Clinical trial results:
A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group 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	2018-002303-33
Trial protocol	EE DE BE GB HU NL DK SE AT GR BG FI ES CZ HR FR PT SK IT RO
Global end of trial date	28 September 2020
Results information	
Result version number	v1 (current)
This version publication date	10 October 2021
First version publication date	10 October 2021

Trial information

Trial identification	
Sponsor protocol code	EP0092
Additional study identifiers	
ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03739840
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	16 November 2020
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	28 September 2020
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The primary objective was to evaluate the efficacy of the 3 selected dose regimens of padsevonil (PSL) administered concomitantly with up to 3 anti-epileptic drugs (AEDs) compared with placebo for treatment of observable focal-onset seizures in subjects with drug-resistant epilepsy.

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: -

Actual start date of recruitment	06 March 2019
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	7 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Japan: 23
Country: Number of subjects enrolled	Australia: 5
Country: Number of subjects enrolled	Bosnia and Herzegovina: 10
Country: Number of subjects enrolled	Bulgaria: 26
Country: Number of subjects enrolled	Croatia: 8
Country: Number of subjects enrolled	Czechia: 7
Country: Number of subjects enrolled	Denmark: 14
Country: Number of subjects enrolled	Estonia: 8
Country: Number of subjects enrolled	Finland: 3
Country: Number of subjects enrolled	France: 2
Country: Number of subjects enrolled	Germany: 9
Country: Number of subjects enrolled	Greece: 5
Country: Number of subjects enrolled	Hungary: 2
Country: Number of subjects enrolled	Ireland: 4
Country: Number of subjects enrolled	Italy: 2
Country: Number of subjects enrolled	Norway: 1
Country: Number of subjects enrolled	Poland: 19
Country: Number of subjects enrolled	Portugal: 1

Country: Number of subjects enrolled	Romania: 5
Country: Number of subjects enrolled	Serbia: 4
Country: Number of subjects enrolled	Spain: 16
Country: Number of subjects enrolled	Sweden: 4
Country: Number of subjects enrolled	Turkey: 17
Country: Number of subjects enrolled	United Kingdom: 5
Country: Number of subjects enrolled	United States: 29
Country: Number of subjects enrolled	Belgium: 3
Worldwide total number of subjects	232
EEA total number of subjects	139

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)	218
From 65 to 84 years	14
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study started to enroll participants in March 2019 and concluded in September 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. The 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	Subject, Investigator, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Participants randomized to the placebo group received 5-6 placebo tablets to maintain the blinding, twice daily (bid) up to Week 19.

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 100 mg BID

Arm description:

Participants were randomized to receive a combination of tablets of padsevonil 100 mg and placebo (as appropriate) to maintain the blinding, bid up to Week 19.

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 200 mg BID

Arm description:

Participants were randomized to receive a combination of tablets of padsevonil 200 mg and placebo (as

appropriate) to maintain the blinding, bid up to Week 19.

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 400 mg BID

Arm description:

Participants were randomized to receive a combination of tablets of padsevonil 400 mg and placebo (as appropriate) to maintain the blinding, bid up to Week 19

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 100 mg BID	Padsevonil 200 mg BID
Started	56	60	57
Completed Titration and Stabilization	54	58	51
Completed Maintenance Period	46	44	44
Completed	46	44	44
Not completed	10	16	13
Study Early Closure	-	-	1
Due To Sponsor Instruction	-	-	-
Trial Closed By Sponsor	-	1	-
Study Has Been Cancelled By The Sponsor	-	-	-
Program Termination	3	-	1
Consent Withdrawn	1	3	1
Promotor Decision	-	1	-
Premature Closure Of The Study	-	-	1
Sponsor Closed Study- Subject Was Discontinued	1	-	-
Trial Was Closed By Sponsor	-	-	-
Adverse event, non-fatal	2	6	6
Premature Program Termination	-	1	-

Premature Study Termination By Sponsor	-	-	1
Per Sponsor Study Closed	-	1	-
Sponsors Decision	3	2	1
Lack of efficacy	-	1	-
Protocol deviation	-	-	1

Number of subjects in period 1	Padsevonil 400 mg BID
Started	59
Completed Titration and Stabilization	54
Completed Maintenance Period	36
Completed	36
Not completed	23
Study Early Closure	-
Due To Sponsor Instruction	1
Trial Closed By Sponsor	-
Study Has Been Cancelled By The Sponsor	1
Program Termination	1
Consent Withdrawn	1
Promotor Decision	-
Premature Closure Of The Study	-
Sponsor Closed Study- Subject Was Discontinued	-
Trial Was Closed By Sponsor	1
Adverse event, non-fatal	12
Premature Program Termination	-
Premature Study Termination By Sponsor	-
Per Sponsor Study Closed	-
Sponsors Decision	3
Lack of efficacy	3
Protocol deviation	-

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	Subject, Investigator, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Participants randomized to the placebo group received 5-6 placebo tablets to maintain the blinding, bid up to Week 19.

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 100 mg BID

Arm description:

Participants were randomized to receive a combination of tablets of padsevonil 100 mg and placebo (as appropriate) to maintain the blinding, bid up to Week 19.

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 200 mg BID

Arm description:

Participants were randomized to receive a combination of tablets of padsevonil 200 mg and placebo (as appropriate) to maintain the blinding, bid up to Week 19.

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 400 mg BID

Arm description:

Participants were randomized to receive a combination of tablets of padsevonil 400 mg and placebo (as appropriate) to maintain the blinding, bid up to Week 19

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 100 mg BID	Padsevonil 200 mg BID
Started	46	44	44
Started Conversion Period	33 [1]	31 [2]	29 [3]
Completed Conversion Period	33 [4]	31 [5]	29 [6]
Started Taper and Safety Follow-up	19 [7]	18 [8]	21 [9]
Completed Taper and Safety Follow-up	15 [10]	16 [11]	18 [12]
Enrolled in EP0093	27 [13]	26 [14]	23 [15]
Completed	42	42	41
Not completed	4	2	3
Sponsor's Decision	-	1	-
Sponsor Closed Study- Subject Was Discontinued	-	1	-
Trial Closed By Sponsor Decision	-	-	1
Adverse event, non-fatal	3	-	-
Sponsor Decision + Subject Refusal	-	-	1
Early Study Closure	-	-	1
Sponsor Decision To Terminate The Study	1	-	-
Consent Withdrawn	-	-	-

Number of subjects in period 2	Padsevonil 400 mg BID
Started	36
Started Conversion Period	28 [16]
Completed Conversion Period	28 [17]
Started Taper and Safety Follow-up	13 [18]
Completed Taper and Safety Follow-up	12 [19]
Enrolled in EP0093	23 [20]
Completed	35
Not completed	1
Sponsor's Decision	-
Sponsor Closed Study- Subject Was Discontinued	-
Trial Closed By Sponsor Decision	-

Adverse event, non-fatal	-
Sponsor Decision + Subject Refusal	-
Early Study Closure	-
Sponsor Decision To Terminate The Study	-
Consent Withdrawn	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 100 mg BID 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 200 mg BID 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 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.
[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 100 mg BID 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.
[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 200 mg BID 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 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.

[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 Padsevonil 100 mg BID 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 200 mg BID 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 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.
[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 Padsevonil 100 mg BID 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 200 mg BID 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 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.
[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 Padsevonil 100 mg BID 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 200 mg BID 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 400 mg BID 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 400 mg BID 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 400 mg BID 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 400 mg BID 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 400 mg BID 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 5-6 placebo tablets to maintain the blinding, twice daily (bid) up to Week 19.	
Reporting group title	Padsevonil 100 mg BID
Reporting group description:	
Participants were randomized to receive a combination of tablets of padsevonil 100 mg and placebo (as appropriate) to maintain the blinding, bid up to Week 19.	
Reporting group title	Padsevonil 200 mg BID
Reporting group description:	
Participants were randomized to receive a combination of tablets of padsevonil 200 mg and placebo (as appropriate) to maintain the blinding, bid up to Week 19.	
Reporting group title	Padsevonil 400 mg BID
Reporting group description:	
Participants were randomized to receive a combination of tablets of padsevonil 400 mg and placebo (as appropriate) to maintain the blinding, bid up to Week 19	

Reporting group values	Placebo	Padsevonil 100 mg BID	Padsevonil 200 mg BID
Number of subjects	56	60	57
Age Categorical Units: Participants			
<=18 years	1	0	4
Between 18 and 65 years	52	57	48
>=65 years	3	3	5
Age Continuous Units: years			
arithmetic mean	41.9	40.7	39.5
standard deviation	± 13.6	± 13.0	± 14.3
Sex: Female, Male Units: Participants			
Female	34	34	29
Male	22	26	28
Race/Ethnicity, Customized Units: Subjects			
American Indian or Alaska Native	1	0	0
Asian	5	5	7
Black	0	1	1
Native Hawaiian or Other Pacific Islander	0	2	0
White	49	50	49
Other/mixed	1	2	0

Reporting group values	Padsevonil 400 mg BID	Total	
Number of subjects	59	232	

Age Categorical Units: Participants			
<=18 years	0	5	
Between 18 and 65 years	56	213	
>=65 years	3	14	
Age Continuous Units: years			
arithmetic mean	39.7		
standard deviation	± 13.6	-	
Sex: Female, Male Units: Participants			
Female	34	131	
Male	25	101	
Race/Ethnicity, Customized Units: Subjects			
American Indian or Alaska Native	0	1	
Asian	7	24	
Black	1	3	
Native Hawaiian or Other Pacific Islander	0	2	
White	51	199	
Other/mixed	0	3	

End points reporting groups

Reporting group title	Placebo
Reporting group description:	
Participants randomized to the placebo group received 5-6 placebo tablets to maintain the blinding, twice daily (bid) up to Week 19.	
Reporting group title	Padsevonil 100 mg BID
Reporting group description:	
Participants were randomized to receive a combination of tablets of padsevonil 100 mg and placebo (as appropriate) to maintain the blinding, bid up to Week 19.	
Reporting group title	Padsevonil 200 mg BID
Reporting group description:	
Participants were randomized to receive a combination of tablets of padsevonil 200 mg and placebo (as appropriate) to maintain the blinding, bid up to Week 19.	
Reporting group title	Padsevonil 400 mg BID
Reporting group description:	
Participants were randomized to receive a combination of tablets of padsevonil 400 mg and placebo (as appropriate) to maintain the blinding, bid up to Week 19	
Reporting group title	Placebo
Reporting group description:	
Participants randomized to the placebo group received 5-6 placebo tablets to maintain the blinding, bid up to Week 19.	
Reporting group title	Padsevonil 100 mg BID
Reporting group description:	
Participants were randomized to receive a combination of tablets of padsevonil 100 mg and placebo (as appropriate) to maintain the blinding, bid up to Week 19.	
Reporting group title	Padsevonil 200 mg BID
Reporting group description:	
Participants were randomized to receive a combination of tablets of padsevonil 200 mg and placebo (as appropriate) to maintain the blinding, bid up to Week 19.	
Reporting group title	Padsevonil 400 mg BID
Reporting group description:	
Participants were randomized to receive a combination of tablets of padsevonil 400 mg and placebo (as appropriate) to maintain the blinding, bid up to Week 19	
Subject analysis set title	Placebo (FAS)
Subject analysis set type	Full analysis
Subject analysis set description:	
Participants randomized to the placebo group received 5-6 placebo tablets to maintain the blinding, bid up to Week 19. Participants formed the Full Analysis Set (FAS).	
Subject analysis set title	Padsevonil 100 mg BID (FAS)
Subject analysis set type	Full analysis
Subject analysis set description:	
Participants were randomized to receive a combination of tablets of padsevonil 100 mg and placebo (as appropriate) to maintain the blinding, bid up to Week 19. Participants formed the FAS.	
Subject analysis set title	Padsevonil 200 mg BID (FAS)
Subject analysis set type	Full analysis
Subject analysis set description:	
Participants were randomized to receive a combination of tablets of padsevonil 200 mg and placebo (as appropriate) to maintain the blinding, bid up to Week 19. Participants formed the FAS.	
Subject analysis set title	Padsevonil 400 mg BID (FAS)
Subject analysis set type	Full analysis
Subject analysis set description:	
Participants were randomized to receive a combination of tablets of padsevonil 400 mg and placebo (as	

appropriate) to maintain the blinding, bid up to Week 19. Participants formed the FAS.

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

Subject analysis set description:

Participants randomized to the placebo group received 5-6 placebo tablets to maintain the blinding, bid up to Week 19. Participants formed the Safety Set (SS).

Subject analysis set title	Padsevonil 100 mg BID (SS)
Subject analysis set type	Safety analysis

Subject analysis set description:

Participants were randomized to receive a combination of tablets of padsevonil 100 mg and placebo (as appropriate) to maintain the blinding, bid up to Week 19. Participants formed the SS.

Subject analysis set title	Padsevonil 200 mg BID (SS)
Subject analysis set type	Safety analysis

Subject analysis set description:

Participants were randomized to receive a combination of tablets of padsevonil 200 mg and placebo (as appropriate) to maintain the blinding, bid up to Week 19. Participants formed the SS.

Subject analysis set title	Padsevonil 400 mg BID (SS)
Subject analysis set type	Safety analysis

Subject analysis set description:

Participants were randomized to receive a combination of tablets of padsevonil 400 mg and placebo (as appropriate) to maintain the blinding, bid up to Week 19. Participants formed the SS.

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

Subject analysis set description:

Participants randomized to the placebo group received 5-6 placebo tablets to maintain the blinding, bid up to Week 19. Participants formed the Safety Set (SS).

Subject analysis set title	Padsevonil 100 mg BID Treatment Period (SS)
Subject analysis set type	Safety analysis

Subject analysis set description:

Participants were randomized to receive a combination of tablets of padsevonil 100 mg and placebo (as appropriate) to maintain the blinding, bid up to Week 19. Participants formed the SS.

Subject analysis set title	Padsevonil 200 mg BID Treatment Period (SS)
Subject analysis set type	Safety analysis

Subject analysis set description:

Participants were randomized to receive a combination of tablets of padsevonil 200 mg and placebo (as appropriate) to maintain the blinding, bid up to Week 19. Participants formed the SS.

Subject analysis set title	Padsevonil 400 mg BID Treatment Period (SS)
Subject analysis set type	Safety analysis

Subject analysis set description:

Participants were randomized to receive a combination of tablets of padsevonil 400 mg and placebo (as appropriate) to maintain the blinding, bid up to Week 19. 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 open-label extension (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 of 400 mg/day for the OLE. Participants formed the Safety Set (SS).

Subject analysis set title	Padsevonil 100 mg BID 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 100 mg bid was gradually adapted (increased or decreased) in a blinded way to reach the entry dose of 400 mg/day for the OLE. Participants formed the SS.

Subject analysis set title	Padsevonil 200 mg BID 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 200 mg bid was gradually adapted (increased or decreased) in a blinded way to reach the entry dose of 400 mg/day for the OLE. Participants formed the SS.

Subject analysis set title	Padsevonil 400 mg BID 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 400 mg bid was gradually adapted (increased or decreased) in a blinded way to reach the entry dose of 400 mg/day 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 discontinued before the end of the 12-Week Maintenance Period. Participants initially randomized to the placebo group received 5-6 placebo tablets to maintain the blinding and have been gradually tapered off the IMP over a 3-Week period followed by 1-week drug-free period. Afterward, 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 100mg BID 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 discontinued before the end of the 12-Week Maintenance Period. Participants initially randomized to padsevonil 100 mg bid have been gradually tapered off the IMP over a 3-Week period followed by 1-week drug-free period. Afterward, participants had a Safety Follow-Up visit 30 days after the last IMP intake. Participants formed the SS.

Subject analysis set title	Padsevonil 200mg BID 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 discontinued before the end of the 12-Week Maintenance Period. Participants initially randomized to padsevonil 200 mg bid have been gradually tapered off the IMP over a 3-Week period followed by 1-week drug-free period. Afterward, participants had a Safety Follow-Up visit 30 days after the last IMP intake. Participants formed the SS.

Subject analysis set title	Padsevonil 400mg BID 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 discontinued before the end of the 12-Week Maintenance Period. Participants initially randomized to padsevonil 200 mg bid have been gradually tapered off the IMP over a 3-Week period followed by 1-week drug-free period. Afterward, participants had a Safety Follow-Up visit 30 days after the last IMP intake. Participants formed the SS.

Primary: 75% responder rate from Baseline over the 12-week Maintenance Period

End point title	75% responder rate from Baseline over the 12-week Maintenance Period

End point description:

The 75 % responder rate, where a responder was 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. Here, number of participants were included who were evaluable for the assessment.

End point type	Primary

End point timeframe:

From Baseline over the 12 Week Maintenance Period (up to Week 16)

End point values	Placebo (FAS)	Padsevonil 100 mg BID (FAS)	Padsevonil 200 mg BID (FAS)	Padsevonil 400 mg BID (FAS)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	54	59	56	56
Units: percentage of participants				
number (not applicable)	13.0	15.3	12.5	14.3

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 (Yes, No) and log-transformed Baseline seizure frequency as a continuous covariate.

Comparison groups	Placebo (FAS) v Padsevonil 100 mg BID (FAS)
Number of subjects included in analysis	113
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.803 [1]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.15
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.39
upper limit	3.38

Notes:

[1] - 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 (Yes, No) and log-transformed Baseline seizure frequency as a continuous covariate.

Comparison groups	Placebo (FAS) v Padsevonil 200 mg BID (FAS)
Number of subjects included in analysis	110
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.772 [2]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.84

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.27
upper limit	2.65

Notes:

[2] - 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 (Yes, No) and log-transformed Baseline seizure frequency as a continuous covariate.

Comparison groups	Placebo (FAS) v Padsevonil 400 mg BID (FAS)
Number of subjects included in analysis	110
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.989 [3]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.01
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.33
upper limit	3.08

Notes:

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

Primary: Percentage of Participants With Treatment-Emergent Adverse Events (TEAEs)

End point title	Percentage of Participants With Treatment-Emergent Adverse Events (TEAEs)[4]

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. A TEAE was defined as any event not present before the initiation of the first dose of study treatment or any unresolved event already present before initiation of the first dose that worsened in intensity following exposure to the 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:

[4] - 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 100 mg BID (SS)	Padsevonil 200 mg BID (SS)	Padsevonil 400 mg BID (SS)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	55	60	57	59
Units: percentage of participants				
number (not applicable)	69.1	83.3	78.9	84.7

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of Participants With Treatment-Emergent Adverse Events (TEAEs) leading to study withdrawal

End point title	Percentage of Participants With Treatment-Emergent Adverse Events (TEAEs) leading to study withdrawal[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. A TEAE was defined as any event not present before the initiation of the first dose of study treatment or any unresolved event already present before initiation of the first dose that worsened in intensity following exposure to the 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 100 mg BID (SS)	Padsevonil 200 mg BID (SS)	Padsevonil 400 mg BID (SS)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	55	60	57	59
Units: percentage of participants				
number (not applicable)	7.3	10.0	10.5	20.3

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of Participants With Treatment-Emergent Serious Adverse Events (SAEs)

End point title	Percentage of Participants With Treatment-Emergent Serious Adverse Events (SAEs)[6]

End point description:

A Serious Adverse Event (SAE) is any untoward medical occurrence that at any dose: Results in death, is life-threatening, requires inpatient hospitalization or prolongation of existing hospitalization, is a congenital anomaly or birth defect, is as 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. A TEAE was defined as any

event not present before the initiation of the first dose of study treatment or any unresolved event already present before initiation of the first dose that worsened in intensity following exposure to the 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 100 mg BID (SS)	Padsevonil 200 mg BID (SS)	Padsevonil 400 mg BID (SS)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	55	60	57	59
Units: percentage of participants				
number (not applicable)	9.1	3.3	1.8	10.2

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 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. Here, number of participants were included who were evaluable for the assessment.

End point type	Secondary

End point timeframe:

From Baseline over the 12 Week Maintenance Period (up to Week 16)

End point values	Placebo (FAS)	Padsevonil 100 mg BID (FAS)	Padsevonil 200 mg BID (FAS)	Padsevonil 400 mg BID (FAS)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	54	59	56	56
Units: log e seizures per 28 days				
least squares mean (confidence interval 95%)	-0.41 (-0.6133 to -0.2025)	-0.35 (-0.54906 to -0.15705)	-0.47 (-0.67559 to -0.27382)	-0.47 (-0.67267 to -0.27361)

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	Placebo (FAS) v Padsevonil 100 mg BID (FAS)
Number of subjects included in analysis	113
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.687 [7]
Method	ANCOVA
Parameter estimate	Percent reduction
Point estimate	-5.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-38.1
upper limit	19.2

Notes:

[7] - Adjusted p-values are 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	Placebo (FAS) v Padsevonil 400 mg BID (FAS)
Number of subjects included in analysis	110
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.687 [8]
Method	ANCOVA
Parameter estimate	Percent reduction
Point estimate	6.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-22.9
upper limit	28.6

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	Placebo (FAS) v Padsevonil 200 mg BID (FAS)
Number of subjects included in analysis	110
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.687 [9]
Method	ANCOVA
Parameter estimate	Percent reduction
Point estimate	6.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-22.7
upper limit	28.7

Notes:

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

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) were 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. Here, number of participants were included who were evaluable for the assessment.

End point type	Secondary

End point timeframe:

From Baseline over the 12 Week Maintenance Period (up to Week 16)

End point values	Placebo (FAS)	Padsevonil 100 mg BID (FAS)	Padsevonil 200 mg BID (FAS)	Padsevonil 400 mg BID (FAS)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	54	59	56	56
Units: percent change				
arithmetic mean (standard deviation)	22.34 (± 44.56)	11.72 (± 81.52)	30.29 (± 39.58)	22.41 (± 62.80)

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

Dose group comparisons to Placebo p-value are based on the Wilcoxon-Mann-Whitney test. Hodges Lehmann nonparametric effect estimates and corresponding two-sided 95% asymptotic confidence intervals are provided for the effect difference between each PSL dose and placebo.

Comparison groups	Placebo (FAS) v Padsevonil 100 mg BID (FAS)

Number of subjects included in analysis	113
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.737 [10]
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Median difference (final values)
Point estimate	3.25
Confidence interval	
level	95 %
sides	2-sided
lower limit	-17.08
upper limit	20.36

Notes:

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

Statistical analysis title	Statistical analysis 3

Statistical analysis description:

Dose group comparisons to Placebo p-value are based on the Wilcoxon-Mann-Whitney test. Hodges Lehmann nonparametric effect estimates and corresponding two-sided 95% asymptotic confidence intervals are provided for the effect difference between each PSL dose and placebo.

Comparison groups	Placebo (FAS) v Padsevonil 400 mg BID (FAS)
Number of subjects included in analysis	110
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.341 [11]
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Median difference (net)
Point estimate	9.31
Confidence interval	
level	95 %
sides	2-sided
lower limit	-10.92
upper limit	28.21

Notes:

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

Statistical analysis title	Statistical analysis 2

Statistical analysis description:

Dose group comparisons to Placebo p-value are based on the Wilcoxon-Mann-Whitney test. Hodges Lehmann nonparametric effect estimates and corresponding two-sided 95% asymptotic confidence intervals are provided for the effect difference between each PSL dose and placebo.

Comparison groups	Placebo (FAS) v Padsevonil 200 mg BID (FAS)
Number of subjects included in analysis	110
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.458 [12]
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Median difference (net)
Point estimate	6.17

Confidence interval	
level	95 %
sides	2-sided
lower limit	-10
upper limit	21.91

Notes:

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

Secondary: 50% responder rate from Baseline over the 12-week Maintenance Period

End point title	50% responder rate from Baseline 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. Here, number of participants were included who were evaluable for the assessment.

End point type	Secondary

End point timeframe:

From Baseline over the 12 Week Maintenance Period (up to Week 16)

End point values	Placebo (FAS)	Padsevonil 100 mg BID (FAS)	Padsevonil 200 mg BID (FAS)	Padsevonil 400 mg BID (FAS)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	54	59	56	56
Units: percentage of participants				
number (not applicable)	27.8	35.6	33.9	42.9

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 (Yes, No) and log-transformed Baseline seizure frequency as a continuous covariate.

Comparison groups	Placebo (FAS) v Padsevonil 100 mg BID (FAS)
Number of subjects included in analysis	113
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.425 [13]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.4

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.61
upper limit	3.18

Notes:

[13] - 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 (Yes, No) and log-transformed Baseline seizure frequency as a continuous covariate

Comparison groups	Placebo (FAS) v Padsevonil 200 mg BID (FAS)
Number of subjects included in analysis	110
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.625 [14]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.23
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.53
upper limit	2.85

Notes:

[14] - 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 (Yes, No) and log-transformed Baseline seizure frequency as a continuous covariate

Comparison groups	Placebo (FAS) v Padsevonil 400 mg BID (FAS)
Number of subjects included in analysis	110
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.125 [15]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.84
upper limit	4.34

Notes:

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

Adverse events information

Timeframe for reporting adverse events:

TEAEs were collected from Baseline until Safety Follow-Up (up to Week 23)

Adverse event reporting additional description:

TEAEs counts are for the number of study participants who entered the respective study period regardless of whether or not they completed the previous period. This is the reason for the difference in number of participants in Taper and SFU period in adverse events section and participant flow.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	22.1

Reporting groups

Reporting group title	Padsevonil 100 mg BID Treatment Period (SS)

Reporting group description:

Participants were randomized to receive a combination of tablets of padsevonil 100 mg and placebo (as appropriate) to maintain the blinding, bid up to Week 19. Participants formed the SS.

Reporting group title	Placebo Treatment Period (SS)

Reporting group description:

Participants randomized to the placebo group received 5-6 placebo tablets to maintain the blinding, bid up to Week 19. Participants formed the Safety Set (SS).

Reporting group title	Padsevonil 200 mg BID Treatment Period (SS)

Reporting group description:

Participants were randomized to receive a combination of tablets of padsevonil 200 mg and placebo (as appropriate) to maintain the blinding, bid up to Week 19. 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 open-label extension (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 of 400 mg/day for the OLE. Participants formed the Safety Set (SS).

Reporting group title	Padsevonil 400 mg BID Treatment Period (SS)

Reporting group description:

Participants were randomized to receive a combination of tablets of padsevonil 400 mg and placebo (as appropriate) to maintain the blinding, bid up to Week 19. Participants formed the SS.

Reporting group title	Padsevonil 100 mg BID 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 100 mg bid was gradually adapted (increased or decreased) in a blinded way to reach the entry dose of 400 mg/day for the OLE. Participants formed the SS.

Reporting group title	Padsevonil 200 mg BID 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 200 mg bid was gradually adapted (increased or decreased) in a blinded way to reach the entry dose of 400 mg/day for the OLE. Participants formed the SS.

Reporting group title	Padsevonil 400 mg BID 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 400 mg bid was gradually adapted (increased or decreased) in a blinded way to reach the entry dose of 400 mg/day 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 group received 5-6 placebo tablets to maintain the blinding and 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 100 mg BID 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 100 mg bid 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 200 mg BID 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 200 mg bid 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 400 mg BID 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 400 mg bid 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	Padsevonil 100 mg BID Treatment Period (SS)	Placebo Treatment Period (SS)	Padsevonil 200 mg BID Treatment Period (SS)
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 60 (0.00%)	3 / 55 (5.45%)	1 / 57 (1.75%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			
Injury, poisoning and procedural complications			
Radius fracture			
subjects affected / exposed	0 / 60 (0.00%)	0 / 55 (0.00%)	0 / 57 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin laceration			
subjects affected / exposed	0 / 60 (0.00%)	1 / 55 (1.82%)	0 / 57 (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
Subdural haematoma			

subjects affected / exposed	0 / 60 (0.00%)	1 / 55 (1.82%)	0 / 57 (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
Wrist fracture			
subjects affected / exposed	0 / 60 (0.00%)	0 / 55 (0.00%)	0 / 57 (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
Contusion			
subjects affected / exposed	0 / 60 (0.00%)	0 / 55 (0.00%)	0 / 57 (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
Humerus fracture			
subjects affected / exposed	0 / 60 (0.00%)	0 / 55 (0.00%)	0 / 57 (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
Rib fracture			
subjects affected / exposed	0 / 60 (0.00%)	0 / 55 (0.00%)	0 / 57 (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			
Abortion induced			
subjects affected / exposed	0 / 60 (0.00%)	1 / 55 (1.82%)	0 / 57 (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			
Epilepsy			
subjects affected / exposed	0 / 60 (0.00%)	0 / 55 (0.00%)	1 / 57 (1.75%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Focal dyscognitive seizures			
subjects affected / exposed	0 / 60 (0.00%)	1 / 55 (1.82%)	0 / 57 (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			

subjects affected / exposed	0 / 60 (0.00%)	0 / 55 (0.00%)	0 / 57 (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 / 60 (0.00%)	0 / 55 (0.00%)	0 / 57 (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			
Pneumothorax			
subjects affected / exposed	0 / 60 (0.00%)	0 / 55 (0.00%)	0 / 57 (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			
Aggression			
subjects affected / exposed	0 / 60 (0.00%)	0 / 55 (0.00%)	0 / 57 (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
Emotional disorder			
subjects affected / exposed	0 / 60 (0.00%)	0 / 55 (0.00%)	0 / 57 (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
Suicidal ideation			
subjects affected / exposed	0 / 60 (0.00%)	0 / 55 (0.00%)	0 / 57 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Muscular weakness			
subjects affected / exposed	0 / 60 (0.00%)	0 / 55 (0.00%)	0 / 57 (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			
Hyponatraemia			

subjects affected / exposed	0 / 60 (0.00%)	0 / 55 (0.00%)	0 / 57 (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 400 mg BID Treatment Period (SS)	Padsevonil 100 mg BID Conversion Period (SS)
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 33 (3.03%)	5 / 59 (8.47%)	0 / 31 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			
Injury, poisoning and procedural complications			
Radius fracture			
subjects affected / exposed	0 / 33 (0.00%)	1 / 59 (1.69%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin laceration			
subjects affected / exposed	0 / 33 (0.00%)	0 / 59 (0.00%)	0 / 31 (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
Subdural haematoma			
subjects affected / exposed	0 / 33 (0.00%)	0 / 59 (0.00%)	0 / 31 (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
Wrist fracture			
subjects affected / exposed	0 / 33 (0.00%)	1 / 59 (1.69%)	0 / 31 (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
Contusion			
subjects affected / exposed	1 / 33 (3.03%)	0 / 59 (0.00%)	0 / 31 (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
Humerus fracture			

subjects affected / exposed	1 / 33 (3.03%)	0 / 59 (0.00%)	0 / 31 (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
Rib fracture			
subjects affected / exposed	1 / 33 (3.03%)	0 / 59 (0.00%)	0 / 31 (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
Surgical and medical procedures			
Abortion induced			
subjects affected / exposed	0 / 33 (0.00%)	0 / 59 (0.00%)	0 / 31 (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			
Epilepsy			
subjects affected / exposed	0 / 33 (0.00%)	1 / 59 (1.69%)	0 / 31 (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 / 33 (0.00%)	0 / 59 (0.00%)	0 / 31 (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			
subjects affected / exposed	0 / 33 (0.00%)	0 / 59 (0.00%)	0 / 31 (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 / 33 (0.00%)	0 / 59 (0.00%)	0 / 31 (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			
Pneumothorax			
subjects affected / exposed	0 / 33 (0.00%)	0 / 59 (0.00%)	0 / 31 (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			
Aggression			
subjects affected / exposed	0 / 33 (0.00%)	1 / 59 (1.69%)	0 / 31 (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
Emotional disorder			
subjects affected / exposed	0 / 33 (0.00%)	0 / 59 (0.00%)	0 / 31 (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
Suicidal ideation			
subjects affected / exposed	0 / 33 (0.00%)	0 / 59 (0.00%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Muscular weakness			
subjects affected / exposed	0 / 33 (0.00%)	1 / 59 (1.69%)	0 / 31 (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
Metabolism and nutrition disorders			
Hyponatraemia			
subjects affected / exposed	0 / 33 (0.00%)	1 / 59 (1.69%)	0 / 31 (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

Serious adverse events	Padsevonil 200 mg BID Conversion Period (SS)	Padsevonil 400 mg BID Conversion Period (SS)	Placebo Taper and SFU Period (SS)
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 29 (0.00%)	0 / 28 (0.00%)	1 / 27 (3.70%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			
Injury, poisoning and procedural complications			
Radius fracture			
subjects affected / exposed	0 / 29 (0.00%)	0 / 28 (0.00%)	0 / 27 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Skin laceration			
subjects affected / exposed	0 / 29 (0.00%)	0 / 28 (0.00%)	0 / 27 (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
Subdural haematoma			
subjects affected / exposed	0 / 29 (0.00%)	0 / 28 (0.00%)	0 / 27 (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
Wrist fracture			
subjects affected / exposed	0 / 29 (0.00%)	0 / 28 (0.00%)	0 / 27 (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
Contusion			
subjects affected / exposed	0 / 29 (0.00%)	0 / 28 (0.00%)	0 / 27 (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
Humerus fracture			
subjects affected / exposed	0 / 29 (0.00%)	0 / 28 (0.00%)	0 / 27 (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
Rib fracture			
subjects affected / exposed	0 / 29 (0.00%)	0 / 28 (0.00%)	0 / 27 (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			
Abortion induced			
subjects affected / exposed	0 / 29 (0.00%)	0 / 28 (0.00%)	0 / 27 (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			
Epilepsy			
subjects affected / exposed	0 / 29 (0.00%)	0 / 28 (0.00%)	0 / 27 (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 / 29 (0.00%)	0 / 28 (0.00%)	0 / 27 (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			
subjects affected / exposed	0 / 29 (0.00%)	0 / 28 (0.00%)	0 / 27 (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 / 29 (0.00%)	0 / 28 (0.00%)	0 / 27 (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			
Pneumothorax			
subjects affected / exposed	0 / 29 (0.00%)	0 / 28 (0.00%)	0 / 27 (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			
Aggression			
subjects affected / exposed	0 / 29 (0.00%)	0 / 28 (0.00%)	0 / 27 (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
Emotional disorder			
subjects affected / exposed	0 / 29 (0.00%)	0 / 28 (0.00%)	1 / 27 (3.70%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Suicidal ideation			
subjects affected / exposed	0 / 29 (0.00%)	0 / 28 (0.00%)	1 / 27 (3.70%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Muscular weakness			

subjects affected / exposed	0 / 29 (0.00%)	0 / 28 (0.00%)	0 / 27 (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			
Hyponatraemia			
subjects affected / exposed	0 / 29 (0.00%)	0 / 28 (0.00%)	0 / 27 (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 100 mg BID Taper and SFU Period (SS)	Padsevonil 200 mg BID Taper and SFU Period (SS)	Padsevonil 400 mg BID Taper and SFU Period (SS)
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 30 (6.67%)	0 / 31 (0.00%)	1 / 32 (3.13%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			
Injury, poisoning and procedural complications			
Radius fracture			
subjects affected / exposed	0 / 30 (0.00%)	0 / 31 (0.00%)	0 / 32 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin laceration			
subjects affected / exposed	0 / 30 (0.00%)	0 / 31 (0.00%)	0 / 32 (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
Subdural haematoma			
subjects affected / exposed	0 / 30 (0.00%)	0 / 31 (0.00%)	0 / 32 (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
Wrist fracture			
subjects affected / exposed	0 / 30 (0.00%)	0 / 31 (0.00%)	0 / 32 (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
Contusion			

subjects affected / exposed	0 / 30 (0.00%)	0 / 31 (0.00%)	0 / 32 (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
Humerus fracture			
subjects affected / exposed	0 / 30 (0.00%)	0 / 31 (0.00%)	0 / 32 (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
Rib fracture			
subjects affected / exposed	0 / 30 (0.00%)	0 / 31 (0.00%)	0 / 32 (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			
Abortion induced			
subjects affected / exposed	0 / 30 (0.00%)	0 / 31 (0.00%)	0 / 32 (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			
Epilepsy			
subjects affected / exposed	0 / 30 (0.00%)	0 / 31 (0.00%)	0 / 32 (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 / 30 (0.00%)	0 / 31 (0.00%)	0 / 32 (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			
subjects affected / exposed	1 / 30 (3.33%)	0 / 31 (0.00%)	0 / 32 (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	0 / 30 (0.00%)	0 / 31 (0.00%)	1 / 32 (3.13%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal			

disorders			
Pneumothorax			
subjects affected / exposed	1 / 30 (3.33%)	0 / 31 (0.00%)	0 / 32 (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
Psychiatric disorders			
Aggression			
subjects affected / exposed	0 / 30 (0.00%)	0 / 31 (0.00%)	0 / 32 (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
Emotional disorder			
subjects affected / exposed	0 / 30 (0.00%)	0 / 31 (0.00%)	0 / 32 (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
Suicidal ideation			
subjects affected / exposed	0 / 30 (0.00%)	0 / 31 (0.00%)	0 / 32 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Muscular weakness			
subjects affected / exposed	0 / 30 (0.00%)	0 / 31 (0.00%)	0 / 32 (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			
Hyponatraemia			
subjects affected / exposed	0 / 30 (0.00%)	0 / 31 (0.00%)	0 / 32 (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	Padsevonil 100 mg BID Treatment Period (SS)	Placebo Treatment Period (SS)	Padsevonil 200 mg BID Treatment Period (SS)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	37 / 60 (61.67%)	25 / 55 (45.45%)	40 / 57 (70.18%)

Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	0 / 60 (0.00%)	0 / 55 (0.00%)	3 / 57 (5.26%)
occurrences (all)	0	0	4
Contusion			
subjects affected / exposed	1 / 60 (1.67%)	3 / 55 (5.45%)	2 / 57 (3.51%)
occurrences (all)	1	4	2
Vascular disorders			
Hypotension			
subjects affected / exposed	1 / 60 (1.67%)	0 / 55 (0.00%)	0 / 57 (0.00%)
occurrences (all)	1	0	0
Nervous system disorders			
Somnolence			
subjects affected / exposed	10 / 60 (16.67%)	2 / 55 (3.64%)	19 / 57 (33.33%)
occurrences (all)	11	2	22
Dizziness			
subjects affected / exposed	14 / 60 (23.33%)	4 / 55 (7.27%)	10 / 57 (17.54%)
occurrences (all)	14	5	13
Headache			
subjects affected / exposed	10 / 60 (16.67%)	8 / 55 (14.55%)	9 / 57 (15.79%)
occurrences (all)	22	13	16
Memory impairment			
subjects affected / exposed	0 / 60 (0.00%)	1 / 55 (1.82%)	3 / 57 (5.26%)
occurrences (all)	0	1	3
Tremor			
subjects affected / exposed	3 / 60 (5.00%)	1 / 55 (1.82%)	0 / 57 (0.00%)
occurrences (all)	5	1	0
Disturbance in attention			
subjects affected / exposed	1 / 60 (1.67%)	1 / 55 (1.82%)	5 / 57 (8.77%)
occurrences (all)	1	1	5
Balance disorder			
subjects affected / exposed	1 / 60 (1.67%)	0 / 55 (0.00%)	3 / 57 (5.26%)
occurrences (all)	1	0	3
Dysarthria			
subjects affected / exposed	0 / 60 (0.00%)	1 / 55 (1.82%)	0 / 57 (0.00%)
occurrences (all)	0	1	0

Seizure			
subjects affected / exposed	0 / 60 (0.00%)	1 / 55 (1.82%)	4 / 57 (7.02%)
occurrences (all)	0	1	5
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	5 / 60 (8.33%)	4 / 55 (7.27%)	7 / 57 (12.28%)
occurrences (all)	5	4	7
Asthenia			
subjects affected / exposed	6 / 60 (10.00%)	2 / 55 (3.64%)	3 / 57 (5.26%)
occurrences (all)	6	2	4
Gait disturbance			
subjects affected / exposed	2 / 60 (3.33%)	0 / 55 (0.00%)	2 / 57 (3.51%)
occurrences (all)	2	0	3
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	1 / 60 (1.67%)	3 / 55 (5.45%)	3 / 57 (5.26%)
occurrences (all)	1	5	4
Diarrhoea			
subjects affected / exposed	1 / 60 (1.67%)	3 / 55 (5.45%)	0 / 57 (0.00%)
occurrences (all)	1	4	0
Psychiatric disorders			
Insomnia			
subjects affected / exposed	1 / 60 (1.67%)	0 / 55 (0.00%)	5 / 57 (8.77%)
occurrences (all)	1	0	6
Irritability			
subjects affected / exposed	4 / 60 (6.67%)	3 / 55 (5.45%)	3 / 57 (5.26%)
occurrences (all)	4	3	3
Anxiety			
subjects affected / exposed	0 / 60 (0.00%)	1 / 55 (1.82%)	1 / 57 (1.75%)
occurrences (all)	0	1	2
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	1 / 60 (1.67%)	4 / 55 (7.27%)	4 / 57 (7.02%)
occurrences (all)	1	4	4
Metabolism and nutrition disorders			

Decreased appetite			
subjects affected / exposed	0 / 60 (0.00%)	1 / 55 (1.82%)	3 / 57 (5.26%)
occurrences (all)	0	1	3

Non-serious adverse events	Placebo Conversion Period (SS)	Padsevonil 400 mg BID Treatment Period (SS)	Padsevonil 100 mg BID Conversion Period (SS)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	7 / 33 (21.21%)	41 / 59 (69.49%)	0 / 31 (0.00%)
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	0 / 33 (0.00%)	2 / 59 (3.39%)	0 / 31 (0.00%)
occurrences (all)	0	2	0
Contusion			
subjects affected / exposed	1 / 33 (3.03%)	1 / 59 (1.69%)	0 / 31 (0.00%)
occurrences (all)	1	1	0
Vascular disorders			
Hypotension			
subjects affected / exposed	2 / 33 (6.06%)	0 / 59 (0.00%)	0 / 31 (0.00%)
occurrences (all)	2	0	0
Nervous system disorders			
Somnolence			
subjects affected / exposed	1 / 33 (3.03%)	20 / 59 (33.90%)	0 / 31 (0.00%)
occurrences (all)	1	23	0
Dizziness			
subjects affected / exposed	0 / 33 (0.00%)	18 / 59 (30.51%)	0 / 31 (0.00%)
occurrences (all)	0	19	0
Headache			
subjects affected / exposed	0 / 33 (0.00%)	5 / 59 (8.47%)	0 / 31 (0.00%)
occurrences (all)	0	8	0
Memory impairment			
subjects affected / exposed	0 / 33 (0.00%)	6 / 59 (10.17%)	0 / 31 (0.00%)
occurrences (all)	0	6	0
Tremor			
subjects affected / exposed	0 / 33 (0.00%)	4 / 59 (6.78%)	0 / 31 (0.00%)
occurrences (all)	0	4	0
Disturbance in attention			

subjects affected / exposed	0 / 33 (0.00%)	2 / 59 (3.39%)	0 / 31 (0.00%)
occurrences (all)	0	2	0
Balance disorder			
subjects affected / exposed	0 / 33 (0.00%)	2 / 59 (3.39%)	0 / 31 (0.00%)
occurrences (all)	0	2	0
Dysarthria			
subjects affected / exposed	0 / 33 (0.00%)	5 / 59 (8.47%)	0 / 31 (0.00%)
occurrences (all)	0	5	0
Seizure			
subjects affected / exposed	0 / 33 (0.00%)	0 / 59 (0.00%)	0 / 31 (0.00%)
occurrences (all)	0	0	0
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	1 / 33 (3.03%)	14 / 59 (23.73%)	0 / 31 (0.00%)
occurrences (all)	1	15	0
Asthenia			
subjects affected / exposed	0 / 33 (0.00%)	2 / 59 (3.39%)	0 / 31 (0.00%)
occurrences (all)	0	2	0
Gait disturbance			
subjects affected / exposed	0 / 33 (0.00%)	4 / 59 (6.78%)	0 / 31 (0.00%)
occurrences (all)	0	4	0
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	0 / 33 (0.00%)	1 / 59 (1.69%)	0 / 31 (0.00%)
occurrences (all)	0	1	0
Diarrhoea			
subjects affected / exposed	0 / 33 (0.00%)	2 / 59 (3.39%)	0 / 31 (0.00%)
occurrences (all)	0	2	0
Psychiatric disorders			
Insomnia			
subjects affected / exposed	0 / 33 (0.00%)	4 / 59 (6.78%)	0 / 31 (0.00%)
occurrences (all)	0	4	0
Irritability			
subjects affected / exposed	1 / 33 (3.03%)	3 / 59 (5.08%)	0 / 31 (0.00%)
occurrences (all)	1	3	0
Anxiety			

subjects affected / exposed	0 / 33 (0.00%)	3 / 59 (5.08%)	0 / 31 (0.00%)
occurrences (all)	0	3	0
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	1 / 33 (3.03%)	1 / 59 (1.69%)	0 / 31 (0.00%)
occurrences (all)	1	1	0
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	0 / 33 (0.00%)	1 / 59 (1.69%)	0 / 31 (0.00%)
occurrences (all)	0	1	0

Non-serious adverse events	Padsevonil 200 mg BID Conversion Period (SS)	Padsevonil 400 mg BID Conversion Period (SS)	Placebo Taper and SFU Period (SS)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	1 / 29 (3.45%)	1 / 28 (3.57%)	2 / 27 (7.41%)
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	1 / 29 (3.45%)	0 / 28 (0.00%)	1 / 27 (3.70%)
occurrences (all)	1	0	1
Contusion			
subjects affected / exposed	1 / 29 (3.45%)	0 / 28 (0.00%)	0 / 27 (0.00%)
occurrences (all)	1	0	0
Vascular disorders			
Hypotension			
subjects affected / exposed	0 / 29 (0.00%)	0 / 28 (0.00%)	0 / 27 (0.00%)
occurrences (all)	0	0	0
Nervous system disorders			
Somnolence			
subjects affected / exposed	0 / 29 (0.00%)	0 / 28 (0.00%)	0 / 27 (0.00%)
occurrences (all)	0	0	0
Dizziness			
subjects affected / exposed	0 / 29 (0.00%)	0 / 28 (0.00%)	1 / 27 (3.70%)
occurrences (all)	0	0	1
Headache			
subjects affected / exposed	0 / 29 (0.00%)	0 / 28 (0.00%)	0 / 27 (0.00%)
occurrences (all)	0	0	0
Memory impairment			

subjects affected / exposed	0 / 29 (0.00%)	0 / 28 (0.00%)	0 / 27 (0.00%)
occurrences (all)	0	0	0
Tremor			
subjects affected / exposed	0 / 29 (0.00%)	1 / 28 (3.57%)	0 / 27 (0.00%)
occurrences (all)	0	1	0
Disturbance in attention			
subjects affected / exposed	0 / 29 (0.00%)	0 / 28 (0.00%)	0 / 27 (0.00%)
occurrences (all)	0	0	0
Balance disorder			
subjects affected / exposed	0 / 29 (0.00%)	0 / 28 (0.00%)	0 / 27 (0.00%)
occurrences (all)	0	0	0
Dysarthria			
subjects affected / exposed	0 / 29 (0.00%)	0 / 28 (0.00%)	0 / 27 (0.00%)
occurrences (all)	0	0	0
Seizure			
subjects affected / exposed	0 / 29 (0.00%)	0 / 28 (0.00%)	0 / 27 (0.00%)
occurrences (all)	0	0	0
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	0 / 29 (0.00%)	0 / 28 (0.00%)	0 / 27 (0.00%)
occurrences (all)	0	0	0
Asthenia			
subjects affected / exposed	0 / 29 (0.00%)	0 / 28 (0.00%)	0 / 27 (0.00%)
occurrences (all)	0	0	0
Gait disturbance			
subjects affected / exposed	0 / 29 (0.00%)	0 / 28 (0.00%)	0 / 27 (0.00%)
occurrences (all)	0	0	0
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	0 / 29 (0.00%)	0 / 28 (0.00%)	0 / 27 (0.00%)
occurrences (all)	0	0	0
Diarrhoea			
subjects affected / exposed	0 / 29 (0.00%)	0 / 28 (0.00%)	0 / 27 (0.00%)
occurrences (all)	0	0	0
Psychiatric disorders			

Insomnia			
subjects affected / exposed	0 / 29 (0.00%)	0 / 28 (0.00%)	0 / 27 (0.00%)
occurrences (all)	0	0	0
Irritability			
subjects affected / exposed	0 / 29 (0.00%)	0 / 28 (0.00%)	0 / 27 (0.00%)
occurrences (all)	0	0	0
Anxiety			
subjects affected / exposed	0 / 29 (0.00%)	0 / 28 (0.00%)	0 / 27 (0.00%)
occurrences (all)	0	0	0
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	0 / 29 (0.00%)	0 / 28 (0.00%)	0 / 27 (0.00%)
occurrences (all)	0	0	0
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	0 / 29 (0.00%)	0 / 28 (0.00%)	0 / 27 (0.00%)
occurrences (all)	0	0	0

Non-serious adverse events	Padsevonil 100 mg BID Taper and SFU Period (SS)	Padsevonil 200 mg BID Taper and SFU Period (SS)	Padsevonil 400 mg BID Taper and SFU Period (SS)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	6 / 30 (20.00%)	4 / 31 (12.90%)	2 / 32 (6.25%)
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	0 / 30 (0.00%)	1 / 31 (3.23%)	1 / 32 (3.13%)
occurrences (all)	0	1	1
Contusion			
subjects affected / exposed	1 / 30 (3.33%)	0 / 31 (0.00%)	0 / 32 (0.00%)
occurrences (all)	1	0	0
Vascular disorders			
Hypotension			
subjects affected / exposed	0 / 30 (0.00%)	0 / 31 (0.00%)	0 / 32 (0.00%)
occurrences (all)	0	0	0
Nervous system disorders			
Somnolence			
subjects affected / exposed	1 / 30 (3.33%)	0 / 31 (0.00%)	0 / 32 (0.00%)
occurrences (all)	1	0	0
Dizziness			

subjects affected / exposed	0 / 30 (0.00%)	0 / 31 (0.00%)	0 / 32 (0.00%)
occurrences (all)	0	0	0
Headache			
subjects affected / exposed	4 / 30 (13.33%)	2 / 31 (6.45%)	1 / 32 (3.13%)
occurrences (all)	12	2	1
Memory impairment			
subjects affected / exposed	0 / 30 (0.00%)	0 / 31 (0.00%)	0 / 32 (0.00%)
occurrences (all)	0	0	0
Tremor			
subjects affected / exposed	0 / 30 (0.00%)	0 / 31 (0.00%)	0 / 32 (0.00%)
occurrences (all)	0	0	0
Disturbance in attention			
subjects affected / exposed	0 / 30 (0.00%)	0 / 31 (0.00%)	0 / 32 (0.00%)
occurrences (all)	0	0	0
Balance disorder			
subjects affected / exposed	0 / 30 (0.00%)	1 / 31 (3.23%)	0 / 32 (0.00%)
occurrences (all)	0	1	0
Dysarthria			
subjects affected / exposed	0 / 30 (0.00%)	0 / 31 (0.00%)	0 / 32 (0.00%)
occurrences (all)	0	0	0
Seizure			
subjects affected / exposed	0 / 30 (0.00%)	0 / 31 (0.00%)	0 / 32 (0.00%)
occurrences (all)	0	0	0
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	0 / 30 (0.00%)	0 / 31 (0.00%)	0 / 32 (0.00%)
occurrences (all)	0	0	0
Asthenia			
subjects affected / exposed	0 / 30 (0.00%)	1 / 31 (3.23%)	0 / 32 (0.00%)
occurrences (all)	0	1	0
Gait disturbance			
subjects affected / exposed	0 / 30 (0.00%)	0 / 31 (0.00%)	0 / 32 (0.00%)
occurrences (all)	0	0	0
Gastrointestinal disorders			

Nausea			
subjects affected / exposed	0 / 30 (0.00%)	0 / 31 (0.00%)	0 / 32 (0.00%)
occurrences (all)	0	0	0
Diarrhoea			
subjects affected / exposed	0 / 30 (0.00%)	0 / 31 (0.00%)	0 / 32 (0.00%)
occurrences (all)	0	0	0
Psychiatric disorders			
Insomnia			
subjects affected / exposed	0 / 30 (0.00%)	0 / 31 (0.00%)	0 / 32 (0.00%)
occurrences (all)	0	0	0
Irritability			
subjects affected / exposed	0 / 30 (0.00%)	0 / 31 (0.00%)	0 / 32 (0.00%)
occurrences (all)	0	0	0
Anxiety			
subjects affected / exposed	0 / 30 (0.00%)	0 / 31 (0.00%)	0 / 32 (0.00%)
occurrences (all)	0	0	0
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	0 / 30 (0.00%)	0 / 31 (0.00%)	0 / 32 (0.00%)
occurrences (all)	0	0	0
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	0 / 30 (0.00%)	0 / 31 (0.00%)	0 / 32 (0.00%)
occurrences (all)	0	0	0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
21 January 2020	Protocol Amendment 1 was dated 21 Jan 2020; at the time, 143 study participants had received IMP. The primary rationale for the global amendment was to update the name of the legal form of the Sponsor, UCB Biopharma. At the time, Belgium had adopted a new Code of Companies and Associations, resulting in a mandatory change of the name of the legal form of the entity “société privée à responsabilité limitée”, abbreviated “SPRL”, to “société à responsabilité limitée”, abbreviated “SRL”. In addition, the following changes were introduced: • A summary of the known and expected risks and benefits of PSL was included. • The changes introduced by the local Protocol Amendment 0.1 for China were incorporated: - The percentage of Chinese study participants planned to be randomized in the study increased from 10% to 20% in response to a request by the Chinese Center for Drug Evaluation. - It was specified that the exploratory PK analysis would not be done in Chinese study participants. - The blood volumes required for hematology and chemistry were revised to meet the requirements of the central laboratory. • The changes introduced by the local Protocol Amendment 0.2 for Switzerland were incorporated: - The following language regarding expedited reporting of SAEs was added to meet a request by Swissmedic: “Expedited reporting to regulatory authorities will be in line with local laws”.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported