STATISTICAL ANALYSIS PLAN

An Open Label, Multicenter, Safety and Pharmacokinetic Study of YKP3089

As Adjunctive Therapy in Subjects with Partial Onset Seizures

(Phase 3)

PROTOCOL YKP3089C021 Amendment 4

28 July 2017

Statistical Analysis Plan Version 5.0

05 September 2018

SPONSOR: SK Life Science Inc.
22-10 Route 208 South
Fair Lawn, NJ 07410

1 REVISION HISTORY

Version	Date	Author	Description
1.0	25Sep2017	QDS	Based on Protocol Amendment 3
2.0	19Jun2018	QDS	Updated per Protocol Amendment 4 and additional requests from SKLSI after meeting with FDA
3.0	26Jul2018	QDS	Clarifications for Physical Exam, C-SSRS visit windows. Updated definition for duration of epilepsy. Removed analyses for overall compliance. Administrative changes for subjects disposition, clinical laboratory tests, vital signs analyses
4.0	23Aug2018	QDS	Removed reference to Screen Failures as an analysis population. Removed all analyses by country and region. PK Section: AED plasma concentration analysis will be based on Central Lab results Included Study Assessment Flowchart from Protocol Amendment 4 in Appendix 1
5.0	05Sep2018	QDS	Updated analyses for LFTs to include all baseline values (ie, not restricted to normal baseline)

2 SIGNATURE / APPROVAL PAGE

AUTHORS

Dana L Creanga 07Sep2018

Dana L Creanga, PhD — Date

Statistician, Quality Data Services, Inc.

APPROVERS

7 Sep 2018

Fang Dong — Date

Head, Statistics and Data Management, SK Life Science, Inc

7-SEP-2018

Marc Kamin, MD — Date

Chief Medical Officer, SK Life Science, Inc.

TABLE OF CONTENTS

3 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

AE	Adverse event
AED	Antiepileptic drug
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ATC	Anatomical therapeutic chemical classification system
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
CRO	Clinical Research Organization
CSR	Clinical study report
C-SSRS	Columbia Suicide Severity Rating Scale
CT	Computed tomography
CYP	Cytochrome P450
EC	Ethics Committee
ECG	Electrocardiogram
eCRF	Electronic case report form
EEG	Electroencephalograph
EMEA	Evaluation of Medicinal Products
FDA	Food and Drug Administration
ICH	International Conference on Harmonisation
IND	Investigational new drug
IRB	Institutional Review Board
IWRS	Interactive Web response system
kg	Kilogram
MedDRA	Medical Dictionary for Regulatory Activities Terminology
mg	Milligrams
mg/day	Milligrams per Day
mg/day/week	Milligrams per Day per Week
mg/week	Milligrams per Week
MRI	Magnetic resonance imaging
PK	Pharmacokinetic
QC	Quality Control
QDS	Quality Data Services
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Standard deviation
SE	Safety evaluable
SKLSI	SK Life Science Inc.

SOC	System Organ Class
TEAE	Treatment Emergent Adverse Event
TLF	Tables, listings, figures
VPA	Valproic acid (divalproex sodium)
WHO DD	World Health Organization Drug Dictionary

4 INTRODUCTION

This statistical analysis plan (SAP) describes the statistical methodology to be used for the reporting and statistical analysis of safety and pharmacokinetic (PK) clinical data as collected under SK Life Science clinical study protocol YKP3089C021 (amendment 4, 28 July 2017).

All statistical methods in this SAP are in regulatory compliance with the specifications as detailed in the International Conference on Harmonization (ICH) Guidelines:

- E3: Structure and Content of Clinical Study Reports;
- E6: Guideline for Good Clinical Practice; and
- E9: Statistical Principles for Clinical Trials.

Table, listing and figure templates (TLFs) for this study are presented in separate TLF documents.

All analyses described, statistical populations and TLFs programmed mentioned in this SAP are to be included in sections 14 and 16 of the clinical study report (CSR). All computer outputs detailing the statistical computations are to appear in an appendix: Statistical Documentation in the CSR as specified in the ICH E3 Guidance.

The signatures on this statistical analysis plan indicate approval of the safety and PK statistical analyses as detailed in each section of this SAP. These sections are agreed upon by SK Life Science (the Sponsor) and QDS (the Vendor).

This SAP may be revised at the end of the clinical investigation and prior to database lock to reflect specific details regarding protocol deviations and/or other data analysis clarifications (if needed).

This SAP supersedes any statistical considerations which were identified in the study protocol. Substantial differences from the study protocol are identified in this plan. If additional analyses are required to supplement the planned analyses then they will be performed and identified in the appropriate section of the CSR.

Computer program validation methods are to be agreed upon by the Sponsor and Vendor. Quality Control (QC) of all statistical components including derived SAS analysis datasets and TLFs will be performed by the Vendor prior to delivery to the Sponsor. All computational methods will be checked for accuracy. All “SAS

Notes generated from the computers programs will be checked for appropriateness.

.

5 STUDY OBJECTIVES

The objective of this Phase 3 study is to evaluate the safety and pharmacokinetics of YKP3089 and concomitant anti epileptic drugs (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 AND VISIT SCHEDULE

This is a multicenter, open label study in subjects with poorly controlled partial seizures. The study will consist of a:

- screening period,
- open-label titration phase,
- open label maintenance phase
- taper and follow up.

The study will enroll:

- Subjects on stable doses of phenytoin
- Subjects on stable doses of phenobarbital
- Subjects on stable doses of other concomitant AEDs

from approximately 80-110 sites (US and other countries)t

At least 20 subjects taking phenytoin and at least 20 subjects taking phenobarbital are to be enrolled. Additional subjects taking AEDs other than phenytoin or phenobarbital are to be enrolled in order to expose at least 1,000 subjects for 6 months to further evaluate long term safety.

Details about inclusion / exclusion criteria are included in Protocol Sections 7.3 and 7.4.

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.

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

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 200 mg/day as described in the table below:

Table 1. YKP3089 Initial Up-Titration for subjects on phenytoin and 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

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 200 mg/day) at 2-week intervals as described in the table below:

Table 2. 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

During titration phase, the investigator may add, remove, or adjust the dosage of any concomitant AEDs, as clinically indicated:

Table 3. 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
Adjustment of Phenytoin or Phenobarbital	Allowed	Not Applicable

Monotherapy with YKP3089 will not be allowed. If clinically indicated, titration can be stopped below 200 mg/day. A minimum dose of 50 mg/day is necessary to continue in the study.

During open label maintenance phase:

(1) For subjects taking phenytoin or phenobarbital, 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.

(2) 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.

(3) The investigator may add (except phenytoin or phenobarbital), remove, or adjust the dosage of any concomitant AEDs, as clinically indicated:

Table 4. 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

Subjects who are withdrawn from the open-label treatment period will taper YKP3089 according to the schedule described in Table 5, unless for safety reasons the investigator judges it necessary to discontinue study drug immediately.

Table 5. 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

Details about scheduled procedures during titration phase, open label maintenance phase and taper follow-up are included in Protocol Section 6.1.2.1.

Study schedule and assessments flow chart is included in Appendix 1.

7 STUDY ENDPOINTS

7.1 Pharmacokinetic Endpoints

Population pharmacokinetic analyses of potential effects of covariates on the pharmacokinetics of YKP3089 including other concomitant AEDs will be based on the sparse PK blood sample approach. The results for population PK analyses will be reported in a separate document. Summary results for plasma concentration are discussed in the SAP and will be included in the CSR.

7.2 Safety Endpoints

Safety endpoints will include:

- Exposure (YKP3089 and concomitant phenytoin /phenobarbital AEDs)
- Adverse events (treatment emergent, serious adverse events, discontinuations due to adverse events)
- Overall discontinuation rates
- Concomitant Medications
- Vital signs
- Physical exams
- Clinical laboratory evaluations

- Columbia Suicide Severity Rating Scale (C-SSRS)
- 12-lead ECGs

8 STUDY PROCEDURES AND ASSESSMENTS

The study will include multiple study visits during the 3 years duration. Titration phase will include 7 study visits (Visit 2 to Visit 8), Maintenance phase will include up to 5 visits (Visit 9 to Visit 14). Visit 15 is considered 14-days after last dose follow-up visit. Subjects who benefit from treatment, may continue in an Open-Label Extension beyond year one with visits occurring every 3 months.

8.1 Screening and Baseline

At the time of enrollment in the study, all subjects will sign the informed consent.

Demographic data (Date of Birth, Sex, Race and Ethnicity), characterizing enrolled subjects will be collected on the Demographics eCRF.

Height and weight at baseline will be recorded on the Vital Signs eCRF.

The subject's date of past and present medical conditions, prior to study enrollment, will be recorded on a Medical History eCRF. Medical history data will include the Body System, verbatim text, start date, and end date or ongoing.

The subject's epilepsy/seizure history including past and current seizures will be recorded on an Epilepsy/Seizure History eCRFs. Seizure identification and Etiology data will also be collected.

Physical Examination at screening (full examination) will be recorded on the Physical Exam eCRF. These data will include Body System, a normal/abnormal indication, and a description of the abnormality.

All non-AED medications taken by the subject up to the first dose of the study drug will be recorded on the Prior and Concomitant Medications eCRF. These data will include the verbatim medication name, indication for use, dose, route, frequency, start date, and end date or ongoing indication.

A full neurologic evaluation examination will also be performed at screening and recorded on the eCRF. If the subject has not had a recent (within the last 10 years) CT or MRI, one will be performed and entered on the eCRF. An electrocardiogram (EEG) may also be performed and entered on the eCRF. At baseline visit, a brief neurologic examination may be performed (if needed).

Twelve-lead ECGs overall interpretation and results will be collected at screening and will be entered on an eCRF.

Clinical laboratory evaluations (including blood and urine) will be collected at screening and results will be returned electronically for inclusion in the clinical database.

Serum or urine pregnancy test results, where applicable, will be entered into the eCRF.

The baseline version of the Columbia Suicide Rating Scale (C-SSRS) will be assessed at Visit 1 and entered on the eCRF.

8.2 Safety and Tolerability Measures

8.2.1 Adverse Events

Adverse event (AE) assessments will be recorded on the Adverse Events eCRF. The term AE is used to include both serious and non-serious AEs.

Adverse events will be assumed to be treatment emergent unless (through comparison of full or partial dates) the onset date of the adverse event is specified as outside the treatment period or its exclusion from the treatment emergent period can be definitely ascertained from the end date or available month and year components of either of the start or end dates. An AE is also considered treatment emergent if the onset date is before the start of study treatment [Visit 2 /Day 1 + 1] but the severity worsened following that. If the AE onset date is missing or partial, the date will be compared as far as possible with the date of first dose of study treatment. Treatment emergent AEs (TEAEs) occurring during the study treatment period from the first dose of study drug medication up to and including 14 days after the end of treatment (i.e., not present at baseline or worsened in severity following start of treatment) will be reported as TEAEs.

For each AE, the following will be collected: the verbatim term for the AE, start date, end date or indication of ongoing, severity, indication of Serious AE, SAE criterion, relationship to study drug, action taken, and outcome. AEs will be coded using MedDRA version 20.0.

The onset day of the AE will be the difference between the date of onset of the AE and the date the study drug medication was first dispensed + 1. The duration of the AE will be the difference between the end date of the AE and its onset date + 1.

AE relationship to study drug can be classified by the investigator as definite, probable, possible, remote or unrelated. AEs severity can be rated as mild, moderate or severe.

AEs are classified as serious or non-serious. A serious adverse event (SAE) 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

Adverse events (including SAEs) are collected through the length of study for all enrolled subjects and for screen failures.

8.2.2 Other Safety Measures

Concomitant medications and concomitant procedures will be recorded on the Prior and Concomitant eCRF and Concomitant Procedures eCRF, respectively.

Concomitant AED administration since last visit will be recorded on the eCRF page.

Vital signs will be recorded on the Vital Signs eCRF. These data will include blood pressure, heart rate (supine for 5 minutes), temperature, respiratory rate, and weight.

Physical examinations will be recorded on the Physical Exam eCRF. These data will include Body System, normal/abnormal indication, and a description of the abnormality.

Routine 12-lead ECGs will be performed periodically during the study. Parameters including Heart rate, PR interval, QRS interval, RR interval, QT interval, and QTcF will be measured. These results will be recorded on the eCRF.

A brief neurologic evaluation examination will be made and recorded on the eCRF.

Clinical laboratory evaluations will be collected and returned electronically and not entered on an eCRF. Clinical Laboratory Evaluations will include the following:

- Hematology: hemoglobin, hematocrit, white blood count with differential, RBC count, platelet count, and calculated indices.

- Serum chemistry: blood urea nitrogen (BUN), calcium, chloride, creatinine, glucose, total bilirubin, direct bilirubin, alkaline phosphatase, aspartate transaminase (AST), alanine aminotransferase (ALT), total protein, albumin, globulin, sodium, potassium, phosphorus, and glucose. Serum creatinine will be used to calculate the creatinine clearance.

- Urinalysis: pH, specific gravity, protein, glucose, ketone, bilirubin, blood, nitrite, urobilinogen, and microscopic examination

- Pregnancy Tests – All females of child-bearing potential will undergo a serum pregnancy test for β-hCG (β-human chorionic gonadotropin).

All safety laboratory samples will be analyzed by a central laboratory.

The follow-up version of the Columbia Suicide Rating Scale (C-SSRS) will be assessed at Visit 2 and all subsequent visits throughout the study and entered on the eCRF.

8.3 Study Drug Exposure and Compliance

Information on subject drug compliance will be recorded on the study drug dispensing eCRF and the Study drug accountability eCRF. These data will include the dates and amount of drug dispensed and returned.

End of study data will be recorded on the End of Study eCRF. These data will include completion status, date of completion or discontinuation, primary reason for discontinuation, lost to follow-up information.

9 STUDY SUBJECTS

9.1 Determination of Sample Size and Randomization

No formal sample size estimation was involved for this long-term safety study. At least 20 subjects taking phenytoin and at least 20 subjects taking phenobarbital are planned to 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.

9.2 Analysis Populations

The following analysis populations (sets) will be defined:

Enrolled Population: 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 Population: All subjects enrolled in the study who received at least one dose of study drug medication will be considered safety evaluable subjects.

For reporting purposes, 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

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

All subjects who have given informed consent to participate in this study but failed one or more of the entry criteria will be considered screen failures.

10 STATISTICAL METHODS

10.1 General Methods

Summary statistics and analyses will be presented by overall (YKP3089) and by safety evaluable subgroups. Categorical variables will be summarized using counts and percentages. Descriptive statistics for continuous variables will include mean, standard deviation, median, minimum, and maximum values. No inferential analysis will be performed.

SAS® version 9.4 or later will be used for all statistical analyses.

10.2 Handling Missing Data

All summary results will be based on observed data, unless otherwise specified in the next sections. Data handling rules for missing or partial dates for concomitant and baseline AEDs and medication are included in Appendix 2.

10.3 Visit Windows for Safety Analyses

The table below presents the visits assigned for safety analyses corresponding to the range of treatment study days (window) during which an actual visit (scheduled or unscheduled) may occur. Note that the windows defined for statistical analysis are different from the ones defined in Protocol Section 9.

Visit windows for laboratory tests, vital signs, and for Columbia Suicide Symptoms and Signs Rating Scale (CSSRS):

Derived Visit	Target Study Day [1]	Window [2]
Baseline (for laboratory tests and vitals)	Day 1	Days <= 1
Baseline (for C-SSRS)	Screening (Visit 1)	NA
Visit 2 (for C-SSRS)	Day 1	Days = 1
Visit 3	Day 15	>= Day 2 to <= Day 22
Visit 4	Day 29	>= Day 23 to <= Day 36

Visit 5	Day 43	>= Day 37 to <= Day 50
Visit 6	Day 57	>= Day 51 to <= Day 64
Visit 7	Day 71	>= Day 65 to <= Day 78
Visit 8	Day 85	>= Day 79 to <= Day 92
Visit 9	Day 99	>= Day 93 to <= Day 106
Visit 10	Day 113	>= Day 107 to <= Day 128
Visit 11	Day 143	>= Day 129 to <= Day 173
Visit 12	Day 203	>= Day 174 to <= Day 233
Visit 13	Day 263	>= Day 234 to <= Day 314
Visit 14	Day 365	>= Day 315 to <= Day 410
3 Months after 1 Year Treatment	Day 456	>= Day 411 to <= Day 501
6 Months after 1 Year Treatment	Day 547	>= Day 502 to <= Day 592
9 Months after 1 Year Treatment	Day 638	>= Day 593 to <= Day 684
12 Months after 1 Year Treatment	Day 730	>= Day 685 to <= Day 775
15 Months after 1 Year Treatment	Day 821	>= Day 776 to <= Day 866
18 Months after 1 Year Treatment	Day 912	>= Day 867 to <= Day 957
21 Months after 1 Year Treatment	Day 1003	>= Day 958 to <= Day 1049
24 Months after 1 Year Treatment	Day 1095	>= Day 1050 to <= Day 1112
Visit 15 (14-day follow-up)	Day of the last dose of study	>= day of the last dose of study drug+14

	drug+14 days	
Termination Visit [3]	Termination Visit during treatment period	

[1] Relative to the date of the first dose of study drug. For example, Day 1 = the date of the first dose of study drug.

[2] The study days evaluated for windows of visits during treatment period are on or prior to the last dose day.

[3] For subjects who decide not to continue in the study at any time (i.e., eCRF check box for "Continuing" is answered 'No'), the Termination Visit is performed (as per Protocol Section 9.1.14). This is available for entry at any time as a separate visit on eCRF. The study day for the termination visit will be assigned relative to the first dose of study drug.

Visit windows for ECG measurements:

Derived Visit	Target Study Day [1]	Window [2]
Baseline	Day 1	Days <= 1
Visit 14	Day 365	>= Day 2 to <= Day 547
12 Months after 1 Year Treatment	Day 730	>= Day 548 to <= Day 914
24 Months after 1 Year Treatment	Day 1095	>= Day 915 to <= Day 1112
Visit 15 (14-day follow-up)	Day of the last dose of study drug+14 days	>= day of the last dose of study drug+14
Termination Visit [3]	Termination Visit during treatment period	

[1] Relative to the date of the first dose of study drug. For example, Day 1 = the date of the first dose of study drug.

[2] The study days evaluated for windows of visits during treatment period are on or prior to the last dose day.

[3] For subjects who decide not to continue in the study at any time (i.e., eCRF check box for "Continuing" is answered 'No'), the Termination Visit

is performed (as per Protocol Section 9.1.14). This is available for entry at any time as a separate visit on eCRF. The study day for the termination visit will be assigned relative to the first dose of study drug.

Visit windows for Physical Exam measurements:

Derived Visit	Target Study Day [1]	Window [2]
Baseline	Day 1	Days <= 1
Visit 3	Day 15	>= Day 2 to <= Day 22
Visit 4	Day 29	>= Day 23 to <= Day 36
Visit 5	Day 43	>= Day 37 to <= Day 50
Visit 6	Day 57	>= Day 51 to <= Day 64
Visit 7	Day 71	>= Day 65 to <= Day 78
Visit 8	Day 85	>= Day 79 to <= Day 92
Visit 9	Day 99	>= Day 93 to <= Day 106
Visit 10	Day 113	>= Day 107 to <= Day 239
Visit 14	Day 365	>= Day 240 to <= Day 547
12 Months after 1 Year Treatment	Day 730	>= Day 548 to <= Day 914
24 Months after 1 Year Treatment	Day 1095	>= Day 915 to <= Day 1112
Visit 15 (14-day follow-up)	Day of the last dose of study drug+14 days	>= day of the last dose of study drug+14
Termination Visit [3]	Termination Visit during treatment period	

[1] Relative to the date of the first dose of study drug. For example, Day 1 = the date of the first dose of study drug.

[2] The study days evaluated for windows of visits during treatment period are on or prior to the last dose day.

[3] For subjects who decide not to continue in the study at any time (i.e., eCRF check box for “Continuing” is answered ‘No’), the Termination Visit is performed (as per Protocol Section 9.1.14). This is available for entry at any time as a separate visit on eCRF. The study day for the termination visit will be assigned relative to the first dose of study drug.

Visit Day is calculated by (Visit date – date of the first dose of study drug + 1).

The following conventions will be used for the derived visits with respect to safety variables:

1. If more than one actual visit date (including the unscheduled visits) falls within the same window, the visit closest to the target study day will be considered for analysis.

2. If 2 actual visit dates within a window are at the same distance from the target study day, the later visit with non-missing data will be considered for analysis. If repeated measurements are all taken on the same day, then the last measurement will be used.

3. Values recorded at Termination Visit will be mapped to the derived visit based on the window where the actual visit date falls in per rules 1 and 2 above.

4. Given the rules for completing the Termination Visit on eCRF (as defined in Protocol Section 9.1.14), the results recorded at Termination Visit will be summarized in the safety tables at both derived visit based on rule 3 above and at Termination Visit.

10.4 Baseline Value and Change from Baseline

For all safety variables that involve eCRF data collected during study visits prior to the first dose of study drug, the baseline value is defined as the last non-missing value obtained immediately prior to the first dose.

Change from baseline variables will be calculated by subtracting the baseline value from the post-baseline derived visit (i.e., for derived Visit 3 to Visit 15 as per table in Section 11.4) for each subject.

11 SUBJECT DISPOSTION, BASELINE CHARACTERIS TICS, AND EXPOSURE

11.1 Subject Disposition

Subject disposition will be summarized by safety evaluable subgroups, overall, and by country.

The number and percentage of subjects who discontinued the study along with the distribution of the reasons for discontinuation will be presented overall and by safety evaluable subgroups.

Since the protocol allows for subjects who are benefiting from treatment with YKP3089 to continue the 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., study completion is included as an option for reasons for discontinuation on eCRF.

For any interim reporting of the results from this study, number of subjects ongoing at the time of interim date of data cut-off will be presented overall and by safety evaluable subgroups.

The number and percentage of subjects in each analysis population will be presented overall, by safety evaluable subgroups (when applicable), by country, and by geographic region.

For subjects who are screen failures, reason for screen failures will be listed in enrollment status listing.

For summary tables the reasons for termination/withdrawal will be summarized for the following categories: adverse event, lost to follow-up, pregnancy, protocol deviation, withdrew consent for reason other than adverse event, other reason, and completed.

By-subject data listings will include reason for termination/withdrawal as recorded on eCRF.

11.2 Protocol Deviations

Protocol deviations will be recorded by monitoring CRO (PPD) and recorded in their tracking system by deviation category. Protocol deviations will be included in a by-subject listing for subjects in safety population.

11.3 Demographic and Baseline Characteristics

The following demographic and other baseline characteristics will be summarized overall and by safety evaluable subgroups in safety population:

- Sex
- Age (years)
- Age groups (18-64 years, >=65 years)
- Race
- Ethnicity
- Weight (kg)
- Height (cm)
- Body Mass Index (BMI) (kg/m^2)

Summary results will include number and percentages (sex, age groups, race, and ethnicity) and mean, standard deviation (SD), median, minimum, maximum (age, weight, height, BMI).

By-subject listings of all baseline characteristics (including childbearing potential) will be generate for all enrolled subjects. A separate listing for demographic characteristics (including childbearing potential) will be prepared for screen failures.

11.4 Drug Exposure, Dosing, and Compliance

The extent of exposure to study drug (YKP3089 and concomitant AED) as recorded on eCRF will be provided in a listing by-subject and by visit.

Drug exposure will be summarized for exposure to YKP3089 (throughout the entire duration of the study for all 3 safety evaluable subgroups) and Phenytoin and Phenobarbital dosing during titration period (including only corresponding safety evaluable subgroups: subjects taking phenytoin and YKP3089, subjects taking phenobarbital and YKP3089, respectively).

The following parameters will be derived for each subject in the ~~ITT/~~safety population:

- Number of days/weeks/months YKP3089 study drug medication was taken

- Number of days on each YKP3089 dose level (12.5 mg up to an including 400 mg or maximum reported daily dose) during the titration phase, the maintenance phase and overall during study.

- Modal YKP3089 daily dose defined as the dose taken the most days during maintenance phase (Visit 9 to Visit 14); in case of ties (i.e., 2 different dose levels taken the same number of days), modal dose will be defined as the highest dose between the two.

- Daily phenytoin dose during titration phase (for subjects taking phenytoin and YKP3089 only)

- Daily phenobarbital dose during titration phase (for subjects taking phenobarbital and YKP3089 only)

11.4.1 Exposure to YKP3089 study drug

The following will be summarized overall and by safety evaluable subgroups:

- Length of exposure (weeks and months)
- Number and percentages of subjects by time intervals (0-<1 weeks, 1-<2 weeks, 2-<4 weeks, 4 - <12 weeks, 12 - <24 weeks, 24-<48 weeks, 48-<96 weeks, >=96 weeks)
- Number and percentage of subjects by exposure categories: >= 1 dose, >=6 months, >=12 months, >=18 months, >=24 months, >=36 months

For any interim reporting of the results from this study, only applicable exposure categories based on maximum duration of exposure observed will be included in the summary tables).

Derivation for length of exposure to YKP3089:

- Length of exposure to YKP3089 (days) = (stop date – start date + 1).

- Length of exposure to YKP3089 (weeks) = length of exposure to YKP3089 (days)/7

- Length of exposure to YKP3089 (months) = length of exposure to YKP3089 (days)/30.4

Start and stop dates are define as per rules below:

Analysis Period	Subject Participation	
	Enrolled and discontinued study	**Enrolled and ongoing at date of data cut-off**
Overall	Start Date = First dose date Stop Date = last dose date	Start date = First dose date Stop Date = date of data cut-off
Titration Phase	Start date = First dose date Stop Date = Visit 9 date OR Last dose date	Start date = First dose date Stop Date = Visit 9 date OR date of data cut-off
Maintenance Phase	Start Date = Visit 9 date + 1 Stop Date = Last dose date	Start Date = Visit 9 date + 1 Stop Date = date of data cut-off

Descriptive statistics (mean, standard deviation, median, minimum, and maximum) will be provided to summarize the length of exposure (in weeks and in months) for each safety evaluable subgroup and overall. Similar summary results will be prepared by modal dose within each safety evaluable subgroup.

The number and percentage of subjects at each dose level will be summarized by safety evaluable subgroup and overall for the titration phase, the maintenance phase and overall during study. The length of exposure to YKP3089 at each dose level (from 12.5 mg up to maximum daily dose reported in study) will be summarized using descriptive statistics (mean, standard deviation, median, minimum, and maximum).

Dosing duration will also be expressed in terms of total subject years of exposure to YKP3089, calculated as the sum of all subject exposure days, divided by 365.25.

11.4.2 Phenytoin and Phenobarbital Dosing during Titration Phase

A by-subject data listing including phenytoin and phenobarbital dosing starting with baseline records up to an including end of titration (Visit 9) or early discontinuation for subjects who discontinue before Visit 9 will be prepared

separately for the two safety evaluable subgroups: subjects taking phenytoin and YKP3089, subjects taking phenobarbital and YKP3089, respectively.

Daily dose of phenytoin/phenobarbital will be computed using frequency and dose as recorded on eCRF: total daily dose (mg) = dose (mg) x frequency.

At each visit post-baseline during titration phase (ie, for visits up to an including Visit 9) change in phenytoin/phenobarbital total daily dose will be assessed for each subject based on comparison to the daily dose at the previous visit. The following variables will be derived:

1. Change from previous visit total daily dose of phenytoin/phenobarbital = total daily dose at current visit – total daily dose at the previous visit.

2. Change in total daily dose of phenytoin/phenobarbital categories:

    - no change, if total daily dose at current visit – total daily dose at the previous visit = 0.0

    - increase, if total daily dose at current visit – total daily dose at the previous visit > 0.0

    - decrease, if total daily dose at current visit – total daily dose at the previous visit < 0.0

3. Change from baseline total daily dose of phenytoin/phenobarbital = total daily dose at current visit – total daily dose at baseline.

4. Percent change from previous visit total daily dose of phenytoin/phenobarbital = [(total daily dose at current visit – total daily dose at the previous visit)/(total daily dose at the previous visit)] x 100. Note: percent change will have negative values in the change represents a decrease, positive values if the change represents an increase and will be 0% if there is no change.

5. Percent change from baseline total daily dose of phenytoin/phenobarbital = [(total daily dose at current visit – total daily dose at the baseline)/(total daily dose at the baseline)] x 100. Note: percent change will have negative values in the change represents a decrease, positive values if the change represents an increase and will be 0% if there is no change

Using baseline and end of titration phase total daily dose phenytoin/phenobarbital, the following variables will be derived:

- Change from baseline to end of titration phase (Visit 9 or early discontinuation, whichever is earlier) will be computed as (total daily dose of phenytoin/phenobarbital at the end of titration – baseline total daily dose of phenytoin/phenobarbital.

6. Change in total daily dose of phenytoin/phenobarbital categories:

    - no change, if total daily dose at end of titration phase – total daily dose at baseline = 0.0

    - increase, if total daily dose at end of titration phase – total daily dose at baseline > 0.0

    - decrease, if total daily dose at end of titration phase – total daily dose at baseline < 0.0

- Percent change from baseline to end of titration phase (Visit 9 or early discontinuation, whichever is earlier) will be computed as [(total daily dose of phenytoin/phenobarbital at the end of titration – baseline total daily dose of phenytoin/phenobarbital)/ baseline total daily dose of phenytoin/phenobarbital] x 100.

The following summary results will be prepared for the two safety evaluable subgroups: subjects taking phenytoin and YKP3089, subjects taking phenobarbital and YKP3089, respectively:

- Summary statistics (n, mean, SD, standard error, median, minimum, maximum) for :

    - baseline total daily dose of phenytoin/phenobarbital

    - end of titration phase total daily dose of phenytoin/phenobarbital

    - change from baseline to end of titration in total daily dose of phenytoin/phenobarbital

    - increase from baseline to end of titration in total daily dose of phenytoin/phenobarbital (including only subjects with an increase in total daily dose of phenytoin/phenobarbital)

    - decrease from baseline to end of titration in total daily dose of phenytoin/phenobarbital (including only subjects with a decrease in total daily dose of phenytoin/phenobarbital)

- percent change from baseline to end of titration in total daily dose of phenytoin/phenobarbital
- total daily dose of phenytoin/phenobarbital by post-baseline visit.
- change from previous visit total daily dose of phenytoin/phenobarbital (reported by visit)
- increase from previous visit total daily dose of phenytoin/phenobarbital (reported by visit and including only subjects with an increase in total daily dose of phenytoin/phenobarbital for the respective visit)
- decrease from previous visit total daily dose of phenytoin/phenobarbital (reported by visit and including only subjects with a decrease in total daily dose of phenytoin/phenobarbital for the respective visit)
- percent change from previous visit total daily dose of phenytoin/phenobarbital (reported by visit)
- change from baseline total daily dose of phenytoin/phenobarbital (reported by visit)
- percent change from baseline total daily dose of phenytoin/phenobarbital (reported by visit)

- Number and percentage of subjects:
  - no change from baseline to end of titration phase in total daily dose of phenytoin/phenobarbital
  - increase from baseline to end of titration phase in total daily dose of phenytoin/phenobarbital
  - decrease from baseline to end of titration phase in total daily dose of phenytoin/phenobarbital
  - reporting “no change from previous visit” during titration phase (ie, subjects with “no change” in total daily dose of phenytoin/phenobarbital for all post-baseline visits).

  - reporting at least one increase in total daily dose during titration phase (ie, subjects with at least one “increase” in total daily dose of phenytoin/phenobarbital for all post-baseline visits).
  - reporting at least one decrease in total daily dose during titration phase (ie, subjects with at least one “decrease” in total daily dose of phenytoin/phenobarbital for all post-baseline visits).
  - reporting decreases in total daily dose during titration phase: by number of decreases (1, 2, 3, >3)

- Plots by visit for percent change from baseline in total daily dose of phenytoin/phenobarbital to each post-baseline visits during titration phase
- Plots by visit for observed mean total daily dose of phenytoin/phenobarbital

11.5 Prior and Concomitant Medications and Procedures

Baseline AED medications are defined as AED medications that started prior to and are ongoing at the time of the first dose.

Concomitant AED medications are defined as AEDs that started prior to and are ongoing at the time of the first dose of study medication or started after the first dose of study medication.

Prior medications are defined as non-AED medications with a start date and stop date prior to the first dose of study medication.

Concomitant medications are defined as non-AED medications with a start date on or after the first dose of study medication (Day 1) or started prior to and are ongoing at the time of the first dose of study medication.

Concomitant procedures are defined as procedures with a start date on or after the first dose of study medication (Day 1).

Prior and concomitant therapies will be coded to a World Health Organization Drug Dictionary (WHO DD) term including ATC classification (Version March 2016 or a later version available at the time of data cut-off). A by-subject listing of baseline AEDs, concomitant AEDs, prior and concomitant non-AEDs use, and concomitant procedures will be produced.

The use of baseline and concomitant AEDs, prior non-AEDs, and concomitant non-AEDs will be summarized by safety evaluable subgroup and overall for subjects in the safety population. The number and percentage of subjects taking each medication will be presented by ATC Classification.

In addition, a summary table for:

- Number of baseline AEDs (0, 1, 2,->2)
- Number of baseline AEDs per subject (mean, standard deviation, median, minimum, and maximum number of AEDs)

will be prepared for safety population (overall and by safety evaluable subgroups).

11.6 Medical and Seizure/Epilepsy History

Medical history will be summarized (number and percentage of subjects) by body system overall and by safety evaluable subgroups using safety population. The medical history data will also be presented in a by-subject listing. Female reproductive history will be presented in a by-subject listing.

Epilepsy classification and history of seizures by type, current and past seizures will be summarized overall and by safety evaluable subgroups for safety population and will be included in by-subject listings.

Duration of epilepsy diagnosis (years) will be estimated as the number of years between year of diagnosis and date (year) of the informed consent

11.7 EEG, MRI or CT Scan Results

All EEG, MRI or CT Scan results will be listed by-subject. These results will also be summarized at baseline overall and by safety evaluable subgroups for the safety population.

12 PHARMACOKINETIC AND PHARMACODYNAMIC ENDP OINTS AND ANALYSIS

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 laboratories using previously validated methods. Assay methodologies will be detailed in separate bioanalytical reports.

Subjects receiving phenobarbital or phenytoin: 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. 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).

Subjects taking other taking concomitant AEDs other than phenobarbital or phenytoin : Samples will be obtained from subjects taking concomitant AEDs other than phenobarbital or phenytoin at US sites. 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).

The collection schedule is included in the table below:

Cohort →	Subjects taking Phenytoin or Phenobarbital	Subjects taking AEDs other than Phenytoin or Phenobarbital
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

Plasma concentrations of YKP3089 and of concomitant AEDs measured in samples collected in this study will be combined with clinical data from previous studies to generate and validate population pharmacokinetic model for YKP3089. Relevant concomitant AEDs will be tested as covariates to evaluate their possible effect on YKP3089 PK. In addition, the effect of YKP3089 on the PK of relevant AEDs (like lamotrigine or lacosamide for instance) will be assessed if deemed appropriate. These analyses will be included in the separate report.

For the CSR, summary tables including descriptive statistics (mean, SD, median, minimum, maximum) for plasma concentrations of the concomitant AEDs and for plasma concentrations of the YKP3089 as per Central Lab results will be prepared by the planned collection timepoints.

13 SAFETY ANALYSIS

Safety analyses will be performed using safety evaluable set. Separate by-subject AEs and SAEs listings will be prepared for screen failures.

Safety will be assessed by the frequency, severity of adverse events, as well as by clinical laboratory test values, 12-lead ECG recordings, vital sign measurements, physical and neurologic examinations, and the Columbia-Suicide Severity rating Scale (C-SSRS).

13.1 Analysis of Adverse Events (treatment -emergent, non -serious, serious, and deaths)

Adverse events will be coded to a Medical Dictionary for Regulatory Activities Terminology (MedDRA) version 20.0 or later version available at the time of data cut-off. Verbatim description and the MedDRA System Organ Class (SOC) and Preferred Term for all adverse events will be contained in the subject data listings of the clinical study report.

For adverse events with partial start date (i.e., with only month and year are recorded), the following imputation rule will be applied: 15th of the month or fist dose date which one comes later. The imputed date will be used to derive TEAE analysis flag. The actual collected date will be displayed in all AE data listings.

All reported adverse events (regardless of treatment-emergent or not) will be included in a by- subject adverse event listing, with separate by-subjects listings for adverse events and serious adverse events reported for screen failures.

Only treatment-emergent adverse events will be included in summary tables.

Treatment emergent adverse events (TEAE) are defined as AEs with onset after the start of study medication, up to last dose date of study medication + 14 days (or analysis cut-off date whichever comes first), or onset before study medication and worsened after starting study medication, up to last dose date of study medication + 14 days (or analysis cut-off date whichever comes first).

An adverse event is regarded as related to study medication if the relationship to study medication is definite, probable, or possible. Adverse events with missing

relationship will be assumed to be treatment related. Adverse events with missing severity will be assumed to be severe in order to perform the most conservative statistical analysis.

Severe adverse events and adverse events related to treatment will be summarized overall and by safety evaluable subgroups.

TEAE Incidence will be computed as number of subjects with AE/ number of subjects in each reporting group (%).

Incidence of TEAEs leading to study drug discontinuation will report only TEAEs with Action Taken = study drug discontinuation.

In TEAE summary tables, system organ classes (SOCs) will be presented in alphabetical order and preferred terms within each SOC will be presented in descending order of frequency in overall YKP3089 group within each SOC, unless specified otherwise.

The planned summary of adverse events tables are listed below:

- Incidence of treatment-emergent adverse events by MedDRA System Organ Class and Preferred Term
- Incidence of treatment-emergent adverse events (TEAEs) in descending order of frequency in all YKP3089 group.
- Incidence of severe treatment-emergent adverse events by MedDRA System Organ Class and Preferred Term
- Incidence of treatment-emergent adverse events related to study medication by MedDRA System Organ Class and Preferred Term
- Incidence of treatment-emergent adverse events by MedDRA System Organ Class, Preferred Term, and by maximum severity
- Incidence of treatment-emergent adverse events leading to study drug discontinuation by MedDRA System Organ Class and Preferred Term
- Incidence of treatment-emergent serious adverse events by MedDRA System Organ Class and Preferred Term

Deaths, other serious adverse events, and adverse events leading to study drug discontinuation, will be listed including the safety evaluable subgroup and YKP3089 dose (if applicable) at onset, start and stop dates of the adverse event, and days on study relative to the start of the study. Details of listings that will be provided for the safety evaluable analysis population are as follows:

- Listing of subjects who died;
- Listing of subjects with treatment-emergent serious adverse events;
- Listing of subjects with non treatment-emergent serious adverse events;
- Listing of subjects with treatment-emergent severe adverse events;
- Listing of subjects with treatment-emergent adverse events leading to study drug discontinuation.

13.2 Analysis of Clinical Laboratory parameters

Individual laboratory values (hematology, chemistry, and urinalysis) will be listed by subject and summarized using descriptive statistics (mean, standard deviation, median, minimum, and maximum) by safety evaluable subgroups and by visit. Both SI and Conventional units will be used in reporting summary results.

Baseline measurement is defined as the last available measurement prior to dosing.

Post-baseline timepoints will be derived as per rules included in Section 10.3.

Individual change from baseline (the last available measurement prior to dosing) in laboratory values will be calculated and summarized descriptively (mean, standard deviation, median, minimum and maximum) for each post-baseline visit. Summary results will be presented by post-baseline timepoints.

Shift tables from baseline to each post-baseline timepoint will be prepared for all laboratory assessments based on the categories of Low, Normal, and High (for numerical results) or Abnormal and Normal (for categorical results).

Overall summary tables for shift from normal/abnormal (low or high) baseline to normal or abnormal post-baseline accounting for all post-baseline results during study will also be prepared. For these summary tables both scheduled and unscheduled post-baseline visits will be considered and subjects will be counted as shift to post-baseline normal if they do not have any abnormal (High or Low) post-baseline results during the treatment period; and as shift to post-baseline abnormal they have at least one post-baseline abnormal (High or Low) post-baseline results.

The following abnormality categories will be derived to evaluate liver function test results:

- AST
    - >= 3 x ULN
    - > 5 x ULN
    - > 10 x ULN
- ALT
    - >= 3 x ULN
    - > 5 x ULN
    - > 10X ULN
- Total Bilirubin
    - > 1 x ULN
    - > 1.5 x ULN
    - >= 2 x ULN
- Alkaline phosphatase
    - > 2 x ULN
    - > 3 x ULN

The number and percentage of subjects with clinical laboratory test values in each category for the laboratory tests listed above will be summarized by each timepoint (including baseline) and overall (ie, anytime post-baseline), and by safety evaluable subgroups.

Pregnancy test results will be listed by subject (females only) by visit.

13.3 Analysis of Electrocardiograms

All ECG results will be listed on a by-subject basis. ECG parameters consist of heart rate (beats /min)), PR interval (msec), RR interval (msec), QRS Interval (msec), QT interval (msec), and QTcF interval (msec). Individual ECG values (parameters) will be listed by subject and visit. Baseline measurement is defined as the last available measurement prior to dosing. Post-baseline timepoints will be derived as per rules included in Section 10.3.

For the safety population the following summary tables will be generated for the ECG data:

- Summary statistics (n, mean, standard deviation, median, minimum, and maximum) of the baseline value, the value at each post-baseline timepoint and the corresponding change from baseline for each continuous ECG parameter,
- Count and percentage of subjects with QTcF absolute value > 450 msec, >480 msec, >500 msec, <360 msec, <340 msec, <320 msec, and <300 msec at each post-baseline timepoint,
- Count and percentage of subjects with a mean change from baseline in QTcF intervals >30 msec, >60 msec >90 msec, <30 msec, <60 msec, and <90 msec at each post-baseline timepoint,
- Count and percentage of subjects with absolute heart rate > 100 bpm at each post-baseline timepoint,
- Count and percentage of subjects with heart rate change from baseline >10 bpm, >20 bpm, and >30 bpm at each post-baseline timepoint,
- ECG overall interpretation shift table from baseline to each post-baseline timepoint based on normal / abnormal categories.
- List of abnormal ECG results by safety evaluable subgroups.

13.4 Analysis of Vital Signs

All vital signs will be listed by-subject. Baseline measurement is defined as the last available measurement prior to the first dose. Post-baseline timepoints will be derived as per rules included in Section 10.3. For the safety population the following summary tables will be generated for vital signs by safety evaluable subgroups and overall for the safety population:

- Summary statistics (n, mean, standard deviation, median, minimum, and maximum) of the baseline value, the observed value at each post-baseline timepoint and the corresponding change from baseline.
- Number and percentage of subjects with at least one post-baseline (scheduled or unscheduled) vital sign measurement meeting any of these criteria:

- Systolic Blood Pressure: <90 mmHg, >140 mmHg, >160 mmHg
- Diastolic Blood Pressure: <50 mmHg, >90 mmHg, >100 mmHg
- Pulse Rate: <60 bpm, >100 bpm
- Body Weight: decrease of ≥7% from baseline and increase of ≥7% from baseline
- Respiratory rate: <12 breaths/min, > 20 breaths/min
- Temperature: >38.0 °C, <36.0 °C

13.5 Analysis of Physical and Neurologic Examination Results

Physical examination will be summarized by body system by safety evaluable subgroups and overall. The number and percentage of subjects will be presented. The physical exam findings will also be presented in a by-subject listing including the verbatim text for each physical exam event.

Observations from the full physical, and brief/full neurological examinations will be listed on a by-subject basis. The full examination findings will also be summarized at baseline and follow-up for each body system for physical examination and neurologic parameter (level of consciousness, mental status, visual fields etc.) for the full neurologic examination by safety evaluable subgroups and overall for the safety population.

Neurological examination results will be tabulated as number and percentage of subjects with normal, abnormal non-clinically significant, abnormal clinically significant for each one of the exams for each post-baseline visit.

Physical examination results will be tabulated as number and percentage of subjects with normal, abnormal non-clinically significant, abnormal clinically significant for each one of the exams for each post-baseline timepoint. Post-baseline timepoints will be derived as per rules included in Section 10.3.

In addition, a shift table of physical examination from baseline to post-baseline timepoint will be prepared using the normal, abnormal non-clinically significant, abnormal clinically significant categories for each one of the exams.

A shift table displaying the changes from baseline to follow-up in physical examination findings will also be presented by body system by safety evaluable

subgroups and overall. A similar table will be prepared for the brief neurologic exam findings.

13.6 Columbia Suicide Symptoms and Signs Rating Scale (CSSRS)

C-SSRS Ideation, Intensity and Behavior are collected at baseline and all post-baseline visits. Summary results of response to each question (number and percentage of subjects) will be reported by safety evaluable subgroups and overall and by study visit. The summary table will include all subjects in the safety population.

At each visit, C-SSRS responses will be mapped into Columbia-Classification Algorithm of Suicide Assessment events on as follows:

- Complete suicide = as captured in the safety database (adverse events and/or reason for discontinuation)
- Suicide attempt: “Yes” on “Actual attempt” question
- Preparatory acts towards imminent suicidal behavior: “Yes” on any of the following
    - “Aborted attempt”, or
    - “Interrupted attempt”, or
    - “Preparatory acts or behavior”.
- Suicidal ideation: “Yes” on any of the following:
    - “Wish to be dead”, or
    - “Non-specific active suicidal thoughts”, or
    - “Active suicidal ideation with any methods (not plan) without intent to act”, or
    - “Active suicidal ideation with some intent to act without specific plan”, or
    - “Active suicidal ideation with specific plan or intent”.

New onset suicidality and worsening suicidality during double-blind-phase will be assessed via a shift analysis from baseline to each post-baseline visit and to any post-baseline visit. The following shift categories will be defined:

Suicidality	Baseline Event	Any post -baseline and by visit event
New onset	No suicidal ideation and no behavior (i.e., no suicide attempt or no preparatory acts towards	Any ideation (i.e., suicide ideation) or any behavior (i.e., complete suicide, suicide attempt, or

	imminent suicidal behavior)	preparatory acts towards imminent suicidal behavior)
Worsening	Suicidal ideation	Complete suicide, or suicide attempt, or preparatory acts towards imminent suicidal behavior
	Preparatory acts towards imminent suicidal behavior	Complete suicide or suicide attempt
	Suicide Attempt	Complete suicide

The number and percentages of subjects in each of the shift categories defined above will be reported by safety evaluable subgroups and overall for all subjects included in the safety population. Missing C-SSRS responses will not be imputed.

14 INTERIM ANALYSIS

An early data cut-off may be applied for the purpose for regulatory safety reporting. The date for the early data cut-off will be noted in the summary tables and in by-subject listings.

15 GENERAL PROGRAMMING SPECIFICATIONS

15.1 Format

Computer generated tables described in this analysis plan will adhere to the following specifications.

(a) Summary tables displaying results by derived visit as defined in Section 10.3.

(b) By-subject listing will display results in chronological order of visit dates and will include both scheduled and unscheduled visits.

(c) The estimated mean and median for a set of values will be reported to one more decimal place than the raw (observed) data and rounded appropriately. The standard errors (or standard deviations [SD]) will be reported to two additional decimal places than the raw (observed) data and rounded appropriately. For example, for age (with raw data in whole years):

N	XX
Mean (SD)	XX.X (X.XX)
LS Mean (SE)	XX.X (X.XX)
Median	XX.X
Range	XX-XX

(d) Data in columns of a table will be formatted as follows:

i. Alphanumeric values will be left-justified (in mixed and upper- and lower-case)
ii. Whole numbers (e.g., counts) will be right justified
iii. Numbers containing fractional portions will be decimal aligned

(e) All fractional numeric values will be reported with a zero to the left of the decimal point (e.g., 0.12-0.3).

(f) Percents will be reported to one decimal place.

(g) Dates will be reported in SAS DATE9. format (eg, 29MAR2007). Missing portions of dates should be represented on subject listings as dashes (--MAR2007). Dates that are missing because they are not

applicable for the subject should be listed as “N/A”, unless otherwise specified.

(h) The table should be typed in Arial 10-point font. The table title should be typed in Bold Initial Caps, Arial 10-point font, beginning with the word Table X, Title.

(i) Header (or footer) information for all tables, figures, and listings (TFLs) will include the protocol number, table status (draft or final) and the date and time the table was created.

(j) Any TFLs generated prior to database lock or completion of TFL validation will be marked “Draft”.

15.2 Validation

All programmed tables, listings, and figures will be validated with independent programming, to include checking the log for any errors or warnings, verifying format of output against the statistical analysis plan, reviewing program output for internal consistency, consistency with other output and accuracy against the source data. Derived datasets will be independently programmed and compared using PROC COMPARE.

16 CHANGES FROM PROTOCOL SPECIFIED ANALYSES

Analysis populations names were revised to be “Enrolled Population” and “Safety Population” from protocol terminology: “*Enrolled subjects” and “Safety evaluable subjects (SE).*

For the purpose of reporting selected baseline and safety summary results, the following geographic regions were defined in the SAP: United States, Europe, Asia, and Rest of the World. The following parameters are to be reported by geographic regions: subject disposition, demographic and baseline characteristics, drug exposure, overall compliance, and overall summary of adverse events.

Laboratory results are to be reported using both standard units and conventional units.

Vital Signs: Protocol Section 12.4 indicates that for blood pressure and heart rate orthostatic results will be included. However, according to Protocol Section 9.3, these vital signs are measured after the subjects have been supine for 5 minutes

only. Therefore, SAP does not include specific summary tables for orthostatic results.

The following analyses and summary results were included in the SAP:

- Analyses for liver function test.
- number and percentage of subjects with at least one post-treatment vital sign measurement meeting pre-specified criteria were included in the SAP.
- phenytoin/phenobarbital total daily dose during titration phase by visit and overall, change and percent change from baseline, change and percent change from previous visit
- number and percentage of subjects with no change, increase, decrease in phenytoin/phenobarbital total daily dose during titration phase

.

17 APPENDIX 1: STUDY AS SESSMENT FLOWCHART:

Visit windows of ± 2 days allowed for Visits 3-10.	Screening	Treatment Period													End of Study Follow-up
		Titration Phase							Maintenance Phase						
Visit windows of ± 7 days allowed for all other open-label visits	Visit 1 Safety baseline	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9	Visit 10	Visit 11	Visit 12	Visit 13	Visit 14 or Termination Visit	After 1 year of treatment	Visit 15
Assessment	**Day -21**	**Day 1**	**Day 15**	**Day 29**	**Day 43**	**Day 57**	**Day 71**	**Day 85**	**Day 99**	**Day 113**	**Day 143**	**Day 203**	**Day 263**	**Day 365**	**Every 3 months[a]**	**14 days after the last dose**
Informed Consent	X															
Inclusion/ exclusion	X	X														
Demographics, medical and seizure history	X															
Vital signs[b]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Height[c] and Weight	X			X								X		X	X[l]	X
Full physical exam	X		X[p]	X[p]	X[p]	X[p]	X[p]	X[p]	X[p]	X[p]				X	X[m]	
Full neurologic exam	X													X		X
Brief neurologic exam[d]		X	X	X	X	X	X	X	X	X	X	X	X		X	
C-SSRS[e]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Visit windows of ± 2 days allowed for Visits 3-10. Visit windows of ± 7 days allowed for all other open-label visits	Screening	Treatment Period													End of Study Follow-up
		Titration Phase							Maintenance Phase						
	Visit 1 Safety baseline	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9	Visit 10	Visit 11	Visit 12	Visit 13	Visit 14 or Termination Visit	After 1 year of treatment	Visit 15
Assessment	**Day -21**	**Day 1**	**Day 15**	**Day 29**	**Day 43**	**Day 57**	**Day 71**	**Day 85**	**Day 99**	**Day 113**	**Day 143**	**Day 203**	**Day 263**	**Day 365**	**Every 3 months[a]**	**14 days after the last dose**
ECG[f]	X													X	X[m]	
Serum pregnancy test[g]	X															X
Urine pregnancy test[g]		X			X				X		X	X	X	X	X[r]	
Clinical Laboratory safety assessment[h]	X		X	X	X	X	X	X	X	X		X	X	X	X[l]	X
Urinalysis	X													X	X[m]	
Concomitant medication	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Drug accountability			X	X	X	X	X	X	X	X	X	X	X	X	X	X
Dispense study drug		X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Adverse events		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
YKP3089 PK Draw[j]								X	X							

Visit windows of ± 2 days allowed for Visits 3-10.	Screening	Treatment Period													End of Study Follow-up
		Titration Phase							Maintenance Phase						
Visit windows of ± 7 days allowed for all other open-label visits	Visit 1 Safety baseline	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9	Visit 10	Visit 11	Visit 12	Visit 13	Visit 14 or Termination Visit	After 1 year of treatment	Visit 15
Assessment	**Day -21**	**Day 1**	**Day 15**	**Day 29**	**Day 43**	**Day 57**	**Day 71**	**Day 85**	**Day 99**	**Day 113**	**Day 143**	**Day 203**	**Day 263**	**Day 365**	**Every 3 months[a]**	**14 days after the last dose**
Phenytoin or phenobarbital PK draw[j]		X[n]		X	X	X	X	X								
Concomitant AED PK Draw[k]		X[n]						X	X							
EEG and MRI or CT scan[o]	X															
Follow up calls		X[q]	X[q]	X[q]	X[q]	X[q]	X[q]	X[q]	X[q]							
Dispense Laminated Safety Card		X	X	X	X	X	X	X	X							

C-SSRS = Columbia Suicide Severity Rating Scale; ECG = electrocardiogram; AED = antiepileptic drug; PHT = phenytoin; PB = phenobarbital.

a. After 12 months of participation in the open-label extension phase, 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.
b. Vital signs include blood pressure, heart rate (supine for 5 minutes), temperature, and respiratory rate.
c. Height measured only at Visit 1.
d. Brief neurological exam should be done only if symptoms require
e. Administer the Baseline/Screening version of the C-SSRS at Screening. Administer the Since Last Visit version at all subsequent visits.
f. 12-lead ECG will be performed once. Additional ECGs should be performed at any other time if clinically indicated.

g. For female subjects of childbearing potential: If pregnancy is suspected at any time during the study, an interim test may be performed in addition to scheduled assessment.
h. Laboratory assessment: Safety assessment includes blood chemistry and hematology. If the subject meets an exclusion criterion at Visit 1, an unscheduled laboratory sampling can be repeated for confirmation.
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.
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.
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 collected for the determination of concomitant AED plasma levels: For subjects that are 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. Collect at visit 8 and/ or 9 depending on stability of dosing (doses must be stable for 2 weeks prior to these visits) of concomitant AEDs and YKP3089 for subjects on concomitant AEDs other than phenytoin or phenobarbital. Concomitant AEDs levels will be obtained only for oxcarbazepine, topiramate, lamotrigine, lacosamide, clobazam, perampanel and levetiracetam.
l. Every 6 months after Visit 14.
m. Every 12 months after Visit 14.
n. 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.
o. If a CT or MRI has not been performed within the last 10 years, one must be performed prior to Visit 2. If an EEG report cannot be obtained, and the subject is otherwise eligible, an EEG may be performed
p. At visit 1, 14, and yearly thereafter, full physical. At visit 3-10, limited physical exam to identify evidence of hypersensitivity signs such as rash, swelling, lymphadenopathy and fever.
q. Site calls to subjects at least once in between the clinic visits to remind them to be vigilant regarding signs and symptoms of DRESS
r. Every 3 months after Visit 14

18 APPENDIX 2: DATA HANDLING RULES FOR MISSING OF PARTIAL START/STOP DATES FOR CONCOMITANT MEDICATIONS, CONCOMITANT AEDS, AND BASELINE AEDS

Concomitant Medications and Concomitant AEDs

If a concomitant medication or AED, as reported on the eCRF, has a partially or completely missing start or end date, use the following algorithm to impute missing components of the date(s). Imputed dates will be used in order to determine prior/concomitant status of a medication.

If a medication has some missing components in both the start and end dates, first impute the end date as follows (only if the medication is not ongoing):

1. If CMENDTC contains only year and month – impute the missing day to the last day of the corresponding month (e.g., 31 for January, or 30 for April) or date of data cut-off (whichever comes first).

2. If CMENDTC contains only year – impute the missing day and month to the 31st of December of the corresponding year or date of data cut-off (whichever comes first).

3. If CMENDTC is completely missing impute to the date of end of the last period/phase defined for the subject or date of data cut-off (whichever comes first).

Note: The end date should remain null for medications that are ongoing.

After having imputed the end date (if needed), impute the therapy start date if it is partial or missing as follows:

4. If CMSTDTC contains only year and month – impute the missing day to the 1st day of the corresponding month.

5. If CMSTDTC contains only year – impute the missing day and month to the 1st of January of the corresponding year.

6. If CMSTDTC is completely missing impute to the date of start of the screening period (of IFC date) or to the medication end date (previously imputed if needed), whichever is earlier.

Baseline AEDs

Baseline AEDs are AEDs that started prior to and are ongoing at the time of the first dose of study medication.

Any AEDs recorded as “prior” in eCRF will be evaluated if it is a baseline AED or not.

(1) If both start and stop dates are missing, the medication will not be considered as Baseline AEDs and will not be counted in number of baseline AEDs.
(2) If an AED is identified as Prior in eCRF and it is “not ongoing” and has partial end date, the following rules will be applied:
    - if CMENDTC contains only year or day -year and year < first dose date year, the medication will not be considered Baseline AED
    - if CMENDTC contains only year or day-year and year >= first dose date year, the medication will be considered Baseline AED
    - if CMENDTC contains only month-year and month-year < first dose date month-year, the medication will not be considered Baseline AED
    - if CMENDTC contains only month-year and month-year >= first dose date month-year, the medication will be considered Baseline AED
    - if CMEDTC contains only day-month (ie, no year), the medication will not be considered Baseline AED
(3) If AEDs are not recorded as “prior” in eCRF, the following rules will be considered if start dates are missing or have partial dates:
    - If CMSTDTC contains only year and month – impute the missing day is the 1st day of the corresponding month.
    - If CMSTDTC contains only year – impute the missing day and month to the 1st of January of the corresponding year.
    - If CMSTDTC is completely missing impute to the date of start of the screening period (of IFC date).
(4) After AED start date is imputed:
    - If the imputed start date > the first dose date, AED will not be considered “prior” AED and will not be considered Baseline AED

- If the imputed start date <= the first dose date, AED will be considered “Prior” AED and will be evaluated as potential Baseline AED. The decision if AED is Baseline AED will be based on CMENDTC [as per rule (2) above].

19 REFERENCES

SAS Institute, Inc., SAS® Version 9.4 software, Cary, NC.

ICH Guidance for Industry: E9 Statistical Principles for Clinical Trials, 1998

ICH Guidance for Industry: E3 Structure and Contents for Clinical Study Report, 1996

ICH Guidance for Industry:E6 Guideline for Good Clinical Practice