subjects affected / exposed	0 / 57 (0.00%)	1 / 9 (11.11%)	0 / 14 (0.00%)
occurrences (all)	0	1	0
Burns second degree			
subjects affected / exposed	0 / 57 (0.00%)	0 / 9 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Nervous system disorders			

Dizziness			
subjects affected / exposed	2 / 57 (3.51%)	0 / 9 (0.00%)	0 / 14 (0.00%)
occurrences (all)	6	0	0
Somnolence			
subjects affected / exposed	2 / 57 (3.51%)	0 / 9 (0.00%)	0 / 14 (0.00%)
occurrences (all)	2	0	0
Headache			
subjects affected / exposed	1 / 57 (1.75%)	1 / 9 (11.11%)	0 / 14 (0.00%)
occurrences (all)	5	1	0
Memory impairment			
subjects affected / exposed	0 / 57 (0.00%)	0 / 9 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Tremor			
subjects affected / exposed	0 / 57 (0.00%)	0 / 9 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Balance disorder			
subjects affected / exposed	0 / 57 (0.00%)	0 / 9 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Nystagmus			
subjects affected / exposed	0 / 57 (0.00%)	0 / 9 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	0 / 57 (0.00%)	0 / 9 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Gait disturbance			
subjects affected / exposed	0 / 57 (0.00%)	0 / 9 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	0 / 57 (0.00%)	0 / 9 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	0 / 57 (0.00%)	0 / 9 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0

Diarrhoea			
subjects affected / exposed	1 / 57 (1.75%)	0 / 9 (0.00%)	0 / 14 (0.00%)
occurrences (all)	1	0	0
Psychiatric disorders			
Irritability			
subjects affected / exposed	0 / 57 (0.00%)	0 / 9 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Anxiety			
subjects affected / exposed	0 / 57 (0.00%)	0 / 9 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Paranoia			
subjects affected / exposed	0 / 57 (0.00%)	0 / 9 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 57 (0.00%)	1 / 9 (11.11%)	0 / 14 (0.00%)
occurrences (all)	0	1	0
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	0 / 57 (0.00%)	0 / 9 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Upper respiratory tract infection			
subjects affected / exposed	0 / 57 (0.00%)	0 / 9 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Urinary tract infection			
subjects affected / exposed	0 / 57 (0.00%)	1 / 9 (11.11%)	0 / 14 (0.00%)
occurrences (all)	0	1	0

Non-serious adverse events	Padsevonil dosing regimen 2 Taper and SFU period (SS)	Padsevonil dosing regimen 3 Taper and SFU period (SS)	Padsevonil dosing regimen 4 Taper and SFU period (SS)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 11 (0.00%)	3 / 24 (12.50%)	4 / 22 (18.18%)
Investigations			
Platelet count decreased			
subjects affected / exposed	0 / 11 (0.00%)	0 / 24 (0.00%)	0 / 22 (0.00%)
occurrences (all)	0	0	0
Anticonvulsant drug level increased			

subjects affected / exposed	0 / 11 (0.00%)	0 / 24 (0.00%)	0 / 22 (0.00%)
occurrences (all)	0	0	0
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	0 / 11 (0.00%)	0 / 24 (0.00%)	0 / 22 (0.00%)
occurrences (all)	0	0	0
Ligament sprain			
subjects affected / exposed	0 / 11 (0.00%)	0 / 24 (0.00%)	0 / 22 (0.00%)
occurrences (all)	0	0	0
Burns second degree			
subjects affected / exposed	0 / 11 (0.00%)	0 / 24 (0.00%)	0 / 22 (0.00%)
occurrences (all)	0	0	0
Nervous system disorders			
Dizziness			
subjects affected / exposed	0 / 11 (0.00%)	1 / 24 (4.17%)	1 / 22 (4.55%)
occurrences (all)	0	1	1
Somnolence			
subjects affected / exposed	0 / 11 (0.00%)	0 / 24 (0.00%)	0 / 22 (0.00%)
occurrences (all)	0	0	0
Headache			
subjects affected / exposed	0 / 11 (0.00%)	2 / 24 (8.33%)	1 / 22 (4.55%)
occurrences (all)	0	2	1
Memory impairment			
subjects affected / exposed	0 / 11 (0.00%)	0 / 24 (0.00%)	1 / 22 (4.55%)
occurrences (all)	0	0	1
Tremor			
subjects affected / exposed	0 / 11 (0.00%)	0 / 24 (0.00%)	0 / 22 (0.00%)
occurrences (all)	0	0	0
Balance disorder			
subjects affected / exposed	0 / 11 (0.00%)	0 / 24 (0.00%)	0 / 22 (0.00%)
occurrences (all)	0	0	0
Nystagmus			
subjects affected / exposed	0 / 11 (0.00%)	0 / 24 (0.00%)	0 / 22 (0.00%)
occurrences (all)	0	0	0
General disorders and administration site conditions			

Fatigue			
subjects affected / exposed	0 / 11 (0.00%)	1 / 24 (4.17%)	0 / 22 (0.00%)
occurrences (all)	0	2	0
Gait disturbance			
subjects affected / exposed	0 / 11 (0.00%)	0 / 24 (0.00%)	0 / 22 (0.00%)
occurrences (all)	0	0	0
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	0 / 11 (0.00%)	0 / 24 (0.00%)	0 / 22 (0.00%)
occurrences (all)	0	0	0
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	0 / 11 (0.00%)	0 / 24 (0.00%)	0 / 22 (0.00%)
occurrences (all)	0	0	0
Diarrhoea			
subjects affected / exposed	0 / 11 (0.00%)	1 / 24 (4.17%)	0 / 22 (0.00%)
occurrences (all)	0	1	0
Psychiatric disorders			
Irritability			
subjects affected / exposed	0 / 11 (0.00%)	0 / 24 (0.00%)	1 / 22 (4.55%)
occurrences (all)	0	0	1
Anxiety			
subjects affected / exposed	0 / 11 (0.00%)	0 / 24 (0.00%)	0 / 22 (0.00%)
occurrences (all)	0	0	0
Paranoia			
subjects affected / exposed	0 / 11 (0.00%)	0 / 24 (0.00%)	0 / 22 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 11 (0.00%)	0 / 24 (0.00%)	0 / 22 (0.00%)
occurrences (all)	0	0	0
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	0 / 11 (0.00%)	0 / 24 (0.00%)	0 / 22 (0.00%)
occurrences (all)	0	0	0
Upper respiratory tract infection			

subjects affected / exposed	0 / 11 (0.00%)	0 / 24 (0.00%)	0 / 22 (0.00%)
occurrences (all)	0	0	0
Urinary tract infection			
subjects affected / exposed	0 / 11 (0.00%)	0 / 24 (0.00%)	1 / 22 (4.55%)
occurrences (all)	0	0	1

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
09 March 2018	Protocol Amendment 1, dated 09 Mar 2018, provided the following key changes: The purpose of this substantial amendment was primarily to increase the potential for the study to be 1 of 2 adequate and well-controlled studies that supported registration. This required an increase in the sample size to allow for pairwise comparisons and the use of the 75% responder rate status as the primary variable for the European Medicines Agency (EMA) (CHMP/EWP/566/98 Rev.2/Corr, 2010). Per EMA guidance, the primary variable in add-on epilepsy studies should have dichotomized the data into responders/nonresponders, where responders were participants who obtained at least a certain predefined percentage reduction of seizure frequency. An improvement of >75% was regarded as clinically more meaningful than >50% and seemed feasible given the premise of greater efficacy of Padsevonil based upon nonclinical animal data and EP0069 results. Therefore, the 75% responder rate was selected as the primary variable, rather than the more commonly used 50% responder rate. Another important addition to the protocol was that the Data Monitoring Committee (DMC) could stop enrollment into a Padsevonil dose arm for safety and tolerability reasons and allocate remaining patients to remaining Padsevonil dose or placebo arms. This addition did not reflect a change in intent. Rather, the plan had been to describe this possibility in the Data Monitoring Committee (DMC) Charter, but it was included in the protocol to avoid disruption to the study via a subsequent amendment in the unlikely event that a dose arm was dropped from the study for safety/tolerability reasons.
12 October 2018	Protocol Amendment 2, dated 12 Oct 2018, provided the following key changes: The purpose of this substantial amendment was to clarify that the primary efficacy analysis was comparing each Padsevonil dose to placebo with Type I error controlled for all comparisons. Multiple Comparison Procedure-Modelling (MCP-Mod) analysis was removed since it would no longer contribute to the overall study conclusion and dose selection for future studies. Other changes included the following: • Updates to study contact information. • Minor refinements to the wording describing responder rate variables. • Correction of the maximum duration of exposure to PSL from 20 to 19 weeks. • Clarification of the rationale for the study to state that dose-response relationship was evaluated with respect to safety as well as efficacy. • Revised other efficacy variable, number of seizure-free days to percentage of seizure-free days. • Revised other efficacy variable, time to return to baseline observable (Type IA1+IB+IC) focal-onset seizure frequency to time to return to baseline 28-day observable seizure count. • Revision of designation of treatment-emergent adverse events (TEAEs), TEAEs leading to withdrawal, and SAEs from “safety variables” to “primary safety variables.” A heading was added for these primary variables. • Clarification of a Schedule of Assessments footnote that questionnaires should have been completed prior to other study procedures, when possible. Previously it was mandated that these be completed prior to other procedures. • Removal of efficiencies of the MCP-Mod model based design and analysis as 1 of the drivers for EP0091 dose selection. In addition, the rationale for selection of intermediate doses was revised due to the elimination of MCP-Mod analysis. •Revision of Inclusion Criterion 2 to account for the fact that use of legal representative/caregiver may not have been legally permitted in some countries.

12 October 2018	Continuation of Protocol Amendment 2 (1) • Modification of Inclusion Criterion 5 to facilitate the acceptance of ambulatory electroencephalograms (EEGs), which were used more frequently in some regions, to require (must versus should) consultation with the UCB Study Physician or representative when determining study participant eligibility based on eye-witness seizure report, home video documentation, or other proof, and to allow substitution of head computed tomography (CT) scan for magnetic resonance imaging (MRI) if MRI was contraindicated. • Modification of Exclusion Criterion 1 to allow rescreening of study participants under certain circumstances. • Clarification of the description of the interpretation of echocardiograms − The original description stated that the echocardiograms would be interpreted at the sites by local cardiologists and then provided to a central reader where they would be interpreted. Given that all echocardiograms were to be centrally read and a report provided within 7 business days of receipt, in the absence of queries, there was no need for a local cardiologist. Therefore, the protocol was modified to say that it was only necessary that the local physician examine the echocardiograms for suitability for central reading and for determination if an expedited review by the central reader was required. It was also made explicit that the central reader was a cardiologist. • Clarification of the Titration Period Dosing Table 7-1 in the protocol, to indicate that this period consisted of Week 1, Week 2, and Week 3 (versus previous unclear designations of Day 1, Week 1 and Week 2). • Clarifications regarding administration of the Seizure Severity Global Item (SSG), Quality of Life Inventory in Epilepsy-31-P (QOLIE-31-P), and Hospital Anxiety and Depression Scale (HADS).
12 October 2018	Continuation of Protocol Amendment 2 (2) • Other modifications to the Statistics section (in addition to those related to the removal of MCP-Mod analysis), such as inclusion of information on handling of dropouts and missing data and further details about the determination of sample size.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported