SK Life Science Inc.
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Paramus, NJ 07652

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

Clinical Study Protocol

May 21, 2015

Amendment 1, October 23, 2015

Amendment 2, April 14, 2016

Amendment 3, June 03, 2016

Amendment 4, July 28, 2017

Amendment 5, June 20, 2019

PROTOCOL SIGNATURE PAGE

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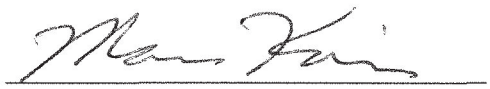

21 JUN 2019

Marc Kamin, MD
Chief Medical Officer,
SK Life Science, Inc.

Date

INVESTIGATOR SIGNATURE PAGE

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By my signature, I confirm that my staff and I have carefully read and understand this protocol or protocol amendment, and agree to comply with the conduct and terms of the study specified herein and with any other study conduct procedures provided by SK Life Science Inc. Date

Investigator's Signature

_____ _____

Print Name

_____

PROTOCOL AMENDMENTS

Amendment 1

Reasons for amendment

1. To increase number of subjects to be enrolled in the study
2. To slow the rate of titration of YKP3089 in subjects taking AEDs other than phenytoin or phenobarbital
3. To allow enrollment of all three groups of subjects (phenytoin, phenobarbital and other concomitant AEDs) concurrently
4. To provide updated YKP3089 exposure, safety and efficacy data
5. To clarify felbamate exclusion requirements
6. To make administrative changes

Amendment 1 Summary of Changes

Section	*Old Text*	*Amended Text*	*Rationale*
1. PROTOCOL SYNOPSIS Study Centers	Approximately 50 sites (multiple countries)	Approximately 75 sites (multiple countries)	To increase number of sites to account for increased number of subjects
1. PROTOCOL SYNOPSIS Number of subjects	Initially at least 20 subjects taking phenytoin and at least 20 subjects taking phenobarbital; followed by an additional approximately 450 subjects taking AEDs other than phenytoin or phenobarbital, at a time to be determined by the Sponsor, to further evaluate long term safety.	At least 20 subjects taking phenytoin and at least 20 subjects taking phenobarbital and approximately an additional 700 subjects taking AEDs other than phenytoin or phenobarbital, to further evaluate long term safety.	To increase number of subjects to be enrolled in the study
1. PROTOCOL SYNOPSIS Design and methodology	*Subjects on concomitant AEDs other than phenytoin or phenobarbital:* The titration phase for subjects on stable doses of other concomitant AEDs will be 4 weeks. Increasing doses of YKP3089 will be administered (50, 100, 150 and 200mg/day) at 1-week intervals. The investigator may add, remove, or adjust the dosage of concomitant AEDs, as clinically indicated in this group of subjects. Monotherapy with YKP3089 will not be allowed.	*Subjects on concomitant AEDs other than phenytoin or phenobarbital:* The titration phase for subjects on stable doses of other concomitant AEDs will be 8 weeks. Increasing doses of YKP3089 will be administered (50, 100, 150 and 200mg/day) at 2-week intervals. The investigator may add, remove, or adjust the dosage of concomitant AEDs, as clinically indicated in this group of subjects. Monotherapy with YKP3089 will not be allowed.	A recent aggregate analysis revealed that the rate of rash/hypersensitivity reactions was lowest when the rate of titration was at 50mg every two weeks
1. PROTOCOL SYNOPSIS Statistics and analyses	The results of the open-label extension will be reported using summary tables, figures, and data listings. Summaries will be presented for demographic information and safety information only.	The results ~~of the open-label extension~~ will be reported using summary tables, figures, and data listings. Summaries will be presented for demographic information and safety information only.	To correct typographical error
3. STUDY ASSESSMENTS Table 1	Colum headers were separate for phenytoin/phenobarbital vs other concomitant AEDs	All subjects have same titration rate with a single set of headers	All subjects will have the same titration rate
4.4.3 Clinical Safety and Efficacy	Cumulatively, approximately 800 subjects have been exposed to YKP3089 in a total of 12 Phase 1 and 3 Phase 2 clinical studies.	Cumulatively, 953 subjects have been exposed to YKP3089 in a total of 14 Phase 1 and 3 Phase 2 clinical studies.	To provide updated exposure, safety and efficacy data

Amendment 2

Reasons for Amendment

1. To increase number of subjects to be enrolled in the study
2. To reduce the initial dose of YKP3089
3. To slow the rate of titration of YKP3089
4. To update the exclusion criteria
5. To provide updated YKP3089 exposure, safety and efficacy data in the introduction
6. To increase the frequency of visits and evaluations during the first 16 weeks of therapy with YKP3089
7. To update the skin/hypersensitivity safety assessments
8. To provide information for two new dosage strengths
9. To update the risk benefit profile in the introduction
10. To make administrative changes

Amendment 2 Summary of Changes

Section	*Old Text*	*Amended Text*	*Rationale*
1. PROTOCOL SYNOPSIS Study Center(s)	Approximately 75 sites (multiple countries)	Approximately 50-100 sites (multiple countries)	To increase number of sites to account for increased number of subjects
1. PROTOCOL SYNOPSIS Number of subjects	At least 20 subjects taking phenytoin and at least 20 subjects taking phenobarbital and approximately an additional 700 subjects taking AEDs other than phenytoin or phenobarbital, to further evaluate long term safety.	At least 20 subjects taking phenytoin and at least 20 subjects taking phenobarbital. Additional subjects taking AEDs other than phenytoin or phenobarbital, will be enrolled in order to expose a total of at least 1,000 subjects for at least 6 months.	To increase number of subjects to be enrolled in the study
1. PROTOCOL SYNOPSIS Design and methodology	The study will consist of a screening period, open-label titration phase, open label maintenance phase and a taper and follow up. **Screening period** The screening period for subjects on stable doses of phenytoin or stable doses of phenobarbital or stable doses of other concomitant AEDs will be up to 21 days. **Titration phase** *Subjects on phenytoin or phenobarbital:* The titration phase for subjects on stable doses of phenytoin or stable doses of phenobarbital will be 8 weeks. Increasing doses of YKP3089 will be administered (50, 100, 150 and 200mg/day) at 2-week intervals. Sparse sampling of phenytoin, phenobarbital and YKP3089 plasma levels will be	The study will consist of a screening period, a 12 week open-label titration phase, an open label maintenance phase and a taper and follow up. Clinic visits during the first 16 weeks of therapy will be every two weeks with a telephone contact between each visit. At each visit during the first 16 weeks physical exams to evaluate signs of hypersensitivity will be performed and laboratory evaluations will be obtained. **Screening period** The screening period for subjects on stable doses of phenytoin or stable doses of phenobarbital or stable doses of other concomitant AEDs will be up to 21 days. **Titration phase** *Subjects on phenytoin or phenobarbital:* The titration phase for subjects on stable doses of phenytoin or stable doses of phenobarbital will be 12 weeks. Increasing doses of YKP3089 will be administered (12.5, 25, 50, 100, 150 and 200mg/day) at 2-week intervals. Sparse sampling of phenytoin, phenobarbital and YKP3089	To reduce the rate of DRESS incidence by lowering initial dose of YKP3089 and slowing the rate of titration

Amendment 3

Reasons for Amendment

1. To allow subjects to increase the target dose up to 400 mg/day

2. Minor administrative changes

Amendment 3 Summary of Changes

Section	*Old Text*	*Amended Text*	*Rationale*
1. PROTOCOL SYNOPSIS Open Label Maintenance Phase Subjects on phenytoin or phenobarbital	If the investigator feels that a subject requires a dose that is lower than 200 mg/day, the dose can be reduced to a minimum of 50 mg/day once the target dose of 200 mg/day was reached. The dose adjustments may occur in weekly increments of 100-mg/day or 50-mg/day. However, the rate of change may be more rapid or slow as clinically indicated. The investigator may add, remove, or adjust the dosage of concomitant AEDs, as clinically indicated. Monotherapy with YKP3089 will not be allowed.	If the investigator feels that a subject requires a dose that is higher than 200 mg/day, the dose can be increased to a maximum of 400 mg/day once the target dose of 200 mg/day was reached The upward dose adjustments should occur every other week in increments of 50-mg/day. If the investigator feels that a subject requires a dose that is lower than 200 mg/day, the dose can be reduced to a minimum of 50 mg/day once the target dose of 200 mg/day was reached. The downward dose adjustments may occur weekly by 100-mg/day or 50-mg/day. However, the downward rate of change may be more rapid or slow as clinically indicated. The investigator may add, remove, or adjust the dosage of concomitant AEDs, as clinically indicated. Monotherapy with YKP3089 will not be allowed.	To increase to a maximum of 400mg/day
PROTOCOL SYNOPSIS Open Label Maintenance Phase Subjects on concomitant AEDs other than phenytoin or phenobarbital	If the investigator feels that a subject requires a dose that is lower than 200 mg/day, the dose can be reduced to a minimum of 50 mg/day once the target dose of 200 mg/day was reached. The dose adjustments may occur in weekly increments of 100-mg/day or 50-mg/day. However, the rate of change may be more rapid or slow as clinically indicated.	For subjects taking other concomitant AEDs, the initial target dose will be 200 mg/day. If the investigator feels that a subject requires a dose that is higher than 200 mg/day, the dose can be increased to a maximum of 400 mg/day once the target dose of 200 mg/day was reached. The upward dose adjustments should occur every other week in increments of 50-mg/day. If the investigator feels that a subject requires a dose that is lower than 200 mg/day, the dose can be reduced to a minimum of 50 mg/day once the target dose of 200 mg/day was reached. The downward dose adjustments may occur weekly by 100-mg/day or 50-mg/day. However, the downward rate of change may be more rapid or slow as clinically indicated.	To increase to a maximum of 400mg/day
Section 4.5 Rationale Section 4.5.2.Dose Justification		After reaching a target dose of 200mg, all subjects will be allowed to titrate up to a maximum dose of 400mg/day of YKP3089. A maximum dose of 400mg/day is justified by the additional efficacy	To increase to a maximum of 400mg/day

Amendment 4

Reasons for Amendment

1. To update inclusion and exclusion criteria to more effectively screen patients for a safety study
2. To update Birth Control Methods Allowable for Enrollment of Subjects
3. To addvital signs details to the Study Assessment table
4. To update screening number assignment
5. To clarify prohibited medications or devices
6. To clarify pharmacokinetics sampling
7. To update Medical Monitor contact information
8. Minor administrative and editorial changes

Amendment 4 Summary of Changes

Section	*Old Text*	*Amended Text*	*Rationale*
3. STUDY ASSESSMENTS Table 1. Study Assessment Flow Chart	b. Vital signs include blood pressure, and heart rate (supine for 5 minutes).	b. Vital signs include blood pressure, heart rate (supine for 5 minutes), temperature, and respiratory rate.	To update vital sign details in the study assessment table
3. STUDY ASSESSMENTS Table 1. Study Assessment Flow Chart	i. Two blood samples will be collected for the determination of YKP3089 plasma levels: the first one will be collected upon subjects' arrival to the study unit; the second one should be collected within 2 to 4 hours after the first blood draw. Collect at visit 8 and/ or 9 depending on stability of dosing (doses must be stable for 2 weeks prior to these visits) of all concomitant AEDs including oxcarbazepine, topiramate, lamotrigine, lacosamide, clobazam, perampanel, levetiracetam, phenytoin and phenobarbital and YKP3089.	i. Two blood samples will be collected for the determination of YKP3089 plasma levels: For patients that are taking YKP3089 in the morning and coming into the visits in the morning, the first blood draw will be collected upon subjects' arrival to the study unit; the second blood draw should be collected within 30 minutes to 2 hours after the medication is taken. Collect at visit 8 and/ or 9 depending on stability of dosing (doses must be stable for 2 weeks prior to these visits) of all concomitant AEDs including oxcarbazepine, topiramate, lamotrigine, lacosamide, clobazam, perampanel, levetiracetam, phenytoin and phenobarbital and YKP3089. YKP3089 PK draw is applicable for subjects on phenytoin and phenobarbital globally and all subjects at US sites.	To clarify pharmacokinetics sampling
3. STUDY ASSESSMENTS Table 1. Study Assessment Flow Chart	j. At Visit 2, a single trough level of phenytoin or phenobarbital will be obtained. At visits 4, 5, 6, 7 and 8 two blood samples will be collected for the determination of phenobarbital and phenytoin plasma levels: the first one will be collected upon subjects' arrival to the study unit; the second one should be collected within 2 to 4 hours after the first blood draw.	j. At Visit 2, a single trough level of phenytoin or phenobarbital will be obtained. At visits 4, 5, 6, 7 and 8 two blood samples will be collected for the determination of phenobarbital and phenytoin plasma levels: For subjects that are taking phenytoin or phenobarbital in the morning and coming into the visits in the morning, the first blood draw will be collected upon subjects' arrival to the study unit; the second blood draw should be collected within 2 to 4 hours after the medication is taken.	To clarify pharmacokinetics sampling
3. STUDY ASSESSMENTS	k. At Visit 2, a single trough level of concomitant AEDs will be obtained. At Visits 8 and 9, two blood samples will be collected for the determination of concomitant AED plasma	k. Concomitant AED PK draw will be done at US sites only. At Visit 2, a single trough level of concomitant AEDs will be obtained. At Visits 8 and 9, two blood samples will be	To clarify pharmacokinetics sampling

Amendment 5

Reason for Amendment Change

1. **Version number and date updated -** Version number and date updated throughout document.

2. **SK Life Science Address update** - SK Life Science, Inc. address updated from: SK Life Science, Inc., 22-10 Route 208 South Fair Lawn, NJ 07410 USA. To: SK Life Science, Inc., 461 From Road, 5th FL, Paramus, NJ 07652 USA

TABLE OF CONTENTS

1 PROTOCOL SYNOPSIS

Name of company	SK Life Science Inc
Title of study	An Open Label, Multicenter, Safety and Pharmacokinetic Study of YKP3089 as Adjunctive Therapy in Subjects with Partial Onset Seizures
Protocol number	YKP3089C021
Phase of development	Phase 3
Study duration	After 12 months of participation in the study, subjects will be evaluated for treatment response. Those who are benefiting from treatment with YKP3089 may continue use of the drug at the discretion of the investigator, until development is stopped by SK Life Science Inc or the product is approved for marketing, or anytime at the discretion of SK Life Science Inc.
Indication	Partial-onset epilepsy
Study center(s)	Approximately 80-110 sites (multiple countries)
Number of subjects	At least 20 subjects taking phenytoin and at least 20 subjects taking phenobarbital. Additional subjects taking AEDs other than phenytoin or phenobarbital, will be enrolled in order to expose a total of at least 1,000 subjects for at least 6 months.
Objectives	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.
Inclusion and exclusion criteria	Subjects to be enrolled in the study include: 1. Subjects on stable doses of phenytoin 2. Subjects on stable doses of phenobarbital 3. Subjects on stable doses of other concomitant AEDs Subjects who meet all inclusion and no exclusion criteria listed in Section 7.3 and Section 7.4 of the protocol are eligible to enroll.

2 LIST OF ABBREVIATIONS

AE	Adverse event
AED	Antiepileptic drug
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUC	Area under the plasma concentration versus time curve
β-hCG	β-human chorionic gonadotropin
CBZ	Carbamazepine
CFR	Code of Federal Regulations
CNS	Central nervous system
C-SSRS	Columbia Suicide Severity Rating Scale
CT	Computed tomography
CYP	Cytochrome P450
DRESS	Drug reaction (or rash) with eosinophilia and systemic symptoms
EC	Ethics committee
ECG	Electrocardiogram
eCRF	Electronic case report form
EEG	Electroencephalograph
FDA	Food and Drug Administration
GABA	Gamma-aminobutyric acid
GCP	Good Clinical Practice
ICH	International Conference on Harmonisation
IND	Investigational new drug
IRB	Institutional review board
IWRS	Interactive Web response system
kg	Kilogram
mg	Milligram
MRI	Magnetic resonance imaging
PHI	Protected health information
PI	Principal Investigator
SAE	Serious adverse event
SKLSI	SK Life Science, Inc.
SUDEP	Sudden unexpected death in epilepsy
SUSAR	Suspected unexpected serious adverse reaction
VNS	Vagal nerve stimulator
VPA	Valproic acid (divalproex sodium)

3 STUDY ASSESSMENTS

Table 1. Study Assessment Flow Chart

4 BACKGROUND AND DOSE SELECTION

4.1 Introduction

This is a protocol for a human research study. This study is being conducted according to US and international standards of Good Clinical Practice (GCP) (Food & Drug Administration [FDA] Title 21 Part 312 and International Conference on Harmonisation [ICH] guidelines), applicable government regulations, and Institutional research policies and procedures.

4.2 Considerations for Studies of Epilepsy

According to the World Health Organization, epilepsy afflicts more than 50 million people worldwide.[1] Epilepsy leads to an increased risk of injury from accidents and an increased rate of mortality and has a significant impact on quality of life. First-generation antiepileptic drugs (AEDs) are still commonly used, even though they can produce a diversity of serious adverse events (SAEs). New AEDs approved since the early 1990s have shown an improved tolerability profile. Nonetheless, approximately 30% of epilepsy cases, particularly those with partial seizures, are refractory to treatment. Many of these patients are taking multiple antiepileptic drugs. It is important to understand any interaction that occurs between them as well as the long term safety profile of YKP3089 when given as adjunctive therapy.

Choice of add-on (adjunctive) design. The initial evaluation of a new antiepileptic drug generally includes a determination of its efficacy in reducing the frequency of seizures in adults who are refractory to treatment with other AEDs.[2,3,4] Because of the risk of exacerbation of seizure severity and frequency upon withdrawal of long-term AED therapy, even in the refractory population, the new AED under study is added to the existing therapy instead of being used as monotherapy. Because partial seizures represent the most common type in both adults and children and claim a disproportionate share of medically refractory cases, they have been the most frequently selected seizure type in the investigation of new AEDs.

4.3 Background

4.3.1 *YKP3089 Structure*

YKP3089 is (R)-(+)-1-(2-chloro-phenyl)-2-tetrazol-2-yl-ethyl ester, which has the chemical formula C_{10} H_{10} Cl $N_{5.}$ YKP3089 is being provided in tablets that contain 50 or 100 mg of the active ingredient. It is a novel small molecule of molecular weight 267.68. Its structure is shown in Figure 1.

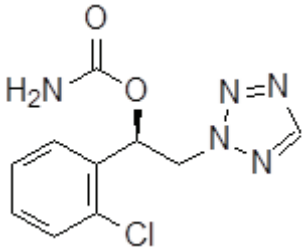

Figure 1. Structure of YKP3089

YKP3089 is a novel small molecule with open INDs for epilepsy (76,809), neuropathic pain (IND 108,178), and anxiety (IND 72,741). It is currently in Phase 2 of development as an antiepileptic agent for partial onset seizures. YKP3089 was shown to be active in standard animal models of epilepsy, neuropathic pain, and anxiety when administered orally.

4.4 Pharmacology

Receptor test systems have shown that YKP3089 does not show significant activity at any of the classical receptor types (eg, adrenergic, GABAergic) or pharmacologic receptors. However, *in vitro* electrophysiology assays showed YKP3089 to be an inhibitor of the slow inactivated state of sodium channels. YKP3089 may also increase inhibitory synaptic transmission by facilitating the release of GABA.

4.4.1 *Absorption, Distribution, Metabolism, and Excretion*

In vitro studies with human microsomes revealed that YKP3089 directly inhibited CYP2B6 (IC_{50} = 280 μM), CYP2C19 (IC_{50} = 170 μM), and CYP3A4/5 (as measured by testosterone 6β-hydroxylation, IC_{50} = 890 μM; and midazolam 1′-hydroxylation, IC_{50} = 720 μM). These IC_{50}

the reciprocal effects of phenytoin and YKP3089, plasma phenytoin exposure increased with co-administration of YKP3089 by 67% (C_{max}) and 84% (AUC) and plasma YKP3089 exposure (C_{max}, AUC) decreased with co-administration of phenytoin by 27 - 28%. Preliminary results of a drug interaction study examining the reciprocal effects of phenobarbital and YKP3089, plasma phenobarbital exposure increased with co-administration of YKP3089 by 34% (C_{max}) and 37% (AUC) and plasma YKP3089 exposure (C_{max}, AUC) decreased with co-administration of phenobarbital by 10-15% based on historical controls.

4.4.2 *Safety Pharmacology and Toxicity Studies*

YKP3089 has been assessed in a large number of safety pharmacology and toxicology studies including single-dose toxicity, repeat-dose toxicity, cardiotoxicity, genetic toxicity, and reproductive toxicity studies in animals. Safety pharmacology studies showed that the doses that produced beneficial central nervous system (CNS) effects of YKP3089 in animal models do not result in obvious negative effects on the CNS. No evidence of cardiovascular effects was observed by telemetric electrocardiography in male monkeys.

Details of the preclinical safety and toxicity studies of YKP3089 can be found in the Investigator's Brochure. The most common AEs in preclinical studies of YKP3089 involved the central nervous system (CNS).

Reproductive toxicity studies showed adverse effects on reproductive performance when the dosage of YKP3089 was high enough to induce maternal toxicity, as evidenced by decreased food consumption and decreased body weight. However, there was no evidence of teratogenicity.

The results of standard genotoxicity studies of YKP3089 were negative. There is no evidence of carcinogenicity in standard testing of two rodent species.

4.4.3 *Clinical Safety and Efficacy*

Cumulatively, 953 subjects have been exposed to YKP3089 in a total of 14 Phase 1 and 3 Phase 2 clinical studies.

The results of the first completed double-blind, randomized, placebo-controlled trial in subjects with partial epilepsy demonstrated that treatment with 200 mg of YKP3089 produced a highly

statistically significant reduction in the frequency of partial onset seizures (Table 2) and seizure free rates (Table 3). YKP3089 was generally well-tolerated. The rate of adverse event withdrawals was similar between the YKP3089 and placebo groups. No life threatening serious adverse events were identified among YKP3089-treated subjects. The most common central nervous system adverse events in the YKP3089 group were somnolence, dizziness, fatigue, and gait disorder.

The second randomized, double-blind, placebo-controlled, dose response trial with a 18 week treatment period enrolled a total of 437 subjects, 108 in a 100 mg YKP3089 group, 110 in a 200 mg YKP3089 group, 111 in a 400 mg YKP3089 group and 109 in a placebo group. The trial confirmed that treatment with 200 mg/day and 400mg/day of YKP3089 produces a highly statistically significant reduction in the frequency of partial onset seizures in patients with partial epilepsy (Table 2) and high seizure free rates (Table 4).

Table 2: Effect Size of Median Percent Reduction and 50% Responder Rate Relative to Placebo in YKP3089 Trials

	YKP3089C013 Study	YKP3089C017 Study		
Dose	200mg	100mg	200mg	400mg
Median Percent Reduction	34.1	11.5	31.0	31.0
50% Responder Rate	28.2	19.0	35.2	38.7

P values in all comparisons were <0.01

Table 3: Seizure free Rates (Completer Population) at 200mg in YKP3089C013

Responder Type	6 Week Maintenance Phase		
	% Responders placebo N = 99	% Responders YKP3089 N = 102	P value
100%	9.1	27.5	0.0003

Table 4: Seizure Free Rates (Completer Population) in YKP3089C017

Responder Type	12 Week Maintenance Phase			
	% Responders	% Responders (YKP3089 100 mg)	% Responders	% Responders

There have been three cases of DRESS syndrome in YKP3089 clinical studies.

Rash and hypersensitivity During the YKP3089 development program there have been other reports of rash and hypersensitivity reactions, some resulting in hospitalization and/or discontinuation. An aggregate analysis of the rate of rash/hypersensitivity and DRESS in subjects exposed to multiple doses of YKP3089 was performed Table 5.

Table 5: Rate of rash/hypersensitivity and DRESS in subjects exposed to multiple doses of YKP3089

	Starting Dose 50 mg with 50 mg Increase Every 2 Weeks		**Starting dose 50 mg with 50 mg Increase Every 1 Week**		**Starting dose 100 mg or more with 100 mg Increase Every 5 to 7 Days**		**Total**	
	Active	Placebo	Active	Placebo	Active	Placebo	Active	Placebo
Subjects Exposed	120	112	363	152	350	37	833	301
Rash/hypersensitivity N (%)	1 (0.8%)	3 (2.7%)	18(5.0%)	4(2.6%)	19 (5.4%)	3 (8.1%)	38 (4.6%)	10 (3.3%)
Dropouts	1 (0.8%)	0	8 (2.2%)	1 (0.6%)	9 (2.5%)	0	18 (2.2%)	1 (0.3%)
DRESS	0	0	1	0	2	0	3	0

The results of the aggregate analysis suggest that lower YKP3089 starting dose and slower titration rate are associated with lower risk of rash/hypersensitivity.

- When YKP3089 dosing was increased weekly or faster, the rate of rash/hypersensitivity reactions was approximately 5%. When YKP3089 was increased by 50 mg increments every 2 weeks, only one case (0.8%) of hypersensitivity reactions was observed.

Two cases DRESS occurred when the first dose of YKP3089 was 100 mg (epilepsy study) or 200 mg (healthy volunteer) followed by rapid titration. The third case, in a healthy volunteer, occurred in a study where the initial dose of YKP3089 was 50 mg/day for 1 week followed by 50 mg weekly increments.

4.5 Rationale

4.5.1 *Study Rationale*

Approximately 30% of epilepsy cases, particularly those with partial seizures, are refractory to treatment. Many of these patients are taking multiple antiepileptic drugs. It is important to understand any interaction that occurs between them as well as the long term safety profile of YKP3089 when given as adjunctive therapy.

Based on healthy volunteer studies with phenytoin and phenobarbital, YKP3089 increases plasma levels of phenobarbital and phenytoin levels. A portion of this open label safety and pharmacokinetic study is designed to understand the impact of adding YKP3089 to an AED regimen including either phenytoin or phenobarbital in subjects with partial epilepsy.

In addition this open label and pharmacokinetic study will enroll subjects taking concomitant AEDs other than phenytoin or phenobarbital to study long term safety and obtain population pharmacokinetic data.

A review of the YKP3089 safety database confirmed three cases of DRESS syndrome among the 953 subjects exposed to the drug.

In order to further characterize the safety profile of YKP3089 while minimizing risk to patients, the following plan was developed:

1. Low starting dose (12.5 mg) and slower titration (dose increase every two weeks)

2. Close monitoring (visits every two weeks) during the first 4 months of treatment to allow early detection of suspected cases of hypersensitivity reaction

3. Evaluation of suspected cases of hypersensitivity reaction to facilitate accurate diagnosis

4. Care of subjects with hypersensitivity reactions to minimize consequences

4.5.2 *Dose Justification*

The target dose of 200 mg/day is based on the efficacy, safety, and tolerability of YKP3089 in previously completed and ongoing studies.

Initiating treatment with YKP3089 at 12.5 mg and then increasing the dose every two weeks is likely to further reduce the risk of many side effects including hypersensitivity reactions. Slowing the titration rates of pharmaceuticals is a well-known procedure for mitigating risk of adverse reactions. Reducing the initial dose and slowing the titration can reduce many central nervous system or gastrointestinal side effects. It has been demonstrated that lowering the initial dose and slowing the titration rate can mitigate the occurrence of rash and possibly the rate of more serious and potentially life threatening adverse cutaneous reactions (Zaccara G, 2007).

After initiating treatment with YKP3089 for two weeks at 12.5 mg and then for two weeks at 25mg YKP3089, subjects taking phenytoin or phenobarbital will titrate YKP3089 upward at a rate of 50mg every other week to a target dose of 200mg/day. This titration is appropriate for this portion of the study because of the known interactions between YKP3089 200mg and phenytoin and phenobarbital. Titrating by 50mg of YKP3089 every other week to steady state will allow better understanding of the clinical impact of any interaction and allow for dosage adjustment of phenytoin or phenobarbital.

Subjects taking concomitant AEDs other than phenytoin or phenobarbital will titrate YKP3089 upward at the same rate to a target dose of 200mg/day.

After reaching a target dose of 200mg, all subjects will be allowed to titrate up to a maximum dose of 400mg/day of YKP3089. A maximum dose of 400mg/day is justified by the additional efficacy seen in the subjects randomized to 400mg/day in the completed dose response study. Seizure free rate effect size in this group approached 20% during the maintenance phase.

4.6 Potential Risks and Benefits

Cumulatively, 953 subjects have been exposed to YKP3089 in a total of 14 Phase 1 and 3 Phase 2 clinical studies.

The potential risks in this study includes,

1. Phenytoin dose related toxicity
2. Risk of phenytoin hypersensitivity syndrome
3. Phenobarbital dose related toxicity
4. Rash / hypersensitivity related to YKP3089 exposure
5. DRESS syndrome related to YKP3089 exposure
6. YKP3089 dose related toxicities

Uncontrolled partial epilepsy is a life threatening disease with significant morbidity and elevated standard mortality rates.

The early signs and symptoms associated with hypersensitivity reaction that may progress to DRESS are readily identifiable by patients and clinicians. When detected and adequately managed, progression to DRESS can be prevented or reversed. The potential benefits of YKP3089 include significant partial seizure frequency reduction and substantial seizure free rates (~18%) in patients who continue to suffer seizures despite history of treatment with multiple AEDs. The current benefit/risk profile in conjunction with the risk minimization measures support the enrollment of partial epilepsy patients into this open-label study to assess the profile of YKP3089 as a potential antiepileptic drug

5 STUDY OBJECTIVES

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 subjects with partial onset seizures
4. Population pharmacokinetics of YKP3089 and concomitant AEDs

6 STUDY DESIGN

6.1 Overview

This multicenter, open label study in subjects with poorly controlled partial seizures will consist of a screening period, open-label titration phase, open label maintenance phase and a taper and follow up. At least 20 subjects taking phenytoin and at least 20 subjects taking phenobarbital will be enrolled. Additional subjects taking AEDs other than phenytoin or phenobarbital, will be enrolled in order to expose at least 1,000 subjects for 6 months to further evaluate long term safety.

6.1.1 *Screening Period*

The screening period for subjects on stable doses of phenytoin or stable doses of phenobarbital or stable doses of other concomitant AEDs will be up to 21 days.

During Screening, assessments will be performed according to the study assessments listed in Table 1 to determine eligibility for the study. Each subject will be informed of his or her rights, and the subject or his or her legally authorized representative must sign an informed consent document indicating understanding of the purpose of the study and required procedures and indicating willingness to participate in the study.

6.1.2 *Open label Treatment Period*

The open label treatment period will consist of a 12 week titration phase followed by an open label maintenance phase.

6.1.2.1 *Titration Phase*

Subjects taking phenytoin or phenobarbital

The titration phase for subjects on stable doses of phenytoin or stable doses of phenobarbital will be 12 weeks. During the 12-week up-titration phase, subjects will increase YKP3089 dose every 2 weeks to a target dose of 200mg/day as described in Table 6.

Table 6. YKP3089 Initial Up-Titration for subjects on phenytoin and phenobarbital

YKP3089 dose (mg/day)

To improve tolerability, the investigator may instruct the subject to take the dose of YKP3089 in the evening. The investigator may alter the timing or amount of an individual dose of any other concomitant AED, but the total daily dose and dosing frequency of any other concomitant AED must remain unchanged during the titration phase.

Subjects taking concomitant AEDs other than phenytoin or phenobarbital

The titration phase for subjects on stable doses of other concomitant AEDs will be 12 weeks. Increasing doses of YKP3089 will be administered (50, 100, 150 and 200mg/day) at 2-week intervals as described in Table7.

Table7. YKP3089 Initial Up-Titration for subjects on concomitant AEDs other than phenytoin or phenobarbital

YKP3089 dose (mg/day)					
Week 1 & 2	Week 3 & 4	Week 5 & 6	Week 7 & 8	Week 9 & 10	Week 11 & 12
12.5	25	50	100	150	200

Prior to initiating YKP3089, subjects at US sites only will have trough concomitant AED levels (oxcarbazepine, topiramate, lamotrigine, lacosamide, clobazam, perampanel and levetiracetam only) drawn at Visit 2. Sites must instruct the subject and schedule the visit accordingly to obtain a trough level. Also the blood must be collected before first dose of YKP3089. To improve tolerability, the investigator may instruct the subject to take the dose of YKP3089 in the evening. The investigator may add, remove, or adjust the dosage of any concomitant AEDs, as clinically indicated (see Table 8 below). Monotherapy with YKP3089 will not be allowed. If clinically indicated, titration can be stopped below 200mg/day. A minimum dose of 50mg/day is necessary to continue in the study.

Table 8. Dose Adjustment Rules during Titration Phase

Cohort →	Subjects taking Phenytoin or Phenobarbital	Subjects taking AEDs other than Phenytoin or Phenobarbital
Adjustments of any Concomitant AEDs	Not Allowed	Allowed
Adjustments of YKP3089	Not Allowed	Allowed

the dose of study medication in the evening or divide the total daily dose into 2 doses. Subjects will follow the schedule of study visits and assessments detailed in Table 1.

After 12 months of participation in the open-label treatment period, subjects will be re-evaluated. Those who are benefiting from treatment with YKP3089 may continue use of the drug at the discretion of the investigator, until development is stopped by SK Life Science Inc or the product is approved for marketing, or anytime at the discretion of SK Life Science Inc.

Table 9. Dose Adjustment Rules during Maintenance Phase

Cohort →	Subjects taking Phenytoin or Phenobarbital	Subjects taking AEDs other than Phenytoin or Phenobarbital
Adjustments of any Concomitant AEDs	Allowed	Allowed
Adjustments of YKP3089	Allowed	Allowed
Adjustment of Phenytoin or Phenobarbital	Allowed	Not Applicable

6.1.2.3 *Taper and follow up*

Subjects who are withdrawn from the open-label treatment period will taper YKP3089 according to the schedule described in Table 10, unless for safety reasons the investigator judges it necessary to discontinue study drug immediately. For subjects taking phenytoin or phenobarbital, discontinuing YKP3089 may reduce the plasma concentration of these AEDs. Doses of phenytoin or phenobarbital may need to be adjusted as clinically indicated.

Table 10. Study Drug Taper Schedule for Subjects Completing Open-Label Treatment

Final open-label dose of YKP3089 (mg/day)	YKP3089 Dose During Taper (mg/day)		
	Week 1	Week 2	Week 3
50 or 100	None		
150 or 200	100	None	None
250 or 300	200	100	None
350 or 400	300	200	100

The follow up visit will take place 14 days after the subject's last dose, following taper and discontinuation of YKP3089; at any time during the open-label treatment; or after 12 months of open-label treatment if there is no additional treatment beyond that point.

6.2 Study Endpoints

6.2.1 *Pharmacokinetic Endpoints*

Sparse PK blood samples will be collected to evaluate YKP3089 and relevant concomitant AED exposure using a population pharmacokinetics approach. This will allow for the investigation of potential effects of covariates on the pharmacokinetics of YKP3089 or other concomitant AEDs. YKP3089 and other concomitant plasma concentration data collected from this study will be pooled with relevant data from other YKP3089 clinical studies for population PK analysis.

6.2.2 *Safety Endpoints*

Safety will be assessed by the nature, frequency, and severity of treatment-emergent spontaneously reported AEs, dropouts due to AEs, overall dropout rates, and changes from baseline in vital signs, physical exams, clinical laboratory evaluations, C-SSRS and 12-lead ECGs, in YKP3089-treated subjects.

7 SELECTION OF STUDY POPULATION

7.1 Study Population and Sites

This trial will be sponsored by SK Life Science Inc. in the United States and other countries.

7.2 Subject Recruitment

Subjects will be selected from the investigator's existing patient population or may be referred by another physician. Sites may also advertise beyond their practice. All advertisements must be approved by the Sponsor and governing ethics committee. Subjects who have provided signed informed consent will need to complete the Screening visit assessments to confirm eligibility for the study.

7.3 Inclusion Criteria

Subjects must satisfy all of the following criteria to be enrolled in the study:

1. Male or female and greater than or equal to 18 years of age at the time of signing the informed consent. The upper age limit is 70 years inclusive.

2. Weight at least 40 kg

3. Written informed consent signed by the subject or legal guardian prior to entering the study in accordance with the ICH GCP guidelines. If the written informed consent is provided by the legal guardian because the subject is unable to do so, a written or verbal assent from the subject must also be obtained. In Germany, only the subject may sign the informed consent form in accordance with ICH guidelines.

4. A diagnosis of partial epilepsy according to the International League Against Epilepsy's Classification of Epileptic Seizures. Diagnosis should have been established by clinical history and an electroencephalogram (EEG) that is consistent with localization related epilepsy; normal interictal EEGs will be allowed provided that the subject meets the other diagnosis criterion (ie, clinical history).

5. Have uncontrolled partial seizures and require additional AED therapy despite having been treated with at least one AED within approximately the last 2 years.

6. Currently on stable antiepileptic treatment regimen:
    g) Subject must have been receiving stable doses of 1 to 3 AEDs for at least 3 weeks prior to Visit 2.
    h) Vagal nerve stimulator (VNS) or deep brain stimulator (DBS) will not be counted as an AED; however, the parameters must remain stable for at least 4 weeks prior to baseline. The VNS or DBS must have been implanted at least 5 months prior to Visit 1.
    i) Benzodiazepines taken at least once per week during the 1 month prior to Visit 1 for epilepsy, or for anxiety or sleep disorder, will be counted as 1 AED and must be continued unchanged throughout the study. Therefore only a maximum of 2 additional approved AEDs will be allowed.

7. Computed tomography (CT) or magnetic resonance imaging (MRI) scan performed within the past 10 years that ruled out a progressive cause of epilepsy. If a CT or MRI has not been performed within the past 10 years, one must be performed prior to dosing.

8. Ability to reach subject by telephone.

9. Use of an acceptable form of birth control by female subjects of childbearing potential (see Section 7.5).

Any potential exception to inclusion criteria allowing *de minimis* (clinically trivial and meaningless) variations must be approved by the medical monitor.

7.4 Exclusion Criteria

Subjects who meet any of the following criteria will be excluded from participating in the study:

1. History of any serious drug-induced hypersensitivity reaction (including but not limited to Stevens Johnson syndrome, toxic epidermal necrolysis, drug reaction with eosinophilia and systemic symptoms) or any drug-related rash requiring hospitalization.

2. History of any drug-induced rash or hypersensitivity reaction with documented nature of the rash or hypersensitivity reaction.

3. History of a first degree relative with a serious cutaneous drug-induced adverse reaction.

4. History of serious systemic disease, including hepatic insufficiency, renal insufficiency, a malignant neoplasm, any disorder in which prognosis for survival is less than 3 months, or any disorder which in the judgment of the investigator will place the subject at excessive risk by participation in a controlled trial.

5. Subjects taking phenytoin must not be taking phenobarbital or primidone; subjects taking phenobarbital must not be taking phenytoin or primidone.

6. Subjects taking concomitant AEDs other than phenytoin or phenobarbital, must not be taking phenytoin or phenobarbital or primidone.

7. Subjects with clinical evidence of phenytoin or phenobarbital toxicity.

7.5 Birth Control Methods Allowable for Enrollment of Subjects

Sexually active female subjects of reproductive potential must practice an approved method of contraception during the entire study and for 30 days after the last dose of study medication. Hormonal contraceptives alone will not be considered an adequate method of contraception.

Women of childbearing/reproductive potential are defined as: Any female who has experienced menarche and does not meet the criteria for "Women Not of Childbearing Potential". Women not of childbearing potential are defined as women who are postmenopausal or permanently sterilised (e.g. tubal occlusion, hysterectomy, bilateral salpingectomy).

Acceptable methods include:

- Hormonal contraception (for at least 3 months prior to Visit 1) in combination with a barrier method.
- Intrauterine device (placement at least 3 months prior to Screening visit)
- Diaphragm with spermicide
- Cervical cap
- Condoms with contraceptive gel/foam or cream
- Surgical sterilization (tubal ligation at least 6 months prior to screening or partner who has had vasectomy at least 6 months prior to screening)
- Postmenopausal (as defined by absent menses for at least 12 months)
- Abstinence; however, if the subject becomes sexually active, 1 of the above methods must be utilized.

There is no need for male subjects enrolled in YKP3089C021 study to use contraception with partners of childbearing potential during their participation in the study.

8 TREATMENTS

8.1 Study Medication Information

8.1.1 *Description of Study Medication*

8.1.1.1 *Physical Description of the Drug*

12.5mg	25mg	50mg	100mg
¼ inch in diameter, round biconvex, tablets debossed with "SK" on one side and "12" on the other side.	10mm in diameter, round, biconvex plain-faced tablets scored on one side.	10mm in diameter, round, biconvex plain-faced tablets scored on one side.	10mm in diameter, round, biconvex plain-faced tablets scored on one side.

8.1.1.2 *Testing*

The sponsor is responsible for testing investigational product to establish stability and storage conditions. The storage specification provided on the labeling reflect results of this testing.

8.1.1.3 *Packaging and Labeling*

YKP3089 will be packaged in high density polyethylene (HDPE) bottles each containing 30 tablets of either 12.5mg or 25mg or 100 tablets of either 50 mg or 100 mg.

8.1.2 ***Supply, Storage, Accountability, and Disposition of Study Medication***

The Sponsor's manufacturing facility will ship a sufficient supply of study medication to each study site directly or from a local depot. The clinical investigator has the responsibility for confirming that all study drug treatment supplies received by the site are inventoried and accounted for throughout the study. A drug receipt log is to be filled out and signed by the person accepting the shipment. It is important that the designated study staff count and verify that the shipment contains all the items noted in the shipment inventory. Any damaged or unusable study drug in a

given shipment will be documented in the study files. The investigator must notify the study Sponsor of any damaged or unusable study treatments that were supplied to the investigator's site.

Subjects or their legal representatives must be told to return all original containers (empty or containing study drug), which will be stored and disposed of according to Sponsor's instructions. Subjects or their legal representatives must also be told to keep study drugs in their original containers and not to combine the contents of different containers.

All study medication must be kept in a secure, locked area or locked cabinet with access restricted to designated study personnel. The tablets will be stored at room temperature in a dry area, protected from light.

Study personnel will keep accurate records of the study medication dispensed to and used by each subject and be available for verification for the Sponsor's site monitor during on-site monitoring visits. The site monitor will periodically check the supplies of study medication held at the site to ensure accountability of all study medication used throughout the study.

At the conclusion of the study, a final inventory will be performed. Any discrepancies will be investigated, resolved, and documented prior to return to the Sponsor for destruction of study drug that has not been dispensed and study drug that has been dispensed and returned.

8.2 Screening and Study Drug Distribution

8.2.1.1 *Screening Number*

The subject will be assigned a screening number by IWRS after signing the informed consent form. The screening number will be an 8-digit number in which the first 2 digits will signify the country, the third, fourth, and fifth digits will signify the site number in that country, and the last 3 digits will be a consecutive number, starting 101, assigned to subjects in the order in which they are screened. Thus, the third screened subject in the second site in the country given number 01 will have screening number 01002103. Screening number should not be reused. Re-screening is not allowed.

8.2.1.2 *Drug Dispensing*

At each visit, the investigator will access the IWRS, enter his or her own user ID and PIN, and provide requested subject details (eg, subject's year of birth). The IWRS will identify open label bottles of tablets to be dispensed. Returned bottles may be re-dispensed to the same subject after drug accountability is performed.

Prior to dispensing, the investigator will record on each open label bottle label the subject number, date dispensed, site number, phone contact, and investigator name.

In addition, the investigator will review the electronic case report form (eCRF) to make sure the medication number printed on each bottle dispensed is populated in the system correctly.

At each visit, the investigator will record the exact dates and exact doses taken since the last visit in the case report form (eCRF). All dosing changes should be recorded in details.

8.3 Prior and Concomitant Treatments

Subjects must be on their current stable daily dosage of phenytoin or phenobarbital or any other concomitant AEDs for at least 3 weeks before Visit 2. They must continue taking the same brand of phenytoin or phenobarbital throughout the titration phase.

Those subjects taking phenytoin every 24 hours will be instructed to take the dose at approximately 8:00 a.m. beginning at least 7 days before Visit 2 and continue this regimen throughout the titration phase. On the day of Visit 2, subject should delay the morning dose until the trough phenytoin plasma sample is obtained. Subjects who are taking phenytoin every 24 hours at bedtime will need to switch to morning dosing at least 7 days before Visit 2. Subjects who take phenytoin every 12 hours will be instructed to take their doses at approximately 8:00 a.m. and 8:00 p.m. beginning at least 7 days before Visit 2 and continue this regimen throughout the titration phase.

Those subjects taking phenobarbital every 24 hours will be instructed to take the dose at approximately 8:00 a.m. beginning at least 7 days before Visit 2 and continue this regimen throughout the titration phase. On the day of Visit 2, subject should delay the morning dose until the trough phenobarbital plasma sample is obtained. Subjects who are taking phenobarbital every 24 hours at bedtime need not switch to morning dosing. Subjects who take phenobarbital every 12

hours will be instructed to take their doses at approximately 8:00 a.m. and 8:00 p.m. beginning at least 7 days before Visit 2 and continue this regimen throughout the titration phase.

Intermittent rescue medication can be used during the open-label treatment period.

Subjects taking AEDs other than phenytoin or phenobarbital at the beginning of the study cannot add phenytoin or phenobarbital to the existing regimen.

8.4 Prohibited Medications or Devices

Medication	Not allowed	Allowed
• Clopidogrel, fluvoxamine, amitriptyline, clomipramine, bupropion, methadone, ifosfamide, cyclophosphamide, efavirenz, natural progesterone fosphenytoin, ethotoin, mephenytoin, primidone, and diazepam	During the study and within 30 days prior to Visit 1	If taken any time before 30 days prior to Visit 1
• Subjects taking phenytoin must not be taking phenobarbital or primidone;	During the study and within 30 days prior to Visit 1	
• Subjects taking phenobarbital must not be taking phenytoin or primidone	During the study and within 30 days prior to Visit 1	
• Vigabatrin and ezogabine	During the study and within 1 year prior to Visit 1	If taken anytime 1 year before Visit 1 (see exclusion criteria for other restrictions specific to Vigabatrin and ezogabine)
• Felbamate	During the study if felbamate was initiated within 18 months prior to Visit 1	If felbamate was initiated more than18 months prior to Visit 1
• Investigational medications or devices other than YKP3089	During the study and within 30 days prior to Visit 1	If taken or used anytime 30 days before Visit 1

8.5 Dosing Instructions for Study Medication

- It is recommended that the study medication is taken once daily in the morning.
- In the event of poor tolerability, the investigator may instruct the subject to take the dose of study medication in the evening.
- During maintenance phase, in the event of poor tolerability, the investigator may instruct the subject to divide the total daily dose of study medication into 2 doses.
- Study medication can be taken with or without food.
- Study medication must be swallowed, not chewed.

9 STUDY PROCEDURES AND ASSESSMENTS

Visit windows of ± 2 days allowed for Visits 3 through 10.

Visit windows of ± 7 days allowed for all other open-label visits.

9.1 Screening

9.1.1 *Visit 1, Day -21*

As shown in Table 1, the following will be performed during Visit 1:

- Obtain informed consent (obtained from the subject prior to any study-related procedures)
- Review and record inclusion and exclusion criteria
- Record medical and seizure history and demographics
- Record vital signs
- Conduct full physical examination (see Appendix A), including height and weight
- Conduct full neurologic examination (see Appendix B)
- Administer C-SSRS (Baseline/Screening version) (see Appendix D: COLUMBIA SUICIDE SEVERITY RATING SCALE (Baseline/Screening))
- Perform 12-lead ECG once
- Perform serum pregnancy test (female subjects of childbearing potential; if positive, subject will not be enrolled)
- Draw blood for laboratory safety assessment
- Obtain urine for urinalysis

- An MRI or CT scan will be performed during screening if the subject has not had a neuroimaging study within 10 years of Visit 1. This will be used to document the absence of an active brain lesion, and a copy of the report will be made available to the Sponsor
- Include the EEG report in the source document. If an EEG report cannot be obtained, and the subject is otherwise eligible, an EEG may be performed during screening.
- Record concomitant medications
- Schedule Visit 2 to occur within 3 weeks of Visit 1

9.1.2 *Visit 2, Day 1*

All subjects who have not discontinued will be scheduled to appear at the clinic for Visit 2. At Visit 2, subjects who continue to meet all of the inclusion criteria and none of the exclusion criteria will receive study drug.

As shown in Table 1, the following will be performed at Visit 2:

- Review and record inclusion and exclusion criteria
- Record vital signs
- Conduct brief neurologic examination if required (Appendix C)
- Administer C-SSRS (Since Last Visit version) (Appendix E)
- Perform urine pregnancy test (for female subjects of childbearing potential)
- Record concomitant medications
- Record AEs
- For subjects taking phenytoin or phenobarbital, draw blood for phenytoin or phenobarbital trough levels
- For subjects taking concomitant AEDs other than phenytoin or phenobarbital at US sites only, draw blood for concomitant AEDs (oxcarbazepine, topiramate, lamotrigine, lacosamide, clobazam, perampanel and levetiracetam only) levels
- Dispense study drug as instructed by IWRS if all of the inclusion criteria and none of the exclusion criteria are met

- The subject may take the first dose of the study medication the same day or the next morning. If the investigator wants to observe the subject after the first dose at the clinic, the first dose can be administered at the site after all other Visit 2 procedures have been completed
- Schedule a return to occur in 2 weeks for Visit 3
- Dispense laminated Hypersensitivity Information safety card
- Call subject in approximately one week to check for any adverse events

9.1.3 *Visit 3, Day 15*

As shown in Table 1, the following will be performed at Visit 3:

- Record vital signs
- Perform limited physical exam for signs of hypersensitivity such as rash, swelling, lymphadenopathy and fever
- Conduct brief neurologic examination if required
- Draw blood for laboratory safety assessment
- Administer C-SSRS (Since Last Visit version)
- Record concomitant medications
- Perform drug accountability
- Record AEs
- Dispense study drug as instructed by IWRS
- Schedule a return to occur in 2 weeks for Visit 4
- Check and dispense laminated Hypersensitivity Information safety card
- Call subject in approximately one week to check for any adverse events

9.1.4 *Visit 4, Day 29*

As shown in Table 1, the following will be performed at Visit 4:

- Record vital signs
- Measure weight
- Perform limited physical exam for signs of hypersensitivity such as rash, swelling, lymphadenopathy and fever

- Conduct brief neurologic examination if required
- Administer C-SSRS (Since Last Visit version)
- Draw blood for laboratory safety assessment
- Record concomitant medications
- Perform drug accountability
- Record AEs
- For subjects taking phenytoin or phenobarbital, draw blood for phenytoin or phenobarbital levels. Two blood samples will be collected: For subjects taking phenytoin or phenobarbital in the morning and coming into the visits in the morning, the first blood draw will be collected upon subjects' arrival to the study unit; the second blood draw should be collected within 30 minutes to 2 hours after the medication is taken.
- Dispense study drug as instructed by IWRS
- Schedule a return to occur in 2 weeks for Visit 5
- Check and dispense laminated Hypersensitivity Information safety card
- Call subject in approximately one week to check for any adverse events

9.1.5 *Visit 5, Day 43*

As shown in Table 1, the following will be performed at Visit 5:

- Record vital signs
- Perform limited physical exam for signs of hypersensitivity such as rash, swelling, lymphadenopathy and fever
- Conduct brief neurologic examination if required
- Draw blood for laboratory safety assessment
- Administer C-SSRS (Since Last Visit version)
- Perform urine pregnancy test (for female subjects of childbearing potential)
- Record concomitant medications
- Perform drug accountability
- Record AEs
- For subjects taking phenytoin or phenobarbital, draw blood for phenytoin or phenobarbital levels. Two blood samples will be collected: For subjects taking phenytoin or phenobarbital in

the morning and coming into the visits in the morning, the first blood draw will be collected upon subjects' arrival to the study unit; the second blood draw should be collected within 30 minutes to 2 hours after the medication is taken.

- Dispense study drug as instructed by IWRS
- Schedule a return to occur in 2 weeks for Visit 6
- Check and dispense laminated Hypersensitivity Information safety card
- Call subject in approximately one week to check for any adverse events

9.1.6 *Visit 6, Day 57*

As shown in Table 1, the following will be assessed at Visit 6:

- Record vital signs
- Perform limited physical exam for signs of hypersensitivity such as rash, swelling, lymphadenopathy and fever
- Conduct brief neurologic examination if required
- Administer C-SSRS (Since Last Visit version)
- Draw blood for laboratory safety assessment
- For subjects taking phenytoin or phenobarbital, draw blood for phenytoin or phenobarbital levels. Two blood samples will be collected: For subjects taking phenytoin or phenobarbital in the morning and coming into the visits in the morning, the first blood draw will be collected upon subjects' arrival to the study unit; the second blood draw should be collected within 30 minutes to 2 hours after the medication is taken.
- Record concomitant medications
- Perform drug accountability
- Record AEs
- Dispense study drug as instructed by IWRS.
- Schedule a return to occur in 2 weeks for Visit 7
- Check and dispense laminated Hypersensitivity Information safety card
- Call subject in approximately one week to check for any adverse events

9.1.7 *Visit 7, Day 71*

As shown in Table 1, the following will be assessed at Visit 7:

- Record vital signs
- Perform limited physical exam for signs of hypersensitivity such as rash, swelling, lymphadenopathy and fever
- Conduct brief neurologic examination if required
- Administer C-SSRS (Since Last Visit version)
- Draw blood for laboratory safety assessment
- For subjects taking phenytoin or phenobarbital, draw blood for phenytoin or phenobarbital levels. Two blood samples will be collected: For subjects taking phenytoin or phenobarbital in the morning and coming into the visits in the morning, the first blood draw will be collected upon subjects' arrival to the study unit; the second blood draw should be collected within 30 minutes to 2 hours after the medication is taken.
- Record concomitant medications
- Perform drug accountability
- Record AEs
- Dispense study drug as instructed by IWRS.
- Schedule a return to occur in 2 weeks for Visit 8
- Check and dispense laminated Hypersensitivity Information safety card
- Call subject in approximately one week to check for any adverse events

9.1.8 *Visit 8, Day 85*

As shown in Table 1, the following will be assessed at Visit 8:

- Record vital signs
- Perform limited physical exam for signs of hypersensitivity such as rash, swelling, lymphadenopathy and fever
- Conduct brief neurologic examination if required
- Administer C-SSRS (Since Last Visit version)

9.1.9 *Visit 9, Day 99*

As shown in Table 1, the following will be assessed at Visit 9:

- Record vital signs
- Perform limited physical exam for signs of hypersensitivity such as rash, swelling, lymphadenopathy and fever
- Conduct brief neurologic examination if required
- Administer C-SSRS (Since Last Visit version)
- Perform urine pregnancy test (for female subjects of childbearing potential)
- Draw blood for laboratory safety assessment
- For subjects taking phenytoin or phenobarbital globally and concomitant AEDs other than phenytoin or phenobarbital in US, draw blood for YKP3089 levels. Two blood samples will be collected: For subjects taking YKP3089 in the morning and coming into the visits in the morning, the first blood draw will be collected upon subjects' arrival to the study unit; the second blood draw should be collected within 30 minutes to 2 hours after the medication is taken.
- For subject taking concomitant AEDs other than phenytoin or phenobarbital at US sites only, draw blood for concomitant AED levels (oxcarbazepine, topiramate, lamotrigine, lacosamide, clobazam, perampanel and levetiracetam only). Two blood samples will be collected: For subjects taking concomitant AEDs in the morning and coming into the visits in the morning, the first blood draw will be collected upon subjects' arrival to the study unit; the second blood draw should be collected within 30 minutes to 2 hours after the medication is taken. For patients that are taking concomitant AEDs in the afternoon and/or coming into the visits in the afternoon, the first blood draw will be collected upon subjects' arrival to the study unit; the second blood draw should be collected within 30 minutes to 2 hours after the first blood draw with timing of the dose, blood draws and strength of previous dose clearly documented.
- Record concomitant medications
- Perform drug accountability
- Record AEs
- Dispense study drug as instructed by IWRS.

- Schedule a return to occur in 2 weeks for Visit 10
- Check and dispense laminated Hypersensitivity Information safety card
- Call subject in approximately one week to check for any adverse events

9.1.10 *Visit 10, Day 113*

As shown in Table 1, the following will be assessed at Visit 10:

- Record vital signs
- Perform limited physical exam for signs of hypersensitivity such as rash, swelling, lymphadenopathy and fever
- Conduct brief neurologic examination if required
- Administer C-SSRS (Since Last Visit version)
- Draw blood for laboratory safety assessment
- Record concomitant medications
- Perform drug accountability
- Record AEs
- Dispense study drug as instructed by IWRS.
- Schedule a return to occur in 4-5 weeks for Visit 11

9.1.11 *Visit 11, Day 143*

As shown in Table 1, the following will be performed at Visit 11:

- Record vital signs
- Conduct brief neurologic exam if required
- Administer C-SSRS (Since Last Visit version)
- Perform urine pregnancy test (for female subjects of child-bearing potential)
- Record concomitant medications
- Perform drug accountability
- Record AEs
- Dispense study drug as instructed by IWRS.
- Schedule a return to occur in 8-9 weeks for Visit 12

9.1.12 *Visit 12, Day 203*

As shown in Table 1, the following will be performed at Visit 12:

- Record vital signs
- Measure weight
- Perform brief neurologic examination if required
- Administer C-SSRS (Since Last Visit version)
- Perform urine pregnancy test (for female subjects of child-bearing potential)
- Draw blood for laboratory safety assessment
- Record concomitant medications
- Perform drug accountability
- Record AEs
- Dispense study drug as instructed by IWRS
- Schedule a return to occur in 8-9 weeks for Visit 13

9.1.13 *Visit 13, Day 263*

As shown in Table 1, the following will be performed at Visit 13:

- Record vital signs
- Conduct brief neurologic exam if required
- Administer C-SSRS (Since Last Visit version)
- Perform urine pregnancy test (for female subjects of child-bearing potential)
- Draw blood for laboratory safety assessment
- Record concomitant medications
- Perform drug accountability
- Record AEs
- Dispense study drug as instructed by IWRS.
- Schedule a return to occur in 14-15 weeks for Visit 14

9.1.14 *Visit 14 or Termination from study—Taper Visit*

As shown in Table 1, the following will be performed at Visit 14 or at the time of early termination from the study.

- Record vital signs
- Measure weight
- Conduct full physical examination
- Conduct full neurologic examination
- Administer C-SSRS (Since Last Visit version)
- Perform 12-lead ECG once
- Perform urine pregnancy test (for female subjects of childbearing potential)
- Draw blood for laboratory safety assessment
- Obtain urine for urinalysis
- Record concomitant medications
- Perform drug accountability
- Record AEs
- For subjects who completed 1 year of open-label treatment, determine whether the subject is benefitting from open-label treatment with YKP3089

For subjects who are benefitting from open-label treatment:

- Dispense open-label medication
- Schedule a return to occur in 3 months for next visit
- See section 9.1.16 for further instructions

For subjects who are <u>not</u> benefitting from open-label treatment or leaving the open-label treatment due to any reasons at any time:

- Dispense taper open-label study drug bottles as instructed by IWRS if needed
- Schedule a return to occur in 2 weeks of the last dose for Visit 15 if tapered
- Schedule a return to occur in 2 weeks for Visit 15 if not tapered

9.1.15 *Visit 15, End of Study Follow-up (14 days from the last dose)*

Visit 15 represents the Follow-up Visit after discontinuation of study drug. This final visit will take place 14 days after the subject's last dose of YKP3089—at any time during the open-label treatment or after 12 months of open-label treatment if there is no additional treatment beyond that point.

As shown in Table 1, the following assessments will be performed at Visit 15:

- Record vital signs
- Measure weight
- Conduct full neurologic examination
- Administer C-SSRS (Since Last Visit version)
- Serum pregnancy test (for female subjects of child-bearing potential)
- Draw blood for laboratory safety assessment
- Record concomitant medications
- Perform drug accountability if tapered
- Record AEs

No study drug will be dispensed.

9.1.16 *Open-Label Extension Beyond Year One*

Subjects who complete Visit 14 and will continue in the open-label treatment beyond year one will adhere to the following visit schedule. The investigator will schedule a return visit in 3 months. Subjects will have study visits every 3 months for a total of 4 visits per study year. The investigator will perform some or all of the following assessments depending up on the visits.

Perform the following every 3 months from Visit 14

- Record vital signs
- Conduct brief neurologic examination if required
- Administer C-SSRS (Since Last Visit version)
- Perform urine pregnancy test (for female subjects of childbearing potential)

- Record concomitant medications
- Perform drug accountability
- Record AEs
- Dispense open-label study drug bottles as instructed by IWRS

Perform the following every 6 months from Visit 14

- Measure weight
- Draw blood for laboratory safety assessment

Perform the following every 12 months from Visit 14

- Perform full physical exam
- Perform 12-lead ECG once
- Obtain urine for urinalysis

This pattern will continue at the discretion of the investigator until development is stopped by SK Life Science Inc, the product is approved for marketing, or anytime at the discretion of SK Life Science Inc.

After the first year of open-label treatment, the visits will be numbered sequentially beginning with Visit 16.

For subjects who discontinue any time after the first year of the open-label treatment, the subject should be brought to the clinic as soon as possible and the investigator will perform the assessments listed under Visit 14. The data collected at this visit will be entered in the Termination Visit page in eCRF. After this visit, the subject will be scheduled to return for Visit 15 (end-of-study follow-up, 14 days after the last dose of study medication).

9.2 Unscheduled Visit

At any time during the study, the subject may have an additional study visit/phone call if the investigator or the subject feels it is necessary. All information, including reason for visit/phone call, AEs, and any procedures performed should be collected in the source documents and recorded in the appropriate section of the eCRF.

9.3 Safety Assessments

Safety will be assessed by the nature, frequency, and severity of treatment-emergent spontaneously reported AEs, dropouts due to AEs, overall dropout rates, and changes from baseline in vital signs, physical and neurologic exams, clinical laboratory evaluations, 12-lead ECGs, and Columbia-Suicide Severity Rating Scale (C-SSRS).

Study subjects will receive the following Hypersensitivity information on a laminated card to carry with them:

- Rash may occur and may progress to Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS).
- Rash or other signs or symptoms of hypersensitivity (e.g., fever, lymphadenopathy, and swelling) may herald a serious medical event and that the patient should report any such occurrence to the investigative site immediately.
- Instructions on whom and where to call in the event a symptom arises and information that can be provided to an emergency room in the event the subject cannot reach the investigator site.
- Reminder to check skin daily for evidence of rash for the first four months of therapy

If a subject reports a rash by telephone, an unscheduled visit should be performed promptly. Any patient with a rash or manifestation of hypersensitivity reaction such as lymphadenopathy, fever, facial swelling must be seen immediately at the study site. If it can definitely be determined that the rash or other symptoms are unrelated to study drug, then the subject can be maintained on YKP3809. If the cause of the rash or other symptoms cannot be definitely determined immediately, then YKP3089 must be discontinued immediately.

The initial physical/rash assessment for hypersensitivity reaction at the investigative site will include the following:

- Measure body temperature

9.4 Pharmacokinetic Evaluations

Time and date of each blood draw and dosing records (time/date/dose) of YKP3089 and AEDs prior to each blood draw will be recorded on the eCRF and other appropriate forms.

Plasma samples will be assayed for YKP3089 and AEDs at a specified bioanalytical laboratory using previously validated methods. Assay methodology will be detailed in separate assay protocols.

For subject taking phenytoin or phenobarbital

These samples will be obtained from subjects taking phenobarbital or phenytoin at any global sites.

At Visit 2, a single trough level of phenytoin or phenobarbital will be obtained. At Visits , 4, 5, 6, 7 and 8, two blood samples will be collected for the determination of phenobarbital or phenytoin plasma levels: For the subjects taking phenytoin or phenobarbital in the morning and coming into the visits in the morning, the first blood draw will be collected upon subjects' arrival to the study unit; the second blood draw should be collected within 30 minutes to 2 hours after the medication is taken. At Visits 8 and 9, two blood samples will be collected for YKP3089 depending on stability of dosing (stable dose all AEDs including YKP3089 for prior 2 weeks).

For subject taking concomitant AEDs other than phenytoin or phenobarbital

These samples will be obtained from subjects taking concomitant AEDs other than phenobarbital or phenytoin at US sites only.

At Visit 2, a single blood sample will be drawn to determine trough level if the subject is taking one of the followings, oxcarbazepine, topiramate, lamotrigine, lacosamide, clobazam, perampanel and levetiracetam. At Visit 8 and/or 9, two blood samples will be drawn from the same subjects to determine plasma levels of YKP3089, oxcarbazepine, topiramate, lamotrigine, lacosamide, clobazam, perampanel and levetiracetam. Collect at visit 8 and/ or 9 depending on stability of dosing (stable dose all AEDs including YKP3089 for prior 2 weeks). At Visit 8 and 9, for the subjects that are taking concomitant AEDs in the morning and coming into the visits in the morning, first blood draw will be collected upon subjects' arrival to the study unit; the second blood draw should be collected within 30 minutes to 2 hours after the medication is taken. For

patients that are taking concomitant AEDs in the afternoon and/or coming into the visits in the afternoon, the first blood draw will be collected upon subjects' arrival to the study unit; the second blood draw should be collected within 30 minutes to 2 hours after the first blood draw with timing of the dose, blood draws and strength of previous dose clearly documented.

The collection schedule is summarized in Table 11 below.

Table 11. Blood Collection Schedule* for YKP3089 and AED Levels

Cohort →	Subjects taking Phenytoin or Phenobarbital	Subjects taking AEDs other than Phenytoin or Phenobarbital –US sites only
Blood collection for YKP3089 levels	Visits 8 and/or 9	Visits 8 and/or 9
Blood collection for phenytoin or phenobarbital levels	Visits 2*, 4, 5, 6, 7 and 8	Not Applicable
Blood collection for concomitant AEDs (other than phenytoin or phenobarbital) levels	None	Visits 2*, 8 and/or 9

* At Visit 2, one sample will be collected; at all other visits, two samples will be collected

Additional Samples

Additional blood samples may be drawn for levels of concomitant AEDs during the open label maintenance phase if the investigator believes that symptoms of toxicity may be related to concomitant AEDs.

10 SAFETY AND ADVERSE EVENTS

10.1 Definitions

10.1.1 *Adverse Events*

An adverse event (AE) is any symptom, sign, illness, or experience that develops or worsens in severity during the course of the study. Intercurrent illnesses or injuries should be regarded as AEs. Abnormal results of diagnostic procedures are considered to be AEs if the abnormality:

- Results in study withdrawal
- Is associated with an SAE
- Is associated with clinical signs or symptoms
- Leads to additional treatment or to further diagnostic tests
- Is considered by the investigator to be of clinical significance

10.1.2 *Serious Adverse Event*

AEs are classified as serious or non-serious. A ***serious adverse event*** is any AE that is:

- Fatal
- Life-threatening
- Requires or prolongs hospital stay
- Results in persistent or significant disability or incapacity
- A congenital anomaly or birth defect
- An important medical event

Important medical events are those that may not be immediately life threatening but are clearly of major clinical significance. They may jeopardize the subject and may require intervention to prevent one of the other serious outcomes noted above. For example, drug overdose or abuse, a seizure that did not result in inpatient hospitalization, or intensive treatment of bronchospasm in an emergency department would typically be considered serious.

10.1.3 *Suspected Adverse Reaction*

Suspected adverse reaction means any AEs for which there is a reasonable possibility that the drug cause the AE. For the purpose of investigational new drug (IND) safety reporting, “reasonable possibility” means there is evidence to suggest a causal relationship between the drug and AE. Suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any AE caused by a drug.

All AEs that do not meet any of the criteria for seriousness should be regarded as ***non-serious AEs***.

10.1.4 *Adverse Event Reporting Period*

The study period during which AEs must be reported is normally defined as the period from the initiation of any study procedures (Visit 1) to the end of the study treatment follow-up. For this study, the AE reporting period is defined as 30 days following the last administration of study treatment for SAEs. For all other AEs, reporting period is defined as 14 days following the last administration of study treatment.

10.1.5 *Preexisting Condition*

A preexisting condition is one that is present at the start of the study. A preexisting condition should be recorded as an AE if the frequency, intensity, or the character of the condition worsens during the study period.

At Visit 1 any clinically significant abnormality should be recorded as a preexisting condition. At the end of the study, any new clinically significant findings/abnormalities that meet the definition of an AE must also be recorded and documented as an AE.

Post-study Adverse Events

All unresolved AEs should be followed by the investigator until the events are resolved, the subject is lost to follow-up, or the AE is otherwise explained. At the last scheduled visit, the investigator should instruct each subject to report any subsequent event(s) that the subject, or the subject's personal physician, believes might reasonably be related to participation in this study.

The investigator should notify the study Sponsor of any death or AE occurring at any time after a subject has discontinued or terminated study participation that may reasonably be related to this study. The Sponsor should also be notified if the investigator should become aware of the development of cancer or of a congenital anomaly in a subsequently conceived offspring of a subject who has participated in this study.

Abnormal Laboratory Values

A clinical laboratory abnormality should be documented as an AE if *any one of the following* conditions is met:

- The laboratory abnormality is not otherwise refuted by a repeat test to confirm the abnormality.
- The abnormality suggests a disease and/or organ toxicity.
- The abnormality is of a degree that requires active management (eg, change of dose, discontinuation of the drug, more frequent follow-up assessments, further diagnostic investigation).

Hospitalization, Prolonged Hospitalization, or Surgery

Any AE that results in hospitalization or prolonged hospitalization should be documented and reported as a serious AE unless specifically instructed otherwise in this protocol. Any condition responsible for surgery should be documented as an AE if the condition meets the criteria for an AE.

Neither the condition, hospitalization, prolonged hospitalization, nor surgery are reported as an AE in the following circumstances:

- Hospitalization or prolonged hospitalization for diagnostic or elective surgical procedures for a preexisting condition. Surgery should ***not*** be reported as an outcome of an AE if the purpose of the surgery was elective or diagnostic and the outcome was uneventful.
- Hospitalization or prolonged hospitalization required to allow efficacy measurement for the study.
- Hospitalization or prolonged hospitalization for therapy of the target disease of the study, unless it is a worsening or increase in frequency of hospital admissions as judged by the clinical investigator.
- An Emergency Room visit is not considered hospitalization.

10.2 Adverse Event Recording and Assessing

All AEs occurring during this clinical trial will be recorded. The investigator will review each event and assess its relationship to drug treatment (unrelated, remote, possible, probable, or definite). Each sign or symptom reported will be graded on a 3-point severity scale (mild, moderate, or severe), and the date of onset, time of onset, and outcome of each event will be noted.

The relationship of each AE to study drug will be assessed using the following definitions:

Definite	• Distinct temporal relationship with drug treatment • Known reaction to agent or chemical group, or predicted by known pharmacology • Event cannot be explained by subject's clinical state or other factors
Probable	• Reasonable temporal relationship with drug treatment • Likely to be known reaction to agent or chemical group, or predicted by known pharmacology • Event cannot easily be explained by subject's clinical state or other factors
Possible	• Reasonable temporal relationship with drug treatment • Event could be explained by subject's clinical state or other factors
Remote	• Poor temporal relationship with drug treatment • Event easily explained by subject's clinical state or other factors
Unrelated	• Event occurring before dosing • Event or intercurrent illness due wholly to factors other than drug treatment

The following definitions for rating severity will be used:

- *Mild*: The AE is easily tolerated and does not interfere with daily activity.
- *Moderate*: The AE interferes with daily activity, but the subject is still able to function.
- *Severe*: The AE is incapacitating and requires medical intervention.

10.3 Reporting of Adverse Events

At each contact with the subject, the investigator must seek information on AEs by specific questioning and, as appropriate, by examination. Information on all AEs should be recorded immediately in the source document and also in the appropriate AE module of the eCRF. All clearly related signs, symptoms, and abnormal diagnostic procedures results should recorded in the source document, though they should be grouped under one diagnosis.

All AEs occurring during the study period must be recorded on the appropriate eCRFs. The clinical course of each event should be followed until resolution, stabilization, or until it has been determined that the study treatment or participation is not the cause. Serious AEs that are still ongoing at the end of the study period must be followed up to determine the final outcome. Any serious AE that occurs after the study period and is considered to be possibly related to the study treatment or study participation should be recorded and reported immediately no later than 24 hours after awareness of the event.

10.3.1 *Study Sponsor Notification by Investigator*

In the event of any fatal or life-threatening SAE, the investigator must inform SK Life Science, Inc. (SKLSI) designee QDS by telephone immediately. Any non-fatal or non-life-threatening SAE, regardless of expectedness or causality, must be reported on the SAE Report Form by scanned and emailed to SKLSI's designee QDS within 24 hours of the investigator's or any other study center personnel's knowledge of the event as described below.

A completed SAE Report Form, the AE record, pertinent medical records, and the Concurrent Medication record from the source documents should be scanned and emailed to SKLSI's designee QDS within 24 hours of the investigator's or any study center personnel's knowledge of a serious event. An updated SAE Report Form should be forwarded to SKLSI's designee QDS within 24 hours of receipt of new/updated information. The SAE Reporting Requirements and contact information are outlined in Table 12.

Seizures in this subject population are anticipated. Therefore, seizures, in and of themselves, will not be considered adverse events. Seizures to be considered adverse events will include those occurring with a measurable increase over the subject's typical seizure frequency or duration; or multiple seizures in a pattern distinguishable from the usual seizure pattern.

Table 12. Serious Adverse Event Reporting Requirements

Type of SAE	Reporting	Reporting	Email address, Telephone Number,

- Study center
- Subject number
- A description of the event
- Date of onset
- Current status
- Whether study treatment was discontinued
- The reason why the event is classified as serious
- Investigator assessment of the association between the event and study treatment

Within the following 48 hours, the investigator must provide further information on the serious AE in the form of a written narrative. This should include a copy of the completed SAE form, and any other diagnostic information that will assist the understanding of the event. Significant new information on ongoing serious AEs should be provided promptly to the study Sponsor.

10.3.2 *Ethics Committee/Institutional Review Board Notification by Investigator*

Reports of all serious AEs (including follow-up information) must promptly be submitted to the Ethics Committee/Institutional Review Board (EC/IRB). Copies of each report and documentation of EC/IRB notification and receipt will be kept in the clinical investigator's binder.

10.3.3 *Regulatory Authority Notification of IND Safety Reports by Sponsor*

The study Sponsor must notify the FDA and all participating investigators in an IND safety report of potential serious risks from clinical trials as soon as possible but in no case later than 15 calendar days after the Sponsor determines that the information qualifies for reporting. This includes any suspected adverse reaction that is both serious and unexpected (SUSAR).

The study Sponsor must notify the FDA of any unexpected fatal or life-threatening suspected adverse reaction as soon as possible but no later than 7 calendar days from the Sponsor's initial receipt of the information.

If a previous AE that was not initially deemed reportable is later found to fit the criteria for reporting, the study Sponsor will submit the AE in a written report to the FDA as soon as possible, but no later than 15 calendar days from the time the determination is made.

The notification of other Regulatory Authorities follows the same procedure and timeframe, per ICH Guidance, as for the FDA.

10.4 Withdrawal of Subject from Study

Subjects may be withdrawn from the study prior to completion of the study if:

- Consent is withdrawn by the subject
- The subject fails to adhere to the protocol requirements
- An intolerable AE is experienced
- The subject becomes pregnant
- The subject is lost to follow-up

When a subject is withdrawn, the discharge procedures must be performed. The reason(s) for the withdrawal must be documented in the subject's eCRF.

11 DATA HANDLING PROCEDURES

11.1 Data Handling and Record Keeping

11.1.1 *Confidentiality*

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act (HIPAA). Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI

The subjects will be told that representatives of the Sponsor, IRB/IEC, or regulatory authorities may inspect their medical records to verify the information collected and that all personal information made available for inspection will be handled in strictest confidence and in accordance with local data protection laws.

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects who have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (ie, that the subject is alive) at the end of his or her scheduled study period.

11.1.2 *Source Documents*

Source data is all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents. Examples of these original documents and data records include hospital records; clinical and office charts; laboratory notes; memoranda; subjects' diaries or evaluation checklists; pharmacy dispensing records; recorded data from automated instruments; copies or transcriptions certified after verification as being accurate and complete; microfiches; photographic negatives; microfilm or magnetic media; x-rays; subject files; and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial.

11.1.3 *Electronic Case Report Forms*

The eCRF is the primary data collection instrument for the study. All data requested on the eCRF must be recorded. All missing data must be explained. Details of the completion of the eCRF will be included in a data entry manual.

11.1.4 *Records Retention*

In compliance with the ICH/GCP guidelines, the investigator/institution will maintain all eCRFs and all source documents that support the data collected from each subject, as well as all study documents as specified in ICH/GCP Section 8, Essential Documents for the Conduct of a Clinical Trial, and all study documents as specified by the applicable regulatory requirement(s).

The investigator/institution will take measures to prevent accidental or premature destruction of these documents. Essential documents must be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal

12 STATISTICAL METHODS AND PLANNED ANALYSES

12.1 Statistical Methods

Categorical variables will be summarized as frequencies and percentages. Descriptive statistics for continuous variables will include number of subjects, mean, median, standard deviation, and minimum and maximum values. SAS® version 9.2 or later will be used for all data summaries. Data will be used as collected.

12.2 Analysis Data Sets

Enrolled subjects: All subjects who successfully meet their entry criteria and who have given informed consent to participate in this study will be considered enrolled subjects.

Safety evaluable subjects (SE): All subjects enrolled in the study who received at least one dose of study drug medication will be considered safety evaluable subjects.

Three safety evaluable subgroups of subjects will be defined:

- Subjects taking phenytoin and YKP3089
- Subjects taking Phenobarbital and YKP3089
- Subjects taking concomitant AEDs other than phenytoin or Phenobarbital and YKP3089

12.3 Baseline Characteristics

All demographic measurements (age, gender, race, ethnicity, height, and weight) and all baseline safety measurements (medical and seizure history, MRI, CAT, ECGs, vital signs, clinical laboratory values, physical and brief neurologic exam, and C-SSRS) will be summarized for all enrolled subjects, for all safety evaluable subjects and by the 3 subgroups of subjects defined in Section 12.2.

12.4 Safety Variable Analyses

All enrolled subjects who took at least one dose of study drug medication will be evaluable for safety. The number and percent of subjects reporting AEs (including treatment-emergent laboratory abnormalities) will be tabulated for all safety evaluable subjects and by the 3 subgroups of subjects defined in Section 12.2. All serious AEs (SAEs) will be tabulated separately as well as included with all reported AEs.

Physical and neurologic assessments, laboratory results, vital signs (including orthostatic measurements, weight and height), concomitant medications, ECGs, and C-SSRS will be summarized using descriptive statistics.

Extent of exposure and dose modifications will be tabulated.

12.5 Pharmacokinetics and Pharmacodynamics Analysis

YKP3089 plasma concentration data collected from this study will be pooled with data from other YKP3089 clinical trials for possible population pharmacokinetic and pharmacodynamic analysis. An integrated population pharmacokinetic model for YKP3089 will be developed. Standard population pharmacokinetic parameters (eg, total body clearance, CL/F) in epilepsy patients and their inter- and intra-individual variability will be estimated. The effects of demographic characteristics, concomitant medication including AEDs, laboratory values, and other subject covariates on YKP3089 pharmacokinetics will be evaluated.

For phenytoin, phenobarbital plasma concentrations obtained during titration phase (Visits 3-6) will be compared with that taken at baseline (Visit 2) to assess the effect of YKP3089 on these two AEDs. The timing of AED sampling in relation to the subject's AED dosing schedule will be factored into the analysis.

For each concomitant AED (oxcarbazepine, topiramate, lamotrigine, lacosamide, clobazam, perampanel and levetiracetam only), plasma concentrations obtained at Visits 8 and or 9 will be compared with that taken at baseline (Visit 2) to assess the effect of YKP3089 on these 7 AEDs. The timing of AED sampling in relation to the subject's AED dosing schedule will be factored into the analysis.

If warranted, the AED plasma concentration data collected from this study will be pooled with data from other YKP3089 studies to assess the potential for an interaction with YKP3089. Results will be displayed descriptively in tabular form.

13 LEGAL ASPECTS, ETHICAL AND ADMINISTRATIVE ISSUES

13.1 Good Clinical Practice

This study is to be conducted according to US and international standards of GCP (FDA Title 21 parts 50 and 312 and ICH guidelines), applicable government regulations, and institutional research policies and procedures. This protocol and any amendments will be submitted to a properly constituted independent EC/IRB, in agreement with local legal prescriptions, for formal approval of the study conduct. The decision of the EC/IRB concerning the conduct of the study will be made in writing to the investigator and a copy of this decision will be provided to the Sponsor before commencement of this study. The investigator should provide a list of EC/IRB members and their affiliate to the Sponsor.

13.2 Documentation of Consent

Written consent of a subject, using the EC/IRB-approved consent form, will be obtained before that subject undergoes any study procedure. The individual who consents the subject must be listed on the delegation log and be authorized to obtain consent. All subjects will have adequate time to ask questions and will be provided with a signed copy of the consent for his/her records. The consenting process will be clearly documented in the subject's chart. The principal investigator is responsible for ensuring that valid consent is obtained and documented for all subjects.

13.3 Delegation of Investigator Responsibilities

The qualified investigator will ensure that all persons assisting the trial are adequately qualified, informed about the protocol, any amendments to the protocol, the study treatments, and their trial-related duties and functions. The qualified investigator will maintain a list of sub-investigators and other appropriately qualified persons to whom he delegates significant trial-related duties.

13.4 Conflict of Interest

Any investigator who has a conflict of interest with this study (patent ownership, royalties, or financial gain greater than the minimum allowable by their institution, etc.) must have the conflict reviewed by a properly constituted Conflict of Interest Committee with a Committee-sanctioned conflict management plan that has been reviewed and approved by the study Sponsor prior to participation in this study.

13.5 Publication Plan

Neither the complete nor any part of the results of the study carried out under this protocol, nor any of the information provided by the Sponsor for the purposes of performing the study, will be published or passed on to any third party without the consent of the study Sponsor. Any investigator involved with this study is obligated to provide the Sponsor with complete test results and all data derived from the study.

13.6 Protocol Amendments

Protocol Amendments will not be implemented without agreement from the Sponsor and prior submission to and written approval from the EC/IRB, except when necessary to eliminate an immediate hazard to the subject.

13.7 Study Monitoring, Auditing, and Inspecting

13.7.1 *Study Monitoring Plan*

This study will be monitored according to the monitoring plan and in accordance with 21 CFR 312.53(d) and ICH guidelines. The investigator will allocate adequate time for such monitoring activities. The investigator will also ensure that the monitor or other compliance or quality assurance reviewer is given access to all the above noted study-related documents and study related facilities (eg, pharmacy, diagnostic laboratory), and has adequate space to conduct the monitoring visit.

13.7.2 *Auditing and Inspecting*

The investigator will permit study-related monitoring, audits, and inspections by the EC/IRB, the Sponsor, government regulatory bodies, and University compliance and quality assurance groups of all study related documents (eg, source documents, regulatory documents, data collection instruments, study data). The investigator will ensure the capability for inspections of applicable study-related facilities (eg, pharmacy, diagnostic laboratory).

Participation as an investigator in this study implies acceptance of potential inspection by government regulatory authorities and applicable University compliance and quality assurance offices.

APPENDIX A: FULL PHYSICAL EXAMINATION

FULL PHYSICAL EXAMINATION					
BODY SYSTEM	**Normal**	**Abnormal, NCS**	**Abnormal, CS**	**Not Done**	**If Abnormal, Specify Findings**
General Appearance	☐	☐	☐	☐	
Head	☐	☐	☐	☐	
EENT	☐	☐	☐	☐	
Neck	☐	☐	☐	☐	
Cardiovascular	☐	☐	☐	☐	
Abdominal	☐	☐	☐	☐	
Respiratory	☐	☐	☐	☐	
Musculoskeletal	☐	☐	☐	☐	
Extremities	☐	☐	☐	☐	
Neurological	☐	☐	☐	☐	
Skin	☐	☐	☐	☐	
Other, specify: _____	☐	☐	☐	☐	
Other, specify: _____	☐	☐	☐	☐	

APPENDIX B: FULL NEUROLOGIC EXAMINATION

FULL NEUROLOGIC EXAMINATION					
GENERAL	**Normal**	**Abnormal, NCS**	**Abnormal, CS**	**Not Done**	**If Abnormal, Specify Findings** – including laterality, as applicable
1. Level of Consciousness	☐	☐	☐	☐	
2. Mental Status	☐	☐	☐	☐	
3. Visual Fields (II)	☐	☐	☐	☐	
4. Eye Movements (III, IV, VI)	☐	☐	☐	☐	
5. Jaw Movement and Facial Sensation (V)	☐	☐	☐	☐	
6. Facial Motion (VII)	☐	☐	☐	☐	
7. Hearing (VIII)	☐	☐	☐	☐	
8. Swallowing, pharynx, larynx (IX, X)	☐	☐	☐	☐	
9. SCM, trapezius (XI)	☐	☐	☐	☐	
10. Tongue (XII)	☐	☐	☐	☐	
11. Biceps Reflexes	☐	☐	☐	☐	
12. Triceps Reflexes	☐	☐	☐	☐	
13. Patellar Reflexes	☐	☐	☐	☐	
14. Achilles Reflexes	☐	☐	☐	☐	
15. Plantar Reflexes	☐	☐	☐	☐	
16. Gait	☐	☐	☐	☐	
17. Romberg	☐	☐	☐	☐	
18. Nystagmus	☐	☐	☐	☐	
19. Tremor	☐	☐	☐	☐	
20. Finger-Nose	☐	☐	☐	☐	
21. Heel-Shin	☐	☐	☐	☐	
22. Rapid Alternating Movements	☐	☐	☐	☐	
23. Muscle Strength	☐	☐	☐	☐	
24. Pin	☐	☐	☐	☐	
25. Vibration	☐	☐	☐	☐	

APPENDIX C: BRIEF NEUROLOGIC EXAMINATION

BRIEF NEUROLOGIC EXAMINATION					
GENERAL	**Normal**	**Abnormal, NCS**	**Abnormal, CS**	**Not Done**	**If Abnormal, Specify Findings** – including laterality, as applicable
1. Level of consciousness	☐	☐	☐	☐	
2. Mental status	☐	☐	☐	☐	
3. Biceps reflexes	☐	☐	☐	☐	
4. Knee reflexes	☐	☐	☐	☐	
5. General movement	☐	☐	☐	☐	
6. Gait	☐	☐	☐	☐	
7. Romberg	☐	☐	☐	☐	
8. Nystagmus	☐	☐	☐	☐	
9. Tremor	☐	☐	☐	☐	
10. Finger-nose	☐	☐	☐	☐	
11. Heel-shin	☐	☐	☐	☐	
12. Rapid alternating movements	☐	☐	☐	☐	

APPENDIX D: COLUMBIA SUICIDE SEVERITY RATING SCALE (BASELINE/SCREENING)

COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

Baseline/Screening Version

Version 1/14/09

Posner, K.; Brent, D.; Lucas, C.; Gould, M.; Stanley, B.; Brown, G.; Fisher, P.; Zelazny, J.; Burke, A.; Oquendo, M.; Mann, J.

Disclaimer:

This scale is intended to be used by individuals who have received training in its administration. The questions contained in the Columbia-Suicide Severity Rating Scale are suggested probes. Ultimately, the determination of the presence of suicidal ideation or behavior depends on the judgment of the individual administering the scale.

Definitions of behavioral suicidal events in this scale are based on those used in ***The Columbia Suicide History Form****, developed by John Mann, MD and Maria Oquendo, MD, Conte Center for the Neuroscience of Mental Disorders (CCNMD), New York State Psychiatric Institute, 1051 Riverside Drive, New York, NY, 10032. (Oquendo M. A., Halberstam B. & Mann J. J., Risk factors for suicidal behavior: utility and limitations of research instruments. In M.B. First [Ed.] Standardized Evaluation in Clinical Practice, pp. 103 -130, 2003.)*

For reprints of the C-SSRS contact Kelly Posner, Ph.D., New York State Psychiatric Institute, 1051 Riverside Drive, New York, New York, 10032; inquiries and training requirements contact posnerk@childpsych.columbia.edu

APPENDIX E: COLUMBIA SUICIDE SEVERITY RATING SCALE (SINCE LAST VISIT)

COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

Since Last Visit

Version 1/14/09

Posner, K.; Brent, D.; Lucas, C.; Gould, M.; Stanley, B.; Brown, G.; Fisher, P.; Zelazny, J.; Burke, A.; Oquendo, M.; Mann, J.

Disclaimer:

This scale is intended for use by trained clinicians. The questions contained in the Columbia-Suicide Severity Rating Scale are suggested probes. Ultimately, the determination of the presence of suicidality depends on clinical judgment.

Definitions of behavioral suicidal events in this scale are based on those used in ***The Columbia Suicide History Form****, developed by John Mann, MD and Maria Oquendo, MD, Conte Center for the Neuroscience of Mental Disorders (CCNMD), New York State Psychiatric Institute, 1051 Riverside Drive, New York, NY, 10032. (Oquendo M. A., Halberstam B. & Mann J. J., Risk factors for suicidal behavior: utility and limitations of research instruments. In M.B. First [Ed.]* Standardized Evaluation in Clinical Practice, *pp. 103 -130, 2003.)*

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