Clinical trial results:
A Multicenter, Double-Blind, Randomized, Placebo-Controlled, Dose-Response Trial of YKP3089 as Adjunctive Therapy in Subjects with Partial Onset Seizures, with Optional Open-Label Extension

Summary

EudraCT number	2013-001858-10
Trial protocol	ES DE CZ GB HU PL BG
Global end of trial date	05 April 2021

Results information

Result version number	v1 (current)
This version publication date	21 April 2022
First version publication date	21 April 2022

Trial information

Trial identification

Sponsor protocol code	YKP3089C017

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01866111
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	SK Life Science, Inc.
Sponsor organisation address	461 From Road, Paramus, United States, NJ 07652
Public contact	Laurie Orlinski, SK Life Science, Inc., 1 201-421-3816, lorlinski@sklsi.com
Scientific contact	Marc Kamin, SK Life Science, Inc., 1 201-421-3830, mkamin@sklsi.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	31 October 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	05 April 2021
Global end of trial reached?	Yes
Global end of trial date	05 April 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study was to determine the effective dose range of YKP3089 as adjunctive therapy for the treatment of partial seizures. The study also evaluated the safety and tolerability of YKP3089 in the partial epilepsy population.

Protection of trial subjects:

This study was conducted according to United States and international standards of Good Clinical Practice (GCP; FDA Title 21 parts 50 and 312 and ICH guidelines), applicable government regulations, and institutional research policies and procedures. Written consent of a subject, using the IEC/IRB-approved consent form, was obtained before the subject underwent any study procedure. All subjects were given adequate time to ask questions and were provided with a signed copy of the consent for his/her records. The consenting process was clearly documented in the subject’s chart. The investigator was responsible for ensuring that valid consent was obtained and documented for all subjects.

Background therapy:

The subjects received standard of treatment. They must have been taken 1 to 3 concomitant AEDs at a stable dose for at least 12 weeks before Randomization. They continued these prescribed AED regimens throughout the double-blind phase of the study. During the open-label extension phase of the study, the Investigators were allowed to change the dosage of concomitant AEDs but the subject couldn't be treated with YKP3089 monotherapy. Intermittent benzodiazepines (other than diaszepam) were allowed as rescue medication once during the baseline period, twice during the treatment phase, and intermittently in the open-label extension.

Evidence for comparator:

This was a placebo-controlled study and placebo was considered as comparator.

Actual start date of recruitment	30 July 2013
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Poland: 48
Country: Number of subjects enrolled	Spain: 27
Country: Number of subjects enrolled	United Kingdom: 8
Country: Number of subjects enrolled	Bulgaria: 37
Country: Number of subjects enrolled	Czechia: 24
Country: Number of subjects enrolled	France: 4
Country: Number of subjects enrolled	Germany: 33
Country: Number of subjects enrolled	Hungary: 15
Country: Number of subjects enrolled	Korea, Republic of: 31
Country: Number of subjects enrolled	Romania: 4

Country: Number of subjects enrolled	Serbia: 28
Country: Number of subjects enrolled	Thailand: 8
Country: Number of subjects enrolled	Ukraine: 23
Country: Number of subjects enrolled	United States: 111
Country: Number of subjects enrolled	Australia: 24
Country: Number of subjects enrolled	Israel: 12
Worldwide total number of subjects	437
EEA total number of subjects	192

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)	427
From 65 to 84 years	10
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

437 patients were randomly assigned in a 1:1:1:1 ratio to placebo or YKP3089 at 100 mg/day, 200 mg/day, or 400 mg/day. Qualifying subjects entered a 6-week titration phase. According to the original protocol all subjects began with a daily dose of 100 mg, followed by weekly increments of 100 mg in the daily dose, to the target dose.

Pre-assignment

Screening details:

At screening, each subject or their legally authorized representative signed an informed consent form (ICF). Assessments were performed to determine a subject's eligibility for the study. Subjects who met all inclusion criteria and none of the exclusion criteria were assigned to one of the treatment arms or placebo.

Period 1

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

Blinding implementation details:

This was a double-blind study. Treatment assignments remained blinded to the subject and all study personnel until the database lock of the double-blind treatment period. Selected individuals from the sponsor and/or designee could be unblinded to the study treatments on a need-to-know basis, if they felt it was medically necessary and that knowledge of the treatment assignment was essential for the patient's care.

Arms

Are arms mutually exclusive?	Yes
Arm title	YKP3089 (100 mg qd)

Arm description:

100 mg YKP3089 was administrated daily during 18-week double-blind treatment period (including a 6-week titration phase and 12-week maintenance phase), followed by a 3-week blinded study drug taper period (for subjects leaving the study) or a 2-week blinded conversion period (for subjects participating in the open-label extension), with a final follow-up visit 2 weeks after the last dose of study drug.

Arm type	Experimental
Investigational medicinal product name	YKP3089 100 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

100 mg were administrated once daily. Subjects were supplied with YKP3089 50 mg and 100 mg tablets to be taken orally in the morning. Study drug could have been taken with or without food.

Arm title	YKP3089 (200 mg qd)

Arm description:

200 mg YKP3089 was administrated daily during 18-week double-blind treatment period (including a 6-week titration phase and 12-week maintenance phase), followed by a 3-week blinded study drug taper period (for subjects leaving the study) or a 2-week blinded conversion period (for subjects participating in the open-label extension), with a final follow-up visit 2 weeks after the last dose of study drug.

Arm type	Experimental

Investigational medicinal product name	YKP3089 200 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

200 mg were administrated once daily. Subjects were supplied with YKP3089 50 mg and 100 mg tablets to be taken orally in the morning. Study drug could have been taken with or without food.

Arm title	YKP3089 (400 mg qd)

Arm description:

400 mg YKP3089 was administrated daily during 18-week double-blind treatment period (including a 6-week titration phase and 12-week maintenance phase), followed by a 3-week blinded study drug taper period (for subjects leaving the study) or a 2-week blinded conversion period (for subjects participating in the open-label extension), with a final follow-up visit 2 weeks after the last dose of study drug.

Arm type	Experimental
Investigational medicinal product name	YKP3089 400 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

400 mg were administrated once daily. Subjects were supplied with YKP3089 50 mg and 100 mg tablets to be taken orally in the morning. Study drug could have been taken with or without food.

Arm title	Placebo

Arm description:

Placebo was administrated daily during 18-week double-blind treatment period (including a 6-week titration phase and 12-week maintenance phase), followed by a 3-week blinded study drug taper period (for subjects leaving the study) or a 2-week blinded conversion period (for subjects participating in the open-label extension), with a final follow-up visit 2 weeks after the last dose of study drug.

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

Dosage and administration details:

Placebo were administrated once daily. Subjects were supplied with Placebo, identical in appearance to the study drug, to be taken orally in the morning. Placebo could have been taken with or without food.

Number of subjects in period 1	YKP3089 (100 mg qd)	YKP3089 (200 mg qd)	YKP3089 (400 mg qd)
Started	108	110	111
Completed	95	90	81
Not completed	13	20	30
Consent withdrawn by subject	-	4	3
Other	-	-	1
Pregnancy	-	-	-
Adverse event	12	15	23
Lost to follow-up	-	-	1

Lack of efficacy	1	-	1
Protocol deviation	-	1	1

Number of subjects in period 1	Placebo
Started	108
Completed	94
Not completed	14
Consent withdrawn by subject	5
Other	3
Pregnancy	1
Adverse event	5
Lost to follow-up	-
Lack of efficacy	-
Protocol deviation	-

Period 2

Period 2 title	Open-Label Extension Phase
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Blinding implementation details:

A total of 356 subjects entered the open-label extension phase from the double-blind treatment period.

Arms

Are arms mutually exclusive?	Yes
Arm title	DB YKP3089 100 mg to YKP3089 OLE

Arm description:

95 subjects from YKP3089 100 mg/day group entered the open-label extension phase from the double-blind treatment period.

Arm type	Experimental
Investigational medicinal product name	YKP3089
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects were supplied with YKP3089 50 mg and 100 mg tablets to be taken orally in the morning. Study drug could have been taken with or without food.
The initial target dose for the open-label extension phase was 300 mg/day. However, if a subject was not able to tolerate the 300 mg/day dose, YKP3089 dose was reduced to a minimum of 50 mg/day. If the investigator felt that a subject required a dose that was higher than 300 mg/day, the dose was increased to a maximum of 400 mg/day once the target dose of 300 mg/day was reached. If 50 mg/day of YKP3089 was not tolerated, the subject was withdrawn from the study. The dose adjustments occurred in weekly increments of 100 mg/day or 50 mg/day.

Arm title	DB YKP3089 200 mg to YKP3089 OLE

Arm description:

90 subjects from YKP3089 200 mg/day group entered the open-label extension phase from the double-blind treatment period.

Arm type	Experimental
Investigational medicinal product name	YKP3089
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects were supplied with YKP3089 50 mg and 100 mg tablets to be taken orally in the morning. Study drug could have been taken with or without food.
The initial target dose for the open-label extension phase was 300 mg/day. However, if a subject was not able to tolerate the 300 mg/day dose, YKP3089 dose was reduced to a minimum of 50 mg/day. If the investigator felt that a subject required a dose that was higher than 300 mg/day, the dose was increased to a maximum of 400 mg/day once the target dose of 300 mg/day was reached. If 50 mg/day of YKP3089 was not tolerated, the subject was withdrawn from the study. The dose adjustments occurred in weekly increments of 100 mg/day or 50 mg/day.

Arm title	DB YKP3089 400 mg to YKP3089 OLE

Arm description:

80 subjects from YKP3089 400 mg/day group entered the open-label extension phase from the double-blind treatment period.

Arm type	Experimental
Investigational medicinal product name	YKP3089
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects were supplied with YKP3089 50 mg and 100 mg tablets to be taken orally in the morning. Study drug could have been taken with or without food.
The initial target dose for the open-label extension phase was 300 mg/day. However, if a subject was not able to tolerate the 300 mg/day dose, YKP3089 dose was reduced to a minimum of 50 mg/day. If the investigator felt that a subject required a dose that was higher than 300 mg/day, the dose was increased to a maximum of 400 mg/day once the target dose of 300 mg/day was reached. If 50 mg/day of YKP3089 was not tolerated, the subject was withdrawn from the study. The dose adjustments occurred in weekly increments of 100 mg/day or 50 mg/day.

Arm title	Placebo DB to YKP3089 OLE

Arm description:

91 subjects from Placebo group entered the open-label extension phase from the double-blind treatment period.

Arm type	Experimental
Investigational medicinal product name	YKP3089
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects were supplied with YKP3089 50 mg and 100 mg tablets to be taken orally in the morning. Study drug could have been taken with or without food.
The initial target dose for the open-label extension phase was 300 mg/day. However, if a subject was not able to tolerate the 300 mg/day dose, YKP3089 dose was reduced to a minimum of 50 mg/day. If the investigator felt that a subject required a dose that was higher than 300 mg/day, the dose was increased to a maximum of 400 mg/day once the target dose of 300 mg/day was reached. If 50 mg/day of YKP3089 was not tolerated, the subject was withdrawn from the study. The dose adjustments occurred in weekly increments of 100 mg/day or 50 mg/day.

Number of subjects in period 2[1]	DB YKP3089 100 mg to YKP3089 OLE	DB YKP3089 200 mg to YKP3089 OLE	DB YKP3089 400 mg to YKP3089 OLE
Started	95	90	80
Completed	21	19	14
Not completed	74	71	66
Consent withdrawn by subject	7	9	3
Death	1	3	2
Other	3	1	3
Adverse event	6	6	7
Lost to follow-up	1	1	3
Entered EAP/Navigator	39	28	32
Lack of efficacy	17	23	14
Protocol deviation	-	-	2

Number of subjects in period 2[1]	Placebo DB to YKP3089 OLE
Started	91
Completed	16
Not completed	75
Consent withdrawn by subject	16
Death	1
Other	3
Adverse event	9
Lost to follow-up	2
Entered EAP/Navigator	30
Lack of efficacy	13
Protocol deviation	1

Notes:

[1] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.
Justification: 356 of 360 subjects entered open-label extension period; 4 subjects have an answer of 'No' to the question 'if subject going to OLE' without more details.

Baseline characteristics

Reporting groups	
Reporting group title	YKP3089 (100 mg qd)
Reporting group description:	
100 mg YKP3089 was administrated daily during 18-week double-blind treatment period (including a 6-week titration phase and 12-week maintenance phase), followed by a 3-week blinded study drug taper period (for subjects leaving the study) or a 2-week blinded conversion period (for subjects participating in the open-label extension), with a final follow-up visit 2 weeks after the last dose of study drug.	
Reporting group title	YKP3089 (200 mg qd)
Reporting group description:	
200 mg YKP3089 was administrated daily during 18-week double-blind treatment period (including a 6-week titration phase and 12-week maintenance phase), followed by a 3-week blinded study drug taper period (for subjects leaving the study) or a 2-week blinded conversion period (for subjects participating in the open-label extension), with a final follow-up visit 2 weeks after the last dose of study drug.	
Reporting group title	YKP3089 (400 mg qd)
Reporting group description:	
400 mg YKP3089 was administrated daily during 18-week double-blind treatment period (including a 6-week titration phase and 12-week maintenance phase), followed by a 3-week blinded study drug taper period (for subjects leaving the study) or a 2-week blinded conversion period (for subjects participating in the open-label extension), with a final follow-up visit 2 weeks after the last dose of study drug.	
Reporting group title	Placebo
Reporting group description:	
Placebo was administrated daily during 18-week double-blind treatment period (including a 6-week titration phase and 12-week maintenance phase), followed by a 3-week blinded study drug taper period (for subjects leaving the study) or a 2-week blinded conversion period (for subjects participating in the open-label extension), with a final follow-up visit 2 weeks after the last dose of study drug.	

Reporting group values	YKP3089 (100 mg qd)	YKP3089 (200 mg qd)	YKP3089 (400 mg qd)
Number of subjects	108	110	111
Age categorical Units: Subjects			
Adults (18-64 years)	106	107	110
From 65-84 years	2	3	1
Age continuous Units: years			
median	37.5	40.5	38.0
full range (min-max)	19 to 66	19 to 69	21 to 66
Gender categorical Units: Subjects			
Female	51	56	59
Male	57	54	52

Reporting group values	Placebo	Total	
Number of subjects	108	437	
Age categorical Units: Subjects			
Adults (18-64 years)	104	427	
From 65-84 years	4	10	

Age continuous Units: years median full range (min-max)	 38.0 19 to 70	 -	
Gender categorical Units: Subjects			
Female	50	216	
Male	58	221	

Subject analysis sets	
Subject analysis set title	ITT population
Subject analysis set type	Intention-to-treat
Subject analysis set description: The ITT population included all randomized subjects.	
Subject analysis set title	MITT population
Subject analysis set type	Modified intention-to-treat
Subject analysis set description: MITT population includes all randomized subjects with at least 1 dose of YKP3089 or placebo and had any postbaseline seizure data.	
Subject analysis set title	MITT-M population
Subject analysis set type	Sub-group analysis
Subject analysis set description: MITT-M population includes all randomized subjects who completed the titration phase, took at least 1 dose of YKP3089 or placebo in the maintenance phase, and had any maintenance phase seizure data.	
Subject analysis set title	PP population
Subject analysis set type	Per protocol
Subject analysis set description: PP population includes all randomized subjects with no major protocol deviations, and had at least 80% compliance with study.	
Subject analysis set title	SE population
Subject analysis set type	Safety analysis
Subject analysis set description: The Safety Evaluable (SE) population was the same as the ITT population.	
Subject analysis set title	OLE-EA population
Subject analysis set type	Sub-group analysis
Subject analysis set description: OLE-EA population includes all subjects who entered in open-label extension phase, took at least one dose of open-label study medication, and had any seizure data recorded in open-label extension seizure diary.	

Reporting group values	ITT population	MITT population	MITT-M population
Number of subjects	437	434	397
Age categorical Units: Subjects			
Adults (18-64 years)	427		
From 65-84 years	10		
Age continuous Units: years median full range (min-max)	 38.0 19 to 70	 	

Gender categorical Units: Subjects			
Female	216		
Male	221		

Reporting group values	PP population	SE population	OLE-EA population
Number of subjects	398	437	355
Age categorical Units: Subjects			
Adults (18-64 years)		427	
From 65-84 years		10	
Age continuous Units: years			
median		38.0	
full range (min-max)		19 to 70	
Gender categorical Units: Subjects			
Female		216	
Male		221	

End points

End points reporting groups

Reporting group title	YKP3089 (100 mg qd)
Reporting group description:	
100 mg YKP3089 was administrated daily during 18-week double-blind treatment period (including a 6-week titration phase and 12-week maintenance phase), followed by a 3-week blinded study drug taper period (for subjects leaving the study) or a 2-week blinded conversion period (for subjects participating in the open-label extension), with a final follow-up visit 2 weeks after the last dose of study drug.	
Reporting group title	YKP3089 (200 mg qd)
Reporting group description:	
200 mg YKP3089 was administrated daily during 18-week double-blind treatment period (including a 6-week titration phase and 12-week maintenance phase), followed by a 3-week blinded study drug taper period (for subjects leaving the study) or a 2-week blinded conversion period (for subjects participating in the open-label extension), with a final follow-up visit 2 weeks after the last dose of study drug.	
Reporting group title	YKP3089 (400 mg qd)
Reporting group description:	
400 mg YKP3089 was administrated daily during 18-week double-blind treatment period (including a 6-week titration phase and 12-week maintenance phase), followed by a 3-week blinded study drug taper period (for subjects leaving the study) or a 2-week blinded conversion period (for subjects participating in the open-label extension), with a final follow-up visit 2 weeks after the last dose of study drug.	
Reporting group title	Placebo
Reporting group description:	
Placebo was administrated daily during 18-week double-blind treatment period (including a 6-week titration phase and 12-week maintenance phase), followed by a 3-week blinded study drug taper period (for subjects leaving the study) or a 2-week blinded conversion period (for subjects participating in the open-label extension), with a final follow-up visit 2 weeks after the last dose of study drug.	
Reporting group title	DB YKP3089 100 mg to YKP3089 OLE
Reporting group description:	
95 subjects from YKP3089 100 mg/day group entered the open-label extension phase from the double-blind treatment period.	
Reporting group title	DB YKP3089 200 mg to YKP3089 OLE
Reporting group description:	
90 subjects from YKP3089 200 mg/day group entered the open-label extension phase from the double-blind treatment period.	
Reporting group title	DB YKP3089 400 mg to YKP3089 OLE
Reporting group description:	
80 subjects from YKP3089 400 mg/day group entered the open-label extension phase from the double-blind treatment period.	
Reporting group title	Placebo DB to YKP3089 OLE
Reporting group description:	
91 subjects from Placebo group entered the open-label extension phase from the double-blind treatment period.	
Subject analysis set title	ITT population
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
The ITT population included all randomized subjects.	
Subject analysis set title	MITT population
Subject analysis set type	Modified intention-to-treat
Subject analysis set description:	
MITT population includes all randomized subjects with at least 1 dose of YKP3089 or placebo and had any postbaseline seizure data.	
Subject analysis set title	MITT-M population
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
MITT-M population includes all randomized subjects who completed the titration phase, took at least 1	

dose of YKP3089 or placebo in the maintenance phase, and had any maintenance phase seizure data.

Subject analysis set title	PP population
Subject analysis set type	Per protocol

Subject analysis set description:

PP population includes all randomized subjects with no major protocol deviations, and had at least 80% compliance with study.

Subject analysis set title	SE population
Subject analysis set type	Safety analysis

Subject analysis set description:

The Safety Evaluable (SE) population was the same as the ITT population.

Subject analysis set title	OLE-EA population
Subject analysis set type	Sub-group analysis

Subject analysis set description:

OLE-EA population includes all subjects who entered in open-label extension phase, took at least one dose of open-label study medication, and had any seizure data recorded in open-label extension seizure diary.

Primary: Percentage Change in Seizure Frequency per 28 Days During the Double-Blind Treatment Period for the United States and Rest of the World

End point title	Percentage Change in Seizure Frequency per 28 Days During the Double-Blind Treatment Period for the United States and Rest of the World

End point description:

The primary efficacy endpoint for the United States and the ROW was defined as the percentage change from pretreatment baseline period in seizure frequency (average monthly seizure rate per 28 days) of Type B, Type C, and Type D seizures during the double-blind treatment period.
The primary efficacy endpoint values below will be based on the MITT population.

End point type	Primary

End point timeframe:

Double-blind treatment period

End point values	YKP3089 (100 mg qd)	YKP3089 (200 mg qd)	YKP3089 (400 mg qd)	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	108	109	111	106
Units: percent				
median (full range (min-max))				
Baseline (n)	9.5 (3.5 to 202)	11 (4 to 418)	9 (4 to 638)	8.4 (4 to 704)
Endpoint (n)	5.8 (0 to 164.6)	5.8 (0 to 373.7)	3.8 (0 to 424.9)	6.8 (0.7 to 640.8)
Change from Baseline (%)	-35.5 (-100 to 206)	-55 (-100 to 191)	-55 (-100 to 167)	-24 (-91 to 198)

Statistical analyses

Statistical analysis title	ANCOVA for Percentage Change in Seizure in DB

Statistical analysis description:

The primary analysis for this primary efficacy endpoint will be based on the MITT population.
The testing strategy for this primary efficacy analysis is to compare each of the YKP3089 dosage groups with the placebo group. Due to multiple treatment comparisons, a step-down procedure will be used to

ensure the overall type I error rate is controlled at the 5% level. The hierarchy for comparisons is YKP3089 200 mg vs placebo, YKP3089 400 mg vs placebo, YKP3089 100 mg vs placebo.

Comparison groups	YKP3089 (100 mg qd) v YKP3089 (200 mg qd) v YKP3089 (400 mg qd) v Placebo
Number of subjects included in analysis	434
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	= 0.007 [2]
Method	ANCOVA

Notes:

[1] - An analysis of covariance (ANCOVA) model will be fit to the ranked values of the primary efficacy endpoint. The ANCOVA will have terms for ranked baseline seizure rate and randomized treatment group. Ties will be handled using TIES=MEAN.
It should be noted that the primary efficacy analysis uses a non-parametric approach. Because of this, effect sizes are not estimated and tested directly, since testing is made on the rank of the primary efficacy value.
[2] - p-value (YKP3089 100 mg qd vs Placebo) = 0.007
p-value (YKP3089 200 mg qd vs Placebo) < 0.001
p-value (YKP3089 400 mg qd vs Placebo) < 0.001

Primary: Responder Rate (at Least 50% Reduction in Seizure Frequency) During the Maintenance Phase for Europe, Australia, New Zealand, and South Africa

End point title	Responder Rate (at Least 50% Reduction in Seizure Frequency) During the Maintenance Phase for Europe, Australia, New Zealand, and South Africa

End point description:

The primary efficacy endpoint for Europe, Australia, New Zealand, and South Africa is the responder rate (responder is defined as a ≥ 50% reduction during the maintenance phase of double-blind treatment period in seizure frequency from baseline period).
The primary efficacy endpoint values below will be based on the MITT-M population.

End point type	Primary

End point timeframe:

During maintenance phase of double-blind treatment period

End point values	YKP3089 (100 mg qd)	YKP3089 (200 mg qd)	YKP3089 (400 mg qd)	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	102	98	95	102
Units: percent				
number (not applicable)				
Responder – Yes (n)	41	55	61	26
Responder – No (n)	61	43	34	76
Responder – Yes (%)	40.2	56.1	64.2	25.5
Responder – No (%)	59.8	43.9	35.8	74.5

Statistical analyses

Statistical analysis title	Fisher Exact Test for Responder Rate in DB

Statistical analysis description:

The primary analysis for this primary efficacy endpoint will be based on the MITT-M population.
The testing strategy for this primary efficacy analysis is to compare each of the YKP3089 dosage groups with the placebo group. Due to multiple treatment comparisons, a step-down procedure will be used to

ensure the overall type I error rate is controlled at the 5% level. The hierarchy for comparisons is YKP3089 200 mg vs placebo, YKP3089 400 mg vs placebo, YKP3089 100 mg vs placebo.

Comparison groups	YKP3089 (100 mg qd) v YKP3089 (200 mg qd) v YKP3089 (400 mg qd) v Placebo
Number of subjects included in analysis	397
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.036 [3]
Method	Fisher exact

Notes:

[3] - p-value (YKP3089 100 mg qd vs Placebo) = 0.036
p-value (YKP3089 200 mg qd vs Placebo) < 0.001
p-value (YKP3089 400 mg qd vs Placebo) < 0.001

Other pre-specified: Percent Change in Seizure Frequency per 28-Day During Open-Label Extension period

End point title	Percent Change in Seizure Frequency per 28-Day During Open-Label Extension period

End point description:

This efficacy endpoint was defined as the percentage change from pretreatment baseline period in seizure frequency (average monthly seizure rate per 28 days) of Type B, Type C, and Type D seizures during the open-label extension phase.
The efficacy endpoint values below will be based on the OLE-EA population.

End point type	Other pre-specified

End point timeframe:

During open-label extension phase

End point values	DB YKP3089 100 mg to YKP3089 OLE	DB YKP3089 200 mg to YKP3089 OLE	DB YKP3089 400 mg to YKP3089 OLE	Placebo DB to YKP3089 OLE
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	95	90	79	91
Units: percent				
median (full range (min-max))				
Percent Change from Baseline	-63.32 (-100.0 to 85.3)	-57.58 (-100.0 to 174.8)	-60.60 (-100.0 to 409.5)	-63.21 (-100.0 to 256.4)

End point values	OLE-EA population			
Subject group type	Subject analysis set			
Number of subjects analysed	355			
Units: percent				
median (full range (min-max))				
Percent Change from Baseline	-61.56 (-100.0 to 409.5)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

During the double-blind treatment period

Adverse event reporting additional description:

The incidence of Treatment-Emergent Adverse Events (TEAEs) was presented in the Safety Evaluable Population (SE population) during the double-blind treatment period. Similar data was observed during Open-Label Extension Phase (OLE-SE Population).

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18.1

Reporting groups

Reporting group title	YKP3089 (100 mg qd)

Reporting group description:

100 mg YKP3089 was administrated daily during 18-week double-blind treatment period (including a 6-week titration phase and 12-week maintenance phase), followed by a 3-week blinded study drug taper period (for subjects leaving the study) or a 2-week blinded conversion period (for subjects participating in the open-label extension), with a final follow-up visit 2 weeks after the last dose of study drug.

Reporting group title	YKP3089 (200 mg qd)

Reporting group description:

200 mg YKP3089 was administrated daily during 18-week double-blind treatment period (including a 6-week titration phase and 12-week maintenance phase), followed by a 3-week blinded study drug taper period (for subjects leaving the study) or a 2-week blinded conversion period (for subjects participating in the open-label extension), with a final follow-up visit 2 weeks after the last dose of study drug.

Reporting group title	YKP3089 (400 mg qd)

Reporting group description:

400 mg YKP3089 was administrated daily during 18-week double-blind treatment period (including a 6-week titration phase and 12-week maintenance phase), followed by a 3-week blinded study drug taper period (for subjects leaving the study) or a 2-week blinded conversion period (for subjects participating in the open-label extension), with a final follow-up visit 2 weeks after the last dose of study drug.

Reporting group title	Placebo

Reporting group description:

Placebo was administrated daily during 18-week double-blind treatment period (including a 6-week titration phase and 12-week maintenance phase), followed by a 3-week blinded study drug taper period (for subjects leaving the study) or a 2-week blinded conversion period (for subjects participating in the open-label extension), with a final follow-up visit 2 weeks after the last dose of study drug.

Serious adverse events	YKP3089 (100 mg qd)	YKP3089 (200 mg qd)	YKP3089 (400 mg qd)
Total subjects affected by serious adverse events			
subjects affected / exposed	10 / 108 (9.26%)	4 / 110 (3.64%)	8 / 111 (7.21%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Investigations			
Alanine aminotransferase increased			

subjects affected / exposed	0 / 108 (0.00%)	0 / 110 (0.00%)	1 / 111 (0.90%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 108 (0.00%)	0 / 110 (0.00%)	1 / 111 (0.90%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immunoglobulins decreased			
subjects affected / exposed	0 / 108 (0.00%)	0 / 110 (0.00%)	1 / 111 (0.90%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Concussion			
subjects affected / exposed	0 / 108 (0.00%)	0 / 110 (0.00%)	0 / 111 (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
Facial bones fracture			
subjects affected / exposed	0 / 108 (0.00%)	0 / 110 (0.00%)	1 / 111 (0.90%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fall			
subjects affected / exposed	0 / 108 (0.00%)	1 / 110 (0.91%)	1 / 111 (0.90%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Femur fracture			
subjects affected / exposed	0 / 108 (0.00%)	1 / 110 (0.91%)	0 / 111 (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
Hand fracture			
subjects affected / exposed	1 / 108 (0.93%)	0 / 110 (0.00%)	0 / 111 (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
Jaw fracture			

subjects affected / exposed	0 / 108 (0.00%)	0 / 110 (0.00%)	0 / 111 (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
Laceration			
subjects affected / exposed	1 / 108 (0.93%)	0 / 110 (0.00%)	0 / 111 (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
Limb injury			
subjects affected / exposed	1 / 108 (0.93%)	0 / 110 (0.00%)	0 / 111 (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
Thermal burn			
subjects affected / exposed	1 / 108 (0.93%)	0 / 110 (0.00%)	0 / 111 (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
Nervous system disorders			
Ataxia			
subjects affected / exposed	0 / 108 (0.00%)	0 / 110 (0.00%)	2 / 111 (1.80%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dizziness			
subjects affected / exposed	0 / 108 (0.00%)	0 / 110 (0.00%)	2 / 111 (1.80%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hemiparesis			
subjects affected / exposed	1 / 108 (0.93%)	0 / 110 (0.00%)	0 / 111 (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
Lethargy			
subjects affected / exposed	1 / 108 (0.93%)	0 / 110 (0.00%)	0 / 111 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nystagmus			

subjects affected / exposed	0 / 108 (0.00%)	0 / 110 (0.00%)	2 / 111 (1.80%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Seizure			
subjects affected / exposed	2 / 108 (1.85%)	1 / 110 (0.91%)	1 / 111 (0.90%)
occurrences causally related to treatment / all	1 / 2	1 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Somnolence			
subjects affected / exposed	0 / 108 (0.00%)	0 / 110 (0.00%)	1 / 111 (0.90%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Status epilepticus			
subjects affected / exposed	0 / 108 (0.00%)	0 / 110 (0.00%)	0 / 111 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	1 / 108 (0.93%)	0 / 110 (0.00%)	0 / 111 (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
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	0 / 108 (0.00%)	0 / 110 (0.00%)	1 / 111 (0.90%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 108 (0.00%)	0 / 110 (0.00%)	0 / 111 (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			
Pulmonary embolism			

subjects affected / exposed	1 / 108 (0.93%)	0 / 110 (0.00%)	0 / 111 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Drug reaction with eosinophilia and systemic symptoms			
subjects affected / exposed	0 / 108 (0.00%)	1 / 110 (0.91%)	0 / 111 (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
Psychiatric disorders			
Suicidal ideation			
subjects affected / exposed	2 / 108 (1.85%)	0 / 110 (0.00%)	0 / 111 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Suicide attempt			
subjects affected / exposed	1 / 108 (0.93%)	0 / 110 (0.00%)	0 / 111 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Abscess jaw			
subjects affected / exposed	0 / 108 (0.00%)	0 / 110 (0.00%)	0 / 111 (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
Infectious colitis			
subjects affected / exposed	0 / 108 (0.00%)	0 / 110 (0.00%)	0 / 111 (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		
Total subjects affected by serious adverse events			
subjects affected / exposed	6 / 108 (5.56%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Investigations			
Alanine aminotransferase increased			

subjects affected / exposed	0 / 108 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Aspartate aminotransferase increased				
subjects affected / exposed	0 / 108 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Immunoglobulins decreased				
subjects affected / exposed	0 / 108 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Injury, poisoning and procedural complications				
Concussion				
subjects affected / exposed	1 / 108 (0.93%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Facial bones fracture				
subjects affected / exposed	0 / 108 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Fall				
subjects affected / exposed	0 / 108 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Femur fracture				
subjects affected / exposed	0 / 108 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hand fracture				
subjects affected / exposed	0 / 108 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Jaw fracture				

subjects affected / exposed	1 / 108 (0.93%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Laceration				
subjects affected / exposed	0 / 108 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Limb injury				
subjects affected / exposed	0 / 108 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Thermal burn				
subjects affected / exposed	0 / 108 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Nervous system disorders				
Ataxia				
subjects affected / exposed	0 / 108 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Dizziness				
subjects affected / exposed	0 / 108 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hemiparesis				
subjects affected / exposed	0 / 108 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Lethargy				
subjects affected / exposed	0 / 108 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Nystagmus				

subjects affected / exposed	0 / 108 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Seizure				
subjects affected / exposed	0 / 108 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Somnolence				
subjects affected / exposed	0 / 108 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Status epilepticus				
subjects affected / exposed	1 / 108 (0.93%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
General disorders and administration site conditions				
Chest pain				
subjects affected / exposed	0 / 108 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Ear and labyrinth disorders				
Vertigo				
subjects affected / exposed	0 / 108 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal disorders				
Gastrooesophageal reflux disease				
subjects affected / exposed	1 / 108 (0.93%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Respiratory, thoracic and mediastinal disorders				
Pulmonary embolism				

subjects affected / exposed	0 / 108 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			
Drug reaction with eosinophilia and systemic symptoms			
subjects affected / exposed	0 / 108 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Suicidal ideation			
subjects affected / exposed	0 / 108 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Suicide attempt			
subjects affected / exposed	0 / 108 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Abscess jaw			
subjects affected / exposed	1 / 108 (0.93%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infectious colitis			
subjects affected / exposed	1 / 108 (0.93%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	YKP3089 (100 mg qd)	YKP3089 (200 mg qd)	YKP3089 (400 mg qd)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	60 / 108 (55.56%)	80 / 110 (72.73%)	92 / 111 (82.88%)
Injury, poisoning and procedural complications			

Fall			
subjects affected / exposed	2 / 108 (1.85%)	3 / 110 (2.73%)	3 / 111 (2.70%)
occurrences (all)	2	3	3
Nervous system disorders			
Somnolence			
subjects affected / exposed	20 / 108 (18.52%)	23 / 110 (20.91%)	40 / 111 (36.04%)
occurrences (all)	20	23	40
Dizziness			
subjects affected / exposed	19 / 108 (17.59%)	22 / 110 (20.00%)	35 / 111 (31.53%)
occurrences (all)	19	22	35
Headache			
subjects affected / exposed	11 / 108 (10.19%)	12 / 110 (10.91%)	12 / 111 (10.81%)
occurrences (all)	11	12	12
Balance disorder			
subjects affected / exposed	3 / 108 (2.78%)	2 / 110 (1.82%)	10 / 111 (9.01%)
occurrences (all)	3	2	10
Nystagmus			
subjects affected / exposed	3 / 108 (2.78%)	4 / 110 (3.64%)	5 / 111 (4.50%)
occurrences (all)	3	4	5
Ataxia			
subjects affected / exposed	2 / 108 (1.85%)	4 / 110 (3.64%)	5 / 111 (4.50%)
occurrences (all)	2	4	5
Dysarthria			
subjects affected / exposed	2 / 108 (1.85%)	3 / 110 (2.73%)	7 / 111 (6.31%)
occurrences (all)	2	3	7
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	13 / 108 (12.04%)	19 / 110 (17.27%)	27 / 111 (24.32%)
occurrences (all)	13	19	27
Gait disturbance			
subjects affected / exposed	1 / 108 (0.93%)	6 / 110 (5.45%)	9 / 111 (8.11%)
occurrences (all)	1	6	9
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	1 / 108 (0.93%)	3 / 110 (2.73%)	5 / 111 (4.50%)
occurrences (all)	1	3	5

Eye disorders			
Diplopia			
subjects affected / exposed	8 / 108 (7.41%)	11 / 110 (10.00%)	17 / 111 (15.32%)
occurrences (all)	8	11	17
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	2 / 108 (1.85%)	3 / 110 (2.73%)	10 / 111 (9.01%)
occurrences (all)	2	3	10
Nausea			
subjects affected / exposed	7 / 108 (6.48%)	1 / 110 (0.91%)	10 / 111 (9.01%)
occurrences (all)	7	1	10
Vomiting			
subjects affected / exposed	2 / 108 (1.85%)	3 / 110 (2.73%)	6 / 111 (5.41%)
occurrences (all)	2	3	6
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	4 / 108 (3.70%)	1 / 110 (0.91%)	6 / 111 (5.41%)
occurrences (all)	4	1	6
Infections and infestations			
Upper respiratory tract infection			
subjects affected / exposed	3 / 108 (2.78%)	4 / 110 (3.64%)	3 / 111 (2.70%)
occurrences (all)	3	4	3
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	3 / 108 (2.78%)	1 / 110 (0.91%)	6 / 111 (5.41%)
occurrences (all)	3	1	6

Non-serious adverse events	Placebo		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	67 / 108 (62.04%)		
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	6 / 108 (5.56%)		
occurrences (all)	6		
Nervous system disorders			
Somnolence			

subjects affected / exposed	9 / 108 (8.33%)		
occurrences (all)	9		
Dizziness			
subjects affected / exposed	15 / 108 (13.89%)		
occurrences (all)	15		
Headache			
subjects affected / exposed	6 / 108 (5.56%)		
occurrences (all)	6		
Balance disorder			
subjects affected / exposed	0 / 108 (0.00%)		
occurrences (all)	0		
Nystagmus			
subjects affected / exposed	1 / 108 (0.93%)		
occurrences (all)	1		
Ataxia			
subjects affected / exposed	1 / 108 (0.93%)		
occurrences (all)	1		
Dysarthria			
subjects affected / exposed	0 / 108 (0.00%)		
occurrences (all)	0		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	9 / 108 (8.33%)		
occurrences (all)	9		
Gait disturbance			
subjects affected / exposed	3 / 108 (2.78%)		
occurrences (all)	3		
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	3 / 108 (2.78%)		
occurrences (all)	3		
Eye disorders			
Diplopia			
subjects affected / exposed	2 / 108 (1.85%)		
occurrences (all)	2		
Gastrointestinal disorders			

Constipation subjects affected / exposed occurrences (all) Nausea subjects affected / exposed occurrences (all) Vomiting subjects affected / exposed occurrences (all)	1 / 108 (0.93%) 1 1 / 108 (0.93%) 1 0 / 108 (0.00%) 0		
Musculoskeletal and connective tissue disorders Back pain subjects affected / exposed occurrences (all)	3 / 108 (2.78%) 3		
Infections and infestations Upper respiratory tract infection subjects affected / exposed occurrences (all)	6 / 108 (5.56%) 6		
Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all)	1 / 108 (0.93%) 1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
07 January 2014	The following is a summary of the major changes implemented with Protocol Amendment 1 (global amendment dated on 07 Jan 2014 for all countries except France, Germany, Korea, and the United Kingdom, for which the amendment date was 09 Jan 2014): • Reduced the initial starting dose to 50 mg/day and slowed the titration rate to improve tolerability. • Clarified the definition of uncontrolled partial seizures. • Provided guidance on contraception for male subjects. • Allowed the first dose of study drug to be given at the investigator's site. • Revised the timelines for the data monitoring committee review of data. • Added a 50 mg/day dosing card.
20 March 2015	The following is a summary of the major changes implemented with Protocol Amendment 2 (global amendment dated 20 Mar 2015 for all countries): • Removed interim analysis. • Provided details of proposed statistical procedures. • Added lacosamide as one of the concomitant AEDs in the pharmacokinetic (PK) analysis.
17 June 2019	The following changes were implemented with Protocol Amendment 3 (global amendment dated 17 Jun 2019 for all countries except Germany for which the amendment date was 16 Aug 2019): • Updated SK Life Science Inc.'s address.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported