



Clinical trial results:

An Open Label, Multicenter, Safety and Pharmacokinetic Study of YKP3089 as Adjunctive Therapy in Subjects with Partial Onset Seizures Summary

EudraCT number	2015-001859-67
Trial protocol	DE ES BG PL CZ HU SE
Global end of trial date	31 March 2021

Results information

Result version number	v1 (current)
This version publication date	05 May 2022
First version publication date	05 May 2022

Trial information

Trial identification

Sponsor protocol code	YKP3089C021
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02535091
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	04 February 2022
Is this the analysis of the primary completion data?	Yes
Primary completion date	31 March 2021
Global end of trial reached?	Yes
Global end of trial date	31 March 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The objective is to evaluate the safety and pharmacokinetics of YKP3089 and concomitant AEDs when administered as adjunctive therapy for the treatment of partial seizures. The evaluations will include:

1. Phenytoin-YKP3089 interaction
2. Phenobarbital-YKP3089 interaction
3. Long term safety of YKP3089 as adjunctive therapy in partial onset seizures
4. Population pharmacokinetics of YKP3089 and concomitant AEDs.

Protection of trial subjects:

This study was conducted according to United States and international standards of Good Clinical Practice (GCP; Food and Drug Administration 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 individuals responsible for obtaining consent were preauthorized and listed on the delegation log. 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 principal investigator was responsible for ensuring that valid consent was obtained and documented for all subjects. Each subject was informed of his or her rights, and the subject or his or her legally authorized representative signed an informed consent document indicating understanding of the purpose of the study and required procedures and indicating willingness to participate in the study.

Background therapy:

Concomitant AEDs are defined as AEDs that started prior to and are ongoing at the time of the first dose of study medication or started after the first dose of study medication. The most common concomitant AEDs taken by at least 15% of all subjects were levetiracetam (40.6%), lamotrigine (33.5%), carbamazepine (27.8%), lacosamide (25.1%) and clobazam (15.1%).

Evidence for comparator:

It's not a comparator study.

Actual start date of recruitment	03 November 2015
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Chile: 20
Country: Number of subjects enrolled	Korea, Republic of: 48
Country: Number of subjects enrolled	Mexico: 114
Country: Number of subjects enrolled	Russian Federation: 46
Country: Number of subjects enrolled	Serbia: 41
Country: Number of subjects enrolled	Thailand: 3
Country: Number of subjects enrolled	Ukraine: 170

Country: Number of subjects enrolled	United States: 410
Country: Number of subjects enrolled	Argentina: 9
Country: Number of subjects enrolled	Australia: 104
Country: Number of subjects enrolled	Poland: 55
Country: Number of subjects enrolled	Spain: 129
Country: Number of subjects enrolled	Sweden: 8
Country: Number of subjects enrolled	Bulgaria: 50
Country: Number of subjects enrolled	Czechia: 24
Country: Number of subjects enrolled	Germany: 53
Country: Number of subjects enrolled	Hungary: 56
Worldwide total number of subjects	1340
EEA total number of subjects	375

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)	1298
From 65 to 84 years	42
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

A total of 1340 subjects received study treatment in the study: 83 in the YKP3089 and phenytoin treatment group, 37 in the YKP3089 and phenobarbital treatment group, and 1220 in the YKP3089 and Other AEDs treatment group.

Pre-assignment

Screening details:

The screening period for subjects on stable doses of phenytoin, stable doses of phenobarbital, or stable doses of other concomitant AEDs was up to 21 days. 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 a treatment group.

Period 1

Period 1 title	Open-Label Treatment Period (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Blinding implementation details:

This was an open-label study.

Arms

Are arms mutually exclusive?	Yes
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Arm title	YKP3089 and Phenytoin
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Arm description:

83 subjects were administrated with YKP3089 and Phenytoin, for a 12-month open label treatment period which consisted of 12-week titration phase followed by an open-label maintenance phase. After 12 months of participation in the open-label treatment period, subjects were re-evaluated. Those who are benefiting from treatment with YKP3089 may continue use of the drug at the discretion of the investigator.

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 12.5 mg, 25 mg, 50 mg, and 100 mg tablets to be taken orally once daily. Subjects in the United States were also supplied with 150 mg and 200 mg tablets. Study drug could have been taken with or without food. The target dose was 200 mg/day. After reaching the target dose of 200 mg/day, all subjects were allowed to titrate up to a maximum dose of 400 mg/day of YKP3089.

Arm title	YKP3089 and Phenobarbital
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Arm description:

37 subjects were administrated with YKP3089 and Phenobarbital, for a 12-month open label treatment period which consisted of 12-week titration phase followed by an open-label maintenance phase. After 12 months of participation in the open-label treatment period, subjects were re-evaluated. Those who are benefiting from treatment with YKP3089 may continue use of the drug at the discretion of the investigator.

Arm type	Experimental
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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 12.5 mg, 25 mg, 50 mg, and 100 mg tablets to be taken orally once daily. Subjects in the United States were also supplied with 150 mg and 200 mg tablets. Study drug could have been taken with or without food. The target dose was 200 mg/day. After reaching the target dose of 200 mg/day, all subjects were allowed to titrate up to a maximum dose of 400 mg/day of YKP3089.

Arm title	YKP3089 and Other AEDs
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Arm description:

1220 subjects were administrated with YKP3089 and Other AEDs, for a 12-month open label treatment period which consisted of 12-week titration phase followed by an open-label maintenance phase.

After 12 months of participation in the open-label treatment period, subjects were re-evaluated. Those who are benefiting from treatment with YKP3089 may continue use of the drug at the discretion of the investigator.

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 12.5 mg, 25 mg, 50 mg, and 100 mg tablets to be taken orally once daily. Subjects in the United States were also supplied with 150 mg and 200 mg tablets. Study drug could have been taken with or without food. The target dose was 200 mg/day. After reaching the target dose of 200 mg/day, all subjects were allowed to titrate up to a maximum dose of 400 mg/day of YKP3089.

Number of subjects in period 1	YKP3089 and Phenytoin	YKP3089 and Phenobarbital	YKP3089 and Other AEDs
Started	83	37	1220
Completed	22	5	236
Not completed	61	32	984
Adverse Event	9	4	170
Other	4	3	81
Lost to follow-up	-	1	19
Withdrew Consent Other Than Adverse Event	14	5	121
Entered EAP/Navigator	34	18	575
Pregnancy	-	-	7
Protocol deviation	-	1	11

Baseline characteristics

Reporting groups

Reporting group title	YKP3089 and Phenytoin
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Reporting group description:

83 subjects were administrated with YKP3089 and Phenytoin, for a 12-month open label treatment period which consisted of 12-week titration phase followed by an open-label maintenance phase. After 12 months of participation in the open-label treatment period, subjects were re-evaluated. Those who are benefiting from treatment with YKP3089 may continue use of the drug at the discretion of the investigator.

Reporting group title	YKP3089 and Phenobarbital
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Reporting group description:

37 subjects were administrated with YKP3089 and Phenobarbital, for a 12-month open label treatment period which consisted of 12-week titration phase followed by an open-label maintenance phase. After 12 months of participation in the open-label treatment period, subjects were re-evaluated. Those who are benefiting from treatment with YKP3089 may continue use of the drug at the discretion of the investigator.

Reporting group title	YKP3089 and Other AEDs
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Reporting group description:

1220 subjects were administrated with YKP3089 and Other AEDs, for a 12-month open label treatment period which consisted of 12-week titration phase followed by an open-label maintenance phase. After 12 months of participation in the open-label treatment period, subjects were re-evaluated. Those who are benefiting from treatment with YKP3089 may continue use of the drug at the discretion of the investigator.

Reporting group values	YKP3089 and Phenytoin	YKP3089 and Phenobarbital	YKP3089 and Other AEDs
Number of subjects	83	37	1220
Age categorical Units: Subjects			
Adults (18-64 years)	76	35	1187
From 65-84 years	7	2	33
Age continuous Units: years			
median	42	41	38.5
full range (min-max)	18 to 72	19 to 70	18 to 70
Gender categorical Units: Subjects			
Female	28	15	624
Male	55	22	596

Reporting group values	Total		
Number of subjects	1340		
Age categorical Units: Subjects			
Adults (18-64 years)	1298		
From 65-84 years	42		
Age continuous Units: years			
median			
full range (min-max)	-		

Gender categorical			
Units: Subjects			
Female	667		
Male	673		

Subject analysis sets

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

Subject analysis set description:

All subjects enrolled in the study who received at least 1 dose of study drug medication were considered safety evaluable subjects.

Subject analysis set title	PK Population
Subject analysis set type	Sub-group analysis

Subject analysis set description:

All subjects enrolled in the study who took at least 1 dose of study drug and with at least 1 blood sample for PK.

Reporting group values	Safety population	PK Population	
Number of subjects	1340	484	
Age categorical			
Units: Subjects			
Adults (18-64 years)	1298		
From 65-84 years	42		
Age continuous			
Units: years			
median	39		
full range (min-max)	18 to 72		
Gender categorical			
Units: Subjects			
Female	667		
Male	673		

End points

End points reporting groups

Reporting group title	YKP3089 and Phenytoin
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Reporting group description:

83 subjects were administrated with YKP3089 and Phenytoin, for a 12-month open label treatment period which consisted of 12-week titration phase followed by an open-label maintenance phase. After 12 months of participation in the open-label treatment period, subjects were re-evaluated. Those who are benefiting from treatment with YKP3089 may continue use of the drug at the discretion of the investigator.

Reporting group title	YKP3089 and Phenobarbital
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Reporting group description:

37 subjects were administrated with YKP3089 and Phenobarbital, for a 12-month open label treatment period which consisted of 12-week titration phase followed by an open-label maintenance phase. After 12 months of participation in the open-label treatment period, subjects were re-evaluated. Those who are benefiting from treatment with YKP3089 may continue use of the drug at the discretion of the investigator.

Reporting group title	YKP3089 and Other AEDs
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Reporting group description:

1220 subjects were administrated with YKP3089 and Other AEDs, for a 12-month open label treatment period which consisted of 12-week titration phase followed by an open-label maintenance phase. After 12 months of participation in the open-label treatment period, subjects were re-evaluated. Those who are benefiting from treatment with YKP3089 may continue use of the drug at the discretion of the investigator.

Subject analysis set title	Safety population
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Subject analysis set type	Safety analysis
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Subject analysis set description:

All subjects enrolled in the study who received at least 1 dose of study drug medication were considered safety evaluable subjects.

Subject analysis set title	PK Population
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Subject analysis set type	Sub-group analysis
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Subject analysis set description:

All subjects enrolled in the study who took at least 1 dose of study drug and with at least 1 blood sample for PK.

Primary: Summary of Treatment-Emergent Adverse Events (TEAEs)

End point title	Summary of Treatment-Emergent Adverse Events (TEAEs) ^[1]
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End point description:

TEAEs were defined as Adverse events (AEs) with onset on or after the start of study medication, up to last dose date of study medication + 14 days or onset before study medication and worsened after starting study medication, up to last dose date of study medication + 14 days.

Long-term administration of YKP3089 as adjunctive therapy to approved AEDs, including phenytoin and phenobarbital, is generally safe and well tolerated.

All cases of hypersensitivity reactions from the clinical and safety databases were reviewed for DRESS and no cases were identified.

No subjects completed suicide.

No significant laboratory or ECG abnormalities were identified.

End point type	Primary
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End point timeframe:

During the course of the study

Notes:

[1] - 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: Descriptive statistics have been used for this primary endpoint.

End point values	YKP3089 and Phenytoin	YKP3089 and Phenobarbital	YKP3089 and Other AEDs	Safety population
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	83	37	1220	1340
Units: percent				
number (not applicable)				
At least 1 TEAE (n)	76	35	1104	1215
At least 1 TEAE (%)	91.6	94.6	90.5	90.7
At least 1 treatment-related TEAE (n)	57	29	923	1009
At least 1 treatment-related TEAE (%)	68.7	78.4	75.7	75.3
TEAE with outcome of death (n)	1	0	5	6
TEAE with outcome of death (%)	1.2	0	0.4	0.4
TEAE leading to study drug discontinuation (n)	9	6	168	183
TEAE leading to study drug discontinuation (%)	10.8	16.2	13.8	13.7
At least 1 serious TEAE (n)	15	6	217	238
At least 1 serious TEAE (%)	18.1	16.2	17.8	17.8
At least 1 severe TEAE (n)	10	4	148	162
At least 1 severe TEAE (%)	12.0	10.8	12.1	12.1

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Exposure to Study Dose

End point title	Exposure to Study Dose
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End point description:

Exposure to Study Dose was measures in Safety Population. Modal daily dose defined as the dose taken the most days during the reporting phase or study; in case of ties modal dose was defined as the highest dose level between the two doses in the tie.

End point type	Other pre-specified
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End point timeframe:

During the course of the study

End point values	YKP3089 and Phenytoin	YKP3089 and Phenobarbital	YKP3089 and Other AEDs	Safety population
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	83	37	1220	1340
Units: weeks/months/mg				
arithmetic mean (standard deviation)				
Length of Exposure (Weeks) – Overall	123.96 (± 62.885)	119.48 (± 81.612)	129.28 (± 65.436)	128.68 (± 65.753)
Length of Exposure (Months) – Overall	28.543 (± 14.4801)	27.512 (± 18.7922)	29.768 (± 15.0675)	29.630 (± 15.1404)
Modal Daily Dose (mg) – Overall	223.34 (± 100.528)	183.11 (± 105.500)	219.32 (± 107.154)	218.57 (± 106.808)
Length of Exposure (Weeks) – Maintenance Phase	122.4 (± 51.89)	136.7 (± 61.93)	131.6 (± 50.33)	131.2 (± 50.75)

Length of Exposure (Months) – Maintenance Phase	28.18 (± 11.949)	31.47 (± 14.261)	30.31 (± 11.589)	30.20 (± 11.686)
Modal Daily Dose (mg) – Maintenance Phase	244.7 (± 82.84)	222.4 (± 85.13)	244.5 (± 88.32)	244.0 (± 87.91)

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Vital Signs: Subjects Meeting Abnormal Criteria (Post-Baseline Measurement)

End point title	Vital Signs: Subjects Meeting Abnormal Criteria (Post-Baseline Measurement)
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End point description:

Subjects with At Least 1 Post-Baseline Measurement Meeting Abnormal Criteria.

Changes in systolic and diastolic blood pressure, pulse rate, respiratory rate, temperature, weight, and height in each safety evaluable group were small and not clinically meaningful.

End point type	Other pre-specified
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End point timeframe:

During the course of the study

End point values	YKP3089 and Phenytoin	YKP3089 and Phenobarbital	YKP3089 and Other AEDs	Safety population
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	83	37	1220	1340
Units: percent				
number (not applicable)				
Systolic blood pressure <90 mmHg (n)	3	3	58	64
Systolic blood pressure <90 mmHg (%)	3.6	8.1	4.8	4.8
Systolic blood pressure >140 mmHg (n)	26	15	310	351
Systolic blood pressure >140 mmHg (%)	31.3	40.5	25.4	26.2
Systolic blood pressure >160 mmHg (n)	7	0	44	51
Systolic blood pressure >160 mmHg (%)	8.4	0	3.6	3.8
Diastolic blood pressure <50 mmHg (n)	0	2	41	43
Diastolic blood pressure <50 mmHg (%)	0	5.4	3.4	3.2
Diastolic blood pressure >90 mmHg (n)	29	12	318	359
Diastolic blood pressure >90 mmHg (%)	34.9	32.4	26.1	26.8
Diastolic blood pressure >100 mmHg (n)	7	2	68	77
Diastolic blood pressure >100 mmHg (%)	8.4	5.4	5.6	5.7
Pulse rate <60 bpm (n)	35	14	446	495
Pulse rate <60 bpm (%)	42.2	37.8	36.6	36.9
Pulse rate >100 bpm (n)	2	1	79	82
Pulse rate >100 bpm (%)	2.4	2.7	6.5	6.1
Body weight: Decrease of ≥7% from baseline (n)	21	12	373	406

Body weight: Decrease of $\geq 7\%$ from baseline (%)	25.3	32.4	30.6	30.3
Body weight: Increase of $\geq 7\%$ from baseline (n)	19	5	272	296
Body weight: Increase of $\geq 7\%$ from baseline (%)	22.9	13.5	22.3	22.1
Respiratory rate <12 breaths/min (n)	2	2	33	37
Respiratory rate <12 breaths/min (%)	2.4	5.4	2.7	2.8
Respiratory rate >20 breaths/min (n)	22	6	247	275
Respiratory rate >20 breaths/min (%)	26.5	16.2	20.2	20.5
Temperature >38.0°C (n)	0	1	5	6
Temperature >38.0°C (%)	0	2.7	0.4	0.4
Temperature <36.0°C (n)	33	12	384	429
Temperature <36.0°C (%)	39.8	32.4	31.5	32.0

Statistical analyses

No statistical analyses for this end point

Other pre-specified: YKP3089 Plasma Levels (mcg/mL)

End point title	YKP3089 Plasma Levels (mcg/mL)
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End point description:

At Visit 8 and Visit 9, 2 blood samples were collected for the determination of YKP3089 plasma levels (YKP3089 and concomitant AED doses must have been stable for 2 weeks prior to these visits), at arrival and 30 minutes to 4 hours after the most recent dose.

Plasma levels of phenytoin and phenobarbital were stable during the titration.

The endpoint values below is based on PK population.

End point type	Other pre-specified
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End point timeframe:

At visit 8 and 9

End point values	YKP3089 and Phenytoin	YKP3089 and Phenobarbital	YKP3089 and Other AEDs	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	83	37	364	
Units: mcg/mL				
arithmetic mean (standard deviation)				
Visit 8 / Arrival at clinic	12.5051 (\pm 5.80730)	12.4071 (\pm 4.71288)	14.6904 (\pm 5.99973)	
Visit 8 / Post-Dose	13.7470 (\pm 6.02498)	14.6900 (\pm 4.44020)	15.8694 (\pm 5.92152)	
Visit 9 / Arrival at clinic	11.8173 (\pm 5.36440)	13.2607 (\pm 5.46875)	15.4764 (\pm 5.94161)	
Visit 9 / Post-Dose	13.4618 (\pm 5.69905)	15.0770 (\pm 5.25885)	16.4892 (\pm 5.87959)	

Statistical analyses

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Treatment-Emergent Adverse Events (TEAEs) were measured during treatment period + 14 days.

Adverse event reporting additional description:

Treatment-Emergent Adverse Events (TEAEs) are defined as AEs with onset on or after the start of study medication, up to last dose date of study medication + 14 days, or onset before study medication and worsened after starting study medication, up to last dose date of study medication + 14 days.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	20.0
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Reporting groups

Reporting group title	YKP3089 and Phenytoin
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Reporting group description:

83 subjects were administrated with YKP3089 and Phenytoin, for a 12-month open label treatment period which consisted of 12-week titration phase followed by an open-label maintenance phase. After 12 months of participation in the open-label treatment period, subjects were re-evaluated. Those who are benefiting from treatment with YKP3089 may continue use of the drug at the discretion of the investigator.

Reporting group title	YKP3089 and Phenobarbital
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Reporting group description:

37 subjects were administrated with YKP3089 and Phenobarbital, for a 12-month open label treatment period which consisted of 12-week titration phase followed by an open-label maintenance phase. After 12 months of participation in the open-label treatment period, subjects were re-evaluated. Those who are benefiting from treatment with YKP3089 may continue use of the drug at the discretion of the investigator.

Reporting group title	YKP3089 and Other AEDs
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Reporting group description:

1220 subjects were administrated with YKP3089 and Other AEDs, for a 12-month open label treatment period which consisted of 12-week titration phase followed by an open-label maintenance phase. After 12 months of participation in the open-label treatment period, subjects were re-evaluated. Those who are benefiting from treatment with YKP3089 may continue use of the drug at the discretion of the investigator.

Serious adverse events	YKP3089 and Phenytoin	YKP3089 and Phenobarbital	YKP3089 and Other AEDs
Total subjects affected by serious adverse events			
subjects affected / exposed	15 / 83 (18.07%)	6 / 37 (16.22%)	217 / 1220 (17.79%)
number of deaths (all causes)	2	0	8
number of deaths resulting from adverse events	1	0	5
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Breast cancer			
subjects affected / exposed	0 / 83 (0.00%)	0 / 37 (0.00%)	4 / 1220 (0.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Fibroadenoma of breast			
subjects affected / exposed	0 / 83 (0.00%)	0 / 37 (0.00%)	1 / 1220 (0.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Glioblastoma			
subjects affected / exposed	0 / 83 (0.00%)	0 / 37 (0.00%)	2 / 1220 (0.16%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Gliosarcoma			
subjects affected / exposed	0 / 83 (0.00%)	0 / 37 (0.00%)	1 / 1220 (0.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Invasive ductal breast carcinoma			
subjects affected / exposed	0 / 83 (0.00%)	0 / 37 (0.00%)	1 / 1220 (0.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oesophageal carcinoma			
subjects affected / exposed	0 / 83 (0.00%)	0 / 37 (0.00%)	1 / 1220 (0.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Papillary thyroid cancer			
subjects affected / exposed	0 / 83 (0.00%)	0 / 37 (0.00%)	1 / 1220 (0.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Prostate cancer			
subjects affected / exposed	1 / 83 (1.20%)	0 / 37 (0.00%)	0 / 1220 (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
Squamous cell carcinoma			
subjects affected / exposed	0 / 83 (0.00%)	0 / 37 (0.00%)	1 / 1220 (0.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tumour haemorrhage			

subjects affected / exposed	0 / 83 (0.00%)	0 / 37 (0.00%)	1 / 1220 (0.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Uterine leiomyoma			
subjects affected / exposed	0 / 83 (0.00%)	0 / 37 (0.00%)	1 / 1220 (0.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Arterial haemorrhage			
subjects affected / exposed	1 / 83 (1.20%)	0 / 37 (0.00%)	0 / 1220 (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
Deep vein thrombosis			
subjects affected / exposed	0 / 83 (0.00%)	0 / 37 (0.00%)	2 / 1220 (0.16%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypovolaemic shock			
subjects affected / exposed	1 / 83 (1.20%)	0 / 37 (0.00%)	0 / 1220 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Surgical and medical procedures			
Hospitalisation			
subjects affected / exposed	0 / 83 (0.00%)	0 / 37 (0.00%)	1 / 1220 (0.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neurolysis			
subjects affected / exposed	0 / 83 (0.00%)	0 / 37 (0.00%)	1 / 1220 (0.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vagal nerve stimulator implantation			
subjects affected / exposed	0 / 83 (0.00%)	0 / 37 (0.00%)	1 / 1220 (0.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pregnancy, puerperium and perinatal			

conditions			
Abortion spontaneous			
subjects affected / exposed	0 / 83 (0.00%)	0 / 37 (0.00%)	2 / 1220 (0.16%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ectopic pregnancy			
subjects affected / exposed	0 / 83 (0.00%)	0 / 37 (0.00%)	1 / 1220 (0.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 83 (0.00%)	0 / 37 (0.00%)	1 / 1220 (0.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chest pain			
subjects affected / exposed	0 / 83 (0.00%)	0 / 37 (0.00%)	3 / 1220 (0.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Complication associated with device			
subjects affected / exposed	0 / 83 (0.00%)	0 / 37 (0.00%)	1 / 1220 (0.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Non-cardiac chest pain			
subjects affected / exposed	0 / 83 (0.00%)	0 / 37 (0.00%)	1 / 1220 (0.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oedema peripheral			
subjects affected / exposed	0 / 83 (0.00%)	0 / 37 (0.00%)	1 / 1220 (0.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pelvic mass			
subjects affected / exposed	0 / 83 (0.00%)	0 / 37 (0.00%)	1 / 1220 (0.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Pyrexia			
subjects affected / exposed	0 / 83 (0.00%)	0 / 37 (0.00%)	1 / 1220 (0.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Serositis			
subjects affected / exposed	0 / 83 (0.00%)	0 / 37 (0.00%)	1 / 1220 (0.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sudden death			
subjects affected / exposed	0 / 83 (0.00%)	0 / 37 (0.00%)	1 / 1220 (0.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	1 / 1
Immune system disorders			
Sarcoidosis			
subjects affected / exposed	0 / 83 (0.00%)	0 / 37 (0.00%)	1 / 1220 (0.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Endometriosis			
subjects affected / exposed	0 / 83 (0.00%)	0 / 37 (0.00%)	2 / 1220 (0.16%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gynaecomastia			
subjects affected / exposed	1 / 83 (1.20%)	0 / 37 (0.00%)	0 / 1220 (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
Ovarian cyst			
subjects affected / exposed	0 / 83 (0.00%)	0 / 37 (0.00%)	2 / 1220 (0.16%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pelvic haemorrhage			
subjects affected / exposed	0 / 83 (0.00%)	0 / 37 (0.00%)	1 / 1220 (0.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Vaginal haemorrhage			
subjects affected / exposed	0 / 83 (0.00%)	0 / 37 (0.00%)	2 / 1220 (0.16%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vaginal prolapse			
subjects affected / exposed	0 / 83 (0.00%)	0 / 37 (0.00%)	1 / 1220 (0.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vulvar dysplasia			
subjects affected / exposed	0 / 83 (0.00%)	0 / 37 (0.00%)	1 / 1220 (0.08%)
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			
Acute respiratory failure			
subjects affected / exposed	0 / 83 (0.00%)	0 / 37 (0.00%)	1 / 1220 (0.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Emphysema			
subjects affected / exposed	0 / 83 (0.00%)	0 / 37 (0.00%)	1 / 1220 (0.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Laryngospasm			
subjects affected / exposed	0 / 83 (0.00%)	0 / 37 (0.00%)	1 / 1220 (0.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Neonatal hypoxia			
subjects affected / exposed	0 / 83 (0.00%)	0 / 37 (0.00%)	1 / 1220 (0.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pleuritic pain			
subjects affected / exposed	0 / 83 (0.00%)	0 / 37 (0.00%)	1 / 1220 (0.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Pneumonia aspiration			
subjects affected / exposed	0 / 83 (0.00%)	0 / 37 (0.00%)	1 / 1220 (0.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumothorax			
subjects affected / exposed	0 / 83 (0.00%)	0 / 37 (0.00%)	1 / 1220 (0.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary embolism			
subjects affected / exposed	0 / 83 (0.00%)	0 / 37 (0.00%)	6 / 1220 (0.49%)
occurrences causally related to treatment / all	0 / 0	0 / 0	3 / 6
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory arrest			
subjects affected / exposed	0 / 83 (0.00%)	0 / 37 (0.00%)	1 / 1220 (0.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Affective disorder			
subjects affected / exposed	0 / 83 (0.00%)	0 / 37 (0.00%)	1 / 1220 (0.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aggression			
subjects affected / exposed	0 / 83 (0.00%)	0 / 37 (0.00%)	1 / 1220 (0.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anger			
subjects affected / exposed	1 / 83 (1.20%)	0 / 37 (0.00%)	0 / 1220 (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
Anxiety			
subjects affected / exposed	0 / 83 (0.00%)	0 / 37 (0.00%)	1 / 1220 (0.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anxiety disorder			

subjects affected / exposed	0 / 83 (0.00%)	0 / 37 (0.00%)	1 / 1220 (0.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Confusional state			
subjects affected / exposed	0 / 83 (0.00%)	0 / 37 (0.00%)	1 / 1220 (0.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Depression			
subjects affected / exposed	0 / 83 (0.00%)	0 / 37 (0.00%)	1 / 1220 (0.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Major depression			
subjects affected / exposed	0 / 83 (0.00%)	0 / 37 (0.00%)	2 / 1220 (0.16%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mental status changes			
subjects affected / exposed	0 / 83 (0.00%)	0 / 37 (0.00%)	3 / 1220 (0.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mood disorder due to a general medical condition			
subjects affected / exposed	0 / 83 (0.00%)	0 / 37 (0.00%)	1 / 1220 (0.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Postictal psychosis			
subjects affected / exposed	0 / 83 (0.00%)	0 / 37 (0.00%)	1 / 1220 (0.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychogenic seizure			
subjects affected / exposed	0 / 83 (0.00%)	0 / 37 (0.00%)	1 / 1220 (0.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychotic disorder			

subjects affected / exposed	0 / 83 (0.00%)	0 / 37 (0.00%)	3 / 1220 (0.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	3 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Schizophrenia			
subjects affected / exposed	0 / 83 (0.00%)	0 / 37 (0.00%)	1 / 1220 (0.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Substance use disorder			
subjects affected / exposed	0 / 83 (0.00%)	0 / 37 (0.00%)	1 / 1220 (0.08%)
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 behaviour			
subjects affected / exposed	0 / 83 (0.00%)	0 / 37 (0.00%)	1 / 1220 (0.08%)
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 / 83 (0.00%)	0 / 37 (0.00%)	5 / 1220 (0.41%)
occurrences causally related to treatment / all	0 / 0	0 / 0	3 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Suicide attempt			
subjects affected / exposed	1 / 83 (1.20%)	0 / 37 (0.00%)	4 / 1220 (0.33%)
occurrences causally related to treatment / all	0 / 1	0 / 0	3 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Fibrin D dimer increased			
subjects affected / exposed	0 / 83 (0.00%)	0 / 37 (0.00%)	1 / 1220 (0.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Weight decreased			
subjects affected / exposed	0 / 83 (0.00%)	0 / 37 (0.00%)	1 / 1220 (0.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			

Accidental overdose			
subjects affected / exposed	0 / 83 (0.00%)	0 / 37 (0.00%)	2 / 1220 (0.16%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ankle fracture			
subjects affected / exposed	0 / 83 (0.00%)	1 / 37 (2.70%)	2 / 1220 (0.16%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Burns third degree			
subjects affected / exposed	0 / 83 (0.00%)	0 / 37 (0.00%)	1 / 1220 (0.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cervical vertebral fracture			
subjects affected / exposed	0 / 83 (0.00%)	0 / 37 (0.00%)	1 / 1220 (0.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Concussion			
subjects affected / exposed	0 / 83 (0.00%)	0 / 37 (0.00%)	2 / 1220 (0.16%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fall			
subjects affected / exposed	0 / 83 (0.00%)	1 / 37 (2.70%)	5 / 1220 (0.41%)
occurrences causally related to treatment / all	0 / 0	0 / 1	2 / 6
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Femoral neck fracture			
subjects affected / exposed	0 / 83 (0.00%)	0 / 37 (0.00%)	3 / 1220 (0.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Femur fracture			
subjects affected / exposed	0 / 83 (0.00%)	0 / 37 (0.00%)	1 / 1220 (0.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fibula fracture			

subjects affected / exposed	0 / 83 (0.00%)	0 / 37 (0.00%)	1 / 1220 (0.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Forearm fracture			
subjects affected / exposed	1 / 83 (1.20%)	0 / 37 (0.00%)	0 / 1220 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Head injury			
subjects affected / exposed	0 / 83 (0.00%)	0 / 37 (0.00%)	2 / 1220 (0.16%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Humerus fracture			
subjects affected / exposed	0 / 83 (0.00%)	0 / 37 (0.00%)	1 / 1220 (0.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intentional overdose			
subjects affected / exposed	1 / 83 (1.20%)	0 / 37 (0.00%)	1 / 1220 (0.08%)
occurrences causally related to treatment / all	0 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Jaw fracture			
subjects affected / exposed	0 / 83 (0.00%)	0 / 37 (0.00%)	2 / 1220 (0.16%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Joint dislocation			
subjects affected / exposed	0 / 83 (0.00%)	0 / 37 (0.00%)	1 / 1220 (0.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ligament rupture			
subjects affected / exposed	0 / 83 (0.00%)	0 / 37 (0.00%)	1 / 1220 (0.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ligament sprain			

subjects affected / exposed	0 / 83 (0.00%)	0 / 37 (0.00%)	1 / 1220 (0.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lip injury			
subjects affected / exposed	0 / 83 (0.00%)	0 / 37 (0.00%)	1 / 1220 (0.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower limb fracture			
subjects affected / exposed	0 / 83 (0.00%)	0 / 37 (0.00%)	1 / 1220 (0.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Overdose			
subjects affected / exposed	0 / 83 (0.00%)	0 / 37 (0.00%)	1 / 1220 (0.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Patella fracture			
subjects affected / exposed	0 / 83 (0.00%)	0 / 37 (0.00%)	1 / 1220 (0.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pelvic fracture			
subjects affected / exposed	0 / 83 (0.00%)	0 / 37 (0.00%)	1 / 1220 (0.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skull fracture			
subjects affected / exposed	0 / 83 (0.00%)	0 / 37 (0.00%)	1 / 1220 (0.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal column injury			
subjects affected / exposed	0 / 83 (0.00%)	0 / 37 (0.00%)	1 / 1220 (0.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal compression fracture			

subjects affected / exposed	0 / 83 (0.00%)	0 / 37 (0.00%)	1 / 1220 (0.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Stab wound			
subjects affected / exposed	0 / 83 (0.00%)	0 / 37 (0.00%)	1 / 1220 (0.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subarachnoid haemorrhage			
subjects affected / exposed	0 / 83 (0.00%)	0 / 37 (0.00%)	1 / 1220 (0.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subdural haematoma			
subjects affected / exposed	0 / 83 (0.00%)	0 / 37 (0.00%)	1 / 1220 (0.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Thermal burn			
subjects affected / exposed	0 / 83 (0.00%)	0 / 37 (0.00%)	3 / 1220 (0.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thoracic vertebral fracture			
subjects affected / exposed	0 / 83 (0.00%)	0 / 37 (0.00%)	1 / 1220 (0.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Toxicity to various agents			
subjects affected / exposed	0 / 83 (0.00%)	1 / 37 (2.70%)	0 / 1220 (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
Traumatic intracranial haemorrhage			
subjects affected / exposed	0 / 83 (0.00%)	0 / 37 (0.00%)	1 / 1220 (0.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Congenital, familial and genetic disorders			
Cortical dysplasia			

subjects affected / exposed	0 / 83 (0.00%)	0 / 37 (0.00%)	1 / 1220 (0.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Patent ductus arteriosus			
subjects affected / exposed	0 / 83 (0.00%)	0 / 37 (0.00%)	1 / 1220 (0.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Acute coronary syndrome			
subjects affected / exposed	0 / 83 (0.00%)	0 / 37 (0.00%)	2 / 1220 (0.16%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute myocardial infarction			
subjects affected / exposed	0 / 83 (0.00%)	0 / 37 (0.00%)	2 / 1220 (0.16%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrioventricular block complete			
subjects affected / exposed	0 / 83 (0.00%)	0 / 37 (0.00%)	1 / 1220 (0.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocardial ischaemia			
subjects affected / exposed	0 / 83 (0.00%)	0 / 37 (0.00%)	1 / 1220 (0.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Supraventricular tachycardia			
subjects affected / exposed	0 / 83 (0.00%)	0 / 37 (0.00%)	1 / 1220 (0.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Ataxia			
subjects affected / exposed	1 / 83 (1.20%)	0 / 37 (0.00%)	6 / 1220 (0.49%)
occurrences causally related to treatment / all	1 / 1	0 / 0	4 / 6
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Balance disorder			

subjects affected / exposed	0 / 83 (0.00%)	0 / 37 (0.00%)	2 / 1220 (0.16%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebral atrophy			
subjects affected / exposed	0 / 83 (0.00%)	0 / 37 (0.00%)	1 / 1220 (0.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebral haemorrhage			
subjects affected / exposed	0 / 83 (0.00%)	0 / 37 (0.00%)	1 / 1220 (0.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebral ischaemia			
subjects affected / exposed	0 / 83 (0.00%)	0 / 37 (0.00%)	1 / 1220 (0.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebrovascular accident			
subjects affected / exposed	0 / 83 (0.00%)	0 / 37 (0.00%)	1 / 1220 (0.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dizziness			
subjects affected / exposed	0 / 83 (0.00%)	0 / 37 (0.00%)	5 / 1220 (0.41%)
occurrences causally related to treatment / all	0 / 0	0 / 0	5 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dysarthria			
subjects affected / exposed	0 / 83 (0.00%)	0 / 37 (0.00%)	2 / 1220 (0.16%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Epilepsy			
subjects affected / exposed	0 / 83 (0.00%)	0 / 37 (0.00%)	8 / 1220 (0.66%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 9
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Focal dyscognitive seizures			

subjects affected / exposed	0 / 83 (0.00%)	0 / 37 (0.00%)	1 / 1220 (0.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Generalised tonic-clonic seizure			
subjects affected / exposed	1 / 83 (1.20%)	0 / 37 (0.00%)	2 / 1220 (0.16%)
occurrences causally related to treatment / all	1 / 1	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Headache			
subjects affected / exposed	0 / 83 (0.00%)	0 / 37 (0.00%)	1 / 1220 (0.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolic encephalopathy			
subjects affected / exposed	0 / 83 (0.00%)	0 / 37 (0.00%)	2 / 1220 (0.16%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Migraine			
subjects affected / exposed	0 / 83 (0.00%)	0 / 37 (0.00%)	1 / 1220 (0.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myelopathy			
subjects affected / exposed	0 / 83 (0.00%)	0 / 37 (0.00%)	1 / 1220 (0.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nerve compression			
subjects affected / exposed	0 / 83 (0.00%)	0 / 37 (0.00%)	1 / 1220 (0.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Paraesthesia			
subjects affected / exposed	0 / 83 (0.00%)	0 / 37 (0.00%)	1 / 1220 (0.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Partial seizures with secondary generalisation			

subjects affected / exposed	1 / 83 (1.20%)	0 / 37 (0.00%)	0 / 1220 (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
Poor sucking reflex			
subjects affected / exposed	0 / 83 (0.00%)	0 / 37 (0.00%)	1 / 1220 (0.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Post-traumatic epilepsy			
subjects affected / exposed	0 / 83 (0.00%)	0 / 37 (0.00%)	2 / 1220 (0.16%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Postictal paralysis			
subjects affected / exposed	0 / 83 (0.00%)	0 / 37 (0.00%)	6 / 1220 (0.49%)
occurrences causally related to treatment / all	0 / 0	0 / 0	3 / 6
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Postictal state			
subjects affected / exposed	0 / 83 (0.00%)	0 / 37 (0.00%)	4 / 1220 (0.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Presyncope			
subjects affected / exposed	0 / 83 (0.00%)	0 / 37 (0.00%)	1 / 1220 (0.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Radial nerve palsy			
subjects affected / exposed	0 / 83 (0.00%)	0 / 37 (0.00%)	1 / 1220 (0.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Seizure			
subjects affected / exposed	1 / 83 (1.20%)	1 / 37 (2.70%)	27 / 1220 (2.21%)
occurrences causally related to treatment / all	1 / 1	0 / 3	10 / 33
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Seizure cluster			

subjects affected / exposed	0 / 83 (0.00%)	1 / 37 (2.70%)	2 / 1220 (0.16%)
occurrences causally related to treatment / all	0 / 0	0 / 1	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Somnolence			
subjects affected / exposed	0 / 83 (0.00%)	0 / 37 (0.00%)	3 / 1220 (0.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	3 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal cord compression			
subjects affected / exposed	0 / 83 (0.00%)	0 / 37 (0.00%)	1 / 1220 (0.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Status epilepticus			
subjects affected / exposed	0 / 83 (0.00%)	0 / 37 (0.00%)	7 / 1220 (0.57%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 7
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Syncope			
subjects affected / exposed	0 / 83 (0.00%)	0 / 37 (0.00%)	1 / 1220 (0.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Toxic encephalopathy			
subjects affected / exposed	0 / 83 (0.00%)	0 / 37 (0.00%)	3 / 1220 (0.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transient ischaemic attack			
subjects affected / exposed	0 / 83 (0.00%)	0 / 37 (0.00%)	1 / 1220 (0.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vertebral artery dissection			
subjects affected / exposed	0 / 83 (0.00%)	0 / 37 (0.00%)	1 / 1220 (0.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Wernicke's encephalopathy			

subjects affected / exposed	0 / 83 (0.00%)	0 / 37 (0.00%)	1 / 1220 (0.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	0 / 83 (0.00%)	0 / 37 (0.00%)	1 / 1220 (0.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Glaucoma			
subjects affected / exposed	0 / 83 (0.00%)	0 / 37 (0.00%)	1 / 1220 (0.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Visual acuity reduced			
subjects affected / exposed	0 / 83 (0.00%)	0 / 37 (0.00%)	1 / 1220 (0.08%)
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			
Abdominal pain			
subjects affected / exposed	0 / 83 (0.00%)	0 / 37 (0.00%)	3 / 1220 (0.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal pain upper			
subjects affected / exposed	0 / 83 (0.00%)	0 / 37 (0.00%)	1 / 1220 (0.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Constipation			
subjects affected / exposed	0 / 83 (0.00%)	0 / 37 (0.00%)	2 / 1220 (0.16%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dysphagia			
subjects affected / exposed	0 / 83 (0.00%)	0 / 37 (0.00%)	1 / 1220 (0.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Enteritis			
subjects affected / exposed	0 / 83 (0.00%)	0 / 37 (0.00%)	1 / 1220 (0.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastritis			
subjects affected / exposed	1 / 83 (1.20%)	0 / 37 (0.00%)	0 / 1220 (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
Intestinal obstruction			
subjects affected / exposed	0 / 83 (0.00%)	0 / 37 (0.00%)	1 / 1220 (0.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower gastrointestinal haemorrhage			
subjects affected / exposed	0 / 83 (0.00%)	0 / 37 (0.00%)	1 / 1220 (0.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis acute			
subjects affected / exposed	0 / 83 (0.00%)	0 / 37 (0.00%)	2 / 1220 (0.16%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis chronic			
subjects affected / exposed	0 / 83 (0.00%)	0 / 37 (0.00%)	1 / 1220 (0.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Salivary gland calculus			
subjects affected / exposed	0 / 83 (0.00%)	0 / 37 (0.00%)	1 / 1220 (0.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	1 / 83 (1.20%)	0 / 37 (0.00%)	3 / 1220 (0.25%)
occurrences causally related to treatment / all	0 / 1	0 / 0	1 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			

Bile duct stone			
subjects affected / exposed	0 / 83 (0.00%)	0 / 37 (0.00%)	1 / 1220 (0.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholecystitis			
subjects affected / exposed	0 / 83 (0.00%)	0 / 37 (0.00%)	1 / 1220 (0.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholecystitis acute			
subjects affected / exposed	0 / 83 (0.00%)	0 / 37 (0.00%)	2 / 1220 (0.16%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholelithiasis			
subjects affected / exposed	0 / 83 (0.00%)	0 / 37 (0.00%)	1 / 1220 (0.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Dermatitis allergic			
subjects affected / exposed	0 / 83 (0.00%)	0 / 37 (0.00%)	1 / 1220 (0.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Erythema			
subjects affected / exposed	0 / 83 (0.00%)	0 / 37 (0.00%)	1 / 1220 (0.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Excessive granulation tissue			
subjects affected / exposed	0 / 83 (0.00%)	0 / 37 (0.00%)	1 / 1220 (0.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rash			
subjects affected / exposed	0 / 83 (0.00%)	0 / 37 (0.00%)	1 / 1220 (0.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rash maculo-papular			

subjects affected / exposed	0 / 83 (0.00%)	0 / 37 (0.00%)	1 / 1220 (0.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rash papular			
subjects affected / exposed	0 / 83 (0.00%)	0 / 37 (0.00%)	3 / 1220 (0.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	3 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin disorder			
subjects affected / exposed	0 / 83 (0.00%)	0 / 37 (0.00%)	1 / 1220 (0.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Swelling face			
subjects affected / exposed	0 / 83 (0.00%)	0 / 37 (0.00%)	1 / 1220 (0.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urticaria			
subjects affected / exposed	0 / 83 (0.00%)	0 / 37 (0.00%)	1 / 1220 (0.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 83 (0.00%)	0 / 37 (0.00%)	2 / 1220 (0.16%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nephrolithiasis			
subjects affected / exposed	0 / 83 (0.00%)	0 / 37 (0.00%)	1 / 1220 (0.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Proteinuria			
subjects affected / exposed	0 / 83 (0.00%)	0 / 37 (0.00%)	1 / 1220 (0.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endocrine disorders			

Adrenal mass			
subjects affected / exposed	0 / 83 (0.00%)	0 / 37 (0.00%)	1 / 1220 (0.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Inappropriate antidiuretic hormone secretion			
subjects affected / exposed	0 / 83 (0.00%)	0 / 37 (0.00%)	1 / 1220 (0.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 83 (0.00%)	0 / 37 (0.00%)	1 / 1220 (0.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemarthrosis			
subjects affected / exposed	0 / 83 (0.00%)	0 / 37 (0.00%)	1 / 1220 (0.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intervertebral disc disorder			
subjects affected / exposed	0 / 83 (0.00%)	0 / 37 (0.00%)	1 / 1220 (0.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intervertebral disc protrusion			
subjects affected / exposed	1 / 83 (1.20%)	0 / 37 (0.00%)	1 / 1220 (0.08%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Muscular weakness			
subjects affected / exposed	0 / 83 (0.00%)	0 / 37 (0.00%)	1 / 1220 (0.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteoarthritis			
subjects affected / exposed	0 / 83 (0.00%)	0 / 37 (0.00%)	1 / 1220 (0.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Osteonecrosis			
subjects affected / exposed	0 / 83 (0.00%)	0 / 37 (0.00%)	1 / 1220 (0.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rheumatoid arthritis			
subjects affected / exposed	0 / 83 (0.00%)	0 / 37 (0.00%)	1 / 1220 (0.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal osteoarthritis			
subjects affected / exposed	0 / 83 (0.00%)	0 / 37 (0.00%)	1 / 1220 (0.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Abdominal wall abscess			
subjects affected / exposed	0 / 83 (0.00%)	0 / 37 (0.00%)	1 / 1220 (0.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abscess oral			
subjects affected / exposed	0 / 83 (0.00%)	0 / 37 (0.00%)	1 / 1220 (0.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Appendiceal abscess			
subjects affected / exposed	0 / 83 (0.00%)	0 / 37 (0.00%)	1 / 1220 (0.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Appendicitis			
subjects affected / exposed	0 / 83 (0.00%)	0 / 37 (0.00%)	7 / 1220 (0.57%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 7
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cellulitis			
subjects affected / exposed	0 / 83 (0.00%)	0 / 37 (0.00%)	2 / 1220 (0.16%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Corona virus infection			

subjects affected / exposed	1 / 83 (1.20%)	0 / 37 (0.00%)	0 / 1220 (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
Dengue fever			
subjects affected / exposed	0 / 83 (0.00%)	0 / 37 (0.00%)	1 / 1220 (0.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Encephalitis			
subjects affected / exposed	0 / 83 (0.00%)	0 / 37 (0.00%)	1 / 1220 (0.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis			
subjects affected / exposed	0 / 83 (0.00%)	0 / 37 (0.00%)	2 / 1220 (0.16%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis bacterial			
subjects affected / exposed	0 / 83 (0.00%)	1 / 37 (2.70%)	0 / 1220 (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
Herpes zoster			
subjects affected / exposed	0 / 83 (0.00%)	0 / 37 (0.00%)	2 / 1220 (0.16%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Influenza			
subjects affected / exposed	0 / 83 (0.00%)	0 / 37 (0.00%)	1 / 1220 (0.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Otitis media			
subjects affected / exposed	0 / 83 (0.00%)	0 / 37 (0.00%)	1 / 1220 (0.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			

subjects affected / exposed	2 / 83 (2.41%)	0 / 37 (0.00%)	4 / 1220 (0.33%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia viral			
subjects affected / exposed	0 / 83 (0.00%)	0 / 37 (0.00%)	2 / 1220 (0.16%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	0 / 83 (0.00%)	0 / 37 (0.00%)	1 / 1220 (0.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis neonatal			
subjects affected / exposed	0 / 83 (0.00%)	0 / 37 (0.00%)	1 / 1220 (0.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tonsillitis			
subjects affected / exposed	0 / 83 (0.00%)	0 / 37 (0.00%)	1 / 1220 (0.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	0 / 83 (0.00%)	0 / 37 (0.00%)	4 / 1220 (0.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urosepsis			
subjects affected / exposed	0 / 83 (0.00%)	0 / 37 (0.00%)	2 / 1220 (0.16%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vestibular neuronitis			
subjects affected / exposed	0 / 83 (0.00%)	0 / 37 (0.00%)	1 / 1220 (0.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Dehydration			

subjects affected / exposed	0 / 83 (0.00%)	0 / 37 (0.00%)	1 / 1220 (0.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypernatraemia			
subjects affected / exposed	0 / 83 (0.00%)	0 / 37 (0.00%)	1 / 1220 (0.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypokalaemia			
subjects affected / exposed	0 / 83 (0.00%)	0 / 37 (0.00%)	2 / 1220 (0.16%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyponatraemia			
subjects affected / exposed	0 / 83 (0.00%)	0 / 37 (0.00%)	6 / 1220 (0.49%)
occurrences causally related to treatment / all	0 / 0	0 / 0	4 / 7
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tetany			
subjects affected / exposed	0 / 83 (0.00%)	0 / 37 (0.00%)	1 / 1220 (0.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	YKP3089 and Phenytoin	YKP3089 and Phenobarbital	YKP3089 and Other AEDs
Total subjects affected by non-serious adverse events			
subjects affected / exposed	61 / 83 (73.49%)	29 / 37 (78.38%)	887 / 1220 (72.70%)
Investigations			
Gamma-glutamyltransferase increased			
subjects affected / exposed	0 / 83 (0.00%)	2 / 37 (5.41%)	4 / 1220 (0.33%)
occurrences (all)	0	2	4
Weight decreased			
subjects affected / exposed	3 / 83 (3.61%)	0 / 37 (0.00%)	71 / 1220 (5.82%)
occurrences (all)	3	0	71
Injury, poisoning and procedural complications			

Contusion			
subjects affected / exposed	2 / 83 (2.41%)	2 / 37 (5.41%)	44 / 1220 (3.61%)
occurrences (all)	2	2	44
Fall			
subjects affected / exposed	6 / 83 (7.23%)	2 / 37 (5.41%)	65 / 1220 (5.33%)
occurrences (all)	6	2	65
Ligament sprain			
subjects affected / exposed	3 / 83 (3.61%)	2 / 37 (5.41%)	28 / 1220 (2.30%)
occurrences (all)	3	2	28
Toxicity to various agents			
subjects affected / exposed	8 / 83 (9.64%)	0 / 37 (0.00%)	2 / 1220 (0.16%)
occurrences (all)	8	0	2
Nervous system disorders			
Ataxia			
subjects affected / exposed	4 / 83 (4.82%)	4 / 37 (10.81%)	46 / 1220 (3.77%)
occurrences (all)	4	4	46
Balance disorder			
subjects affected / exposed	10 / 83 (12.05%)	4 / 37 (10.81%)	80 / 1220 (6.56%)
occurrences (all)	10	4	80
Dizziness			
subjects affected / exposed	30 / 83 (36.14%)	13 / 37 (35.14%)	339 / 1220 (27.79%)
occurrences (all)	30	13	339
Dysarthria			
subjects affected / exposed	1 / 83 (1.20%)	3 / 37 (8.11%)	36 / 1220 (2.95%)
occurrences (all)	1	3	36
Headache			
subjects affected / exposed	6 / 83 (7.23%)	7 / 37 (18.92%)	221 / 1220 (18.11%)
occurrences (all)	6	7	221
Memory impairment			
subjects affected / exposed	2 / 83 (2.41%)	2 / 37 (5.41%)	33 / 1220 (2.70%)
occurrences (all)	2	2	33
Nystagmus			
subjects affected / exposed	7 / 83 (8.43%)	1 / 37 (2.70%)	31 / 1220 (2.54%)
occurrences (all)	7	1	31
Seizure			

subjects affected / exposed occurrences (all)	3 / 83 (3.61%) 3	1 / 37 (2.70%) 1	53 / 1220 (4.34%) 53
Somnolence subjects affected / exposed occurrences (all)	22 / 83 (26.51%) 22	17 / 37 (45.95%) 17	377 / 1220 (30.90%) 377
Tremor subjects affected / exposed occurrences (all)	3 / 83 (3.61%) 3	2 / 37 (5.41%) 2	41 / 1220 (3.36%) 41
General disorders and administration site conditions Fatigue subjects affected / exposed occurrences (all)	18 / 83 (21.69%) 18	10 / 37 (27.03%) 10	232 / 1220 (19.02%) 232
Gait disturbance subjects affected / exposed occurrences (all)	7 / 83 (8.43%) 7	3 / 37 (8.11%) 3	62 / 1220 (5.08%) 62
Eye disorders Diplopia subjects affected / exposed occurrences (all)	6 / 83 (7.23%) 6	2 / 37 (5.41%) 2	97 / 1220 (7.95%) 97
Vision blurred subjects affected / exposed occurrences (all)	4 / 83 (4.82%) 4	3 / 37 (8.11%) 3	59 / 1220 (4.84%) 59
Gastrointestinal disorders Constipation subjects affected / exposed occurrences (all)	2 / 83 (2.41%) 2	2 / 37 (5.41%) 2	78 / 1220 (6.39%) 78
Diarrhoea subjects affected / exposed occurrences (all)	4 / 83 (4.82%) 4	5 / 37 (13.51%) 5	70 / 1220 (5.74%) 70
Haemorrhoids subjects affected / exposed occurrences (all)	1 / 83 (1.20%) 1	2 / 37 (5.41%) 2	14 / 1220 (1.15%) 14
Nausea subjects affected / exposed occurrences (all)	5 / 83 (6.02%) 5	1 / 37 (2.70%) 1	100 / 1220 (8.20%) 100
Reproductive system and breast			

disorders			
Erectile dysfunction			
subjects affected / exposed	1 / 83 (1.20%)	3 / 37 (8.11%)	4 / 1220 (0.33%)
occurrences (all)	1	3	4
Psychiatric disorders			
Anxiety			
subjects affected / exposed	4 / 83 (4.82%)	2 / 37 (5.41%)	48 / 1220 (3.93%)
occurrences (all)	4	2	48
Insomnia			
subjects affected / exposed	5 / 83 (6.02%)	2 / 37 (5.41%)	46 / 1220 (3.77%)
occurrences (all)	5	2	46
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	3 / 83 (3.61%)	2 / 37 (5.41%)	50 / 1220 (4.10%)
occurrences (all)	3	2	50
Pain in extremity			
subjects affected / exposed	2 / 83 (2.41%)	2 / 37 (5.41%)	18 / 1220 (1.48%)
occurrences (all)	2	2	18
Infections and infestations			
Ear infection			
subjects affected / exposed	0 / 83 (0.00%)	2 / 37 (5.41%)	14 / 1220 (1.15%)
occurrences (all)	0	2	14
Influenza			
subjects affected / exposed	7 / 83 (8.43%)	2 / 37 (5.41%)	49 / 1220 (4.02%)
occurrences (all)	7	2	49
Otitis media			
subjects affected / exposed	0 / 83 (0.00%)	2 / 37 (5.41%)	3 / 1220 (0.25%)
occurrences (all)	0	2	3
Upper respiratory tract infection			
subjects affected / exposed	10 / 83 (12.05%)	4 / 37 (10.81%)	103 / 1220 (8.44%)
occurrences (all)	10	4	103
Urinary tract infection			
subjects affected / exposed	8 / 83 (9.64%)	2 / 37 (5.41%)	68 / 1220 (5.57%)
occurrences (all)	8	2	68
Viral upper respiratory tract infection			

subjects affected / exposed	8 / 83 (9.64%)	4 / 37 (10.81%)	126 / 1220 (10.33%)
occurrences (all)	8	4	126
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	5 / 83 (6.02%)	2 / 37 (5.41%)	37 / 1220 (3.03%)
occurrences (all)	5	2	37

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
23 October 2015	Amendment 1 (dated October 23, 2015) was issued to make the following changes: <ul style="list-style-type: none">• Increase the number of subjects to be enrolled in the study• Slow the rate of titration of YKP3089 in subjects taking AEDs other than phenytoin or phenobarbital• Allow the enrollment of all 3 groups of subjects (phenytoin, phenobarbital, and other concomitant AEDs) concurrently• Provide updated YKP3089 exposure, safety, and efficacy data• Clarify felbamate exclusion requirements• Make administrative changes.
14 April 2016	Amendment 2 (dated April 14, 2016) was issued to make the following changes: <ul style="list-style-type: none">• Increase the number of subjects to be enrolled in the study• Reduce the initial dose of YKP3089• Slow the rate of titration of YKP3089• Update the exclusion criteria• Provide updated YKP3089 exposure, safety, and efficacy data in the introduction• Increase the frequency of visits and evaluations during the first 16 weeks of therapy with YKP3089• Update the skin/hypersensitivity safety assessments• Provide information for 2 new dosage strengths• Update the risk-benefit profile in the introduction• Make administrative changes.
03 June 2016	Amendment 3 (dated June 3, 2016) was issued to make the following changes: <ul style="list-style-type: none">• Allow subjects to increase the target dose up to 400 mg/day• Make minor administrative changes.
28 July 2017	Amendment 4 (dated July 28, 2017) was issued to make the following changes: <ul style="list-style-type: none">• Update inclusion and exclusion criteria to more effectively screen patients for a safety study• Update Birth Control Methods Allowable for Enrollment of Subjects• Add vital signs details to the Study Assessment table• Update screening number assignment• Clarify prohibited medications or devices• Clarify PK sampling• Update medical monitor contact information• Make minor administrative and editorial changes.
20 June 2019	Amendment 5 (dated June 20, 2019) was issued to make the following changes: SKLSI Address Updated – from 22-10 Route 208 South Fair Lawn, NJ to 461 From Road, Paramus, NJ 07652

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported