Clinical trial results:
A PHASE 2, MULTICENTER, DOUBLE-BLIND, RANDOMIZED, ADJUNCTIVE PLACEBO-CONTROLLED TRIAL WITH AN OPEN-LABEL EXTENSION TO EVALUATE THE EFFICACY AND SAFETY OF YKP3089 IN SUBJECTS WITH TREATMENT RESISTANT PARTIAL ONSET SEIZURES

Summary

EudraCT number	2011-000901-37
Trial protocol	PL
Global end of trial date	28 January 2021

Results information

Result version number	v1 (current)
This version publication date	25 May 2022
First version publication date	25 May 2022

Trial information

Trial identification

Sponsor protocol code	YKP3089C013

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01397968
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	SK Life Science, Inc
Sponsor organisation address	461 From Road, Paramus, New Jersey, United States, 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 2014213830, 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	28 January 2021
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	28 January 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the efficacy of YKP3089 when titrated from 50 to 200 milligram per day (mg/day) in reducing seizure frequency when compared to baseline in subjects with partial onset seizures not fully controlled despite their treatment with 1 to 3 concomitant antiepileptic drugs.

Protection of trial subjects:

This study was conducted according to United States and international standards of Good Clinical Practice (Food and Drug Administration Title 21 Part 312 and International Conference on Harmonization guidelines), applicable government regulations and Institutional research policies and procedures.

Background therapy:

Subjects must have been taking 1-3 concomitant antiepileptic drugs, which they continued to take as prescribed, throughout the study. Subjects could not have any dose changes in their current antiepileptic drug therapy for at least 12 weeks prior to randomization, and doses were to remain stable throughout the double-blind treatment period.

Evidence for comparator:

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

Actual start date of recruitment	06 July 2011
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	India: 51
Country: Number of subjects enrolled	Korea, Republic of: 41
Country: Number of subjects enrolled	Poland: 44
Country: Number of subjects enrolled	United States: 86
Worldwide total number of subjects	222
EEA total number of subjects	44

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	0

months)	
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	222
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This Phase 2 double-blind study with an open-label extension (OLE) was conducted in subjects with treatment resistant partial onset seizures at 40 investigational sites. Investigational sites in India did not participate in the OLE phase. A total of 222 subjects were randomized in a 1:1 ratio to YKP3089 or placebo in this study.

Pre-assignment

Screening details:

The study consisted of a baseline phase (8 weeks), a double-blind treatment period (6-week titration and 6-week maintenance phase), and an OLE phase. The OLE phase was designed without a pre-specified number of weeks. Subject disposition for the double-blind treatment period is based on Randomized Population.

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:

During the double-blind period, the packaging and labeling of the clinical trial medication maintained the double-blind design of the trial. The treatment administered was not known to the subjects or the study personnel at the clinical site. Selected individuals from the Sponsor and/or designee and at the contract research organization (CRO) may have been unblinded to the study treatments on a need-to-know basis as described in the CRO’s Standard Operating Procedures on blinding and unblinding.

Arms

Are arms mutually exclusive?	Yes
Arm title	Double-Blind Treatment Period: YKP3089

Arm description:

Subjects received YKP3089 50 mg orally once daily starting on Day 1 for the first 2 weeks. If well tolerated the dose was increased to 100 mg/day for the next 2 weeks. If well tolerated the dose was then increased to 150 mg/day for the next 2 weeks. If well tolerated the dose was then increased to 200 mg/day for the final 6-week maintenance phase. Subjects who reported side effects may, instead of increasing the dose, remained on the same dose (50 mg, 100 mg, or 150 mg) and not titrated until the following visit.

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

Dosage and administration details:

YKP3089 capsules with dosages described above in Arm description were administrated orally once daily in the morning (with or without breakfast) from Day 1 to the end of double-blind treatment period.

Arm title	Double-Blind Treatment Period: Placebo

Arm description:

Subjects received placebo (matching with YKP3089) orally once daily starting on Day 1 and throughout the 6-week titration phase and 6-week maintenance phase.

Arm type	Placebo

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

Placebo (matching with YKP3089) capsules were administrated orally once daily in the morning (with or without breakfast) from Day 1 to the end of double-blind treatment period.

Number of subjects in period 1	Double-Blind Treatment Period: YKP3089	Double-Blind Treatment Period: Placebo
Started	113	109
Completed	102	99
Not completed	11	10
Consent withdrawn by subject	5	4
Adverse event, non-fatal	4	4
Other	-	1
Lost to follow-up	2	-
Protocol deviation	-	1

Period 2

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

Arms

Arm title	OLE Phase: YKP3089

Arm description:

Subjects who continued in the OLE phase received YKP3089 100 mg orally once daily starting on Day 1 of the OLE phase (Day 85 of study) and then increased by 50 mg/day increments every 2 weeks until reaching the maximum of 400 mg/day based on the same tolerability requirement used in the double-blind treatment period.

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

Dosage and administration details:

YKP3089 capsules or tablets with dosages described above in Arm description were administrated orally once daily in the morning (with or without breakfast) from Day 1 to the end of OLE phase. The OLE phase could continue until development was stopped by the Sponsor, the product was approved for marketing or anytime at the discretion of the Sponsor. The OLE phase disposition is based on OLE Safety Evaluable Population, which is defined as all subjects treated in double-blind who continued into

OLE phase and took at least 1 dose of open-label study medication.

Number of subjects in period 2[1]	OLE Phase: YKP3089
Started	149
Completed	37
Not completed	112
Consent withdrawn by subject	31
Adverse event, non-fatal	16
Other	12
Lost to follow-up	5
Pregnancy	1
Entered Extended Access Program/Navigator	47

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: Only subjects who completed the double-blind treatment period and still met inclusion/exclusion criteria except for seizure frequency were entered into the OLE phase. Please note, sites from India did not participate in the OLE phase.

Baseline characteristics

Reporting groups

Reporting group title	Double-Blind Treatment Period: YKP3089

Reporting group description:

Subjects received YKP3089 50 mg orally once daily starting on Day 1 for the first 2 weeks. If well tolerated the dose was increased to 100 mg/day for the next 2 weeks. If well tolerated the dose was then increased to 150 mg/day for the next 2 weeks. If well tolerated the dose was then increased to 200 mg/day for the final 6-week maintenance phase. Subjects who reported side effects may, instead of increasing the dose, remained on the same dose (50 mg, 100 mg, or 150 mg) and not titrated until the following visit.

Reporting group title	Double-Blind Treatment Period: Placebo

Reporting group description:

Subjects received placebo (matching with YKP3089) orally once daily starting on Day 1 and throughout the 6-week titration phase and 6-week maintenance phase.

Reporting group values	Double-Blind Treatment Period: YKP3089	Double-Blind Treatment Period: Placebo	Total
Number of subjects	113	109	222
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	36.2	37.5	
standard deviation	± 11.27	± 11.38	-
Gender categorical Units: Subjects			
Female	58	51	109
Male	55	58	113
Race Units: Subjects			
White	57	58	115
Black or African American	3	2	5
Asian	49	45	94
American Indian or Alaska Native	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0
Other	1	2	3
Unknown	3	2	5
Ethnicity Units: Subjects			
Hispanic or Latino	4	3	7
Not Hispanic or Latino	105	101	206
Not Reported	4	5	9

End points

End points reporting groups

Reporting group title	Double-Blind Treatment Period: YKP3089

Reporting group description:

Subjects received YKP3089 50 mg orally once daily starting on Day 1 for the first 2 weeks. If well tolerated the dose was increased to 100 mg/day for the next 2 weeks. If well tolerated the dose was then increased to 150 mg/day for the next 2 weeks. If well tolerated the dose was then increased to 200 mg/day for the final 6-week maintenance phase. Subjects who reported side effects may, instead of increasing the dose, remained on the same dose (50 mg, 100 mg, or 150 mg) and not titrated until the following visit.

Reporting group title	Double-Blind Treatment Period: Placebo

Reporting group description:

Subjects received placebo (matching with YKP3089) orally once daily starting on Day 1 and throughout the 6-week titration phase and 6-week maintenance phase.

Reporting group title	OLE Phase: YKP3089

Reporting group description:

Subjects who continued in the OLE phase received YKP3089 100 mg orally once daily starting on Day 1 of the OLE phase (Day 85 of study) and then increased by 50 mg/day increments every 2 weeks until reaching the maximum of 400 mg/day based on the same tolerability requirement used in the double-blind treatment period.

Primary: Percent Change From Baseline in Seizure Frequency Per 28 Days During Double-Blind Treatment Period

End point title	Percent Change From Baseline in Seizure Frequency Per 28 Days During Double-Blind Treatment Period

End point description:

Percent change (reduction) was calculated as (baseline seizure frequency per 28 days – double-blind period seizure frequency per 28 days) / baseline seizure frequency per 28 days x 100. Baseline seizure frequency per 28 Days = number of seizures over baseline period (56 days prior to study Day 1) divided by the number of days in the interval multiplied by 28. The Intention-to-Treat (ITT) population included all randomized subjects who took at least 1 single dose of YKP3089 (or placebo) and had at least 1 efficacy evaluation. The analysis for the primary endpoint is based on ITT population.

End point type	Primary

End point timeframe:

From Day 1 to the end of the double-blind treatment period (Week 12)

End point values	Double-Blind Treatment Period: YKP3089	Double-Blind Treatment Period: Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	113	108		
Units: percent change				
median (full range (min-max))	55.6 (-417.3 to 100.0)	21.5 (-588.0 to 100.0)		

Statistical analyses

Statistical analysis title	Percent Change from Baseline in Seizure Frequency
Comparison groups	Double-Blind Treatment Period: YKP3089 v Double-Blind Treatment Period: Placebo
Number of subjects included in analysis	221
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [1]
Method	Wilcoxon rank-sum test

Notes:

[1] - The p-value is based on a Wilcoxon rank-sum test assessing if the median percent change in seizure frequency for the treatment group is significantly different from the median percent change in seizure frequency for the placebo subjects.

Secondary: Responder Rate (at Least 50% Reduction in Seizure Frequency) During Double-Blind Treatment Period

End point title	Responder Rate (at Least 50% Reduction in Seizure Frequency) During Double-Blind Treatment Period

End point description:

The main secondary endpoint was the responder rate (responder is defined as a subject with ≥ 50% reduction in seizure frequency during the double-blind treatment period). The ITT population included all randomized subjects who took at least 1 single does of YKP3089 (or placebo) and had at least 1 efficacy evaluation. The analysis for this secondary endpoint is based on ITT population.

End point type	Secondary

End point timeframe:

From Day 1 to the end of the double-blind treatment period (Week 12)

End point values	Double-Blind Treatment Period: YKP3089	Double-Blind Treatment Period: Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	113	108		
Units: percentage of responder subjects				
number (not applicable)	50.4	22.2		

Statistical analyses

Statistical analysis title	Logistic Regression Analysis for Responder Rate

Statistical analysis description:

The odds ratio, 95% confidence interval and p-value (YKP3089 versus placebo) are based on a logistic regression model with terms for treatment, country, and baseline seizure frequency (Wald chi-square).

Comparison groups	Double-Blind Treatment Period: YKP3089 v Double-Blind Treatment Period: Placebo
Number of subjects included in analysis	221
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	3.94

Confidence interval	
level	95 %
sides	2-sided
lower limit	2.14
upper limit	7.24

Secondary: Percent Change From Baseline in Seizure Frequency of Simple Partial Seizure With Motor Component (Type B) per 28 Days During Double-Blind Treatment Period

End point title	Percent Change From Baseline in Seizure Frequency of Simple Partial Seizure With Motor Component (Type B) per 28 Days During Double-Blind Treatment Period

End point description:

The 3 partial seizure types included simple partial seizure with motor component (Type B), complex partial seizures (Type C) and secondarily generalized tonic-clonic seizures (Type D). This secondary endpoint assessed the percent change for Type B seizure frequency. Percent change (reduction) was calculated as (baseline seizure frequency per 28 days – double-blind period seizure frequency per 28 days) / baseline seizure frequency per 28 days x 100. Baseline seizure frequency per 28 Days = number of seizures over baseline period (56 days prior to study Day 1) divided by the number of days in the interval multiplied by 28. The ITT population included all randomized subjects who took at least 1 single does of YKP3089 (or placebo) and had at least 1 efficacy evaluation. The analysis for this secondary endpoint is based on ITT population.

End point type	Secondary

End point timeframe:

From Day 1 to the end of the double-blind treatment period (Week 12)

End point values	Double-Blind Treatment Period: YKP3089	Double-Blind Treatment Period: Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	30	26		
Units: percent change				
median (full range (min-max))	76.3 (-122.0 to 100.0)	27.8 (-749.3 to 100.0)		

Statistical analyses

Statistical analysis title	Percent Change from Baseline in Seizure Frequency

Statistical analysis description:

Analysis was performed in Seizure Frequency (Type B).

Comparison groups	Double-Blind Treatment Period: YKP3089 v Double-Blind Treatment Period: Placebo

Number of subjects included in analysis	56
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0448 [2]
Method	Wilcoxon rank-sum test

Notes:

[2] - The p-value is based on a Wilcoxon rank-sum test assessing if the median seizure frequency at post baseline for the treatment group is significantly different from the median seizure frequency for the placebo subjects.

Secondary: Percent Change From Baseline in Seizure Frequency of Complex Partial Seizures (Type C) per 28 Days During Double-Blind Treatment Period

End point title	Percent Change From Baseline in Seizure Frequency of Complex Partial Seizures (Type C) per 28 Days During Double-Blind Treatment Period

End point description:

The 3 partial seizure types included simple partial seizure with motor component (Type B), complex partial seizures (Type C) and secondarily generalized tonic-clonic seizures (Type D). This secondary endpoint assessed the percent change for Type C seizure frequency. Percent change (reduction) was calculated as (baseline seizure frequency per 28 days – double-blind period seizure frequency per 28 days) / baseline seizure frequency per 28 days x 100. Baseline seizure frequency per 28 Days = number of seizures over baseline period (56 days prior to study Day 1) divided by the number of days in the interval multiplied by 28. The ITT population included all randomized subjects who took at least 1 single does of YKP3089 (or placebo) and had at least 1 efficacy evaluation. The analysis for this secondary endpoint is based on ITT population.

End point type	Secondary

End point timeframe:

From Day 1 to the end of the double-blind treatment period (Week 12)

End point values	Double-Blind Treatment Period: YKP3089	Double-Blind Treatment Period: Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	87	89		
Units: percent change				
median (full range (min-max))	55.6 (-366.7 to 100.0)	21.1 (-234.0 to 100.0)		

Statistical analyses

Statistical analysis title	Percent Change from Baseline in Seizure Frequency

Statistical analysis description:

Analysis was performed in Seizure Frequency (Type C).

Comparison groups	Double-Blind Treatment Period: YKP3089 v Double-Blind Treatment Period: Placebo

Number of subjects included in analysis	176
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0009 [3]
Method	Wilcoxon rank-sum test

Notes:

[3] - The p-value is based on a Wilcoxon rank-sum test assessing if the median seizure frequency at post baseline for the treatment group is significantly different from the median seizure frequency for the placebo subjects.

Secondary: Percent Change From Baseline in Seizure Frequency of Secondarily Generalized Tonic-Clonic Seizures (Type D) per 28 Days During Double-Blind Treatment Period

End point title	Percent Change From Baseline in Seizure Frequency of Secondarily Generalized Tonic-Clonic Seizures (Type D) per 28 Days During Double-Blind Treatment Period

End point description:

The 3 partial seizure types included simple partial seizure with motor component (Type B), complex partial seizures (Type C) and secondarily generalized tonic-clonic seizures (Type D). This secondary endpoint assessed the percent change for Type D seizure frequency. Percent change (reduction) was calculated as (baseline seizure frequency per 28 days – double-blind period seizure frequency per 28 days) / baseline seizure frequency per 28 days x 100. Baseline seizure frequency per 28 Days = number of seizures over baseline period (56 days prior to study Day 1) divided by the number of days in the interval multiplied by 28. The ITT population included all randomized subjects who took at least 1 single does of YKP3089 (or placebo) and had at least 1 efficacy evaluation. The analysis for this secondary endpoint is based on ITT population.

End point type	Secondary

End point timeframe:

From Day 1 to the end of the double-blind treatment period (Week 12)

End point values	Double-Blind Treatment Period: YKP3089	Double-Blind Treatment Period: Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	38	37		
Units: percent change				
median (full range (min-max))	77.0 (-146.6 to 100.0)	33.0 (-880.0 to 100.0)		

Statistical analyses

Statistical analysis title	Percent Change from Baseline in Seizure Frequency

Statistical analysis description:

Analysis was performed in Seizure Frequency (Type D).

Comparison groups	Double-Blind Treatment Period: YKP3089 v Double-Blind Treatment Period: Placebo

Number of subjects included in analysis	75
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0117 [4]
Method	Wilcoxon rank-sum test

Notes:

[4] - The p-value is based on a Wilcoxon rank-sum test assessing if the median seizure frequency at post baseline for the treatment group is significantly different from the median seizure frequency for the placebo subjects.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Treatment-emergent adverse events (TEAEs) were reported during the double-blind treatment period.

Adverse event reporting additional description:

Adverse events (AEs) that occur up to 7 days following the subject's last dose of double-blind study drug are included as TEAEs. Double-blind safety evaluable population included all randomized subjects who took at least 1 dose of YKP3089 (or placebo). AEs are reporting in Safety evaluable population. Similar AEs data was observed during OLE phase.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	16.0

Reporting groups

Reporting group title	Double-Blind Treatment Period: YKP3089

Reporting group description:

Subjects received YKP3089 50 mg orally once daily starting on Day 1 for the first 2 weeks. If well tolerated the dose was increased to 100 mg/day for the next 2 weeks. If well tolerated the dose was then increased to 150 mg/day for the next 2 weeks. If well tolerated the dose was then increased to 200 mg/day for the final 6-week maintenance phase. Subjects who reported side effects may, instead of increasing the dose, remained on the same dose (50 mg, 100 mg, or 150 mg) and not titrated until the following visit.

Reporting group title	Double-Blind Treatment Period: Placebo

Reporting group description:

Subjects received placebo (matching with YKP3089) orally once daily starting on Day 1 and throughout the 6-week titration phase and 6-week maintenance phase.

Serious adverse events	Double-Blind Treatment Period: YKP3089	Double-Blind Treatment Period: Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 113 (1.77%)	4 / 109 (3.67%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Investigations			
Arteriogram coronary normal			
subjects affected / exposed	0 / 113 (0.00%)	1 / 109 (0.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Convulsion			
subjects affected / exposed	0 / 113 (0.00%)	1 / 109 (0.92%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Status epilepticus			
subjects affected / exposed	0 / 113 (0.00%)	2 / 109 (1.83%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Drug hypersensitivity			
subjects affected / exposed	1 / 113 (0.88%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	1 / 113 (0.88%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Double-Blind Treatment Period: YKP3089	Double-Blind Treatment Period: Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	84 / 113 (74.34%)	69 / 109 (63.30%)	
Nervous system disorders			
Balance disorder			
subjects affected / exposed	9 / 113 (7.96%)	1 / 109 (0.92%)	
occurrences (all)	11	1	
Dizziness			
subjects affected / exposed	25 / 113 (22.12%)	18 / 109 (16.51%)	
occurrences (all)	49	21	
Headache			
subjects affected / exposed	14 / 113 (12.39%)	14 / 109 (12.84%)	
occurrences (all)	19	16	
Nystagmus			
subjects affected / exposed	11 / 113 (9.73%)	0 / 109 (0.00%)	
occurrences (all)	15	0	
Somnolence			

subjects affected / exposed	25 / 113 (22.12%)	13 / 109 (11.93%)	
occurrences (all)	36	15	
Tremor			
subjects affected / exposed	7 / 113 (6.19%)	3 / 109 (2.75%)	
occurrences (all)	24	6	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	12 / 113 (10.62%)	7 / 109 (6.42%)	
occurrences (all)	15	8	
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	6 / 113 (5.31%)	0 / 109 (0.00%)	
occurrences (all)	6	0	
Diarrhea			
subjects affected / exposed	6 / 113 (5.31%)	0 / 109 (0.00%)	
occurrences (all)	9	0	
Nausea			
subjects affected / exposed	13 / 113 (11.50%)	5 / 109 (4.59%)	
occurrences (all)	17	5	
Vomiting			
subjects affected / exposed	6 / 113 (5.31%)	2 / 109 (1.83%)	
occurrences (all)	7	2	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	1 / 113 (0.88%)	6 / 109 (5.50%)	
occurrences (all)	1	8	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	7 / 113 (6.19%)	1 / 109 (0.92%)	
occurrences (all)	7	1	
Upper respiratory tract infection			
subjects affected / exposed	8 / 113 (7.08%)	5 / 109 (4.59%)	
occurrences (all)	9	6	
Urinary tract infection			
subjects affected / exposed	8 / 113 (7.08%)	2 / 109 (1.83%)	
occurrences (all)	8	2	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
09 May 2011	To amend inclusion/exclusion criteria to allow subjects receiving carbamazepine into the study.
01 November 2011	To add an OLE to obtain long-term safety and tolerability data in subjects with treatment resistant partial onset seizures. To allow subjects under the care of guardians to participate in the study.
28 November 2011	To allow subjects with a body mass index up to 40 to participate in the study.
10 September 2012	To allow subjects to convert from double-blind to open-label treatment without a taper. Clarified exclusion criteria. To provide results of the second carbamazepine - YKP3089 interaction study.
12 November 2012	To allow subjects in the OLE to continue open-label treatment beyond 1 year and also to collect long term safety data for YKP3089.
10 April 2013	To add additional safety assessments for subjects with treatment-emergent rash.
10 October 2013	To provide the results of a multiple ascending dose study that targeted 400, 500 and 600 mg/day doses of YKP3089. To allow subjects in the OLE to increase the target dose up to 400 mg/day.
11 September 2015	To allow subjects in the OLE to take YKP3089 in tablet formulation.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported