



Clinical trial results:

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

Summary

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

Results information

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

Trial information

Trial identification

| | |
|-----------------------|-------------|
| Sponsor protocol code | YKP3089C017 |
|-----------------------|-------------|

Additional study identifiers

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

Notes:

Sponsors

| | |
|------------------------------|---|
| Sponsor organisation name | SK Life Science, Inc. |
| Sponsor organisation address | 461 From Road, Paramus, United States, NJ 07652 |
| Public contact | Laurie Orlinski, SK Life Science, Inc., 1 201-421-3816, lorlinski@sklsi.com |
| Scientific contact | Marc Kamin, SK Life Science, Inc., 1 201-421-3830, mkamin@sklsi.com |

Notes:

Paediatric regulatory details

| | |
|--|----|
| Is trial part of an agreed paediatric investigation plan (PIP) | No |
| Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial? | No |
| Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial? | No |

Notes:

Results analysis stage

| | |
|--|-----------------|
| Analysis stage | Final |
| Date of interim/final analysis | 31 October 2021 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 05 April 2021 |
| Global end of trial reached? | Yes |
| Global end of trial date | 05 April 2021 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

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

Protection of trial subjects:

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

Background therapy:

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

Evidence for comparator:

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

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

Notes:

Population of trial subjects

Subjects enrolled per country

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

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

Notes:

| Subjects enrolled per age group | |
|---|-----|
| In utero | 0 |
| Preterm newborn - gestational age < 37 wk | 0 |
| Newborns (0-27 days) | 0 |
| Infants and toddlers (28 days-23 months) | 0 |
| Children (2-11 years) | 0 |
| Adolescents (12-17 years) | 0 |
| Adults (18-64 years) | 427 |
| From 65 to 84 years | 10 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

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

Pre-assignment

Screening details:

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

Period 1

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

Blinding implementation details:

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

Arms

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

Arm description:

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

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

Dosage and administration details:

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

| | |
|------------------|---------------------|
| Arm title | YKP3089 (200 mg qd) |
|------------------|---------------------|

Arm description:

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

| | |
|----------|--------------|
| Arm type | Experimental |
|----------|--------------|

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

Dosage and administration details:

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

| | |
|------------------|---------------------|
| Arm title | YKP3089 (400 mg qd) |
|------------------|---------------------|

Arm description:

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

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

Dosage and administration details:

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

| | |
|------------------|---------|
| Arm title | Placebo |
|------------------|---------|

Arm description:

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

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

Dosage and administration details:

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

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

| | | | |
|--------------------|---|---|---|
| Lack of efficacy | 1 | - | 1 |
| Protocol deviation | - | 1 | 1 |

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

Period 2

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

Blinding implementation details:

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

Arms

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

Arm description:

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

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

Dosage and administration details:

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

The initial target dose for the open-label extension phase was 300 mg/day. However, if a subject was not able to tolerate the 300 mg/day dose, YKP3089 dose was reduced to a minimum of 50 mg/day. If the investigator felt that a subject required a dose that was higher than 300 mg/day, the dose was increased to a maximum of 400 mg/day once the target dose of 300 mg/day was reached. If 50 mg/day of YKP3089 was not tolerated, the subject was withdrawn from the study. The dose adjustments occurred in weekly increments of 100 mg/day or 50 mg/day.

| | |
|------------------|----------------------------------|
| Arm title | DB YKP3089 200 mg to YKP3089 OLE |
|------------------|----------------------------------|

Arm description:

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

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

Dosage and administration details:

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

The initial target dose for the open-label extension phase was 300 mg/day. However, if a subject was not able to tolerate the 300 mg/day dose, YKP3089 dose was reduced to a minimum of 50 mg/day. If the investigator felt that a subject required a dose that was higher than 300 mg/day, the dose was increased to a maximum of 400 mg/day once the target dose of 300 mg/day was reached. If 50 mg/day of YKP3089 was not tolerated, the subject was withdrawn from the study. The dose adjustments occurred in weekly increments of 100 mg/day or 50 mg/day.

| | |
|------------------|----------------------------------|
| Arm title | DB YKP3089 400 mg to YKP3089 OLE |
|------------------|----------------------------------|

Arm description:

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

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

Dosage and administration details:

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

The initial target dose for the open-label extension phase was 300 mg/day. However, if a subject was not able to tolerate the 300 mg/day dose, YKP3089 dose was reduced to a minimum of 50 mg/day. If the investigator felt that a subject required a dose that was higher than 300 mg/day, the dose was increased to a maximum of 400 mg/day once the target dose of 300 mg/day was reached. If 50 mg/day of YKP3089 was not tolerated, the subject was withdrawn from the study. The dose adjustments occurred in weekly increments of 100 mg/day or 50 mg/day.

| | |
|------------------|---------------------------|
| Arm title | Placebo DB to YKP3089 OLE |
|------------------|---------------------------|

Arm description:

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

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

Dosage and administration details:

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

The initial target dose for the open-label extension phase was 300 mg/day. However, if a subject was not able to tolerate the 300 mg/day dose, YKP3089 dose was reduced to a minimum of 50 mg/day. If the investigator felt that a subject required a dose that was higher than 300 mg/day, the dose was increased to a maximum of 400 mg/day once the target dose of 300 mg/day was reached. If 50 mg/day of YKP3089 was not tolerated, the subject was withdrawn from the study. The dose adjustments occurred in weekly increments of 100 mg/day or 50 mg/day.

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

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

Notes:

[1] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.

Justification: 356 of 360 subjects entered open-label extension period; 4 subjects have an answer of 'No' to the question 'if subject going to OLE' without more details.

Baseline characteristics

Reporting groups

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

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

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

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

Subject analysis sets

| | |
|----------------------------|--------------------|
| Subject analysis set title | ITT population |
| Subject analysis set type | Intention-to-treat |

Subject analysis set description:

The ITT population included all randomized subjects.

| | |
|----------------------------|-----------------------------|
| Subject analysis set title | MITT population |
| Subject analysis set type | Modified intention-to-treat |

Subject analysis set description:

MITT population includes all randomized subjects with at least 1 dose of YKP3089 or placebo and had any postbaseline seizure data.

| | |
|----------------------------|--------------------|
| Subject analysis set title | MITT-M population |
| Subject analysis set type | Sub-group analysis |

Subject analysis set description:

MITT-M population includes all randomized subjects who completed the titration phase, took at least 1 dose of YKP3089 or placebo in the maintenance phase, and had any maintenance phase seizure data.

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

Subject analysis set description:

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

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

Subject analysis set description:

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

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

Subject analysis set description:

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

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

| | | | |
|---------------------------------------|-----|--|--|
| Gender categorical Units: Subjects | | | |
| Female | 216 | | |
| Male | 221 | | |

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

End points

End points reporting groups

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

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

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

Subject analysis set description:

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

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

Subject analysis set description:

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

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

Subject analysis set description:

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

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

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

End point description:

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

The primary efficacy endpoint values below will be based on the MITT population.

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Double-blind treatment period

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

Statistical analyses

| | |
|-----------------------------------|---|
| Statistical analysis title | ANCOVA for Percentage Change in Seizure in DB |
|-----------------------------------|---|

Statistical analysis description:

The primary analysis for this primary efficacy endpoint will be based on the MITT population.

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

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

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

Notes:

[1] - An analysis of covariance (ANCOVA) model will be fit to the ranked values of the primary efficacy endpoint. The ANCOVA will have terms for ranked baseline seizure rate and randomized treatment group. Ties will be handled using TIES=MEAN.

It should be noted that the primary efficacy analysis uses a non-parametric approach. Because of this, effect sizes are not estimated and tested directly, since testing is made on the rank of the primary efficacy value.

[2] - p-value (YKP3089 100 mg qd vs Placebo) = 0.007

p-value (YKP3089 200 mg qd vs Placebo) < 0.001

p-value (YKP3089 400 mg qd vs Placebo) < 0.001

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

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

End point description:

The primary efficacy endpoint for Europe, Australia, New Zealand, and South Africa is the responder rate (responder is defined as a $\geq 50\%$ reduction during the maintenance phase of double-blind treatment period in seizure frequency from baseline period).

The primary efficacy endpoint values below will be based on the MITT-M population.

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

During maintenance phase of double-blind treatment period

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

Statistical analyses

| | |
|-----------------------------------|--|
| Statistical analysis title | Fisher Exact Test for Responder Rate in DB |
|-----------------------------------|--|

Statistical analysis description:

The primary analysis for this primary efficacy endpoint will be based on the MITT-M population.

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

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

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

Notes:

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

p-value (YKP3089 200 mg qd vs Placebo) < 0.001

p-value (YKP3089 400 mg qd vs Placebo) < 0.001

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

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

End point description:

This efficacy endpoint was defined as the percentage change from pretreatment baseline period in seizure frequency (average monthly seizure rate per 28 days) of Type B, Type C, and Type D seizures during the open-label extension phase.

The efficacy endpoint values below will be based on the OLE-EA population.

| | |
|----------------|---------------------|
| End point type | Other pre-specified |
|----------------|---------------------|

End point timeframe:

During open-label extension phase

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

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

Statistical analyses

Adverse events

Adverse events information

Timeframe for reporting adverse events:

During the double-blind treatment period

Adverse event reporting additional description:

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

| | |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

Dictionary used

| | |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

| | |
|--------------------|------|
| Dictionary version | 18.1 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|---------------------|
| Reporting group title | YKP3089 (100 mg qd) |
|-----------------------|---------------------|

Reporting group description:

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

| | |
|-----------------------|---------------------|
| Reporting group title | YKP3089 (200 mg qd) |
|-----------------------|---------------------|

Reporting group description:

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

| | |
|-----------------------|---------------------|
| Reporting group title | YKP3089 (400 mg qd) |
|-----------------------|---------------------|

Reporting group description:

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

| | |
|-----------------------|---------|
| Reporting group title | Placebo |
|-----------------------|---------|

Reporting group description:

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

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

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

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

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

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 1 / 108 (0.93%) | 0 / 110 (0.00%) | 0 / 111 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Skin and subcutaneous tissue disorders | | | |
| Drug reaction with eosinophilia and systemic symptoms | | | |
| subjects affected / exposed | 0 / 108 (0.00%) | 1 / 110 (0.91%) | 0 / 111 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Psychiatric disorders | | | |
| Suicidal ideation | | | |
| subjects affected / exposed | 2 / 108 (1.85%) | 0 / 110 (0.00%) | 0 / 111 (0.00%) |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Suicide attempt | | | |
| subjects affected / exposed | 1 / 108 (0.93%) | 0 / 110 (0.00%) | 0 / 111 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infections and infestations | | | |
| Abscess jaw | | | |
| subjects affected / exposed | 0 / 108 (0.00%) | 0 / 110 (0.00%) | 0 / 111 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infectious colitis | | | |
| subjects affected / exposed | 0 / 108 (0.00%) | 0 / 110 (0.00%) | 0 / 111 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|-----------------|--|--|
| Serious adverse events | Placebo | | |
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 6 / 108 (5.56%) | | |
| number of deaths (all causes) | 0 | | |
| number of deaths resulting from adverse events | 0 | | |
| Investigations | | | |
| Alanine aminotransferase increased | | | |

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

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

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

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

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

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

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

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

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

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

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

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|-----------------|---|
| 07 January 2014 | The following is a summary of the major changes implemented with Protocol Amendment 1 (global amendment dated on 07 Jan 2014 for all countries except France, Germany, Korea, and the United Kingdom, for which the amendment date was 09 Jan 2014): <ul style="list-style-type: none">• Reduced the initial starting dose to 50 mg/day and slowed the titration rate to improve tolerability.• Clarified the definition of uncontrolled partial seizures.• Provided guidance on contraception for male subjects.• Allowed the first dose of study drug to be given at the investigator's site.• Revised the timelines for the data monitoring committee review of data.• Added a 50 mg/day dosing card. |
| 20 March 2015 | The following is a summary of the major changes implemented with Protocol Amendment 2 (global amendment dated 20 Mar 2015 for all countries): <ul style="list-style-type: none">• Removed interim analysis.• Provided details of proposed statistical procedures.• Added lacosamide as one of the concomitant AEDs in the pharmacokinetic (PK) analysis. |
| 17 June 2019 | The following changes were implemented with Protocol Amendment 3 (global amendment dated 17 Jun 2019 for all countries except Germany for which the amendment date was 16 Aug 2019): <ul style="list-style-type: none">• Updated SK Life Science Inc.'s address. |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported