SK Life Science Inc
461 From Road, 5th floor
Paramus, NJ 07652

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

Clinical Study Protocol

June 12, 2013

Amendment 1, January 7, 2014

Amendment 2, March 20, 2015

Amendment 3, June 17, 2019

CONFIDENTIAL

Type of document:	☐ Protocol ☒ Protocol Amendment
Protocol title:	A Multicenter, Double-Blind, Randomized, Placebo-Controlled, Dose-Response Trial of YKP3089 as Adjunctive Therapy in Subjects with Partial Onset Seizures, with Optional Open-Label Extension
Protocol number:	YKP3089C017
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Sponsor's name:	SK Life Science Inc
Sponsor's address:	461 From Road, 5th floor Paramus, NJ 07652
Project medical officer:	Marc Kamin, MD

PROTOCOL SIGNATURE PAGE

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Original protocol date: June 12, 2013

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SPONSOR APPROVAL:

Marc Kamin

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.

Investigator's Signature Date

_____ _____

Print Name

_____

PROTOCOL AMENDMENTS

Amendment 3

Reasons for amendment

1. Administrative changes to update the Sponsor's address.

Amendment 3
Summary of Change

Section	*Old Text*	*Amended Text*	*Rationale*
Title Page	22-10 Route 208 South Fair Lawn, NJ 07410	461 From Road, 5th floor Paramus, NJ 07652	Address change

PROTOCOL AMENDMENTS

Amendment 2

Reasons for amendment

2. To remove interim analysis

3. To provide details of proposed statistical procedures

4. To add Lacosamide as one of the concomitant AED in the pharmacokinetic analysis

Section	*Old Text*	*Amended Text*	*Rationale*
1.PROTOCOL SYNOPSIS Design and methodology	An interim analysis will be performed on available data from the first 160 to 240 subjects randomly assigned to study drug (approximately 40 to 60 per group) who have completed or discontinued early during the double-blind treatment period of the study to obtain necessary efficacy and safety information on YKP3089 only for the purpose of planning of future studies. The results of the interim analysis will not be revealed to the investigators, subjects, or SK Life Science Inc or designated staff who are directly involved in the conduct of the study. The results will not be used to revise the trial design or the analysis methods.	-text deleted-	Management decided not to conduct interim analysis for planning of future studies
1.PROTOCOL SYNOPSIS Statistics and analyses	**Primary efficacy analysis**: The primary efficacy variable is the percent reduction in seizure frequency (average 28-day seizure rate) of complex partial and/or secondarily generalized and/or simple partial motor seizures during the double-blind phase relative to the pretreatment baseline. An analysis of covariance (ANCOVA) model will be fit to the ranked values of the primary efficacy variable. If the coefficient of the ranked baseline variable is statistically significant, then the final ranked analysis will be considered the primary analysis. If the baseline coefficient is not statistically significant, then a Wilcoxon rank-sum test will serve as the primary analysis. **Secondary Efficacy Analyses**: The secondary efficacy variable will be the response to treatment, defined as a	The primary efficacy endpoint to be evaluated for registration in the United States and the Rest of the World is the percent change from the pretreatment baseline phase in seizure frequency (average monthly seizure rate per 28 days) of all simple partial motor, complex partial, or secondarily generalized seizures compared with the double-blind treatment phase. The primary efficacy endpoint to be evaluated for registration in the countries of Europe, Australia, New Zealand, and South Africa is the responder rate defined as a 50% or greater reduction during the maintenance phase of the double blind period in the seizure frequency from baseline.	To clarify the efficacy analyses based on country specific regulatory requirements

Section	*Old Text*	*Amended Text*	*Rationale*
	50% or greater reduction during the double blind phase in the seizure frequency from baseline for the ITT subjects. The data will be summarized using frequencies and percentages. The data will also be analyzed with a logistic regression model predicting the probability of response. Dose level will be the only covariate in the model. **Other Efficacy and Safety Analyses:** The percentage of subjects who become seizure-free (all seizure types) during the maintenance phase of the double-blind treatment period will also be analyzed. Responder rates for partial seizure subtypes (including simple partial with motor component, complex partial, and secondarily generalized tonic-clonic seizures) will be summarized. Outcome measurements such as quality of life and clinical global impression change will be analyzed. Safety will be assessed by the frequency, severity, and timing 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). **Open-Label Extension:** 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. **Interim Analysis:** An interim analysis will be conducted to obtain efficacy and safety information for planning of	**The primary Efficacy Analysis for United States, and the Rest of the World:** The primary efficacy analysis of the primary endpoint will be based on the MITT population. The testing strategy for the primary efficacy endpoint is to compare each of the YKP3089 dosage groups with the placebo group. Due to multiple treatment comparisons, a step-down procedure will be used to ensure the overall type I error rate is controlled at the 5% level. Each of the YKP3089 dosage groups will be compared with the placebo group according to the following hierarchy: 1. 200-mg dosage group versus placebo group 2. 400-mg dosage group versus placebo group 3. 100-mg dosage group versus placebo group The 200-mg dosage group will be compared with the placebo group at a 2-sided 0.05 level as the first step. If no statistically significant difference is detected between the 200-mg dosage group and the placebo group, the procedure will stop and it will be concluded that none of the YKP3089 dosages are efficacious. If a statistically significant difference is detected between the 200-mg dosage group and the placebo group in favor of the 200-mg dosage group, the	

Section	*Old Text*	*Amended Text*	*Rationale*
	new YKP3089 studies. Demographic and baseline characteristics, efficacy, and safety data from the first 160 to 240 subjects randomly assigned to study drug and who have completed or discontinued early from the double-blind treatment period will be analyzed.	procedure will proceed to the next step to compare the 400-mg dosage group with the placebo group at a 2-sided 0.05 level. If a statistically significant difference is detected between the 400-mg dosage group and the placebo group in favor of the 400-mg dosage group, the procedure will proceed to the next step to compare the 100-mg dosage group with the placebo group at a 2-sided 0.05 level. An analysis of covariance (ANCOVA) model will be fit to the ranked values of the primary efficacy endpoint. The ANCOVA will have terms for ranked baseline seizure rate and randomized treatment group. **The Primary Efficacy Analysis for Europe, Australia, New Zealand, and South Africa:** The primary efficacy analysis of the primary endpoint will be based on the MITT-M population. The testing strategy for the primary efficacy endpoint (responder rate) is to compare each of the YKP3089 dosage groups with the placebo group. A step-down procedure will be used to ensure the type I error rate due to multiple treatment comparisons is controlled at the 5% level. Each of the YKP3089 dosage groups will be compared with the placebo group according to the following hierarchy:	

Section	*Old Text*	*Amended Text*	*Rationale*
		1. 200-mg dosage group versus placebo group 2. 400-mg dosage group versus placebo group 3. 100-mg dosage group versus placebo group The 200-mg dosage group will be compared with the placebo group at a 2-sided 0.05 level as the first step. If no statistically significant difference is detected between the 200-mg dosage group and the placebo group, the procedure will stop and it will be concluded that none of the YKP3089 dosages are efficacious. If a statistically significant difference is detected between the 200-mg dosage group and the placebo group in favor of the 200-mg dosage group, the procedure will proceed to the next step to compare the 400-mg dosage group with the placebo group at a 2-sided 0.05 level. If a statistically significant difference is detected between the 400-mg dosage group and the placebo group in favor of the 400-mg dosage group, the procedure will proceed to the next step to compare the 100-mg dosage group with the placebo group at a 2-sided 0.05 level. The data will be summarized using frequencies and percents of subjects achieving at least a 50% response to treatment, the responder rate. The responder data will be analyzed using a chi-square test.	

Section	*Old Text*	*Amended Text*	*Rationale*
		Other Efficacy and Safety Analyses: The percentage of subjects who have a 75%, 90% and 100% seizure reduction during the double blind period and the maintenance phase. Responder rates for partial seizure subtypes (including simple partial with motor component, complex partial, and secondarily generalized tonic-clonic seizures) will be summarized. Outcome measurements such as quality of life and clinical global impression change will be analyzed. Safety will be assessed by the frequency, severity, and timing 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). **Open-Label Extension:** The results of the open-label extension will be reported at a later date using summary tables, figures, and data listings. Summaries will be presented for demographic information and safety information only.	
6.2 Study Endpoints	**6.2.1 Primary Efficacy Variable** The primary efficacy variable is the percentage reduction in seizure frequency (average 28-day seizure rate) of	The primary efficacy endpoints reflect the United States Food and Drug Administration (FDA) recommendation of percent reduction in seizure frequency for registration which is adopted by many countries in the rest of the world, and the	To clarify the efficacy endpoints based on country

Section	*Old Text*	*Amended Text*	*Rationale*
	complex partial and/or secondarily generalized and/or simple partial motor seizures during the double blind treatment period, relative to the pretreatment baseline period. The frequency of seizures will be calculated by the actual seizure count multiplied by 28, divided by the number of days in the period; in effect, frequency count is normalized to 28 days. The percent reduction is calculated as 100 * [B-D]/B, where B is the seizure frequency during baseline, D is seizure frequency in the double-blind treatment period, and reductions in seizure frequency yield a positive value. **6.2.2 Secondary Efficacy Variable** The secondary efficacy variable is the response to treatment, which is defined as at least a 50% reduction in the average 28-day seizure rate during the double blind treatment period relative to the pretreatment baseline period. **6.2.3 Other Efficacy Variables** Other efficacy variables include: • Seizure freedom during the double-blind maintenance phase • Percentage reduction in:	European Agency for the Evaluation of Medicinal Products (EMEA) recommendation of the responder rate for registration in Europe, which is also adopted by Australia, New Zealand, and South Africa. **6.2.1 Primary Efficacy Endpoint in the United States and the Rest of the World** The primary efficacy endpoint to be evaluated for registration in the United States and the Rest of the World is the percent change from the pretreatment baseline phase in seizure frequency (average monthly seizure rate per 28 days) of all simple partial motor, complex partial, or secondarily generalized seizures compared with the double-blind treatment phase. The baseline rate (B) is calculated by counting the number of seizures over the baseline period and dividing by the number of days in the interval with non-missing seizure data and then multiplying by 28. The double-blind rate (D) is calculated in a similar manner. The percent change is equal to 100*(D-B)/B. Simple partial seizures without a motor/visual component will not be counted. This value will be undefined if B=0. For the primary efficacy analysis, there will not be any baseline values with zero seizures. However, for the analysis of seizure sub-types,	specific regulatory requirements

Section	*Old Text*	*Amended Text*	*Rationale*
	o Complex partial and/or secondarily generalized tonic-clonic and/or simple partial motor seizures o Secondarily generalized tonic-clonic seizure only	there is a possibility that B may be zero. In this case, B will be set to a value of 1. **6.2.2 Primary Efficacy Endpoint in the countries of Europe, Australia, New Zealand, and South Africa** The primary efficacy endpoint to be evaluated for registration in the countries of Europe, Australia, New Zealand, and South Africa is the responder rate defined as a 50% or greater reduction during the maintenance phase of the double blind period in the seizure frequency from baseline. The responder endpoint is a binary indicator endpoint defined as 1 if the primary endpoint is <= -50%, and 0 otherwise. **6.2.3 Secondary Efficacy Endpoint in the countries of Europe, Australia, New Zealand, and South Africa** The secondary efficacy endpoint to be evaluated for registration in the countries of Europe, Australia, New Zealand and South Africa is the percent change from the pretreatment baseline phase in seizure frequency (average monthly seizure rate per 28 days) of all simple partial motor, complex partial, or secondarily generalized seizures compared with the maintenance phase of the double-blind	

Section	*Old Text*	*Amended Text*	*Rationale*
		treatment phase. The baseline rate (B) is calculated by counting the number of seizures over the baseline period and dividing by the number of days in the interval with non-missing seizure data and then multiplying by 28. The double-blind rate (D) is calculated in a similar manner. The percent change is equal to 100*(D-B)/B. Simple partial seizures without a motor/visual component will not be counted. This value will be undefined if B=0. For the primary efficacy analysis, there will not be any baseline values with zero seizures. However, for the analysis of seizure sub-types, there is a possibility that B may be zero. In this case, B will be set to a value of 1. **6.2.4 Secondary Efficacy Endpoint in the United States and the Rest of the World** The secondary efficacy endpoint to be evaluated for registration in the United States and the Rest of the World is the responder rate defined as a 50% or greater reduction during the double blind period in the seizure frequency from baseline. The responder endpoint is a binary indicator endpoint defined as 1 if the primary endpoint is <= -50%, and 0 otherwise.	

Section	*Old Text*	*Amended Text*	*Rationale*
		6.2.5 Additional Secondary Efficacy Endpoints • Higher response rates of (defined by cutoffs of -75%, -90% and -100%) simple partial seizures with motor component plus complex partial seizures plus secondarily generalized tonic clonic seizures during the double-blind period and maintenance phase. • Percentage change in other seizure types will be calculated in the same way as the primary endpoint except for selecting the specific seizure types: o Complex partial o Secondarily generalized tonic-clonic o Simple partial motor	
6.2.7 Pharmacokinetic and Pharmacodynamic Endpoints	Pharmacokinetic and Pharmacodynamic Endpoints Trough AED levels (oxcarbazepine [OXC], topiramate [TPM], carbamazepine [CBZ], valproate [VPA], lamotrigine [LTG], and levetiracetam (LEV) only) during the baseline will be compared to those during the treatment period in subjects randomized to 100, 200, or 400 mg/day YKP3089 or placebo to determine potential drug interactions. In addition, YKP3089 blood levels of	Pharmacokinetic Endpoints Trough AED levels (oxcarbazepine [OXC], topiramate [TPM], carbamazepine [CBZ], valproate [VPA], lamotrigine [LTG], lacosamide (LMD) and levetiracetam (LEV) only) during the baseline will be compared to those during the treatment period in subjects randomized to 100, 200, or 400 mg/day YKP3089 or placebo to determine potential drug interactions.	Lacosamide was added as additional AED to be analyzed and text modified to clarify PK end points

Section	*Old Text*	*Amended Text*	*Rationale*
	subjects randomized to 100, 200, or 400 mg/day will be used to assess whether or not there are any correlations between the levels and reduction in seizure frequency.		
6.4 Interim Analysis	An interim analysis will be conducted to obtain efficacy and safety information for planning of future YKP3089 studies. Details of the statistical analysis plan for the interim analysis are provided in Section 12.11	No interim analysis will be performed.	Management decided not to conduct interim analysis for planning of future studies
9.5 Clinical Laboratory & Pharmacokinetic Evaluations	…… blood samples will be drawn to determine plasma levels of concomitant AED (OXC, TPM, CBZ, VPA, LTG, and LEV only) prior to study drug administration (Visit 3)…	…… blood samples will be drawn to determine plasma levels of concomitant AED (OXC, TPM, CBZ, VPA, LTG, LMD and LEV only) prior to study drug administration (Visit 3)…	Lacosamide was added as additional AED to be analyzed
12.2 Statistical Methods	Summary statistics and analyses will include the data from the dose-titration period and will be presented by randomized treatment group. Categorical variables will be summarized as frequencies and percentages. Descriptive statistics for continuous variables will include sample size, mean, median, standard deviation, and minimum and maximum values. SAS® version 9.2 or later will be used for all data summaries, statistical analyses, and data listings. Inferential statistical tests will be 2-sided and will employ a tolerance for type I error (alpha, α) of 0.05. Data will be used as collected. If an observation is missing, then	Summary statistics and analyses will be presented by the treatment group category assigned to the subject regardless of the dosage of drug administered. Categorical variables will be summarized as frequencies and percentages. Descriptive statistics for continuous variables will include sample size, mean, median, standard deviation, and minimum and maximum values. SAS® version 9.2 or later will be used for all data summaries, statistical analyses, and data listings. Inferential statistical tests will be 2-sided and will employ a tolerance for type I error (alpha, α) of 0.05.	To add details of handling of missing data and definitions of various analysis populations

Section	*Old Text*	*Amended Text*	*Rationale*
	the missing value will be imputed using the last observation carried forward (LOCF) method.	Data will be used as collected. Full details of the analysis plan will be included in the Statistical Analysis Plan (SAP) and finalized prior to any un-blinding of efficacy data. ***Analyses of Missing Data*** The primary efficacy endpoint definition in the United States and Rest of the world states that seizure rates will be calculated using days with non-missing seizure data. The definition does not explicitly account for days with missing data, i.e., days during which the presence or absence of seizures was not recorded in personal diaries. However the definition implicitly accounts for missing data in that it is identical to a definition in which days with missing data are assumed to have the same seizure rate as days with non-missing data. Similar to the United States definition of the primary efficacy endpoint, the primary endpoint (responder) definition in the countries of Europe, Australia, New Zealand and South Africa implicitly accounts for missing data during maintenance phase in that it is identical to a definition in which days with missing data are assumed to have the same seizure rate as days with non-missing data. An additional analysis will be performed in which subjects who dropped out during the titration phase will be included in the analysis by having their maintenance phase data imputed	

Section	*Old Text*	*Amended Text*	*Rationale*
		using the available titration data. The same approach will be used for missing data in the analysis of all secondary efficacy end points.	
12.3 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. Intention-to-treat (ITT): All subjects randomly assigned to study drug will be considered intention-to-treat subjects. Modified intention-to-treat (MITT) subjects: All subjects randomly assigned to study drug who have taken at least 1 dose of YKP3089 (or placebo) and have a post-dose evaluation will be considered modified intention-to-treat subjects. Per protocol population: All subjects randomly assigned to study drug who have no major protocol violations and have at least 80% drug compliance will be considered per-protocol subjects. Safety evaluable subjects (SE): All MITT subjects will be considered safety evaluable subjects.	For all populations, subjects will be analyzed according to the target (randomized) dosage group including subjects who fail to achieve the target dosage during the titration phase. Enrolled subjects: All subjects who have given informed consent to participate in this study will be considered enrolled subjects. Intention-to-treat (ITT): All randomized subjects will be considered intention-to-treat subjects. Modified intention-to-treat (MITT) subjects: All randomized subjects who have taken at least one dose of YKP3089 (or placebo) and have any post-baseline seizure data will be considered modified intention-to-treat subjects. Modified intention-to-treat (MITT-M) subjects in Maintenance phase: All randomized subjects who have completed the titration phase and have taken at least one dose of YKP3089 (or placebo) in the maintenance phase and have any maintenance phase seizure data will be considered modified intention-to-treat subjects in the maintenance phase.	To add details regarding various analysis populations

Section	*Old Text*	*Amended Text*	*Rationale*
		Per protocol population (PP): All randomized subjects who have no major protocol violations and have at least 80% drug compliance will be considered per-protocol subjects. Safety evaluable subjects (SE): All ITT subjects.	
12.5 Primary Efficacy Analyses	The primary efficacy analysis will be performed after all randomized subjects who have completed or discontinued early from the double-blind treatment period. It will be based on the ITT population. The primary efficacy variable is percent change in seizure frequency per 28 days for the ITT subjects during the double-blind treatment period relative to the baseline period. Seizure frequency will be calculated as the number of seizures during the maintenance phase divided by the number of days treated in the maintenance phase multiplied by 28. The cumulative distribution functions for each dose group will be presented as a descriptive summary. An analysis of covariance (ANCOVA) model will be fit to the ranked values of the primary efficacy variable. If the coefficient on the ranked baseline variable is statistically significant, then the final ranked analysis will be considered the primary analysis. If the baseline coefficient is not statistically significant, then a Wilcoxon rank-sum test will serve as the primary analysis. The primary efficacy variable will be analyzed using a	**12.5.1 Primary Efficacy Analysis in the United States and the Rest of the World:** The primary efficacy analysis of the primary endpoint will be based on the MITT population. The testing strategy for the primary efficacy endpoint (percent change in seizure frequency) is to compare each of the YKP3089 dosage groups with the placebo group. Due to multiple treatment comparisons, a step-down procedure will be used to ensure the overall type I error rate is controlled at the 5% level. Each of the YKP3089 dosage groups will be compared with the placebo group according to the following hierarchy: 1. 200-mg dosage group versus placebo group 2. 400-mg dosage group versus placebo group 3. 100-mg dosage group versus placebo group The 200-mg dosage group will be compared with the placebo group at a 2-sided 0.05 level as the first step. If no statistically significant difference is detected between the 200-mg dosage group and the	To clarify the primary efficacy analyses based on country specific regulatory requirements

Section	*Old Text*	*Amended Text*	*Rationale*
	hierarchical step-down approach to provide control of the type 1 error rate. The first comparison will be 400 mg/day vs placebo. If this test is significant at the 0.05 level, then the next lower dose 200 mg/day will be compared with placebo. If that test is also statistically significant, the lowest dose 100 mg/day will be tested. The sequential testing will stop if a dose fails to be shown superior to placebo at the 0.05 level of statistical significance.	placebo group, the procedure will stop and it will be concluded that none of the YKP3089 dosages are efficacious. If a statistically significant difference is detected between the 200-mg dosage group and the placebo group in favor of the 200-mg dosage group, the procedure will proceed to the next step to compare the 400-mg dosage group with the placebo group at a 2-sided 0.05 level. If a statistically significant difference is detected between the 400-mg dosage group and the placebo group in favor of the 400-mg dosage group, the procedure will proceed to the next step to compare the 100-mg dosage group with the placebo group at a 2-sided 0.05 level. An analysis of covariance (ANCOVA) model will be fit to the ranked values of the primary efficacy endpoint. The ANCOVA will have terms for ranked baseline seizure rate and randomized treatment group. Ties will be handled using the default option in SAS. It should be noted that the primary efficacy analysis uses a non-parametric approach. Because of this, effect sizes are not estimated and tested directly, since testing is made on the rank of the primary efficacy value. However, summary tables for the actual (not the ranked) primary efficacy endpoint will be presented. Descriptive results of the primary efficacy end point will be provided for the subjects who were titrated under the original protocol. **12.5.2 Primary Efficacy Analyses in the countries of Europe, Australia, New Zealand, and South Africa**	

Section	*Old Text*	*Amended Text*	*Rationale*
		The primary efficacy analysis of the primary endpoint will be based on the MITT-M population. The testing strategy for the primary efficacy endpoint (responder rate) is to compare each of the YKP3089 dosage groups with the placebo group. A step-down procedure will be used to ensure the type I error rate due to multiple treatment comparisons is controlled at the 5% level. Each of the YKP3089 dosage groups will be compared with the placebo group according to the following hierarchy: 1. 200-mg dosage group versus placebo group 2. 400-mg dosage group versus placebo group 3. 100-mg dosage group versus placebo group The 200-mg dosage group will be compared with the placebo group at a 2-sided 0.05 level as the first step. If no statistically significant difference is detected between the 200-mg dosage group and the placebo group, the procedure will stop and it will be concluded that none of the YKP3089 dosages are efficacious. If a statistically significant difference is detected between the 200-mg dosage group and the placebo group in favor of the 200-mg dosage group, the procedure will proceed to the next step to compare the 400-mg dosage group with the placebo group at a 2-sided 0.05 level. If a statistically significant difference is detected between the 400-mg dosage group and the placebo group in favor of the 400-mg dosage group, the procedure will proceed to the next step to compare the	

Section	*Old Text*	*Amended Text*	*Rationale*
		100-mg dosage group with the placebo group at a 2-sided 0.05 level. The data will be summarized using frequencies and percents of subjects achieving at least a 50% response to treatment, the responder rate. The responder data will be analyzed using a chi-square test.	
12.6 Secondary Efficacy Analyses	The secondary efficacy variable is the response to treatment, which is defined as at least a 50% reduction in the average 28-day seizure rate during the double blind treatment period relative to the pretreatment baseline period for the ITT subjects. The data will be summarized using frequencies and percents of subjects achieving at least a 50% response to treatment, the responder rate. The data will also be modeled using a logistic regression model predicting the probability of response. Dose level will be the only covariate in the model.	**12.6.1 Secondary Efficacy Analysis in the countries of Europe, Australia, New Zealand, and South Africa** The secondary efficacy analysis will be based on the MITT-M population. The secondary efficacy analysis is to compare each of the YKP3089 dosage groups with the placebo group for the percent reduction in seizure frequency. An analysis of covariance (ANCOVA) model will be fit to the ranked values of the change in seizure frequency during the maintenance phase. The ANCOVA will have terms for ranked baseline seizure rate and randomized treatment group. Ties will be handled using the default option in SAS. It should be noted that the efficacy analysis uses a non-parametric approach. Because of this, effect sizes are not estimated and tested directly, since testing is made on the rank of the change in seizure frequency. However, summary tables for the actual (not the ranked) change in seizure	To clarify the secondary efficacy analyses based on country specific regulatory requirements

Section	*Old Text*	*Amended Text*	*Rationale*
		frequency will be presented. **12.6.2 Secondary Efficacy Analysis in the United States and the Rest of the World** The secondary efficacy analysis will be based on the MITT population. The secondary efficacy analysis is to compare each of the YKP3089 dosage groups with the placebo group for the responder rate. The data will be summarized using frequencies and percents of subjects achieving at least a 50% response to treatment, the responder rate. The responder data will be analyzed using a chi-square test.	
12.7 Additional Efficacy Analyses	**12.7 Additional Efficacy Analyses** The primary efficacy variable will also be analyzed based on the MITT population (if this population differs appreciably from the ITT population) and the per-protocol population. In addition, the maintenance phase data will be analyzed for the ITT population. This analysis will use all available double-blind period data for subjects who withdraw before reaching the maintenance phase. The maintenance phase data will also be used to test for a	**12.7 Additional Secondary Efficacy Analyses** These secondary efficacy analyses will be based on the MITT or MITT-M population. • Higher response rate of (75, 90 and 100%) of simple partial seizures with motor component plus complex partial seizures plus secondarily generalized tonic clonic seizures during the double-blind period and maintenance phase will be summarized.	To provide details of additional secondary efficacy analyses

Section	*Old Text*	*Amended Text*	*Rationale*
	dose-response relationship and to compare the YKP3089 doses to each other. The percentage of subjects who become seizure free (all seizure types) during the maintenance phase of the double-blind treatment period will also be analyzed. Seizure frequency reductions and responder rates for partial seizure subtypes including simple partial with motor component, complex partial, and secondarily generalized tonic-clonic seizures will also be analyzed. Outcome measurements will be summarized by visits or analyzed by appropriate models.	• Median percent change for partial seizure subtypes (including simple partial with motor component, complex partial, and secondarily generalized tonic-clonic seizures) will be summarized. • Seizure rate over time will be analyzed using following scheme o A moving average for each dose group will be computed using 4 week periods with 2 week overlap beginning from Visit 3 (V3-V5, V4-V6, V5-V6+2 weeks and so on) • For the QOLIE-31 analysis, changes from baseline (Visit 3) to the the final value (defined as the last observation obtained in the double-blind phase) (Visit 9) for each treatment group will be summarized using descriptive statistics. Differences between each treatment group and the placebo group in the change from baseline will also be summarized using descriptive statistics. The minimally important change (MIC) was defined as a change from baseline ≥11.8 at the End Point for the weighted overall QOLIE-31 score. The incidence of subjects meeting the MIC criteria will be summarized by treatment group. • CGIC will be summarized using descriptive	

Section	*Old Text*	*Amended Text*	*Rationale*
		statistics for each treatment group and the placebo group.	
12.8 Safety Variable Analyses	All MITT subjects will be evaluable for safety. The number and percent of subjects reporting AEs (including treatment-emergent laboratory abnormalities) will be tabulated by randomized treatment group. 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), ECGs, and C-SSRS will be summarized using descriptive statistics.	All ITT subjects will be evaluable for safety. The number and percent of subjects reporting AEs (including treatment-emergent laboratory abnormalities) will be tabulated by randomized treatment group. 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), ECGs, and C-SSRS will be summarized using descriptive statistics.	To clarify safety analysis population
12.9 Pharmacokinetic and Pharmacodynamic Analysis	**12.9 Pharmacokinetic and Pharmacodynamic Analysis** Individual plasma concentrations of YKP3089 will be tabulated with the corresponding time related to study drug administration by dose group. 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	**12.9 Pharmacokinetic Analysis** Individual plasma concentrations of YKP3089 will be tabulated with the corresponding time related to study drug administration by dose group. Descriptive statistical analyses will be performed on the plasma concentrations of the YKP3089 obtained during steady-state treatment (Visit 7 and 8). Descriptive statistical analyses will be performed on the plasma concentrations of the concomitant AEDs obtained during steady-state concomitant treatment (Visit 7 and 8) and those at baseline (Visit 3) to assess the effect of YKP3089 on these AEDs.	To clarify PK analysis plan

Section	*Old Text*	*Amended Text*	*Rationale*
	effects of demographic characteristics, concomitant medication including AEDs, laboratory values, and other subject covariates on YKP3089 pharmacokinetics will be evaluated. For each concomitant AED (OXC, TPM, CBZ, VPA, LTG, LEV only), plasma concentrations obtained during steady-state concomitant treatment (Visits 7 and 8) will be compared with that taken at baseline (Visit 3) to assess the effect of YKP3089 on these 6 AEDs. The timing of AED sampling in relation to the subject's AED dosing schedule will be factored into the analysis. The difference between subjects receiving active and placebo treatments will be assessed. 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 by individual study drug dose.		
12.10 Open-Label Extension Analyses	The results of the open-label extension will be reported using summary tables, figures, and data listings.	The results of the open-label extension will be reported at a later date using summary tables, figures, and data listings.	To clarify the timing of reporting of the open label data
12.11 Interim Analysis	The objective of the interim analysis is to obtain necessary efficacy and safety information on YKP3089 for planning	No interim analysis will be performed.	Management decided not to conduct

Section	*Old Text*	*Amended Text*	*Rationale*
	future studies. There is no plan for stopping the study based on the interim analysis of efficacy. The study will proceed without changes in the protocol, as the interim analysis results will not be used to revise the trial design or method of analysis. Therefore, in theory no type 1 error rate spending should be necessary. This interim analysis will be based on the available data from the first 160 to 240 randomized subjects (approximately 40 to 60 per group) from a total of 400 subjects. The size of this cohort will depend upon a number of considerations, including the rate of enrollment. The cutoff will be the time point that the last subject of this cohort completes the 18-week double-blind treatment, or the time at which the last subject from this group drops out of the study. The demographics and baseline characteristics, efficacy, and safety data from these subjects will be analyzed. An independent statistician who is not involved with any other trial activity will analyze the interim data. The interim analysis results will be available to and reviewed by an interim analysis committee consisting of clinicians and statisticians who are not directly involved with any other trial activity. The decisions or recommendations from the interim analysis committee will be communicated only to		interim analysis for planning of future studies

Section	*Old Text*	*Amended Text*	*Rationale*
	limited individuals who are involved with planning future studies. All decisions or recommendations that are communicated outside of the committee will be properly documented. In addition, these results may be made available to regulatory agencies. The results of the interim analysis will not be revealed to the investigators, subjects, or SK Life Science Inc or designated staff who are directly involved in the conduct of the study. Details of the following aspects will be pre-specified in the interim analysis plan: • Timing of the interim analysis • Data to be analyzed • Level of unblinding • Possible actions based on the interim analysis • The role and composition of the interim analysis committee and interim analysis statistician • Communication of the interim analysis results • Data analysis methods		

The amendment must be reviewed and approved or have a favorable opinion from the Institutional Review Board/ Ethics Committee, prior to being implemented.

Amendment 1

Reasons for amendment

1. To provide the results of a completed Phase 1 multiple ascending dose study targeting YKP3089 doses of 400mg, 500mg and 600mg/day
2. To provide the results of a completed Phase 2 randomized, double-blind, placebo-controlled study that evaluated the efficacy and safety of YKP3089 200mg as adjunctive therapy for partial seizures.
3. To reduce the initial starting dose to 50mg and slow the titration rate to improve tolerability
4. To clarify the definition of uncontrolled partial seizures
5. To provide guidance on contraception for male subjects
6. To allow the first dose of study drug to be given at the investigator's site
7. To revise the timelines for the data monitoring committee review of data
8. To add a 50mg dosing card
9. To make minor administrative changes

Section	*Old Text*	*Amended Text*	*Rationale*
1.PROTOCOL SYNOPSIS Design and methodology	Subjects will first enter a titration phase lasting up to 6 weeks, during which the daily dose will be increased by 100 mg every week until the target dose is reached. Subjects having tolerability issues for the first time during Weeks 2 to 5 will have their dose reduced by 100 mg once. Subsequent to this reduction, subjects will recommence the upward titration by 50 mg increments towards their target dose until Week 6. Subjects having tolerability issues for a second time until Week 8 or having tolerability issues for the first time during Week 6 will have their dose reduced by 50 mg once and must remain at that dose for the remainder of the study.	Subjects will first enter a 6-week titration phase, during which the initial dose will be 50mg/day. The planned increase in the daily dose will be 50mg/day/week increments until 200mg is reached and after which the dose will be increased by 100mg/day/week in subjects randomized to 400mg/day. Subjects having tolerability issues for the first time during Weeks 2 to 6 will have their dose reduced by 50 or100 mg depending on their attained dose at the time (Reduce by 50mg if taking 100mg, 150mg or 200mg; reduce by 100mg if on 300mg or 400mg).Subsequent to this reduction, subjects may at the discretion of the investigator, recommence the upward titration by 50 mg weekly increments towards their target dose until Week 6. If the subject cannot tolerate the new upward titration, the daily dose can be reduced one time by 50 mg through the end of week 8.	To improve tolerability, the dose and the titration rate is reduced
Table 1. Study Assessment Flowchart for Double-Blind Study	EEG or MRI or CT scan	EEG and MRI or CT scan	Text changed to correct typographical error
4.4.4 Clinical safety	Approximately 400 human subjects have been exposed to YKP3089 in 12 completed (11 Phase 1 and 1 proof-of-concept) and 3 ongoing clinical studies (1 Phase 2a and 2 Phase 1 studies).	Approximately 400 human subjects have been exposed to YKP3089 in 15 completed (13 Phase 1, 1 proof-of-concept) and 1 Phase 2a). In a multiple ascending dose study in healthy volunteers,	Text revised to update safety results from recently completed

Section	*Old Text*	*Amended Text*	*Rationale*
	In a multiple ascending dose study in healthy volunteers, when doses of 250 to 300 mg once daily were given from Day 1, somnolence, dizziness, and decreases in mean systolic blood pressure have been seen, but no serious AEs have been reported. Horizontal nystagmus, ataxia, and gait disturbance have also been observed in normal volunteers receiving 250 and 300 mg once daily. These reactions resolved after YKP3089 was discontinued at the end of the study. At 300 mg once daily, a mean shortening of the QTc_F interval of 10 to 15 msec was observed. In an ongoing Phase 1 multiple ascending dose study that remains blinded, subjects are titrated from a starting dose of 200 mg once daily to a target dose of 400, 500, or 600 mg once daily by 100-mg increments every 5 to 7 days. To date, adverse events in the first and second cohorts are generally mild, with no discernible pattern other than drowsiness. Two subjects taking YKP3089 discontinued from the cohort targeting 500 mg once daily because of an adverse event that was probably related to YKP3089. One subject discontinued for facial swelling and rash. The other subject discontinued because of an antiepileptic hypersensitivity syndrome with symptoms consistent with DRESS syndrome. Dosing was discontinued during the blinded phase of treatment with 600 mg once daily because	when doses of 250 to 300 mg once daily were given from Day 1, somnolence, dizziness, and decreases in mean systolic blood pressure have been seen, but no serious AEs have been reported. Horizontal nystagmus, ataxia, and gait disturbance have also been observed in normal volunteers receiving 250 and 300 mg once daily. These reactions resolved after YKP3089 was discontinued at the end of the study. At 300 mg once daily, a mean shortening of the QTc_F interval of 10 to 15 msec was observed. In another, now completed Phase 1 multiple ascending dose study in healthy volunteers, YKP3089C018, subjects were titrated from a starting dose of 200 mg once daily to a target dose of 400, 500, or 600 mg once daily by 100-mg increments every 5 to 7 days. Adverse events in the first and second cohorts were generally mild, with no discernible pattern other than drowsiness. All subjects following daily administration of 600 mg YKP3089 experienced multiple neurological adverse events including somnolence, ataxia, and nystagmus. Many of these AEs were probably related to the study drug and at least 2 subjects had exceeded their maximum tolerated dose. Based on the overall condition of the remaining subjects, the study was stopped. Two subjects taking YKP3089 discontinued from the cohort targeting 500 mg once daily because of an adverse event that was probably related to YKP3089. One subject discontinued for facial	clinical studies

Section	*Old Text*	*Amended Text*	*Rationale*
	of ataxia. In addition, a 41-year-old male subject receiving 600 once daily of YKP3089 was hospitalized because of head trauma subsequent to a fall and an altered state of consciousness. In an ongoing Phase 2a, double-blind, randomized, adjunctive therapy, placebo-controlled trial to evaluate the efficacy and safety of YKP3089 in subjects with treatment-resistant partial-onset seizures, subjects start with a 50-mg daily dose, which is increased by 50 mg every 2 weeks to a target dose of 200 mg once daily. There is a 6-week titration and 6-week maintenance period, followed by a 1-week taper period. Subjects who complete the double-blind period are eligible to enter an open-label extension. The sponsor remains blinded to results. A data monitoring committee has reviewed safety data from 100 subjects who have completed the double-blind period of the study and found no reason to alter the conduct of the study. Two suspected unexpected serious adverse reaction (SUSAR) have occurred: an early manifestation of a drug hypersensitivity reaction characterized by flushed erythema of palms and soles with mild itching of ears and a status epilepticus during tapering of the study medication. During the open-label extension, 2 notable serious adverse events occurred: one case of	swelling and rash. The other subject discontinued because of an antiepileptic hypersensitivity syndrome with symptoms consistent with DRESS syndrome. In addition, a 41-year-old male subject receiving 600 once daily of YKP3089 was hospitalized for one day because of head trauma subsequent to a fall and an altered state of consciousness. A recently completed Phase 2a, randomized, double-blind, placebo-controlled study, YKP3089C013, evaluated the efficacy and safety of 200mg of YKP3089 as adjunctive therapy for the treatment of partial seizures. YKP3089 treatment began with a 50-mg daily dose, which was increased by 50 mg every 2 weeks to a target dose of 200 mg once daily. There was a 6-week titration and 6-week maintenance period, followed by a 1-week taper period. Subjects who completed the double-blind period were eligible to enter an open-label extension. In the Phase 2a study, 113 subjects received YKP3089 and 109 received placebo. Comparison of the primary efficacy endpoint, median percent reduction in partial seizure frequency, demonstrated a highly statistically significant effect in favor of the YKP3089 group, 55% vs 21%, $p<0.0001$. Initial efficacy was observed at doses of 50-100mg/day and maintained throughout the 12 week study. Review of the safety data indicated that 4% of subjects in the	

Section	*Old Text*	*Amended Text*	*Rationale*
	sudden unexpected death in epilepsy (SUDEP) and one case of suicide. They were considered remotely related or unrelated to study drug.	active and 4% of subjects in the placebo-group dropped out because of adverse events. Two-thirds of subjects completed the study at the target dose of 200mg/day. The most common central nervous system adverse events in the YKP3089 group were somnolence, dizziness, fatigue, and gait disorder Two suspected unexpected serious adverse reaction (SUSAR) occurred in YKP3089 treated subjects: an early manifestation of a drug hypersensitivity reaction characterized by flushed erythema of palms and soles with mild itching of ears and a status epilepticus during tapering. During the open-label extension, 2 notable serious adverse events occurred in YKP3089 treated subjects: one case of sudden unexpected death in epilepsy (SUDEP) and one case of suicide. They were considered remotely related or unrelated to study drug.	
4.5.1 Double-Blind Dose Selection	The primary objective of this study is to determine the effective dose range of YKP3089 as adjunctive therapy for the treatment of partial seizures. According to a blinded review of an ongoing Phase 2a double-blind, randomized, placebo-controlled trial involving subjects with partial epilepsy, few subjects dropped out and 2 serious adverse events were related to YKP3089. Some subjects did not reach the maximum target dose of 200 mg. However, a daily dose of up to 500 mg was generally well tolerated by healthy volunteers in a multiple ascending dose extension	The primary objective of this study is to determine the effective dose range of YKP3089 as adjunctive therapy for the treatment of partial seizures. During the initial design of this protocol, a blinded review of the ongoing Phase 2a randomized, double-blind, placebo-controlled study YKP3089C013, revealed that few subjects dropped out and that only the two previously described serious adverse events were related to YKP3089. Some subjects did not reach the maximum target dose of 200 mg. In the multiple ascending dose study, YKP3089C018, a daily dose of up to 500 mg was	Text added to provide rationale for lower initial dose and slower titration rate

Section	*Old Text*	*Amended Text*	*Rationale*
	trial. In the open-label extension portion of the Phase 2a study, some subjects reportedly began to have clinically significant improvement in their seizure frequency only when they started taking a daily dose of 100 to 200 mg. A dose range of 200 to 400 mg/day should therefore be broad enough to identify efficacious doses. A 100-mg daily dose was chosen to determine the minimum effective dose. Although a dose of 500 mg once daily has generally been well tolerated by healthy volunteers, the maximum dose in this study will be 400 mg once daily, to account for potential adverse pharmacodynamic interaction with the concomitant antiepileptic drugs. The Phase 2a study titrated the daily dose upward by 50 mg every 2 weeks. However, the healthy volunteers in the ongoing multiple ascending dose study started with a daily dose of 200 mg, titrated upward by 100 mg every 5 to 7 days, and are tolerating the faster titration rate. Therefore, this study will begin with a daily dose of 100 mg, followed by weekly increments of 100 mg in the daily dose, to a target dose of up to 400 mg once daily.	generally well tolerated by healthy volunteers. In the open-label extension portion of the Phase 2a study, some subjects reportedly began to have clinically significant improvement in their seizure frequency only when they started taking a daily dose of 100 to 200 mg. It was concluded that a dose range of 200 to 400 mg/day should therefore be broad enough to identify efficacious doses. A 100-mg daily dose was chosen to determine the minimum effective dose. Although a dose of 500 mg once daily has generally been well tolerated by healthy volunteers, the maximum dose chosen for the study was 400 mg once daily, to account for potential adverse pharmacodynamic interaction with the concomitant antiepileptic drugs. Although the Phase 2a study titrated the daily dose upward by 50 mg every 2 weeks the healthy volunteers in the recently completed multiple ascending dose study initiated therapy with a daily dose of 200 mg, titrated upward by 100 mg every 5 to 7 days to 400 and 500mg/day, and generally well tolerated the faster titration rate. Therefore, it was initially decided that in the current study subjects would begin with a daily dose of 100 mg, followed by weekly increments of 100 mg in the daily dose, to the target dose. Recently, a blinded review of the tolerability profile in the	

Section	*Old Text*	*Amended Text*	*Rationale*
		first 9 subjects randomized in this study, YKP3089C017, was performed. Three subjects had study drug dose reduction and subsequently discontinued because of adverse events within four weeks of randomization. One of these subjects, a 47 year old male with a history of partial epilepsy, head trauma and a right hemiparesis, developed significant somnolence and ataxia and was hospitalized for increasing right hemiparesis. Asymptomatic pulmonary emboli were found incidentally during the hospitalization. Two other subjects had study drug dose reductions because of adverse events and are continuing therapy. The adverse events reported by these subjects are consistent with the adverse event profile of YKP3089 reported in previous studies of YKP3089, including somnolence, dizziness and ataxia; however the frequency of discontinuation and dose reductions is higher than initially expected. Although only a small number of subjects have been exposed to the new titration rate, to ensure that the results of this study can be interpreted correctly, the titration rate will be modestly slowed to provide for better tolerability and potentially fewer adverse event dropouts. The initial dose will be reduced to 50mg/day and the titration rate will slow to 50mg/day/week until 200mg is reached and then the dose will be increased by 100mg/week in subjects randomized to 400mg/day. If the subject experiences tolerability issues during the titration that	

Section	*Old Text*	*Amended Text*	*Rationale*
		require intervention by the investigator, the study drug dose will be reduced by 50 or 100mg depending on the attained dose at that time. (Reduce by 50mg if taking 100mg, 150mg or 200mg; reduce by 100mg if on 300mg or 400mg). The lower dose will be maintained for 7-13 days and then the investigator, at his/her discretion, may recommence an upward titration to the target dose. These changes are being made based on a blinded review of the data and will not impact the integrity of this double-blind placebo-controlled dose response study.	
4.6 Potential Risks and Benefits	Approximately 400 human subjects have been exposed to YKP3089 in 12 completed (11 phase 1 and 1 proof-of-concept) and 3 ongoing clinical studies (1 Phase 2a and 2 Phase 1). In an ongoing Phase 2a proof-of-concept study involving subjects with partial-onset seizures, only 2 SAEs have been related to YKP3089: an early manifestation of a drug hypersensitivity reaction characterized by flushed erythema of palms and soles with mild itching of ears and a status epilepticus during tapering of the study medication. In the open-label extension, 1 case of SUDEP and 1 suicide have been observed. In an ongoing Phase 1 drug interaction study with YKP3089 and phenytoin, a case of antiepileptic-induced	Approximately 400 human subjects have been exposed to YKP3089 in 15 completed (13 Phase 1, 1 proof-of-concept and 1 Phase 2a). In the completed Phase 2a randomized double-blind, placebo-controlled study in subjects with partial-onset seizures, only 2 SAEs have been related to YKP3089: an early manifestation of a drug hypersensitivity reaction characterized by flushed erythema of palms and soles with mild itching of ears and a status epilepticus during tapering of the study medication. In the open-label extension, one case of SUDEP and one case of suicide have been observed. No significant laboratory or electrocardiographic abnormalities were identified. In a completed Phase 1 drug interaction study with YKP3089 and phenytoin, a case of antiepileptic-induced	Text updated to provide results of recently completed clinical studies

Section	*Old Text*	*Amended Text*	*Rationale*
	hypersensitivity syndrome was observed. Rash and mucosal ulcers developed after 14 days of phenytoin treatment and 1 dose of YKP3089. The investigator deemed this SAE not related to YKP3089 and characterized it as phenytoin-induced hypersensitivity syndrome. As described previously, in an ongoing Phase 1 multiple ascending dose study, 1 subject developed fever, rash, leukocytosis, eosinophilia, and hepatic enzyme and electrolyte abnormalities. The drug was stopped and the signs and symptoms resolved thereafter. This was diagnosed as an antiepileptic hypersensitive syndrome with symptoms consistent with DRESS syndrome and probably related to YKP3089. In Phase 1 trials and in a Phase 2a proof-of-concept trial where treatment assignment is known, a total of 11 of 256 (4.3%) YKP3089-treated subjects reported rashes and 2 of 60 (3.3%) placebo treated subjects reported rashes. The preclinical antiepileptic profile of YKP3089 and a proof-of-concept study suggest that YKP3089 could provide additional seizure control in patients with poorly controlled epilepsy.	hypersensitivity syndrome was observed. Rash and mucosal ulcers developed after 14 days of phenytoin treatment and one dose of YKP3089. The investigator deemed this SAE not related to YKP3089 and characterized it as phenytoin-induced hypersensitivity syndrome. As described previously, in a completed Phase 1 multiple ascending dose study, one subject developed fever, rash, leukocytosis, eosinophilia, and hepatic enzyme and electrolyte abnormalities. The drug was stopped and the signs and symptoms resolved thereafter. This was diagnosed as an antiepileptic hypersensitive syndrome with symptoms consistent with DRESS syndrome and probably related to YKP3089. The incidence of rashes in YKP3089 and placebo treated subjects in completed Phase 1 trials and in a Phase 2a studies is approximately 4% in each group. At this time, the preclinical antiepileptic profile of YKP3089 and the first Phase 2a randomized, double-blind, placebo-controlled study suggest that YKP3089 could provide additional seizure control in patients with poorly controlled epilepsy with limited safety risks.	

<table>
<tr><th>Section</th><th>Old Text</th><th>Amended Text</th><th>Rationale</th></tr>
<tr><td>6.1 Overview</td><td>Subjects will first enter a 6-week titration phase, during which the planned increase in the daily dose will be 100 mg per week. Subjects will then enter a 12-week double-blind maintenance phase.</td><td>Subjects will first enter a 6-week titration phase, during which the initial dose will be 50mg/day. The planned increase in the daily dose will be 50mg/day/week increments until 200mg is reached and after which the dose will be increased by 100mg/day/week in subjects randomized to 400mg/day 100 mg per week. Subjects will then enter a 12-week double-blind maintenance phase.</td><td>Text revised to lower the initial dose and the titration rate</td></tr>
<tr><td>6.1.2.1 Titration Phase</td><td>During the initial 6-week up-titration phase of the double-blind treatment period, subjects assigned to receive YKP3089 will receive blinded study medication according to the dosage schedule shown in Table 3

Table 3. YKP3089 Initial Double-Blind Up-Titration
<table><tr><td rowspan="2">YKP3089 target dose (mg/day)</td><td></td><td></td><td colspan="3">YKP3089 dose (mg/day)</td></tr><tr><td>Week 1</td><td>Week 2</td><td>Week 3</td><td>Week 4</td><td>Week 5 + 6</td></tr><tr><td>100</td><td>100</td><td>100</td><td>100</td><td>100</td><td>100</td></tr><tr><td>200</td><td>100</td><td>200</td><td>200</td><td>200</td><td>200</td></tr><tr><td>400</td><td>100</td><td>200</td><td>300</td><td>400</td><td>400</td></tr></table>
During Week 1, no dose reduction will be permitted. Subjects who have significant tolerability issues should discontinue treatment with study drug. If study drug is not tolerated for the first time at any time during Weeks 2 through 5, subjects may have one 100-mg reduction in their daily dose. For subjects in the 100-mg group, the 100-mg dose reduction will only be simulated because the</td><td>During the initial 6-week up-titration phase of the double-blind treatment period, subjects assigned to receive YKP3089 will receive blinded study medication according to the dosage schedule shown in Table 3

Table 3. YKP3089 Initial Double-Blind Up-Titration
<table><tr><td rowspan="2">YKP3089 target dose (mg/day)</td><td></td><td></td><td colspan="4">YKP3089 dose (mg/day)</td></tr><tr><td>Week 1</td><td>Week 2</td><td>Week 3</td><td>Week 4</td><td>Week 5</td><td>Week 6</td></tr><tr><td>100</td><td>50</td><td>100</td><td>100</td><td>100</td><td>100</td><td>100</td></tr><tr><td>200</td><td>50</td><td>100</td><td>150</td><td>200</td><td>200</td><td>200</td></tr><tr><td>400</td><td>50</td><td>100</td><td>150</td><td>200</td><td>300</td><td>400</td></tr></table>
During Week 1, no dose reduction will be permitted. Subjects who have significant tolerability issues should discontinue treatment with study drug. If study drug is not tolerated for the first time at any time during Weeks 2 through 6, subjects may a reduction in their daily dose. The size of the reduction will depend on the dose at the time poor tolerability is noted (Reduce by 50mg if taking 100mg, 150mg or 200mg; reduce</td><td>Table and text changed to provide lower starting dose and slower titration rate</td></tr>
</table>

Section	*Old Text*	*Amended Text*	*Rationale*
	minimum dose to be tested is 100 mg. Subjects will remain at the reduced dose level for a minimum of 7 days and up to 13 days. Thereafter, the subjects will recommence the upward titration at 50-mg increments in the daily dose once a week towards the target dose until week 6. If the subject cannot tolerate the new upward titration, the daily dose can be reduced one time by 50 mg through the end of week 8. Subjects having tolerability issues during Week 6 for the first time will have their dose reduced by 50 mg once and will remain at that dose for the rest of the study. For the 100-mg group, the 50-mg dose reduction will only be simulated because the minimum dose to be tested is 100 mg. No upward titration will be allowed after Week 6. No two consecutive dose reductions will be allowed. If a tolerability issue occurs, dosage adjustments need to be made at a scheduled visit or at an unscheduled visit at the discretion of the investigator. At the visit, the subject will be issued a new set of cards to be determined by interactive web response system (IWRS). To improve tolerability, the investigator may instruct the subject to take the dose of study medication in the evening. The investigator may alter the timing or amount of an individual dose of a concomitant AED, but the total daily dose and dosing frequency of the concomitant AED must	by 100mg if on 300mg or 400mg). Subjects will remain at the reduced dose level for a minimum of 7 days and up to 13 days. Thereafter, the subjects may at the discretion of the investigator, recommence the upward titration at 50-mg increments in the daily dose once a week towards the target dose until week 6. If the subject cannot tolerate the new upward titration, the daily dose can be reduced one time by 50 mg through the end of week 8. No upward titration will be allowed after Week 6. No two consecutive dose reductions will be allowed. If a tolerability issue occurs, dosage adjustments need to be made at a scheduled visit or at an unscheduled visit at the discretion of the investigator. At the visit, the subject will be issued a new set of cards to be determined by the interactive web response system (IWRS). To improve tolerability, the investigator may instruct the subject to take the dose of study medication in the evening. The investigator may alter the timing or amount of an individual dose of a concomitant AED, but the total daily dose and dosing frequency of the concomitant AED must remain unchanged during the double-blind phase. During titration, the investigator may instruct the subject to	Language added to provide an additional step to improve tolerability during titration

<table>
<tr><th>Section</th><th>Old Text</th><th>Amended Text</th><th>Rationale</th></tr>
<tr><td></td><td>remain unchanged during the double-blind phase.</td><td>hold the daily dose of the study drug up to a maximum of 2 days per week.</td><td></td></tr>
<tr><td>6.1.2.3 Blinded Study Drug Taper: Termination at End of Double-Blind Phase</td><td>Table 4. Blinded Study Drug Taper Schedule
<table><tr><td rowspan="2">Final Double-Blind Dose of YKP3089 (mg/day)</td><td colspan="3">YKP3089 Dose During Taper (mg/day)</td></tr><tr><td>Week 1</td><td>Week 2</td><td>Week 3</td></tr><tr><td>0 (placebo) or 100</td><td>0</td><td>0</td><td>0</td></tr><tr><td>150 or 200</td><td>100</td><td>0</td><td>0</td></tr><tr><td>250 or 300</td><td>200</td><td>100</td><td>0</td></tr><tr><td>350 or 400</td><td>300</td><td>200</td><td>100</td></tr></table></td><td>Table 4. Blinded Study Drug Taper Schedule
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<tr><td>6.1.4.1 Blinded Study Drug Conversion Period: Subjects Entering the Open-Label Phase</td><td>Subjects will have a 2-week double-blind conversion period at the beginning of the open-label extension phase of the study. In order to keep the treatment blind, subjects from all four dose groups will be converted to a single dose group of 300 mg/day after two weeks of blinded conversion period. This conversion period will begin at Visit 9. Subjects will follow the study medication schedule shown in Table 5. The daily dose will consist of 4 tablets of YKP3089 or placebo (depending on the dose regimen assigned during the double-blind phase) from a blinded blister card plus tablets (1 for Week 1 and 2 for Week 2) from an open-label bottle of 100-mg YKP3089 tablets taken every morning. Starting at Visit 11, the subjects will take three 100-mg tablets from the open-label bottle every morning.</td><td>Subjects will have a 2-week double-blind conversion period at the beginning of the open-label extension phase of the study. In order to keep the treatment blind, subjects from all four dose groups will be converted to a target dose of 300 mg/day after two weeks of blinded conversion period. This conversion period will begin at Visit 9. Subjects will follow the study medication schedule shown in Table 5. The daily dose will consist of 4 tablets of YKP3089 or placebo (depending on the dose regimen assigned during the double-blind phase) from a blinded blister card plus tablets (2 for Week 1 and 4 for Week 2) from an open-label bottle of 50-mg YKP3089 tablets taken every morning. Starting at Visit 11, the subjects will take three 100-mg tablets from the open-label bottle every morning.</td><td>Text revised/added to provide 50mg open label tablets during blinded conversion to open label treatment</td></tr>
</table>

Section	*Old Text*	*Amended Text*	*Rationale*

Table 5. Blinded Study Drug Conversion to Open-Label Target of 300 mg/day YKP3089

YKP3089 dose group (mg/day) during double-blind period	Dose of YKP3089 (mg/day)[a]					
	Dispensed at Visit 9				Dispensed at Visit 11	
	Week 1		Week 2		Week 3	
	From Card	From Open-Label Bottle	From Card	From Open-Label Bottle	From Card	From Open-Label Bottle
0 (placebo)	0	100	0	200	No card	300
100	100	100	100	200	No card	300
150/200	100	100	100	200	No card	300
250/300	200	100	100	200	No card	300
350/400	200	100	100	200	No card	300

[a]The total daily dose is the amount taken from the blister card plus the amount taken from the bottle of 100-mg tablets (eg, the placebo group from the double-blind phase receives placebo from the blister card and a 100-mg tablet from the bottle every day during Week 1 of the conversion period, placebo from the blister card and two 100-mg tablets from the bottle every day during Week 2 of the conversion period, and then three 100-mg tablets from the bottle per day starting in Visit 11).

Table 5. Blinded Study Drug Conversion to Open-Label Target of 300 mg/day YKP3089

YKP3089 dose group (mg/day) during double-blind period	Dose of YKP3089 (mg/day)[a]					
	Dispensed at Visit 9				Dispensed at Visit 11	
	Week 1		Week 2		Week 3	
	From Card	From Open-Label Bottle	From Card	From Open-Label Bottle	From Card	From Open-Label Bottle
0 (placebo)/50	0	2X50	0	4X50	No card	300
100	100	2X50	100	4X50	No card	300
150/200	100	2X50	100	4X50	No card	300
250/300	200	2X50	100	4X50	No card	300
350/400	200	2X50	100	4X50	No card	300

[a]The total daily dose is the amount taken from the blister card plus the amount taken from the bottle of 50-mg tablets (eg, the placebo group from the double-blind phase receives placebo from the blister card and two 50-mg tablets from the bottle every day during Week 1 of the conversion period, placebo from the blister card and four 50-mg tablets from the bottle every day during Week 2 of the conversion period, and then three 100-mg tablets from the bottle per day starting in Visit 11).

Section	*Old Text*	*Amended Text*	*Rationale*
	Investigator can increase or decrease the open-label dosage by 100 mg if clinically indicated (ie, recurrence of seizures, adverse events) during the conversion period.	During the first week of the conversion period, the investigator can increase or decrease the open-label dosage by 50-100 mg if clinically indicated (ie, recurrence of seizures, adverse events). During the second week of the conversion period, the investigator can decrease the open-label dosage by 50-200 mg or increase the open label dosage by a maximum of 100 mg if clinically indicated (ie, recurrence of seizures, adverse events). **All dose adjustments must be made with tablets from the open label bottles. All tablets from the cards must be taken on Week 1 and Week 2 during the conversion period.** Although the target dose for subjects is 300mg at Visit 11, subjects may be taking 50-400 mg at Visit 11 depending upon tolerability and efficacy during the conversion period. Doses of concomitant AEDs may be adjusted during the conversion phase.	
6.1.4.2 Open-Label Extension Treatment Phase	The initial target dose for the open-label extension will be 300 mg/day. However, if a subject is not tolerating the 300 mg/day dose, YKP3089 dose may be reduced to a minimum of 100 mg/day. If the investigator feels that a subject requires a dose that is higher than 300 mg/day, the dose can be increased to a maximum of 400 mg/day once the target dose of 300 mg/day was reached. The dose adjustments may occur in weekly increments of 100	The initial target dose for the open-label extension will be 300 mg/day. However, if a subject is not tolerating the 300 mg/day dose, YKP3089 dose may be reduced to a minimum of 50 mg/day. If the investigator feels that a subject requires a dose that is higher than 300 mg/day, the dose can be increased to a maximum of 400 mg/day once the target dose of 300 mg/day was reached. The dose adjustments may occur in weekly increments of 100 mg/day or 50-mg/day. However,	Text added to allow minimum open label treatment dose of 50mg/day

<table>
<tr><th>Section</th><th>Old Text</th><th>Amended Text</th><th>Rationale</th></tr>
<tr><td></td><td>mg/day or 50-mg/day. However, the rate of change may be more rapid or slow as clinically indicated. No dose reductions are permitted if subject is taking 100 mg/day YKP3089. If 100 mg/day YKP3089 is not tolerated, the subject will withdraw from the study</td><td>the rate of change may be more rapid or slow as clinically indicated. No dose reductions are permitted if the subject is taking 50 mg/day YKP3089. If 50 mg/day YKP3089 is not tolerated, the subject will withdraw from the study.</td><td></td></tr>
<tr><td>6.1.4.3 Study Drug Taper: Subjects Leaving the Open-Label Extension</td><td>Table 6. Study Drug Taper Schedule for Subjects Completing Open-Label Extension
<table>
<tr><td rowspan="2">Final open-label dose of YKP3089 (mg/day)</td><td colspan="3">YKP3089 Dose During Taper (mg/day)</td></tr>
<tr><td>Week 1</td><td>Week 2</td><td>Week 3</td></tr>
<tr><td>100</td><td colspan="3">None</td></tr>
<tr><td>150 or 200</td><td>100</td><td>None</td><td>None</td></tr>
<tr><td>250 or 300</td><td>200</td><td>100</td><td>None</td></tr>
<tr><td>350 or 400</td><td>300</td><td>200</td><td>100</td></tr>
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<tr><td>50 or 100</td><td colspan="3">None</td></tr>
<tr><td>150 or 200</td><td>100</td><td>None</td><td>None</td></tr>
<tr><td>250 or 300</td><td>200</td><td>100</td><td>None</td></tr>
<tr><td>350 or 400</td><td>300</td><td>200</td><td>100</td></tr>
</table></td><td>Text added to provide taper schedule for subject treated with 50mg/day YKP3089 during open label treatment</td></tr>
<tr><td>6.1.5 Dose Adjustments of Study Drug and Concomitant AEDs</td><td>During week 1, no dose reduction will be permitted. Subjects who have significant tolerability issues should discontinue treatment with study drug. If study drug is not tolerated at some point during weeks 2 through 5, subjects may have one (and only one) 100-mg reduction in the daily dose. For the 100-mg group, the 100-mg dose reduction will only be simulated because the minimum dose to be tested is 100 mg. Subjects will remain at the reduced dose level for a minimum of 7 days and up to 13 days. Thereafter, the subjects will recommence the upward titration to the target dose at 50-mg increments in the daily dose once a week until week 6. If the subject cannot tolerate the new upward titration, the daily dosage can be</td><td>During week 1, no dose reduction will be permitted. Subjects who have significant tolerability issues should discontinue treatment with study drug. If study drug is not tolerated at some point during weeks 2 through 6, subjects may have a reduction in the daily dose. The size of the reduction will depend on the dose at the time poor tolerability is noted (Reduce by 50mg if taking 100mg, 150mg or 200mg; reduce by 100mg if on 300mg or 400mg). Subjects will remain at the reduced dose level for a minimum of 7 days and up to 13 days. Thereafter, the subjects may, at the discretion of the investigator, recommence the upward titration to the target dose at 50-mg increments in the daily dose once a week until week 6. If the subject cannot tolerate the new upward</td><td>Text revised to clarify dose adjustments</td></tr>
</table>

Section	*Old Text*	*Amended Text*	*Rationale*
	reduced once by 50 mg up through the end of Week 8. Subjects having tolerability issues during Week 6 for the first time will have their dose reduced by 50 mg once and will remain at that dose for the rest of the study. For the 100-mg group, the 50-mg dose reduction will only be simulated because the minimum dose to be tested is 100 mg. No upward titration will be allowed after Week 6. No two consecutive dose reductions will be allowed. Dosage adjustments related to tolerability issues need to be made at a scheduled visit or at an unscheduled visit at the discretion of the investigator. At the visit, the subject will be issued a new card or set of cards to be determined by IWRS. For further instruction on dose adjustments, please refer to study manual. The investigator may instruct the subject to take the dose of study medication in the evening if clinically indicated and consistent with other aspects of the protocol. The investigator may alter the timing or amount of an individual dose of a concomitant AED, but the total daily dose and dosing frequency of the concomitant AED must remain unchanged during the double-blind phase. The initial target dose for the open-label extension will be 300 mg/day. However, if a subject is not tolerating the 300	titration, the daily dosage can be reduced once by 50 mg up through the end of Week 8.. No upward titration will be allowed after Week 6. No two consecutive dose reductions will be allowed. Dosage adjustments related to tolerability issues need to be made at a scheduled visit or at an unscheduled visit at the discretion of the investigator. At the visit, the subject will be issued a new card or set of cards to be determined by IWRS. For further instruction on dose adjustments, please refer to study manual. The initial target dose for the open-label extension will be 300 mg/day. However, if a subject is not tolerating the 300 mg/day dose, YKP3089 dose may be reduced to a minimum of 50 mg/day. If the investigator feels that a subject requires higher than 300 mg/day, the dose can be increased to a maximum of 400 mg/day once the target dose of 300 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. No dose reductions are permitted if subject is taking 50 mg/day YKP3089. If 50 mg/day YKP3089 is not tolerated, the subject will withdraw from the study. Monotherapy with YKP3089 will not be allowed. The investigator may add, remove, or adjust the dosage of concomitant AEDs, as	

Section	*Old Text*	*Amended Text*	*Rationale*
	mg/day dose, YKP3089 dose may be reduced to a minimum of 100 mg/day. If the investigator feels that a subject requires higher than 300 mg/day, the dose can be increased to a maximum of 400 mg/day once the target dose of 300 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. No dose reductions are permitted if subject is taking 100 mg/day YKP3089. If 100 mg/day YKP3089 is not tolerated, the subject will withdraw from the study. Monotherapy with YKP3089 will not be allowed. The investigator may add, remove, or adjust the dosage of concomitant AEDs, as clinically indicated. In the event of poor tolerability, the investigator may instruct the subject to take the dose of study medication in the evening or divide the total daily dose into 2 doses.	clinically indicated. In the event of poor tolerability, the investigator may instruct the subject to take the dose of study medication in the evening or divide the total daily dose into 2 doses.	
7.3 Inclusion Criteria	5. Have uncontrolled partial seizures despite having been treated with at least 2 different AEDs within approximately the last 2 years.	5. Have uncontrolled partial seizures despite having been treated with at least one AED within approximately the last 2 years.	Text changed to define uncontrolled partial seizures
7.5 Birth Control Methods Allowable for Enrollment of	7.5 Birth Control Methods Allowable for Enrollment of Female Subjects	7.5 Birth Control Methods Allowable for Enrollment of Subjects	Title changed to provide contraception guidance for both male and

Section	*Old Text*	*Amended Text*	*Rationale*
Female Subjects	-	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).	female subjects Text added to provide definition for women of child bearing potential
	-	There is no need for male subjects enrolled in YKP3089C017 to use contraception with partners of childbearing potential during their participation in the study.	Text added to provide contraception language for male subjects
8.1.1.3 Packaging and Labeling	For the double-blind phase and the blinded conversion to open-label phase, 50 mg and 100 mg YKP3089 and matching placebo tablets will be packaged in 2-panel blister cards—one panel for the label and the other for the medication. There will be 8 blister card types, one for each of the possible daily doses in this study: placebo, 100, 150, 200, 250, 300, 350, and 400 mg. Each medication panel of the blister card will contain nine rows and four columns of tablets for 7 days of treatment plus 2 extra days for a total of 9 days. Each row will contain the same total dose.	For the double-blind phase and the blinded conversion to open-label phase, 50 mg and 100 mg YKP3089 and matching placebo tablets will be packaged in 2-panel blister cards—one panel for the label and the other for the medication. There will be 9 blister card types, one for each of the possible daily doses in this study: placebo, 50, 100, 150, 200, 250, 300, 350, and 400 mg. Each medication panel of the blister card will contain nine rows and four columns of tablets for 7 days of treatment plus 2 extra days for a total of 9 days. Each row will contain the same total dose.	Text added to include 50mg cards to the blister card types

Section	*Old Text*	*Amended Text*	*Rationale*
8.1.2 Blinding of Study Medication	Neither the investigator nor the site staff will know the contents of the tablets administered; however, this information will be readily available in the event of an emergency. Investigators may perform emergency unblinding using the IWRS system immediately, without prior contact to the study's Medical Monitor, if they feel it is medically necessary and that knowledge of the treatment assignment is essential for the patient's care. If such an emergency unblinding is necessary, investigators should promptly document and explain to the Medical Monitor or Sponsor any premature unblinding of the investigational product.	Neither the investigator nor the site staff will know the contents of the tablets administered; however, this information will be readily available in the event of an emergency.	Text added to provide unblinding information
8.2.1.4 Drug Dispensing	Open-Label Extension If a subject enters the open-label extension, he/she will enter a blinded dose-conversion period. At Visit 9, during the conversion period, the subject will receive 2 blinded blister cards as directed by the IWRS system and an open-label bottle of YKP3089 containing one hundred 100 mg tablets. The subject will be instructed to take medication from each blister card on dates specified on the card. In addition, for the first week, the subject will take one 100-mg tablet from the bottle. For the second week, the subject will be instructed to take two 100-mg tablets from the bottle.	Open-Label Extension If a subject enters the open-label extension, he/she will enter a blinded dose-conversion period. At Visit 9, during the conversion period, the subject will receive 2 blinded blister cards as directed by the IWRS system and an open-label bottle of YKP3089 containing one hundred 50 mg tablets. The subject will be instructed to take medication from each blister card on dates specified on the card. In addition, for the first week, the subject will take two 50-mg tablet from the bottle. For the second week, the subject will be instructed to take four 50-mg tablets from the bottle.	Text updated for use of 50mg tablets

Section	*Old Text*	*Amended Text*	*Rationale*
9.1.3 Visit 3, Day 1 (Randomization)	• Instruct the subject to take the first dose of the study medication the next morning.	• Instruct the subject to take the first dose of the study medication 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 on the day of randomization <u>after all other Visit 3 procedures have been completed</u>. For these subjects, seizures which occur after the first dose must be counted and entered in to the CRF.	Language added to allow subjects to have their first dose of the study medication administered at the study site
9.3.2 Visit 11, Day 141	The initial target dose for the open-label extension will be 300 mg once daily. The dose of YKP3089 may be reduced to a minimum of 100 mg once daily or increased to a maximum of 400 mg once daily by 100-mg or 50-mg increments.	The initial target dose for the open-label extension will be 300 mg once daily. The dose of YKP3089 may be reduced to a minimum of 50 mg once daily or increased to a maximum of 400 mg once daily by 100-mg or 50-mg increments.	Text updated for the use of 50mg tablets
13.7.2 Data Monitoring Committee	The DMC will have access to all unblinded safety data. The DMC will perform the following reviews: 1. Review of the safety of the first 60 subjects completing titration. 2. Review of the safety of the first 120 subjects completing titration. 3. Review of the safety of the first 150 subjects completing double-blind phase. 4. Review of the safety of the first 300 subjects completing double-blind phase.	The DMC will have access to all unblinded safety data. The DMC will perform the following reviews: 1. Review of the safety of the first 40 subjects completing titration. 2. Review of the safety of the first 80 subjects completing titration. 3. Review of the safety of the first 120 subjects completing double-blind phase. 4. Review of the safety of the first 240 subjects completing double-blind phase.	Due to the changes to the titration rate, all DMC meetings will occur earlier in the course of the study.

The amendment must be reviewed and approved or have a favorable opinion from the Institutional Review Board/ Ethics Committee, prior to being implemented.

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1 PROTOCOL SYNOPSIS

Name of company	SK Life Science Inc
Title of study	A Multicenter, Double-Blind, Randomized, Placebo-Controlled, Dose-Response Trial of YKP3089 as Adjunctive Therapy in Subjects with Partial-Onset Seizures, with Optional Open-Label Extension
Protocol number	YKP3089C017
Phase of development	Phase 2b
Study duration	Baseline phase: 8 weeks Double-blind up-titration: 6 weeks Double-blind maintenance phase: 12 weeks Double-blind crossover to open-label extension: 2 weeks Blinded study drug taper: 3 weeks Open-label extension phase: Until development is stopped by SK Life Science Inc, or the product is approved for marketing, or any time at the discretion of SK Life Science Inc.
Indication	Partial-onset epilepsy
Study center(s)	Approximately 100 sites (multiple countries)
Number of subjects	400 randomized
Objectives	The primary objective of this study is to determine the effective dose range of YKP3089 as adjunctive therapy for the treatment of partial seizures. The trial will also evaluate the safety and tolerability of YKP3089 in the partial epilepsy population.
Inclusion and exclusion criteria	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. Men and women 18 to 70 years of age, inclusive, will be permitted to enroll in this study. During the baseline, subjects must have at least 8 partial seizures, including only simple partial seizures with motor component, complex partial seizures, or secondarily generalized seizures without a seizure-free interval of greater than 25 days any time during the 8-week baseline despite appropriate doses of at least 1 and no more than 3 concomitant

	AEDs. Subjects must have at least 3 of these partial seizures during each of the two consecutive 4-week periods in the baseline. Patients who meet the above seizure criteria and continue to meet other inclusion/exclusion criteria will be randomly assigned to the treatment.
Design and methodology	This is a multicenter, double-blind, randomized, placebo-controlled dose-response study, with an 8-week prospective baseline and an 18-week double-blind treatment period (including a 6-week titration phase and 12-week maintenance phase), followed by a 3-week blinded study drug taper period (for subjects leaving the study) or a 2-week blinded conversion period (for subjects who will participate in the open-label extension). Subjects who meet inclusion/exclusion criteria will first undergo an 8-week baseline period to assess seizure frequency. During the baseline, subjects must have at least 8 partial seizures including only simple partial seizures with motor component, complex partial seizures, or secondarily generalized seizures without a seizure-free interval of greater than 25 days any time during the 8-week period. Subjects must have at least 3 of these partial seizures during each of the two consecutive 4-week periods in the baseline. Subjects with a high enough seizure frequency will be randomly assigned in a 1:1:1:1 ratio to receive placebo or to receive YKP3089 100, 200, or 400 mg given once per day in the morning. Subjects will first enter a 6-week titration phase, during which the initial dose will be 50mg/day. The planned increase in the daily dose will be 50mg/day/week increments until 200mg is reached and after which the dose will be increased by 100mg/day/week in subjects randomized to 400mg/day. Subjects having tolerability issues for the first time during Weeks 2 to 6 will have their dose reduced by 50 or100 mg depending on their attained dose at the time (Reduce by 50mg if taking 100mg, 150mg or 200mg; reduce by 100mg if on 300mg or 400mg).Subsequent to this reduction, subjects may at the discretion of the investigator, recommence the upward titration by 50 mg weekly increments towards their target dose until Week 6. If the subject cannot tolerate the new upward titration, the daily dose can be reduced one time by 50 mg through the end of week 8. Subjects will then enter a 12-week double-blind maintenance phase. Only subjects who complete the double-blind maintenance phase will be given the option to continue treatment in an open-label extension. Those who choose not to enter the open-label extension or who withdraw prematurely will taper off the study drug. For those subjects not entering the open-label extension, the taper phase will last 3 weeks, followed by a final visit 14 days after the last dose of study drug. The open-label extension will start with a 2-week blinded crossover period, during which all subjects will be converted to open-label YKP3089 at a target dose of 300 mg once daily.

Test product and dose	YKP3089 50 and 100 mg tablets Target doses: 100, 200 or 400-mg per day
Reference therapy & dose	Placebo
Statistics and analyses	The primary efficacy endpoint to be evaluated for registration in the United States and the Rest of the World is the percent change from the pretreatment baseline phase in seizure frequency (average monthly seizure rate per 28 days) of all simple partial motor, complex partial, or secondarily generalized seizures compared with the double-blind treatment phase. The primary efficacy endpoint to be evaluated for registration in the countries of Europe, Australia, New Zealand, and South Africa is the responder rate defined as a 50% or greater reduction during the maintenance phase of the double blind period in the seizure frequency from baseline. **The Primary Efficacy Analysis for United States, and the Rest of the World:** The primary efficacy analysis of the primary endpoint will be based on the MITT population. The testing strategy for the primary efficacy endpoint is to compare each of the YKP3089 dosage groups with the placebo group. Due to multiple treatment comparisons, a step-down procedure will be used to ensure the overall type I error rate is controlled at the 5% level. Each of the YKP3089 dosage groups will be compared with the placebo group according to the following hierarchy: 1. 200-mg dosage group versus placebo group 2. 400-mg dosage group versus placebo group 3. 100-mg dosage group versus placebo group The 200-mg dosage group will be compared with the placebo group at a 2-sided 0.05 level as the first step. If no statistically significant difference is detected between the 200-mg dosage group and the placebo group, the procedure will stop and it will be concluded that none of the YKP3089 dosages are efficacious. If a statistically significant difference is detected between the 200-mg dosage group and the placebo group in favor of the 200-mg dosage group, the procedure will proceed to the next step to compare the 400-mg dosage group with the placebo group at a 2-sided 0.05 level. If a statistically significant difference is detected between the 400-mg dosage group and the placebo group in favor of the 400-mg dosage group, the procedure will proceed to the next step to compare the 100-mg dosage group with the placebo group at a 2-sided 0.05 level.

	An analysis of covariance (ANCOVA) model will be fit to the ranked values of the primary efficacy endpoint. The ANCOVA will have terms for ranked baseline seizure rate and randomized treatment group. **The primary Efficacy Analysis for Europe, Australia, New Zealand, and South Africa:** The primary efficacy analysis of the primary endpoint will be based on the MITT-M population. The testing strategy for the primary efficacy endpoint (responder rate) is to compare each of the YKP3089 dosage groups with the placebo group. A step-down procedure will be used to ensure the type I error rate due to multiple treatment comparisons is controlled at the 5% level. Each of the YKP3089 dosage groups will be compared with the placebo group according to the following hierarchy: 1. 200-mg dosage group versus placebo group 2. 400-mg dosage group versus placebo group 3. 100-mg dosage group versus placebo group The 200-mg dosage group will be compared with the placebo group at a 2-sided 0.05 level as the first step. If no statistically significant difference is detected between the 200-mg dosage group and the placebo group, the procedure will stop and it will be concluded that none of the YKP3089 dosages are efficacious. If a statistically significant difference is detected between the 200-mg dosage group and the placebo group in favor of the 200-mg dosage group, the procedure will proceed to the next step to compare the 400-mg dosage group with the placebo group at a 2-sided 0.05 level. If a statistically significant difference is detected between the 400-mg dosage group and the placebo group in favor of the 400-mg dosage group, the procedure will proceed to the next step to compare the 100-mg dosage group with the placebo group at a 2-sided 0.05 level. The data will be summarized using frequencies and percents of subjects achieving at least a 50% response to treatment, the responder rate. The responder data will be analyzed using a chi-square test. **Other Efficacy and Safety Analyses:** The percentage of subjects who have a 75%, 90% and 100% seizure reduction during the double blind period and the maintenance phase. Responder rates for partial seizure subtypes (including simple partial with motor component, complex partial, and secondarily generalized tonic-clonic seizures) will be summarized. Outcome measurements such as quality of life and clinical global impression change will be analyzed. Safety will be assessed by the frequency, severity, and timing 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). **Open-Label Extension:** The results of the open-label extension will be reported at a later date using summary tables, figures, and data listings. Summaries will be presented for demographic information and safety information only.

2 LIST OF ABBREVIATIONS

AE	Adverse event
AED	Antiepileptic drug
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
AST	Aspartate aminotransferase
AUC_{0-24}	Area under the plasma concentration versus time curve from 0 to 24 hours after dosing
β-hCG	β-human chorionic gonadotropin
BUN	Blood urea nitrogen
CBZ	Carbamazepine
CFR	Code of Federal Regulations
CNS	Central nervous system
CRO	Clinical Research Organization
C-SSRS	Columbia Suicide Severity Rating Scale
CT	Computed tomography
CYP	Cytochrome P450
DDD	Defined daily dose
DMC	Data Monitoring Committee
DRESS syndrome	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
HIPAA	Health Insurance Portability and Accountability Act
HPDE	High-density polyethylene
ICH	International Conference on Harmonisation
IND	Investigational new drug
IRB	Institutional review board
ITT	Intention to treat
IWRS	Interactive Web response system
kg	Kilogram
LEV	Levetiracetam
LOCF	Last observation carried forward
LTG	Lamotrigine
mg/kg	Milligrams per kilogram
mg/kg/day	Milligrams per kilogram per day
MRI	Magnetic resonance imaging
OXC	Oxcarbazepine
PBR	Phenobarbital (phenobarbitone)
PHI	Protected health information

PHT	Phenytoin
PI	Principal Investigator
PTZ	Pentylenetetrazol
SAE	Serious adverse event
SKLSI	SK Life Science, Inc.
SUDEP	Sudden unexpected death in epilepsy
SUSAR	Suspected unexpected serious adverse reaction
TPM	Topiramate
VNS	Vagal nerve stimulator
VPA	Valproic acid (divalproex sodium)

3 STUDY ASSESSMENTS

Table 1. Study Assessment Flowchart for Double-Blind Study

Visit windows of ± 2 days are allowed for visits 1 through 6 Visit windows of ± 3 days are allowed for visits 7 through 10	Screening / Baseline Period			Double-Blind Treatment Period (18 weeks)						Follow-up Period[b] (5 weeks)
	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9 or Early Termi-nation[a]	Visit 10
	Baseline Seizure Count		Safety baseline	Titration Phase (Day 2-43)			Maintenance Phase (Day 44-127)			
Assessment	**Day-56**	**Day-28**	**Day 1[l]**	**Day 15[m]**	**Day 29[m]**	**Day 43**	**Day 71**	**Day 99**	**Day 127**	**Day 162**
Informed consent	X									
Inclusion/exclusion	X		X							
Medical and seizure history	X									
Seizure Identification Form	X									
Vital signs[c]	X	X	X	X	X	X	X	X	X	X
Height[d] and weight	X		X		X		X		X	X
Full physical examination	X									X
Full neurologic examination	X								X	
Brief neurologic exam			X	X	X	X	X	X		X
C-SSRS[e]	X		X	X	X	X	X	X	X	X
ECG	X[f]		X			X			X	
Serum pregnancy test[g]	X									X
Urine pregnancy test[g]			X						X	
Laboratory safety assessment[h]	X		X			X			X	X
Urinalysis	X		X						X	X
YKP3089 levels[i]							X	X		
Concomitant AED levels[j]			X				X	X		
EEG and MRI or CT scan[k]	X									
Concomitant medications	X	X	X	X	X	X	X	X	X	X

Dispense/review/ collect seizure diary	X	X	X	X	X	X	X	X	X	X
Randomization			X							
Drug accountability				X	X	X	X	X	X	X
Dispense study drug			X	X	X	X	X	X	X[a]	
Adverse events		X	X	X	X	X	X	X	X	X
CGIC[n]									X	
QOLIE-31-P[o]			X						X	

C-SSRS = Columbia-Suicide Severity Rating Scale; ECG = electrocardiogram; AED = antiepileptic drug; MRI = magnetic resonance imaging ; CT = computed tomography EEG = Electroencephalogram. CGIC = Clinical Global Impression of Change, QOLIE-31-P = Quality of Life in Epilepsy-31-Problems

a. Subjects who do not plan to enter the optional open-label phase will have a blinded study drug taper. Subjects who plan to enter the open-label phase will have a blinded crossover at the beginning of the open-label phase.
b. Subjects who do not plan to enter the open-label phase will participate in Visit 10 Follow-up on Day 162. All subjects who plan to enter the open-label phase will enter the open-label phase at Visit 9 and not participate in Visit 10 Follow-up.
c. Vital signs include blood pressure and heart rate (supine for 5 minutes followed by standing for 3 minutes); respiration rate and oral temperature in the supine position.
d. Height measured only at Visit 1.
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 3 times with a minimum of 2 minutes between recordings.
g. For female subjects of childbearing potential: If pregnancy is suspected at any time during the study, an interim test may be performed.
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. Local laboratories may be used if necessary.
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.
j. Trough levels of concomitant AEDs should be obtained whenever possible. If this is not feasible due to the time of the clinic visit, appointments should be made so that the time of the blood draws are consistent with the last dose of concomitant AEDs throughout the study.
k. If a CT or MRI has not been performed within the last 10 years, one must be performed prior to randomization. If an EEG report cannot be obtained, and the subject is otherwise eligible, an EEG may be performed
l. Seizures occurring on Day 1 will not be counted in the study. Day 1 values will be used as safety baseline. Dosing will commence on Day 2.
m. Subjects will be contacted by phone on Days 8, 22 and 36 to assess tolerability and the occurrence of any early treatment-emergent adverse events and to reinforce compliance
n. The investigator will complete the questionnaire at Visit 9 (end of maintenance or early termination if applicable)
o. The subject will complete the questionnaire at Visit 3 and Visit 9 (end of maintenance or early termination if applicable). This questionnaire is only to be implemented in the countries where it is available and validated for the spoken language(s).

Table 2. Study Assessment Flow Chart for Open-Label Extension Phase

Visit windows of ± 3 days allowed for Visits 9 and Visit 17 (end of study follow-up visit) Visit windows of ± 2 days allowed for Visits 11 and 12. Visit windows of ± 7 days allowed for all other open-label visits	Treatment								End of Study Follow-up
	Visit 9 First Day of Open-Label Phase	**Visit 11**	**Visit 12**	**Visit 13**	**Visit 14**	**Visit 15**	**Visit 16 or Termination Visit**	**Post 1 year**	**Visit 17**
Assessment	**Day 127[a]**	**Day 141**	**Day 155**	**Day 239**	**Day 323**	**Day 407**	**Day 491**	**Every 3 months[b]**	**14 days after the last dose**
Inclusion/exclusion[c]	X								
Vital signs[d]	X	X	X	X	X	X	X	X	X
Weight	X			X		X	X	X[e]	X
Full physical examination	X						X	X[f]	
Full neurologic examination	X						X		X
Brief neurologic exam		X		X		X		X[e]	
C-SSRS[g]	X	X	X	X	X	X	X	X	X
ECG[h]	X		X				X	X[f]	
Serum pregnancy test[i]									X
Urine pregnancy test[i]	X		X		X		X	X[e]	
Laboratory safety assessment[j]	X		X		X		X	X[e]	X
Urinalysis	X				X		X	X[f]	X
Concomitant medication	X	X	X	X	X	X	X	X	X
Dispense/review/ collect seizure diary	X	X	X	X	X	X	X	X	
Drug accountability	X	X	X	X	X	X	X	X	X
Dispense study drug	X	X	X	X	X	X	X	X	
Adverse events	X	X	X	X	X	X	X	X	X

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

a. Visit 9 is the same as Visit 9 at the end of double-blind maintenance phase, except that study drug for 2-week blinded crossover period to open-label extension will be dispensed to subjects who will participate in the open-label extension.
b. 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.
c. Subject should continue to meet the inclusion and exclusion criteria except for seizure frequency.
d. Vital signs include blood pressure and heart rate (supine for 5 minutes followed by standing for 3 minutes). Respiration rate and oral temperature in the supine position.
e. Every 6 months after Visit 16.
f. Every 12 months after Visit 16.
g. Administer the Since Last Visit version of the C-SSRS.
h. 12-lead ECG. Additional ECGs should be performed at any other time if clinically indicated.
i. If pregnancy is suspected at any time during the study, an interim test may be performed.
j. Laboratory assessment: Safety assessment includes blood chemistry and hematology.

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. Therefore, the efficacy of YKP3089 in this population is worthy of investigation.

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.

Optimization of inclusion criteria. There is no formal definition of intractability in epilepsy, but subjects whose seizures persist despite therapy with 2 or more AEDs have been shown to have a poor response to subsequent AED regimens.[5] Failure may be characterized as a persistence of any seizure pattern during treatment with a given AED that, in the judgment of the investigator,

has been administered at appropriate doses and for sufficient periods of time. To ensure that enrolled subjects meet a rigorous criterion of medical intractability, treatments with at least 3 different AEDs must have failed (note that these may include AEDs that subjects are currently receiving). Establishing an 8-week prospective baseline and specifying a minimum of 8 seizures during that time (with at least 3 partial seizures during each of the two consecutive 4-week periods) and with no more than 25 consecutive days of freedom from seizures reduces the variability in the pretreatment seizure count and thereby increases the power of detection of significant changes in seizure frequency during the treatment period with the study drug.

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. It is a novel small molecule of molecular weight 267.68. Its structure is shown in Figure 1.

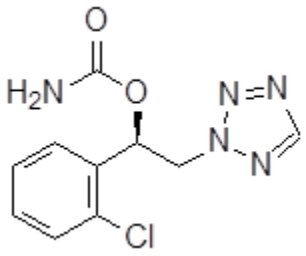


Figure 1. Structure of YKP3089

4.4 Pharmacology

YKP3089 is a novel small molecule that is currently in Phase 2 of development as an antiepileptic agent (IND 76,809). Nonclinical testing of YKP3089 suggested a broad spectrum of antiepileptic effects, as well as therapeutic potential for treatment of neuropathic pain and possible future investigations of treatment of anxiety. The mechanism of action of YKP3089 is currently unknown. Additional details can be found in the current YKP3089 Investigator's Brochure.

4.4.1 *Antiepileptic Activity of YKP3089*

YKP3089 has shown evidence of antiepileptic effects in standard preclinical models, as described in the current version of the Investigator's Brochure:

- The maximal electroshock test, which is used to identify compounds that prevent seizure spread
- The 6 Hz corneal stimulation model, which is a model of psychomotor seizures and therapy-resistant epilepsy
  - The pentylenetetrazol (PTZ, Metrazol®) test, which is used to identify compounds that raise seizure threshold
- Test for inhibition of seizures provoked by picrotoxin or bicuculline, which antagonize $GABA_A$ receptors. Bicuculline can also block Ca^{2+}-activated potassium channels.
- Test for inhibition of seizures induced by pilocarpine, potentiated by lithium carbonate. Pilocarpine is administered to rats to induce sustained convulsions that resemble status epilepticus and are followed by widespread damage to the forebrain.

No specific receptor has been identified as being involved in the mechanism of action of YKP3089. In vitro studies of panels of receptors showed no significant activation or inactivation. Nor did YKP3089 show significant potential to interact with voltage- or receptor-gated channels, although some effects on currents mediated by γ-aminobutyric acid (GABA) were noted. In vitro electrophysiology assays showed YKP3089 to be an inhibitor of the inactivated state of sodium channels. Thus, the mechanism of antiepileptic activity for YKP3089 is unknown and may be novel. Details of these studies can be found in the current version of the Investigator's Brochure.

4.4.2 *Absorption, Distribution, Metabolism, and Excretion*

Preclinical and clinical studies have shown that YKP3089 is well absorbed after oral administration under fasting and fed conditions. A single ascending dose study showed that the half-life of YKP3089 in human subjects was 50.2 ± 15.0 hours (mean ± SD) for a 100-mg oral dose, 54.7 ± 16.1 hours for a 200-mg oral dose, and 60.4 ± 11.2 hours for a 300-mg oral dose. These values suggest that YKP3089 is suitable for once-daily oral dosage. Details of these preclinical and clinical studies can be found in the current version of the Investigator's Brochure.

Protein binding in human plasma was concentration-independent at the range of 0.114 to 1.4 µg/mL. The protein-bound fraction in human plasma was 61%, with 39% free fraction. [^{14}C] YKP3089 was preferentially bound to human albumin protein (~66.7%) and not to α_1-acid glycoprotein.

A bioavailability study showed that YKP3089 undergoes minimal first-pass metabolism in humans. Preclinical studies showed that YKP3089 did not produce any strong inhibitions or inductions of cytochrome P450 (CYP) isozymes, UDP-dependent glucuronosyltransferase, or phenol sulfate transferase. Studies of the metabolism of YKP3089 showed several possible metabolic pathways. However, only the parent compound and the metabolite produced by glucuronidation of the carbamate nitrogen were recovered in human plasma. This suggests limited potential for metabolite toxicity.

A mass balance study in human subjects indicated limited penetration of YKP3089 and its metabolites into cellular elements of blood. More than 50% of the radioactivity from a radiolabeled dose of YKP3089 was excreted in urine and feces within 24 hours; 93% was excreted within 312 hours. For more information, see the Investigator's Brochure.

Clinical studies of drug-drug interactions showed that YKP3089 had no pharmacokinetic interaction with divalproex. Co-administration of YKP3089 did produce a 19% decrease in exposure to carbamazepine (CBZ) plus CBZ epoxide; however, this decrease was not considered clinically relevant. Co-administration of YKP3089 with an oral contraceptive (1 mg norethindrone and 0.035 mg ethinyl estradiol) showed that the contraceptive had no effect on the pharmacokinetics of YKP3089; however, the YKP3089 apparently increased the area under the concentration-time curve from 0 to 24 hours postdose (AUC_{0-24}) for norethindrone by 37%. Details of the drug-drug interaction studies can be found in the current version of the Investigator's Brochure.

4.4.3 *Safety Pharmacology and Toxicity Studies*

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). The incidence and severity of these signs increased with

increasing dose, and the signs resolved during the recovery periods. In mice and rats, the median neurotoxic dose of YKP3089 was calculated to be between 50 and 350 mg/kg, a dose greater than that required to elicit antiepileptic effects (ie, 3 to 30 mg/kg).

In a special neurotoxicity safety pharmacology study in cynomolgus monkeys, no evidence of drug-induced epileptic convulsions was observed at 30, 40, or 60 mg/kg/day administered for 4 days. Severe toxicity was noted at 40 and 60 mg/kg/day requiring euthanasia of 1 animal and halting of dosing for 3 others before the end of the scheduled 4 days of administration. At 60 mg/kg/day, myoclonus and/or intention tremors were noted in 2 of 6 animals.

YKP3089 had no effect on cardiac (ECG) or circulatory function in monkeys, as measured by telemetry. Nor was there evidence of cardiotoxicity in studies of rats or monkeys. YKP3089 at doses up to 30 mg/kg had no effect on pulmonary function or cause bronchoconstriction.

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. No tests of carcinogenicity have been conducted.

4.4.4 *Clinical Safety*

Approximately 400 human subjects have been exposed to YKP3089 in 15 completed (13 Phase 1, 1 proof-of-concept) and 1 Phase 2a).

In a multiple ascending dose study in healthy volunteers, when doses of 250 to 300 mg once daily were given from Day 1, somnolence, dizziness, and decreases in mean systolic blood pressure have been seen, but no serious AEs have been reported. Horizontal nystagmus, ataxia, and gait disturbance have also been observed in normal volunteers receiving 250 and 300 mg once daily. These reactions resolved after YKP3089 was discontinued at the end of the study. At 300 mg once daily, a mean shortening of the QTc_F interval of 10 to 15 msec was observed.

In another, now completed Phase 1 multiple ascending dose study in healthy volunteers, YKP3089C018, subjects were titrated from a starting dose of 200 mg once daily to a target dose

of 400, 500, or 600 mg once daily by 100-mg increments every 5 to 7 days. Adverse events in the first and second cohorts are generally mild, with no discernible pattern other than drowsiness. All subjects following daily administration of 600 mg YKP3089 experienced multiple neurological adverse events including somnolence, ataxia, and nystagmus. Many of these AEs were probably related to the study drug and at least 2 subjects had exceeded their maximum tolerated dose. Based on the overall condition of the remaining subjects, the study was stopped. Two subjects taking YKP3089 discontinued from the cohort targeting 500 mg once daily because of an adverse event that was probably related to YKP3089. One subject discontinued for facial swelling and rash. The other subject discontinued because of an antiepileptic hypersensitivity syndrome with symptoms consistent with DRESS syndrome. In addition, a 41-year-old male subject receiving 600 once daily of YKP3089 was hospitalized for one day because of head trauma subsequent to a fall and an altered state of consciousness.

A recently completed Phase 2a, randomized, double-blind, placebo-controlled study, YKP3089C013, evaluated the efficacy and safety of 200mg of YKP3089 as adjunctive therapy for the treatment of partial seizures. YKP3089 treatment began with a 50-mg daily dose, which was increased by 50 mg every 2 weeks to a target dose of 200 mg once daily. There was a 6-week titration and 6-week maintenance period, followed by a 1-week taper period. Subjects who completed the double-blind period were eligible to enter an open-label extension.

In the Phase 2a study , 113 subjects received YKP3089 and 109 received placebo. Comparison of the primary efficacy endpoint, median percent reduction in partial seizure frequency, demonstrated a highly statistically significant effect in favor of the YKP3089 group, 55% vs 21%, $p<0.0001$. Initial efficacy was observed at doses of 50-100mg/day and maintained throughout the 12 week study. Review of the safety data indicated that 4% of subjects in the active and 4% of subjects in the placebo-group dropped out because of adverse events. Two-thirds of subjects completed the study at the target dose of 200mg/day. The most common central nervous system adverse events in the YKP3089 group were somnolence, dizziness, fatigue, and gait disorder

Two suspected unexpected serious adverse reaction (SUSAR) occurred in YKP3089 treated subjects: an early manifestation of a drug hypersensitivity reaction characterized by flushed

erythema of palms and soles with mild itching of ears and a status epilepticus during tapering. During the open-label extension, 2 notable serious adverse events occurred in YKP3089 treated subjects: one case of sudden unexpected death in epilepsy (SUDEP) and one case of suicide. They were considered remotely related or unrelated to study drug.

4.5 Dose Justification

4.5.1 *Double-Blind Dose Selection*

The primary objective of this study is to determine the effective dose range of YKP3089 as adjunctive therapy for the treatment of partial seizures. During the initial design of this protocol, a blinded review of the ongoing Phase 2a randomized, double-blind, placebo-controlled study YKP3089C013, revealed that few subjects dropped out and that only the two previously described serious adverse events were related to YKP3089. Some subjects did not reach the maximum target dose of 200 mg. In the multiple ascending dose study, YKP3089C018, a daily dose of up to 500 mg was generally well tolerated by healthy volunteers.

In the open-label extension portion of the Phase 2a study, some subjects reportedly began to have clinically significant improvement in their seizure frequency only when they started taking a daily dose of 100 to 200 mg. It was concluded that a dose range of 200 to 400 mg/day should therefore be broad enough to identify efficacious doses. A 100-mg daily dose was chosen to determine the minimum effective dose. Although a dose of 500 mg once daily has generally been well tolerated by healthy volunteers, the maximum dose chosen for the study was 400 mg once daily, to account for potential adverse pharmacodynamic interaction with the concomitant antiepileptic drugs.

Although the Phase 2a study titrated the daily dose upward by 50 mg every 2 weeks the healthy volunteers in the recently completed multiple ascending dose study initiated therapy with a daily dose of 200 mg, titrated upward by 100 mg every 5 to 7 days to 400 and 500mg/day, and generally well tolerated the faster titration rate. Therefore, it was initially decided that in the current study subjects would begin with a daily dose of 100 mg, followed by weekly increments of 100 mg in the daily dose, to the target dose.

Recently, a blinded review of the tolerability profile in the first 9 subjects randomized in this study, YKP3089C017, was performed. Three subjects had study drug dose reduction and subsequently discontinued because of adverse events within four weeks of randomization. One of these subjects, a 47 year old male with a history of partial epilepsy, head trauma and a right hemiparesis, developed significant somnolence and ataxia and was hospitalized for increasing right hemiparesis. Asymptomatic pulmonary emboli were found incidentally during the hospitalization. Two other subjects had study drug dose reductions because of adverse events and are continuing therapy. The adverse events reported by these subjects are consistent with the adverse event profile of YKP3089 reported in previous studies of YKP3089, including somnolence, dizziness and ataxia; however the frequency of discontinuation and dose reductions is higher than initially expected.

Although only a small number of subjects have been exposed to the new titration rate, to ensure that the results of this study can be interpreted correctly, the titration rate will be modestly slowed to provide for better tolerability and potentially fewer adverse event dropouts. The initial dose will be reduced to 50mg/day and the titration rate will slow to 50mg/day/week until 200mg is reached and then the dose will be increased by 100mg/week in subjects randomized to 400mg/day. If the subject experiences tolerability issues during the titration that require intervention by the investigator, the study drug dose will be reduced by 50 or 100mg depending on the attained dose at that time. (Reduce by 50mg if taking 100mg, 150mg or 200mg; reduce by 100mg if on 300mg or 400mg). The lower dose will be maintained for 7-13 days and then the investigator, at his/her discretion, may recommence an upward titration to the target dose.

These changes are being made based on a blinded review of the data and will not impact the integrity of this double-blind placebo-controlled dose response study.

4.6 Potential Risks and Benefits

Approximately 400 human subjects have been exposed to YKP3089 in 15 completed (13 Phase 1, 1 proof-of-concept and 1 Phase 2a).

In the completed Phase 2a randomized double-blind, placebo-controlled study in subjects with partial-onset seizures, only 2 SAEs have been related to YKP3089: an early manifestation of a

drug hypersensitivity reaction characterized by flushed erythema of palms and soles with mild itching of ears and a status epilepticus during tapering of the study medication. In the open-label extension, one case of SUDEP and one case of suicide have been observed. No significant laboratory or electrocardiographic abnormalities were identified.

In a completed Phase 1 drug interaction study with YKP3089 and phenytoin, a case of antiepileptic-induced hypersensitivity syndrome was observed. Rash and mucosal ulcers developed after 14 days of phenytoin treatment and one dose of YKP3089. The investigator deemed this SAE not related to YKP3089 and characterized it as phenytoin-induced hypersensitivity syndrome.

As described previously, in a completed Phase 1 multiple ascending dose study, one subject developed fever, rash, leukocytosis, eosinophilia, and hepatic enzyme and electrolyte abnormalities. The drug was stopped and the signs and symptoms resolved thereafter. This was diagnosed as an antiepileptic hypersensitive syndrome with symptoms consistent with DRESS syndrome and probably related to YKP3089.

The incidence of rashes in YKP3089 and placebo treated subjects in completed Phase 1 trials and in a Phase 2a studies is approximately 4% in each group.

At this time, the preclinical antiepileptic profile of YKP3089 and the first Phase 2a randomized, double-blind, placebo-controlled study suggest that YKP3089 could provide additional seizure control in patients with poorly controlled epilepsy with limited safety risks.

5 STUDY OBJECTIVES

The **primary** objective of this study is to determine the effective dose range of YKP3089 as adjunctive therapy for the treatment of partial seizures.

The trial will also evaluate the safety and tolerability of YKP3089 in the partial epilepsy population.

6 STUDY DESIGN

6.1 Overview

This is a multicenter, double-blind, randomized, placebo-controlled study with an 8-week prospective baseline and an 18-week double-blind treatment period (including a 6-week titration phase and 12-week maintenance phase), followed by a 3-week blinded study drug taper period (for subjects leaving the study) or a blinded 2-week conversion period (for subjects participating in the open-label extension), with a final follow-up visit 2 weeks after the last dose of study drug.

Subjects who meet all inclusion criteria and none of the exclusion criteria will first undergo an 8-week baseline to assess seizure frequency. Subjects who have experienced at least 8 seizures during the baseline period without a seizure-free interval of greater than 25 days any time during those 8 weeks will be randomly assigned in a 1:1:1:1 ratio to receive placebo or YKP3089 100, 200, or 400 mg given once per day in the morning. Subjects must have at least 3 partial seizures during each of the two consecutive 4-week periods of the baseline.

Subjects will first enter a 6-week titration phase, during which the initial dose will be 50mg/day. The planned increase in the daily dose will be 50mg/day/week increments until 200mg is reached and after which the dose will be increased by 100mg/day/week in subjects randomized to 400mg/day . Subjects will then enter a 12-week double-blind maintenance phase.

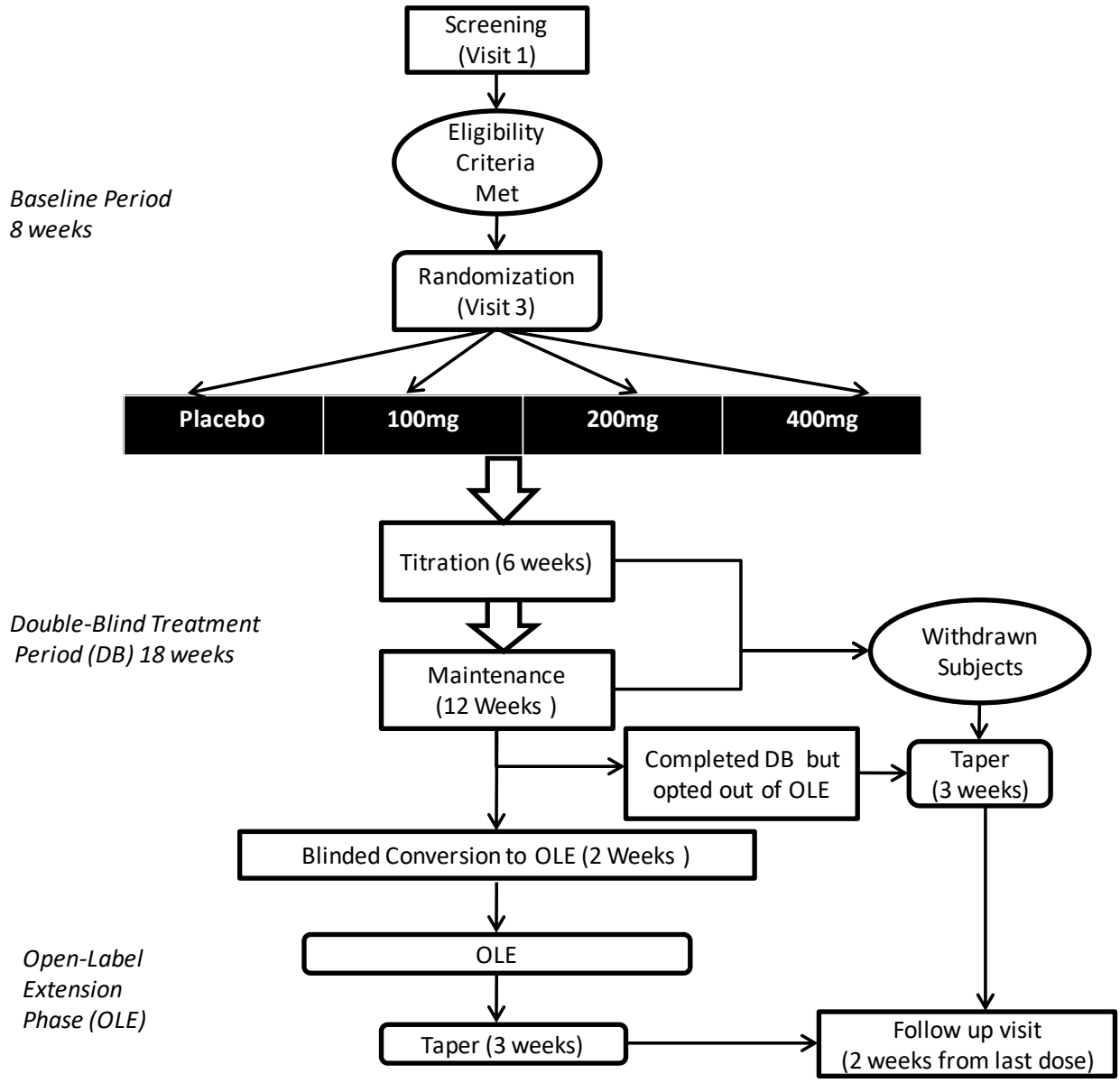
Only subjects who complete the double-blind maintenance phase will be given the option to continue treatment in an open-label extension. Those who choose not to enter the open-label extension or who withdraw prematurely will taper off the study drug.

For those subjects not entering the open-label extension, the taper period will last 3 weeks and will be followed by a final visit 14 days after the last dose of study drug.

Those subjects entering the open-label extension will enter a 2-week blinded crossover period, during which all subjects will be converted to a target dose of 300 mg once daily of open-label YKP3089.

Figure 2 provides an overview of the study design.

Figure 2. Overview of Study Design



6.1.1 *Screening and Pre-Randomization (Baseline Period)*

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. Investigators will be required to fill in a Diagnostic Review Form to be assessed by an independent consulting group (eg, Epilepsy Study Consortium) to ensure consistency of the diagnosis.

In the final determination of eligibility for the trial, screened subjects will be assessed for seizure frequency at the end of the 8-week prospective baseline period.

After the 8-week baseline period, subjects who meet all of the inclusion criteria and none of the exclusion criteria will be randomly assigned to receive placebo or 100, 200, or 400 mg of YKP3089 once daily in the morning. The dosing will start the morning following randomization.

6.1.2 *Double-Blind Treatment Period*

The double-blind treatment period will consist of a 6-week titration phase followed by a 12-week maintenance phase.

6.1.2.1 *Titration Phase*

During the initial 6-week up-titration phase of the double-blind treatment period, subjects assigned to receive YKP3089 will receive blinded study medication according to the dosage schedule shown in Table 3.

Table 3. YKP3089 Initial Double-Blind Up-Titration

YKP3089 target dose (mg/day)			YKP3089 dose (mg/day)			
	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6
100	50	100	100	100	100	100
200	50	100	150	200	200	200
400	50	100	150	200	300	400

During Week 1, no dose reduction will be permitted. Subjects who have significant tolerability issues should discontinue treatment with study drug. If study drug is not tolerated for the first time at any time during Weeks 2 through 6, subjects may have a reduction in their daily dose. The size of the reduction will depend on the dose at the time poor tolerability is noted (Reduce by 50mg if taking 100mg, 150mg or 200mg; reduce by 100mg if on 300mg or 400mg). Subjects will remain at the reduced dose level for a minimum of 7 days and up to 13 days.

Thereafter, the subjects may at the discretion of the investigator, recommence the upward titration at 50-mg increments in the daily dose once a week towards the target dose until week 6. If the subject cannot tolerate the new upward titration, the daily dose can be reduced one time by 50 mg through the end of week 8. No upward titration will be allowed after Week 6. No two consecutive dose reductions will be allowed.

If a tolerability issue occurs, dosage adjustments need to be made at a scheduled visit or at an unscheduled visit at the discretion of the investigator. At the visit, the subject will be issued a new set of cards to be determined by the interactive web response system (IWRS).

To improve tolerability, the investigator may instruct the subject to take the dose of study medication in the evening. The investigator may alter the timing or amount of an individual dose of a concomitant AED, but the total daily dose and dosing frequency of the concomitant AED must remain unchanged during the double-blind phase.

During titration, the investigator may instruct the subject to hold the daily dose of the study drug up to a maximum of 2 days per week.

6.1.2.2 *Double-Blind Maintenance Phase*

After the 6-week up-titration phase, subjects will enter the double-blind maintenance phase. The subjects will be instructed to take their study medication once daily in the morning for 12 weeks. Subjects will follow the schedule of study visits and assessments detailed in Table 1.

The investigator may instruct the subject to take the dose of study medication in the evening if clinically indicated and consistent with other aspects of the protocol. The investigator may alter the timing or amount of an individual dose of a concomitant AED, but the total daily dose and dosing frequency of the concomitant AED must remain unchanged during the double-blind phase. No YKP3089 dose adjustments are permitted after week 8.

6.1.2.3 *Blinded Study Drug Taper: Termination at End of Double-Blind Phase*

Subjects who will not participate in the optional open-label phase will enter a 3-week, double-blind taper period when they complete the maintenance phase or discontinue prematurely. The dosage of YKP3089 will be tapered according to the schedule shown in Table 4. To maintain

blinding during the taper period, YKP3089 or placebo, as appropriate, will be dispensed in blister cards at Visit 9 to all subjects. The taper period will be followed by a Follow-up Visit 14 days after the last dose of study drug. Subjects will follow the schedule of study visits and assessments detailed in Table 1.

During the taper period, investigators will be allowed to adjust the AED dosage or add concomitant AEDs.

Table 4. Blinded Study Drug Taper Schedule

Final Double-Blind Dose of YKP3089 (mg/day)	YKP3089 Dose During Taper (mg/day)		
	Week 1	Week 2	Week 3
0 (placebo)/50/100	0	0	0
150 or 200	100	0	0
250 or 300	200	100	0
350 or 400	300	200	100

6.1.3 *Double-Blind Phase Follow-Up Visit: Subjects Not Entering Open-Label Extension*

Subjects who do not elect to participate in the optional open-label extension will have their Follow-up Visit 14 days after completion of the 18-week double-blind treatment phase and the 3-week blinded study drug taper period. The post-treatment Follow-up Visit (Visit 10) will occur 14 days after last dose of study medication for all subjects ending study participation.

6.1.4 *Open-Label Extension Phase*

Subjects who complete the 12-week double-blind maintenance phase and still meet all inclusion criteria and none of the exclusion criteria except for seizure frequency are eligible to continue in an optional open-label extension phase. For subjects who elect to participate in the optional open-label extension, Visit 9 of the double-blind phase will also be the first visit of the open-label extension.

6.1.4.1 *Blinded Study Drug Conversion Period: Subjects Entering the Open-Label Phase*

Subjects will have a 2-week double-blind conversion period at the beginning of the open-label extension phase of the study. In order to keep the treatment blind, subjects from all four dose groups will be converted to a target dose of 300 mg/day after two weeks of blinded conversion

period. This conversion period will begin at Visit 9. Subjects will follow the study medication schedule shown in Table 5. The daily dose will consist of 4 tablets of YKP3089 or placebo (depending on the dose regimen assigned during the double-blind phase) from a blinded blister card plus tablets (2 for Week 1 and 4 for Week 2) from an open-label bottle of 50-mg YKP3089 tablets taken every morning. Starting at Visit 11, the subjects will take three 100-mg tablets from the open-label bottle every morning.

Table 5. Blinded Study Drug Conversion to Open-Label Target of 300 mg/day YKP3089

YKP3089 dose group (mg/day) during double-blind period	Dose of YKP3089 (mg/day)[a]					
	Dispensed at Visit 9				Dispensed at Visit 11	
	Week 1		Week 2		Week 3	
	From Card	From Open-Label Bottle	From Card	From Open-Label Bottle	From Card	From Open-Label Bottle
0 (placebo)/50	0	2X50	0	4X50	No card	300
100	100	2X50	100	4X50	No card	300
150/200	100	2X50	100	4X50	No card	300
250/300	200	2X50	100	4X50	No card	300
350/400	200	2X50	100	4X50	No card	300

[a]The total daily dose is the amount taken from the blister card plus the amount taken from the bottle of 50-mg tablets (eg, the placebo group from the double-blind phase receives placebo from the blister card and two 50-mg tablets from the bottle every day during Week 1 of the conversion period, placebo from the blister card and four 50-mg tablets from the bottle every day during Week 2 of the conversion period, and then three 100-mg tablets from the bottle per day starting in Visit 11).

During the first week of the conversion period, the investigator can increase or decrease the open-label dosage by 50-100 mg if clinically indicated (ie, recurrence of seizures, adverse events). During the second week of the conversion period, the investigator can decrease the open-label dosage by 50-200 mg or increase the open label dosage by a maximum of 100 mg if clinically indicated (ie, recurrence of seizures, adverse events). **All dose adjustments must be made with tablets from the open label bottles. All tablets from the cards must be taken on Week 1 and Week 2 during the conversion period.**

Although the target dose for subjects is 300mg at Visit 11, subjects may be taking 50-400 mg at Visit 11 depending upon tolerability and efficacy during the conversion period.

Doses of concomitant AEDs may be adjusted during the conversion phase.

6.1.4.2 *Open-Label Extension Treatment Phase*

The initial target dose for the open-label extension will be 300 mg/day. However, if a subject is not tolerating the 300 mg/day dose, YKP3089 dose may be reduced to a minimum of 50 mg/day. If the investigator feels that a subject requires a dose that is higher than 300 mg/day, the dose can be increased to a maximum of 400 mg/day once the target dose of 300 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. No dose reductions are permitted if the subject is taking 50 mg/day YKP3089. If 50 mg/day YKP3089 is not tolerated, the subject will withdraw from the study. Monotherapy with YKP3089 will not be allowed. The investigator may add, remove, or adjust the dosage of concomitant AEDs, as clinically indicated. In the event of poor tolerability, the investigator may instruct the subject to take 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 2. 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.

6.1.4.3 *Study Drug Taper: Subjects Leaving the Open-Label Extension*

Subjects who are withdrawn from the open-label extension study will taper YKP3089 according to the schedule described in Table 6, unless for safety reasons the investigator judges it necessary to discontinue study drug immediately. The investigator is encouraged to discuss the tolerability criteria with the Sponsor or its designee.

Table 6. Study Drug Taper Schedule for Subjects Completing Open-Label Extension

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 final 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.

6.1.5 *Dose Adjustments of Study Drug and Concomitant AEDs*

During week 1, no dose reduction will be permitted. Subjects who have significant tolerability issues should discontinue treatment with study drug. If study drug is not tolerated at some point during weeks 2 through 6, subjects may have a reduction in the daily dose. The size of the reduction will depend on the dose at the time poor tolerability is noted (Reduce by 50mg if taking 100mg, 150mg or 200mg; reduce by 100mg if on 300mg or 400mg). Subjects will remain at the reduced dose level for a minimum of 7 days and up to 13 days. Thereafter, the subjects may, at the discretion of the investigator, recommence the upward titration to the target dose at 50-mg increments in the daily dose once a week until week 6. If the subject cannot tolerate the new upward titration, the daily dosage can be reduced once by 50 mg up through the end of Week 8. No upward titration will be allowed after Week 6. No two consecutive dose reductions will be allowed.

Dosage adjustments related to tolerability issues need to be made at a scheduled visit or at an unscheduled visit at the discretion of the investigator. At the visit, the subject will be issued a new card or set of cards to be determined by IWRS.

For further instruction on dose adjustments, please refer to study manual.

The initial target dose for the open-label extension will be 300 mg/day. However, if a subject is not tolerating the 300 mg/day dose, YKP3089 dose may be reduced to a minimum of 50 mg/day. If the investigator feels that a subject requires higher than 300 mg/day, the dose can be increased to a maximum of 400 mg/day once the target dose of 300 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. No dose reductions are permitted if subject is taking 50 mg/day YKP3089. If 50 mg/day YKP3089 is not tolerated, the subject will withdraw from the study. Monotherapy with YKP3089 will not be allowed. The investigator may add, remove, or adjust the dosage of concomitant AEDs, as clinically indicated. In the event of

poor tolerability, the investigator may instruct the subject to take the dose of study medication in the evening or divide the total daily dose into 2 doses.

6.2 Study Endpoints

The primary efficacy endpoints reflect the United States Food and Drug Administration (FDA) recommendation of percent reduction in seizure frequency for registration which is adopted by many countries in the rest of the world, and the European Agency for the Evaluation of Medicinal Products (EMEA) recommendation of the responder rate for registration in Europe, which is also adopted by Australia, New Zealand, and South Africa.

6.2.1 *Primary Efficacy Endpoint in the United States and the Rest of the World*

The primary efficacy endpoint to be evaluated for registration in the United States and the Rest of the World is the percent change from the pretreatment baseline phase in seizure frequency (average monthly seizure rate per 28 days) of all simple partial motor, complex partial, or secondarily generalized seizures compared with the double-blind treatment phase.

The baseline rate (B) is calculated by counting the number of seizures over the baseline period and dividing by the number of days in the interval with non-missing seizure data and then multiplying by 28. The double-blind rate (D) is calculated in a similar manner. The percent change is equal to 100*(D-B)/B. Simple partial seizures without a motor/visual component will not be counted.

This value will be undefined if B=0. For the primary efficacy analysis, there will not be any baseline values with zero seizures. However, for the analysis of seizure sub-types, there is a possibility that B may be zero. In this case, B will be set to a value of 1.

6.2.2 *Primary Efficacy Endpoint in the countries of Europe, Australia, New Zealand, and South Africa*

The primary efficacy endpoint to be evaluated for registration in the countries of Europe, Australia, New Zealand, and South Africa is the responder rate defined as a 50% or greater reduction during the maintenance phase of the double blind period in the seizure frequency from baseline.

The responder endpoint is a binary indicator endpoint defined as 1 if the primary endpoint is <= -50%, and 0 otherwise

6.2.3 *Secondary Efficacy Endpoint in the countries of Europe, Australia, New Zealand, and South Africa*

The secondary efficacy endpoint to be evaluated for registration in the countries of Europe, Australia, New Zealand and South Africa is the percent change from the pretreatment baseline phase in seizure frequency (average monthly seizure rate per 28 days) of all simple partial motor, complex partial, or secondarily generalized seizures compared with the maintenance phase of the double-blind treatment phase.

The baseline rate (B) is calculated by counting the number of seizures over the baseline period and dividing by the number of days in the interval with non-missing seizure data and then multiplying by 28. The double-blind rate (D) is calculated in a similar manner. The percent change is equal to 100*(D-B)/B. Simple partial seizures without a motor/visual component will not be counted.

This value will be undefined if B=0. For the primary efficacy analysis, there will not be any baseline values with zero seizures. However, for the analysis of seizure sub-types, there is a possibility that B may be zero. In this case, B will be set to a value of 1.

6.2.4 *Secondary Efficacy Endpoint in the United States and the Rest of the World*

The secondary efficacy endpoint to be evaluated for registration in the United States and the Rest of the World is the responder rate defined as a 50% or greater reduction during the double blind period in the seizure frequency from baseline. The responder endpoint is a binary indicator endpoint defined as 1 if the primary endpoint is <= -50%, and 0 otherwise

6.2.5 *Additional Secondary Efficacy Endpoints*

- Higher response rates of (defined by cutoffs of -75%, -90% and -100%) simple partial seizures with motor component plus complex partial seizures plus secondarily generalized tonic clonic seizures during the double-blind period and maintenance phase.

- Percentage change in other seizure types will be calculated in the same way as the primary endpoint except for selecting the specific seizure types:
    - Complex partial
    - Secondarily generalized tonic-clonic
    - Simple partial motor

6.2.6 *Outcome Measurements*

6.2.6.1 *Clinical Global Impression of Change (CGIC)*

The investigator will complete the CGIC questionnaire at Visit 9 (end of maintenance or Early Termination if applicable) to assess the subject's clinical status since starting study drug. This assessment should take into account seizure frequency and severity, the occurrence of AEs, and overall functional status of the subject (Appendix G: Clinical Global Impression of Change (CGIC)).

6.2.6.2 *Quality of Life in Epilepsy Questionnaire (QOLIE-31-P)*

Subjects will complete the QOLIE-31-P at Visit 3 (end of baseline) and Visit 9 (end of maintenance or Early Termination if applicable) to assess their status since starting study drug. Note, the QOLIE-31-P will only be completed by the subject; the caregiver will not be allowed to complete this questionnaire on behalf of the subject (Appendix H: Quality of Life in Epilepsy (QOLIE-31-P))

QOLIE-31-P *must* be completed as described in Appendix H: Quality of Life in Epilepsy (QOLIE-31-P). Subjects *must not* have had any simple motor or complex partial seizures within 4 hours, or generalized seizures within 24 hours before administration of the scale. If subjects have these seizure types but have fully recovered from their seizures, the outcome scale may be administered to the subjects. If subjects have not fully recovered from their seizures, the outcome scale only will be done at an unscheduled visit after recovery from seizures. If subjects experience daily seizures and the visit cannot be rescheduled, the outcome scale will be omitted. If a subject is cognitively impaired and unable to understand the scale or if a subject is unable to read, the subject will be excluded from the completion of the scale.

This questionnaire is only to be implemented in the countries where it is available and validated for the spoken language(s).

6.2.7 *Pharmacokinetic Endpoints*

Trough AED levels (oxcarbazepine [OXC], topiramate [TPM], carbamazepine [CBZ], valproate [VPA], lamotrigine [LTG], lacosamide (LMD) and levetiracetam (LEV) only) during the baseline will be compared to those during the treatment period in subjects randomized to 100, 200, or 400 mg/day YKP3089 or placebo to determine potential drug interactions.

6.3 Safety Assessments

Safety during the double-blind phase 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) in YKP3089-treated subjects compared to placebo-treated subjects.

Any patient who reports a rash by telephone or is observed to have a rash should be carefully evaluated for a drug hypersensitivity syndrome; the evaluation should include hematology and chemistry blood tests. If a subject reports a rash by telephone, an unscheduled visit should be performed promptly.

Adverse Events

Adverse events (AEs) will be reported by the subject (or, when appropriate, by a caregiver, surrogate, or the subject's legally acceptable representative) for the duration of the study. AEs will be followed by the investigator for a length of time as determined by the sponsor. Specific details on AE reporting are provided in Section 11.

Clinical Laboratory Tests

- 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), albumin, 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) at Visits 1 and 10 and urine pregnancy tests performed at the clinical site at Visit 3 & 9 which will be confirmed by a serum pregnancy test if positive.

Electrocardiogram

Triplicate (to be performed 3 times with a minimum of 2 minutes between each recording) and routine 12-lead ECGs will be performed periodically during the study.

Vital Signs

Blood pressure and heart rate will be measured after the subject has been supine for 5 minutes and again after the subject has been standing for 3 minutes. Respiratory rate and oral temperature will be measured with the subject supine.

Physical and Neurologic Examinations

See Appendix A, Appendix B, and Appendix C: BRIEF Neurologic Examination.

6.4 Interim Analysis

No interim analysis will be performed

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. Approximately 520 subjects will be screened to achieve a minimum of 400 subjects randomly assigned to study drug, 100 subjects for each dose group: placebo or 100 mg, 200 mg, or 400 mg YKP3089.

7.2 Subject Recruitment

Subjects will be selected from the principal investigator's and Sub-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, age 18 to 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.

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 despite having been treated with at least one AED within approximately the last 2 years.

6. During the 8-week baseline period, subjects must have at least 8 partial seizures including only simple partial seizures with motor component, complex partial seizures, or secondarily generalized seizures without a seizure-free interval of greater than 25 days any time during the 8 weeks baseline. Subjects must have at least 3 of these partial seizures during each of the two consecutive 4-week segments of the baseline period.

7. Currently on stable antiepileptic treatment regimen:
   a) Subject must have been receiving stable doses of 1 to 3 AEDs for at least 4 weeks prior to screening (Visit 1) to be continued unchanged throughout the study
   b) Vagal nerve stimulator (VNS) will not be counted as an AED; however, the parameters must remain stable for at least 4 weeks prior to baseline. The VNS must have been implanted at least 5 months prior to Visit 1.
   c) 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. See Exclusion Criterion No. 12 for intermittent benzodiazepine rescue parameters.

8. 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 randomization.

9. Ability to reach subject by telephone.

10. 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 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
2. A history of nonepileptic or psychogenic seizures
3. Presence of only nonmotor simple partial seizures or primary generalized epilepsies
4. History of seizure clusters (episodes lasting less than 30 minutes in which multiple seizures occur with such frequency that the initiation and completion of each individual seizure cannot be distinguished) within 3 months prior to Visit 1
5. Presence or previous history of Lennox-Gastaut syndrome
6. Scheduled epilepsy surgery within 8 months after Visit 1
7. Pregnancy or lactation
8. Any clinically significant laboratory abnormality that in the opinion of the investigator would exclude the subject from the study
9. Evidence of significant active hepatic disease. Liver transaminases (AST or ALT) above twice the upper limit of normal or total or direct bilirubin not within normal limits
10. An active CNS infection, demyelinating disease, degenerative neurologic disease, or any CNS disease deemed to be progressive during the course of the study that may confound the interpretation of the study results
11. Any clinically significant psychiatric illness, psychological, or behavioral problems that, in the opinion of the investigator, would interfere with the subject's ability to participate in the study

12. Presence of psychotic disorders and/or unstable recurrent affective disorders evident by use of antipsychotics; presence or recent history (within 6 months) of major depressive episode

13. Use of intermittent rescue benzodiazepines more than once per month (1 to 2 doses in a 24-hour period is considered 1 rescue) in the 1 month period prior to Visit 1

14. History of alcoholism, drug abuse, or drug addiction within the past 2 years

15. Current use of felbamate with less than 18 months of continuous exposure

16. Current use of diazepam, phenytoin, phenobarbital, or metabolites of these drugs (within 1 month of Visit 1)

17. Current or recent (within the past year) use of vigabatrin. Subjects with a prior history of treatment with vigabatrin must have documentation showing no evidence of a vigabatrin associated clinically significant abnormality in a visual perimetry test.

18. History of status epilepticus within 3 months of Visit 1

19. History of 1 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

20. History of AED-associated rash that involved conjunctiva or mucosae or more than one maculopapular rash that required discontinuation

21. Creatinine clearance less than 50 mL/min, as calculated by the Cockcroft-Gault equation

22. Absolute neutrophil count less than 1500/μL

23. Clinical or ECG evidence of serious cardiac disease, including ischemic heart disease, uncontrolled heart failure, and major arrhythmias, or relevant replicated changes in QT intervals (QTcF less than 340 msec or greater than 450 msec in males and greater than 470 msec in females)

24. Platelet counts lower than 80,000/μL in subjects treated with VPA

25. A "yes" answer to Question 1 or 2 of the C-SSRS (Baseline/Screening version) Ideation Section in the past 6 months or a "yes" answer to any of the Suicidal Behavior Questions in the past 2 years.

26. More than 1 lifetime suicide attempt

27. Participation in any other trials involving an investigational product or device within 30 days of screening (or longer, as required by local regulations)

28. Current use of any of the following medications: clopidogrel, fluvoxamine, amitriptyline, clomipramine, bupropion, methadone, ifosfamide, cyclophosphamide, efavirenz, or natural progesterone (within 1 month of Visit 1)

29. History of positive antibody/antigen test for hepatitis B, hepatitis C, or HIV

30. Presence of congenital short QT syndrome

31. A history of any previous exposure to YKP3089

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

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. Note: Although synthetic progestins are acceptable, natural progesterone is not acceptable because of a potential drug-drug interaction with YKP3089.
- 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 YKP3089C017 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*

Tablets of 50 mg and 100 mg of YKP3089 and placebo tablets are 10 mm in diameter, round, biconvex, plain-faced, brown-coated tablets that are scored on one side. All are identical in appearance.

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*

For the double-blind phase and the blinded conversion to open-label phase, 50 mg and 100 mg YKP3089 and matching placebo tablets will be packaged in 2-panel blister cards—one panel for the label and the other for the medication. There will be 9 blister card types, one for each of the possible daily doses in this study: placebo, 50, 100, 150, 200, 250, 300, 350, and 400 mg. Each medication panel of the blister card will contain nine rows and four columns of tablets for 7 days of treatment plus 2 extra days for a total of 9 days. Each row will contain the same total dose.

Picture of the medication panel of the blister card

Date		A	B	C	D
__/__/__	Day 1	◯	◯	◯	◯
__/__/__	Day 2	◯	◯	◯	◯
__/__/__	Day 3	◯	◯	◯	◯
__/__/__	Day 4	◯	◯	◯	◯
__/__/__	Day 5	◯	◯	◯	◯
__/__/__	Day 6	◯	◯	◯	◯
__/__/__	Day 7	◯	◯	◯	◯
__/__/__	Extra 8	◯	◯	◯	◯
__/__/__	Extra 9	◯	◯	◯	◯

The blister card label contains information that meets applicable regulatory requirements. Every blister card will be randomly assigned a unique medication ID #.

For the open-label phase, medication will be packaged in high density polyethylene (HDPE) bottles each containing 100 tablets of either 50 mg or 100 mg of YKP3089.

8.1.2 *Blinding of Study Medication*

Study medication will be both double-blind and open-label. During the double-blind phase, the packaging and labeling of the clinical trial medication will maintain the double-blind design of the trial. The treatment administered will not be known to the subjects or the study personnel at the clinical site. Selected individuals from the Sponsor and/or designee and at the clinical research organization (CRO) may be unblinded to the study treatments on a need-to-know basis as described in the CRO's standard operating procedures (SOP) on blinding and unblinding. The study will be unblinded following database lock according to the CRO's SOP.

Neither the investigator nor the site staff will know the contents of the tablets administered; however, this information will be readily available in the event of an emergency. Investigators may perform emergency unblinding using the IWRS system immediately, without prior contact to the study's Medical Monitor, if they feel it is medically necessary and that knowledge of the treatment assignment is essential for the patient's care. If such an emergency unblinding is necessary, investigators should promptly document and explain to the Medical Monitor or Sponsor any premature unblinding of the investigational product.

The administration of each dose of study drug or placebo will be identical.

For the interim analysis and the data monitoring committee (DMC) reviews, only the statistician and statistical programmer responsible for providing the interim analysis results, key clinical members of the interim analysis committee, and the DMC will be unblinded to the individual treatment assignments.

8.1.3 *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 (active drug or comparator) 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 Randomization and Study Drug Distribution

8.2.1.1 *Screening Number*

The subject will be assigned a screening number 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 number 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 01002003. Re-screened subjects will retain their screening number and the 2 screenings will be differentiated by their screening dates. Only 1 re-screening will be allowed.

In the open-label extension, the subject will retain the same screening number.

8.2.1.2 *Randomization Number*

The randomization number will be assigned by the IWRS using the next available randomization number in the randomization code list for the subject's country.

8.2.1.3 *Randomization Procedure*

Subjects will be assigned with equal chance to 1 of the 4 treatment groups based on a randomization schedule prepared by the designated statistician. The randomization will be balanced using permuted blocks across the 4 treatment groups. The code is computer generated using the plan procedure in the SAS computer program. Validation of the randomization code is performed by quality assurance review. After finalization, the randomization code is placed in a directory with no access by the clinical study team. Once database closure has been completed, a request for unblinding is sent to the project biostatistician, at which time the code is broken and disseminated to the clinical study team for statistical analysis and clinical review.

8.2.1.4 *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 initials and subject's date of birth). The IWRS will identify blinded blister cards and/or open label bottles of tablets to be dispensed appropriate to the phase of study.

Prior to dispensing, the investigator will record on each blister card label the subject number, study week number, date dispensed, site number, visit number, phone contact, and investigator name. The investigator will record adjacent to Day numbers on the card itself the date on which each dose is to be taken. On each dispensed open label bottle, the investigator will record 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 card and bottle dispensed are populated in the system correctly.

Double blind Phase

At Visit 3, if the subject meets the criteria for randomization, the IWRS will provide a subject randomization number. The system will then identify the unique medication number on each of 2 blister cards to be dispensed to the subject. Each blister card provides a 1-week supply of medication plus 2 extra days supply to serve as a reserve as needed. At subsequent visits, after the subject information has been entered, the system will identify medication numbers for 2 blister cards during the titration phase or four blister cards during the maintenance phase to be dispensed to the subject. During a double blind taper, 3 blister cards will be dispensed.

Prior to dispensing, the investigator will record on each blister card label the subject number, study week number, date dispensed, site number, visit number, phone contact, and investigator name. The investigator will record adjacent to Day numbers on the card itself the date on which each dose is to be taken. In addition, the investigator will record in the electronic case report form (eCRF) the medication number printed on each card dispensed.

Open-Label Extension

If a subject enters the open-label extension, he/she will enter a blinded dose-conversion period. At Visit 9, during the conversion period, the subject will receive 2 blinded blister cards as directed by the IWRS system and an open-label bottle of YKP3089 containing one hundred 50-mg tablets. The subject will be instructed to take medication from each blister card on dates specified on the card. In addition, for the first week, the subject will take two 50-mg tablet from the bottle. For the second week, the subject will be instructed to take four 50-mg tablets from the bottle.

After the conversion period, the subject will enter the open-label treatment period and will receive open-label bottles containing YKP3089 (50- or 100-mg) tablets at each visit. At each visit, the IWRS system will be accessed to obtain bottle numbers. The returned bottles may be re-dispensed to the same subject after drug accountability is performed.

Dose Adjustments

If a tolerability issue occurs, all dosage reductions need to be made at a scheduled visit or at an unscheduled visit at the discretion of the investigator. At the visit, the subject must return all the remaining medication cards. The subject will be issued one or more replacement cards to be determined by interactive web response system (IWRS).

8.3 Prior and Concomitant Treatments

Subjects must be taking 1 to 3 concomitant AEDs at a stable dosage for at least 12 weeks before Randomization. They should continue these prescribed AED regimens unchanged throughout the double-blind phase of the study. To improve tolerability issues, the investigator may alter the timing or amount of an individual dose of a concomitant AED, but the total daily dose and dosing frequency of the concomitant AED must remain unchanged during the double-blind phase. During the open-label extension phase of the study, the investigator will be allowed to change the dosage of concomitant AEDs. Concomitant AEDs can be changed, but the subject should not be treated with YKP3089 monotherapy. Intermittent benzodiazepines (other than diazepam) may be taken as rescue medication once during the baseline period and twice during the treatment phase (2 doses in a 24-hour period is considered 1 rescue). Intermittent rescue medication can be used during the open-label extension.

8.4 Prohibited Medications or Devices

Medication	Not allowed	Allowed
• Clopidogrel, fluvoxamine, amitriptyline, clomipramine, bupropion, methadone, ifosfamide, cyclophosphamide, efavirenz, and natural progesterone • Diazepam, phenytoin, phenobarbital, or metabolites of these drugs	During the study and within 30 days prior to Visit 1	If taken anytime 30 days before Visit 1
• Vigabatrin	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)

• 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

- It is recommended that the study medication is taken once daily in the morning.
- In the event of poor tolerability during double blind phase, the investigator may instruct the subject to take the dose of study medication in the evening
- In the event of poor tolerability during open label phase, the investigator may instruct the subject to take the dose of study medication in the evening or divide the total daily dose into 2 doses
- Study medication can be taken with or without food
- Study medication must be swallowed

9 STUDY PROCEDURES

Visit windows of ± 2 days are allowed for Visits 1 through 6 and visit windows of ± 3 days are allowed for Visits 7 through 10.

9.1 Screening / Baseline / Randomization (Visits 1, 2 and 3)

9.1.1 *Visit 1, Day -56*

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
- Complete Diagnostic Review Form (see Section 9.1.1.1 and Appendix D)
- 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) (Appendix E: COLUMBIA SUICIDE SEVERITY RATING SCALE (Baseline/Screening))
- Perform triplicate 12-lead ECG
- 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 the baseline period if the subject has not had a neuroimaging study within 10 years of Visit 1. This will be used to document the absence of a 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.
- Record concomitant medications
- Dispense seizure diary
- Schedule Visit 2 to occur in 4 weeks

Subjects will be given a diary at each visit to record all of their seizures including the type and number. (see Section 9.1.1.1, Seizure Classification Review and Seizure Diary)**.** The subject's seizure diary will be collected and reviewed at each visit and a new diary will be dispensed.

9.1.1.1 *Seizure Classification Review and Seizure Diary*

Immediately following Visit 1, the principal investigator, sub-investigator or his or her designee will complete the Diagnostic Review Form (see Appendix D), which will include information about the subject and their seizure types. After being signed by the investigator, the Diagnostic Review Form will then be faxed or e-mailed to the independent consulting physician group (eg, Epilepsy Study Consortium) and reviewed to confirm that the reported phenomena are indeed seizures. If corrections, clarifications, or additional information is required, the site will be asked to respond to the query and revise the Diagnostic Review Form. The revised Diagnostic Review Form will be returned to the consortium for a second review. The review process must be

completed and an agreement reached between the principal investigator and the independent consulting physician group (eg, Epilepsy Consortium) regarding seizure classification prior to the subject being randomized.

Once the Diagnostic Review Form is approved, it will be signed by the consortium and returned to the site. The approved Diagnostic Review Form will remain in the subject's medical chart.

9.1.2 *Visit 2, Day −28*

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

- Measure vital signs
- Review of seizure diary with the subject for completion and accuracy
- Record Adverse Events and use of concomitant medication
- Dispense new seizure diary
- Schedule a return to occur in 4 weeks for Visit 3

9.1.3 *Visit 3, Day 1 (Randomization)*

All subjects who have not discontinued will be scheduled to appear at the clinic for Visit 3, which is 1 day before the start of the treatment period of the study. At Visit 3, subjects who continue to meet all of the inclusion criteria and none of the exclusion criteria will be randomly assigned to receive study drug (see Section 8.2.1.3).

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

- Review seizure diary and confirm the subject meets seizure frequency criterion.
- Record vital signs
- Measure weight
- Conduct brief neurologic examination
- Administer C-SSRS (Since Last Visit version)
- Administer Quality of Life in Epilepsy Questionnaire (QOLIE-31-P)
- Perform 12-lead ECG (standard)
- Perform urine pregnancy test (for female subjects of childbearing potential)

- Draw blood for laboratory safety assessment
- Obtain urine for urinalysis
- Draw blood for concomitant AED levels (before first dose of study medication.)
- Record concomitant medications
- Record AEs
- Review and record inclusion and exclusion criteria (including documentation of approved Diagnostic Review Form from the Epilepsy Study Consortium)
- Randomly assign the subject to receive study drug if all of the inclusion criteria and none of the exclusion criteria are met
- Dispense seizure diary
- Dispense study drug as instructed by IWRS
- Instruct the subject to take the first dose of the study medication 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 on the day of randomization after all other Visit 3 procedures have been completed. For these subjects, seizures which occur after the first dose must be counted and entered in to the CRF.
- Schedule a return to occur in 2 weeks for Visit 4

9.2 Double-Blind Treatment Period

9.2.1 *Visit 4, Day 15*

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

- Record vital signs
- Conduct brief neurologic examination
- Administer C-SSRS (Since Last Visit version)
- Record concomitant medications
- Review seizure diary
- Perform drug accountability
- Record AEs
- Dispense seizure diary

- Dispense study drug as instructed by IWRS
- Schedule a return to occur in 2 weeks for Visit 5

9.2.2 *Visit 5, Day 29*

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

- Record vital signs
- Measure weight
- Conduct brief neurologic examination
- Administer C-SSRS (Since Last Visit version)
- Record concomitant medications
- Review of seizure diary
- Perform drug accountability
- Record AEs
- Dispense seizure diary
- Dispense study drug as instructed by IWRS
- Schedule a return to occur in 2 weeks for Visit 6

9.2.3 *Visit 6, Day 43*

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

- Record vital signs
- Conduct brief neurologic examination
- Administer C-SSRS (Since Last Visit version)
- Perform 12-lead ECG (standard)
- Draw blood for laboratory safety assessment
- Record concomitant medications
- Review seizure diary
- Perform drug accountability
- Record AEs
- Dispense seizure diary

- Dispense study drug as instructed by IWRS
- Schedule a return to occur in 4 weeks for Visit 7

9.2.4 *Visit 7, Day 71*

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

- Record vital signs
- Measure weight
- Conduct brief neurologic examination
- Administer C-SSRS (Since Last Visit version)
- Draw blood for YKP3089 levels. 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.
- Draw blood for concomitant AED levels
- Record concomitant medications
- Review of seizure diary
- Perform drug accountability
- Record AEs
- Dispense seizure diary
- Dispense study drug as instructed by IWRS.
- Schedule a return to occur in 4 weeks for Visit 8

9.2.5 *Visit 8, Day 99*

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

- Record vital signs
- Conduct brief neurologic exam
- Administer C-SSRS (Since Last Visit version)
- Draw blood for YKP3089 levels. 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.

- Draw blood for concomitant AED levels
- Record concomitant medications
- Review seizure diary
- Perform drug accountability
- Record AEs
- Dispense seizure diary
- Dispense study drug as instructed by IWRS.
- Schedule a return to occur in 4 weeks for Visit 9

9.2.6 *Visit 9, Day 127, End of Double-Blind Treatment Period (or Early Termination)*

For subjects who will be entering open-label extension phase, see Section 9.3 for required assessments and procedures.

For subjects who will not be entering the open-label extension phase of the study (after completing the double-blind maintenance or terminating prematurely), the procedures to be followed at Visit 9 are shown in Table 1.

At Visit 9, subjects who discontinue treatment at the end of the double-blind phase of the study will receive study drug for the double-blind study taper (see Section 6.1.2.3) and a new seizure diary. They will be scheduled to return to the clinic for the Follow-up Visit (Visit 10), 14 days after the last dose of study drug, which corresponds to Day 162 after the start of treatment with YKP3089 or placebo.

If participation in the study is being terminated before Visit 9, the subject will undergo at the time of termination all of the evaluations scheduled for Visit 9. If the clinical situation warrants a taper period, subjects will be dispensed study drug for the double-blind study taper (see Section 6.1.2.3). They will be scheduled to return to the clinic for the Follow-up Visit (Visit 10), 14 days after the last dose of study drug (see Table 1 and Section 9.2.7).

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

- Record vital signs
- Measure weight

- Perform full neurologic examination
- Administer C-SSRS (Since Last Visit version)
- Administer Quality of Life in Epilepsy Questionnaire (QOLIE-31-P)
- Administer Clinical Global Impression of Change (CGIC)
- Perform 12-lead ECG (standard)
- Perform urine pregnancy test (for female subjects of child-bearing potential)
- Draw blood for laboratory safety assessment
- Obtain urine for urinalysis
- Record concomitant medications
- Review seizure diary
- Perform drug accountability
- Record AEs
- Dispense seizure diary
- Dispense study drug (taper) as instructed by IWRS
- Schedule a return to occur in 5 weeks for Visit 10

9.2.7 *Visit 10, Day 162 or 14 Days after Last Dose of Study Drug*

Visit 10 represents the Follow-up Visit scheduled for 14 days after the last dose of study drug for subjects who are discontinuing at the end of the double-blind phase of the study and for subjects who discontinue early. There is no Visit 10 for subjects who are entering the open-label phase of the study.

At Visit 10 (or at the Follow-up Visit scheduled for 14 days after the last dose of study drug for subjects who discontinue early), the following will be assessed, as shown in Table 1:

- Record vital signs
- Measure weight
- Perform full physical examination
- Conduct brief 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
- Obtain urine for urinalysis
- Record concomitant medications
- Review seizure diary
- Perform drug accountability
- Record AEs

Visit 10 represents the end of study participation for subjects who are discontinuing after the double-blind phase. No study drug will be dispensed at Visit 10. For information about Visits 9 and 11 for subjects who will continue in the open-label extension phase, see Section 9.3.

9.3 Open-Label Extension Phase

The open-label extension phase begins at Visit 9, when the subjects who are to continue in the open-label phase start a blinded study drug conversion period (See Section 9.3.1) instead of the blinded study drug taper that is intended for subjects who are discontinuing after the double-blind treatment period (see 9.2.6).

Visit windows of ± 3 days are allowed for visits 9 and end of study Follow-up Visit, visit windows of ± 2 days are allowed for visits 11 and 12, and visit windows of ± 7 days are allowed for all other open-label visits.

9.3.1 *Visit 9, Day 127: Open-Label Phase*

All subjects who have not discontinued and plan to enter the open-label phase of the study will undergo Visit 9 assessments as shown in Table 2:

- Review and record inclusion/exclusion criteria (the same as for the double-blind phase except for seizure frequency)
- Record vital signs
- Measure weight
- Conduct full physical examination
- Conduct full neurologic examination
- Administer C-SSRS (Since Last Visit version)

- Perform 12-lead ECG
- Perform urine pregnancy test (for female subjects of childbearing potential)
- Draw blood for laboratory safety assessment
- Obtain urine for urinalysis
- Record concomitant medication
- Review seizure diary
- Perform drug accountability
- Review AEs
- Dispense seizure diary
- Dispense study drug (double-blind blister card and open-label bottle) as instructed by IWRS.
- Schedule a return to occur in 2 weeks for Visit 11. Note: There is no Visit 10 for subjects who have not discontinued and who enter the open-label phase of the study.

9.3.2 *Visit 11, Day 141*

The initial target dose for the open-label extension will be 300 mg once daily. The dose of YKP3089 may be reduced to a minimum of 50 mg once daily or increased to a maximum of 400 mg once daily by 100-mg or 50-mg increments.

As shown in Table 2, the following will be assessed at Visit 11:

- Record vital signs
- Conduct brief neurologic examination
- Administer C-SSRS (Since Last Visit version)
- Record concomitant medications
- Perform drug accountability
- Record AEs
- Review seizure diary
- Dispense seizure diary
- Dispense open-label study drug bottles as instructed by IWRS
- Schedule a return to occur in 2 weeks for Visit 12

At this point, the subjects will have finished the blinded conversion from the double-blind regimen and will be using an open-label regimen. Starting at this visit, changes to the subject's concomitant AED regimen are permitted.

9.3.3 *Visit 12: Day 155*

As shown in Table 2, the following will be assessed at Visit 12:

- Record vital signs
- Administer C-SSRS (Since Last Visit version)
- Perform 12-lead ECG
- Perform urine pregnancy test (for female subjects of childbearing potential)
- Draw blood for laboratory safety assessment
- Record concomitant medications
- Perform drug accountability
- Record AEs
- Review seizure diary
- Dispense seizure diary
- Dispense open-label study drug bottles as instructed by IWRS
- Schedule a return to occur in 12 weeks for Visit 13

9.3.4 *Visit 13, Day 239*

As shown in Table 2, the following assessments will be performed at Visit 13:

- Record vital signs
- Measure weight
- Conduct brief neurologic examination
- Administer C-SSRS (Since Last Visit version)
- Record concomitant medications
- Perform drug accountability
- Record AEs
- Review seizure diary

- Dispense seizure diary
- Dispense open-label study drug bottles as instructed by IWRS
- Schedule a return to occur in 12 weeks for Visit 14

9.3.5 *Visit 14, Day 323*

As shown in Table 2, the following assessments will be performed at Visit 14:

- Record vital signs
- Administer C-SSRS (Since Last Visit version)
- 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
- Review seizure diary
- Dispense seizure diary
- Dispense open-label study drug bottles as instructed by IWRS
- Schedule a return to occur in 12 weeks for Visit 15

9.3.6 *Visit 15, Day 407*

As shown in Table 2, the following assessments will be made at Visit 15:

- Record vital signs
- Measure weight
- Conduct brief neurologic examination
- Administer C-SSRS (Since Last Visit version)
- Record concomitant medications
- Perform drug accountability
- Record AEs
- Review seizure diary

- Dispense seizure diary
- Dispense open-label study drug bottles as instructed by IWRS
- Schedule a return to occur in 12 weeks for Visit 16

9.3.7 *Visit 16, Day 491, or Termination from Open-Label Phase—Taper Visit*

As shown in Table 2, the following will be performed at Visit 16 or at the time of early termination from the open-label phase.

At Visit 16, if clinically indicated, the subjects will begin the study drug taper described in Section 6.1.4.3. At the end of this drug taper, the subject will have discontinued YKP3089. The following assessments will be made at Visit 16:

- Record vital signs
- Measure weight
- Conduct full physical examination
- Conduct full neurologic examination
- Administer C-SSRS (Since Last Visit version)
- Perform 12-lead ECG
- 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
- Review seizure diary

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

- Dispense seizure diary
- Schedule a return to occur in 3 months for next visit
- See section 9.3.9 for further instructions

For subjects leaving the open-label treatment due to any reasons at any time before 1 year or leaving at Visit 16 due to no benefit or any reasons:

- 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 17 if tapered
- Schedule a return to occur in 2 weeks for Visit 17 if not tapered

9.3.8 *Visit 17, End of Study Follow-up (14 days from the last dose)*

Visit 17 represents the Follow-up Visit after discontinuation of study drug in the open-label extension phase. 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 2, the following assessments will be performed at Visit 17:

- 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
- Obtain urine for urinalysis
- Record concomitant medications
- Perform drug accountability
- Record AEs

No study drug will be dispensed.

9.3.9 *Open-Label Extension Beyond Year One*

Subjects who complete Visit 16 and will continue in the open-label extension 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 16

- Record vital signs
- Administer C-SSRS (Since Last Visit version)
- Record concomitant medications
- Perform drug accountability
- Record AEs
- Review seizure diary
- Dispense open-label study drug bottles as instructed by IWRS

Perform the following every 6 months from Visit 16

- Measure weight
- Conduct brief neurologic examination
- Perform urine pregnancy test (for female subjects of childbearing potential)
- Draw blood for laboratory safety assessment

Perform the following every 12 months from Visit 16

- Perform full physical exam
- Perform 12-lead ECG
- 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 18.

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 16. This visit will be assigned the next sequential number. After this visit, the subject will be scheduled to return for Visit 17 (end-of-study follow-up, 14 days after the last dose of study medication).

9.4 Unscheduled Visit/Telephone Contact

Subjects will be contacted by phone on Days 8, 22 and 36 to assess tolerability and the occurrence of any early treatment-emergent adverse events and to reinforce compliance.

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.

9.5 Clinical Laboratory & Pharmacokinetic Evaluations

Clinical laboratory evaluations will be performed at Visits 1, 3, 6, 9, 10, 12, 14, 16, and 17 and every 6 months afterwards or at any time during the study as deemed necessary by the investigator to assess potential health issues or AEs. Samples will be collected at Visits 1, 3, 9, 10, 14, 16 and 17 and every 12 months afterwards for urinalysis. Female subjects (of childbearing potential) will undergo a serum ß-hCG pregnancy test at Visits 1 and 10 and a urine ß-hCG pregnancy test at Visits 3 and 9 or at any time pregnancy is suspected. Additionally, blood samples will be drawn to determine plasma levels of concomitant AED (OXC, TPM, CBZ, VPA, LTG, LMD and LEV only) prior to study drug administration (Visit 3) and during steady-state concomitant treatment with YKP3089 (Visits 7 and 8). At Visits 7 and 8, additional blood samples (~8 mL each) 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. Additional blood samples may be drawn for levels of concomitant AEDs during the double-blind treatment phase if the investigator

believes that symptoms of toxicity may be related to concomitant AEDs, rather than the study drug, and during the open-label extension phase for any reason; these samples will be analyzed by the local laboratory. 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 CRF.

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

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 to the end of the study treatment follow-up, which for this study is 21 days. For this study, the AE reporting period is defined as 30 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.

10.2 General Physical Examination Findings

At Screening and prior to Visit 3, 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.

10.3 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.

10.4 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 CRF. 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.

10.4.1 *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 PPD 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 fax to SKLSI's designee PPD within one business day 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 faxed to SKLSI's designee PPD within one business day 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 PPD within one business day of receipt of new/updated information. The SAE Reporting Requirements and contact information are outlined in Table 7.

Seizures in this refractory subject population are anticipated with the weekly seizure frequency used as a primary study endpoint. 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 7. Serious Adverse Event Reporting Requirements

Type of SAE	Reporting Time Frame	Reporting Method	Telephone Number, Fax Number, or e-mail address
All SAEs	Within 24 hours of awareness	Fax or E-mail*	+ 44 1223 374102 (North America and Rest of world) EMEAASIASafetyCentral.SM@europe.ppdi.com
Fatal or Life-Threatening	Immediate	Telephone	+ 44 1223 374240 (North America and Rest of world)
	Within 24 hours of awareness	Fax or E-mail*	+ 44 1223 374102 (North America and Rest of world) EMEAASIASafetyCentral.SM@europe.ppdi.com

Urgent safety concerns requiring a medical monitor	As Needed	Telephone	+ 1-888-483-7729 (North America) + 44 1223 374240 (Rest of world)

*** The SAE report form must be used for reporting.**

At the time of the initial report, the investigator should provide as much of the following information as possible:

- Study identifier
- 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.

10.4.2 *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.

10.4.3 *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.

10.5 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 discontinuation of clinical development of the investigational product. These documents will be retained for a longer period if required by the applicable regulatory requirements or by an agreement with the Sponsor. It is the responsibility of the Sponsor to inform the investigator/institution as to when these documents no longer need to be retained.

If the responsible investigator retires, relocates, or for other reasons withdraws from the responsibility of keeping the study records, custody must be transferred to a person who will accept the responsibility. The Sponsor must be notified in writing of the name and address of the new custodian. Under no circumstance shall the investigator relocate or dispose of any study documents before having obtained written approval from the Sponsor. If it becomes necessary for the Sponsor or the appropriate regulatory authority to review any documentation relating to this study, the investigator must permit access to such reports.

The following records are considered essential documents:

- Signed informed consent documents for all subjects
- Subject identification code list, Screening log (if applicable), and enrollment log
- Record of all communications between the investigator and the IRB/IEC
- Composition of the IRB/IEC or other applicable statement
- Record of all communications between the investigator and Sponsor (or CRO)
- List of sub-investigators and other appropriately qualified persons to whom the investigator has delegated significant trial-related duties, together with their roles in the study and their signatures
- Compact Disks (CDs) of eCRFs and related documentation of corrections for all subjects
- Drug accountability records
- Record of any body fluids or tissue samples retained
- All other source documents (subject records, hospital records, laboratory records, etc)
- All other documents as listed in *Section 8* of the ICH consolidated guideline on GCP (Essential Documents for the Conduct of a Clinical Trial) and any applicable country requirements.

12 STATISTICAL METHODS AND PLANNED ANALYSES

12.1 Sample size estimation

A sample size of 100 subjects per treatment group will provide 80% power to detect a difference of 16% in median percent reduction in seizure frequency between an active dosage group and placebo group, at a 2-sided significance level of 0.05, assuming a standard deviation of 40%.

12.2 Statistical Methods

Summary statistics and analyses will be presented by the treatment group category assigned to the subject regardless of the dosage of drug administered. Categorical variables will be summarized as frequencies and percentages. Descriptive statistics for continuous variables will include sample size, mean, median, standard deviation, and minimum and maximum values. SAS® version 9.2 or later will be used for all data summaries, statistical analyses, and data

listings. Inferential statistical tests will be 2-sided and will employ a tolerance for type I error (alpha, α) of 0.05. Data will be used as collected. Full details of the analysis plan will be included in the Statistical Analysis Plan (SAP) and finalized prior to any un-blinding of efficacy data.

Analyses of Missing Data

The primary efficacy endpoint definition in the United States and Rest of the world states that seizure rates will be calculated using days with non-missing seizure data. The definition does not explicitly account for days with missing data, i.e., days during which the presence or absence of seizures was not recorded in personal diaries. However the definition implicitly accounts for missing data in that it is identical to a definition in which days with missing data are assumed to have the same seizure rate as days with non-missing data.

Similar to the United States definition of the primary efficacy endpoint, the primary endpoint (responder) definition in the countries of Europe, Australia, New Zealand and South Africa implicitly accounts for missing data during maintenance phase in that it is identical to a definition in which days with missing data are assumed to have the same seizure rate as days with non-missing data. An additional analysis will be performed in which subjects who dropped out during the titration phase will be included in the analysis by having their maintenance phase data imputed using the available titration data.

The same approach will be used for missing data in the analysis of all secondary efficacy end points.

12.3 Analysis Data Sets

For all populations, subjects will be analyzed according to the target (randomized) dosage group including subjects who fail to achieve the target dosage during the titration phase.

Enrolled subjects: All subjects who have given informed consent to participate in this study will be considered enrolled subjects.

Intention-to-treat (ITT): All randomized subjects will be considered intention-to-treat subjects.

Modified intention-to-treat (MITT) subjects: All randomized subjects who have taken at least one dose of YKP3089 (or placebo) and have any post-baseline seizure data will be considered modified intention-to-treat subjects.

Modified intention-to-treat (MITT-M) subjects in Maintenance phase: All randomized subjects who have completed the titration phase and have taken at least one dose of YKP3089 (or placebo) in the maintenance phase and have any maintenance phase seizure data will be considered modified intention-to-treat subjects in the maintenance phase.

Per protocol population (PP): All randomized subjects who have no major protocol violations and have at least 80% drug compliance will be considered per-protocol subjects.

*Safety evaluable subjects (SE): A*ll ITT subjects.

12.4 Baseline Comparability

All demographic measurements (age, gender, height, and weight) and all safety measurements (ECGs, vital signs, and clinical laboratory values) will be summarized by dose level.

12.5 Primary Efficacy Analyses

12.5.1 *Primary Efficacy Analysis in the United States and the Rest of the World:*

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

The testing strategy for the primary efficacy endpoint (percent change in seizure frequency) is to compare each of the YKP3089 dosage groups with the placebo group. Due to multiple treatment comparisons, a step-down procedure will be used to ensure the overall type I error rate is controlled at the 5% level. Each of the YKP3089 dosage groups will be compared with the placebo group according to the following hierarchy:

1. 200-mg dosage group versus placebo group

2. 400-mg dosage group versus placebo group

3. 100-mg dosage group versus placebo group

The 200-mg dosage group will be compared with the placebo group at a 2-sided 0.05 level as the first step. If no statistically significant difference is detected between the 200-mg dosage group and the placebo group, the procedure will stop and it will be concluded that none of the YKP3089 dosages are efficacious. If a statistically significant difference is detected between the 200-mg dosage group and the placebo group in favor of the 200-mg dosage group, the procedure will proceed to the next step to compare the 400-mg dosage group with the placebo group at a 2-sided 0.05 level. If a statistically significant difference is detected between the 400-mg dosage group and the placebo group in favor of the 400-mg dosage group, the procedure will proceed to the next step to compare the 100-mg dosage group with the placebo group at a 2-sided 0.05 level.

An analysis of covariance (ANCOVA) model will be fit to the ranked values of the primary efficacy endpoint. The ANCOVA will have terms for ranked baseline seizure rate and randomized treatment group. Ties will be handled using the default option in SAS

It should be noted that the primary efficacy analysis uses a non-parametric approach. Because of this, effect sizes are not estimated and tested directly, since testing is made on the rank of the primary efficacy value. However, summary tables for the actual (not the ranked) primary efficacy endpoint will be presented.

Descriptive results of the primary efficacy end point will be provided for the subjects who were titrated under the original protocol.

12.5.2 *Primary Efficacy Analyses in the countries of Europe, Australia, New Zealand, and South Africa*

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

The testing strategy for the primary efficacy endpoint (responder rate) is to compare each of the YKP3089 dosage groups with the placebo group. A step-down procedure will be used to ensure the type I error rate due to multiple treatment comparisons is controlled at the 5% level. Each of the YKP3089 dosage groups will be compared with the placebo group according to the following hierarchy:

1. 200-mg dosage group versus placebo group

2. 400-mg dosage group versus placebo group

3. 100-mg dosage group versus placebo group

The 200-mg dosage group will be compared with the placebo group at a 2-sided 0.05 level as the first step. If no statistically significant difference is detected between the 200-mg dosage group and the placebo group, the procedure will stop and it will be concluded that none of the YKP3089 dosages are efficacious. If a statistically significant difference is detected between the 200-mg dosage group and the placebo group in favor of the 200-mg dosage group, the procedure will proceed to the next step to compare the 400-mg dosage group with the placebo group at a 2-sided 0.05 level. If a statistically significant difference is detected between the 400-mg dosage group and the placebo group in favor of the 400-mg dosage group, the procedure will proceed to the next step to compare the 100-mg dosage group with the placebo group at a 2-sided 0.05 level.

The data will be summarized using frequencies and percents of subjects achieving at least a 50% response to treatment, the responder rate. The responder data will be analyzed using a chi-square test.

12.6 Secondary Efficacy Analyses

12.6.1 *Secondary Efficacy Analysis in the countries of Europe, Australia, New Zealand, and South Africa*

The secondary efficacy analysis will be based on the MITT-M population.

The secondary efficacy analysis is to compare each of the YKP3089 dosage groups with the placebo group for the percent reduction in seizure frequency.

An analysis of covariance (ANCOVA) model will be fit to the ranked values of the change in seizure frequency during the maintenance phase. The ANCOVA will have terms for ranked baseline seizure rate and randomized treatment group. Ties will be handled using the default option in SAS.

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

in seizure frequency. However, summary tables for the actual (not the ranked) change in seizure frequency will be presented.

12.6.2 *Secondary Efficacy Analysis in the United States and the Rest of the World*

The secondary efficacy analysis will be based on the MITT population

The secondary efficacy analysis is to compare each of the YKP3089 dosage groups with the placebo group for the responder rate.

The data will be summarized using frequencies and percents of subjects achieving at least a 50% response to treatment, the responder rate. The responder data will be analyzed using a chi-square test.

12.7 Additional Secondary Efficacy Analyses

These secondary efficacy analyses will be based on the MITT or MITT-M population

- Higher response rate of (75, 90 and 100%) of simple partial seizures with motor component plus complex partial seizures plus secondarily generalized tonic clonic seizures during the double-blind period and maintenance phase will be summarized.
- Median percent change for partial seizure subtypes (including simple partial with motor component, complex partial, and secondarily generalized tonic-clonic seizures) will be summarized.
- Seizure rate over time will be analyzed using following scheme
    - A moving average for each dose group will be computed using 4 week periods with 2 week overlap beginning from Visit 3 (V3-V5, V4-V6, V5-V6+2 weeks and so on)
- For the QOLIE-31 analysis, changes from baseline (Visit 3) to the the final value (defined as the last observation obtained in the double-blind phase) (Visit 9) for each treatment group will be summarized using descriptive statistics. Differences between each treatment group and the placebo group in the change from baseline will also be

summarized using descriptive statistics. The minimally important change (MIC) was defined as a change from baseline ≥11.8 at the End Point for the weighted overall QOLIE-31 score. The incidence of subjects meeting the MIC criteria will be summarized by treatment group.

- CGIC will be summarized using descriptive statistics for each treatment group and the placebo group.

12.8 Safety Variable Analyses

All ITT subjects will be evaluable for safety. The number and percent of subjects reporting AEs (including treatment-emergent laboratory abnormalities) will be tabulated by randomized treatment group. 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), ECGs, and C-SSRS will be summarized using descriptive statistics.

12.9 Pharmacokinetic Analysis

Individual plasma concentrations of YKP3089 will be tabulated with the corresponding time related to study drug administration by dose group.

Descriptive statistical analyses will be performed on the plasma concentrations of the YKP3089 obtained during steady-state treatment (Visit 7 and 8)

Descriptive statistical analyses will be performed on the plasma concentrations of the concomitant AEDs obtained during steady-state concomitant treatment (Visit 7 and 8) and those at baseline (Visit 3) to assess the effect of YKP3089 on these AEDs.

12.10 Open-Label Extension Analyses

The results of the open-label extension will be reported at a later date using summary tables, figures, and data listings.

12.11 Interim Analysis

No interim analysis will be performed

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 Institutional Review Board, 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 *Data Monitoring Committee*

The safety of subjects in the study will be monitored by an independent Data Monitoring Committee (DMC). The mandate of the DMC is to provide an independent review of the safety of YKP3089 in subjects with chronic partial seizures.

The DMC will be composed of an unblinded biostatistician and 3 physicians. All members of the DMC will be experienced in the clinical trials process and in the assessment of safety data from clinical trials.

The DMC will have access to all unblinded safety data. The DMC will perform the following reviews:

1. Review of the safety of the first 40 subjects completing titration.
2. Review of the safety of the first 80 subjects completing titration.
3. Review of the safety of the first 120 subjects completing double-blind phase.
4. Review of the safety of the first 240 subjects completing double-blind phase.

These specified reviews are to occur after dose escalation or study completion. The primary data to be reviewed should be adverse events, but all safety data will be made available for review. After completing the review the DMC Chair will prepare a brief report. The DMC can perform other reviews whenever it believes that a review would be informative regarding patient safety. The DMC will not review efficacy data.

The DMC will have a teleconference with the sponsor after each of the above specified milestones. The DMC can schedule a teleconference with the sponsor whenever the DMC identifies a safety issue. The DMC will be granted the authority, after discussion with the sponsor, of restricting dose escalation, adding safety assessments or halting the study temporarily or permanently.

13.7.3 *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: DIAGNOSTIC REVIEW FORM

PLEASE PRINT LEGIBLY

PROTOCOL: YKP3089C017 CONFIDENTIAL

Subject ID #:_____

DIAGNOSTIC REVIEW FORM

Country: _____

Site Number: _____

PI Name: _____

CRA Name: _____

Date of Visit 1: _____

Date Form Was Completed: _____

Name of Individual & Title Completing this Form: _____

Email Address of Person Completing this Form: _____

Name of Investigator Who Reviewed this Form Prior to Submission: _____

The diagnosis of epilepsy usually requires a combination of several elements to ensure patients are not misdiagnosed. Please provide the information used to confidently arrive at the diagnosis of epilepsy for this patient:

1. Age at First Seizure_____

2. Is there a family history of epilepsy in any first degree relative? ☐ Yes ☐ No

   If yes, what is the relationship (parent/sibling/child, etc.)? _____

   What are the seizure types of the family member (if known?)

   □ PRIMARY GENERALIZED TONIC CLONIC CONVULSION □ ABSENCE □ MYOCLONUS
   □ TONIC □ ATONIC □ SIMPLE PARTIAL SEIZURE □ COMPLEX PARTIAL SEIZURE
   □ SECONDARILY GENERALIZED TONIC CLONIC CONVULSION
   □ OTHER (describe): _____

   If Unknown, please check: ☐

3. Is IQ documented? ☐ Yes ☐ No
   a. If yes, please provide:_____ Date Obtained _____

   Is the subject Developmentally Delayed? ☐ Yes ☐ No

4. Other Neurologic Dysfunction (for example: cerebral palsy, aphasia, visual disturbance)

   Please specify: _____

PLEASE PRINT LEGIBLY

PROTOCOL: YKP3089C017 CONFIDENTIAL

Subject ID #:_____

5. EEG

Please fax or email the EEG summary report that identifies the findings indicated below. These reports must be translated into English. **This must be received before this form is reviewed**.

If you are sending us the EEG clip, please send the clip that demonstrates the abnormality checked below. Please point to the abnormality with an arrow.

☐ Normal EEG

☐ Abnormal (Epileptiform)

☐ *Focal spikes*

☐ *Generalized discharges*

☐ *Other*_____

☐ Abnormal EEG (Non-epileptiform only)

Describe: _____

6. Video-EEG

Please submit video EEG report that identifies the findings indicated below.

☐ Not performed

☐ Performed: date _____

Were any seizures captured? ☐ *Yes* ☐ *No*
If yes, were seizures consistent with:

☐ Focal epilepsy

☐ Generalized epilepsy (generalized spike & wave at onset)

☐ Both (Focal & Generalized)

☐ Other _____

7. CT Scan (check procedure and result): ☐ CT Scan performed ☐ CT Scan not performed

☐ Normal

☐ Abnormal (if abnormal please send a copy of the report and indicate abnormality below):

☐ Focal (specify findings)

_____

_____

☐ Diffuse (specify findings)

_____

_____

PLEASE PRINT LEGIBLY

PROTOCOL: YKP3089C017 CONFIDENTIAL

Subject ID #:_____

8. MRI (check procedure and result): ☐ MRI performed ☐ MRI not performed

☐ Normal

☐ Abnormal (if abnormal please send a copy of the report and indicate abnormality below):

☐ Focal (specify findings)

_____

☐ Diffuse (specify findings)

_____

9. Check here to confirm a copy of the seizure diary key is attached.

☐ Yes

☐ No – If not attached, please explain why: _____

Final approval will not be given until the diary is reviewed.

CURRENT SEIZURES (check all that apply)

□ SIMPLE PARTIAL SEIZURE
□ COMPLEX PARTIAL SEIZURE
□ SECONDARILY GENERALIZED TONIC CLONIC CONVULSION
□ PRIMARY GENERALIZED TONIC CLONIC CONVULSION
□ ABSENCE
□ MYOCLONUS
□ TONIC
□ ATONIC
□ OTHER (describe): _____

PREVIOUS SEIZURES

(check all seizures that the subject **had in the past but no longer experiences**)

□ SIMPLE PARTIAL SEIZURE
□ COMPLEX PARTIAL SEIZURE
□ SECONDARILY GENERALIZED TONIC CLONIC CONVULSION
□ PRIMARY GENERALIZED TONIC CLONIC CONVULSION
□ ABSENCE
□ MYOCLONUS
□ TONIC
□ ATONIC
□ OTHER (describe): _____

PLEASE PRINT LEGIBLY

PROTOCOL: YKP3089C017 CONFIDENTIAL

Subject ID #:_____

Table 1: Etiology Classification

Etiology Classification	Present
Genetic or presumed genetic	☐
Epilepsy of unknown cause	☐
Structural	☐
Metabolic	☐

Table 2:Specific Etiologies

Specific Etiologies	Present
a) Viral, bacterial and parasitic infections	☐ Definite ☐ Possible ☐ No
b) Traumatic brain injury	☐ Definite ☐ Possible ☐ No
c) Stroke	☐ Definite ☐ Possible ☐ No
d) Intraventricular hemorrhage	☐ Definite ☐ Possible ☐ No
e) Hypoxic-ischemic encephalopathy	☐ Definite ☐ Possible ☐ No
f) Other metabolic or toxic insults	☐ Definite ☐ Possible ☐ No
g) Neurocutaneous syndromes	☐ Definite ☐ Possible ☐ No
h) Inborn errors of metabolism	☐ Definite ☐ Possible ☐ No
i) Genetic and chromosomal development encephalopathies [1]	☐ Definite ☐ Possible ☐ No
j) Developmental encephalopathy of unknown cause as evidenced by the presence of mental retardation, cerebral palsy, or autism with no evidence of a specific insult of disorder to which cause can be attributed preceding the onset of epilepsy	☐ Definite ☐ Possible ☐ No
k) Malformations of cortical or other brain development with or without known genetic determinants	☐ Definite ☐ Possible ☐ No
l) Neoplasia	☐ Definite ☐ Possible ☐ No
m) Mesial temporal sclerosis[2]	☐ Definite ☐ Possible ☐ No
n) Dementia	☐ Definite ☐ Possible ☐ No
o) Other degenerative neurologic diseases	☐ Definite ☐ Possible ☐ No
p) Genetic or presumed genetic, if known specify: _____	☐ Definite ☐ Possible ☐ No
q) Epilepsy of unknown cause, without relevant abnormalities on examination, cognition, history, or imaging	☐ Definite ☐ Possible ☐ No
r) Other, specify:_____	☐ Definite ☐ Possible ☐ No

If more than one specific etiology is selected, please specify the most likely primary cause of epilepsy:

Primary Cause:

a) ☐ b) ☐ c) ☐ d) ☐ e) ☐ f) ☐ g) ☐ h) ☐ i) ☐ j) ☐ k) ☐ l) ☐ m) ☐ n) ☐ o) ☐ p) ☐

q) ☐ r) ☐

Comments: _____
_____

[1] E.g., Rett, Down, Angelman, and Fragile X syndromes.
[2] Where evidence is lacking that the structural pathology precedes the onset of epilepsy, it is not assumed that such pathology causes epilepsy.

PLEASE PRINT LEGIBLY

PROTOCOL: YKP3089C017 CONFIDENTIAL

Subject ID #:_____

1) **Enter the seizure diary code that corresponds to the seizure description.**
2) **Write a description of the patient's seizure in each box; include as much detail as possible.**
3) **If the patient has more than one description with the same classification, complete two boxes.**

Seizure Diary Code: _____

Description 1:_____

_____

_____

How long does the seizure last? _____

IS THERE LOSS OF AWARENESS DURING THE SEIZURE? □ **yes** □ **no**

Does the patient have a warning? □ **yes** □ **no**

If yes, describe: _____

Please check/tick the classification of the seizure described above.

□ SIMPLE PARTIAL SEIZURE WITHOUT MOTOR/OBSERVABLE COMPONENT

□ SIMPLE PARTIAL SEIZURE WITH MOTOR/OBSERVABLE COMPONENT

□ COMPLEX PARTIAL SEIZURE (ALTERATION OF AWARENESS OR DYSCOGNITIVE FEATURES)

□ PARTIAL SEIZURE CONSISTING OF OR ENDING IN A GENERALIZED TONIC CLONIC CONVULSION

Include all symptoms. Only reporting "a generalized tonic-clonic seizure" does not give our reviewer enough information. Be sure to specify if there is bilateral stiffening followed by bilateral shaking.

□ OTHER_____

Seizure Diary Code: _____

Description 2:_____

_____

_____

How long does the seizure last? _____

IS THERE LOSS OF AWARENESS DURING THE SEIZURE? □ **yes** □ **no**

Does the patient have a warning? □ **yes** □ **no**

If yes, describe: _____

Please check/tick the classification of the seizure described above.

□ SIMPLE PARTIAL SEIZURE WITHOUT MOTOR/OBSERVABLE COMPONENT

□ SIMPLE PARTIAL SEIZURE WITH MOTOR/OBSERVABLE COMPONENT

□ COMPLEX PARTIAL SEIZURE (ALTERATION OF AWARENESS OR DYSCOGNITIVE FEATURES)

□ PARTIAL SEIZURE CONSISTING OF OR ENDING IN A GENERALIZED TONIC CLONIC CONVULSION

Include all symptoms. Only reporting "a generalized tonic-clonic seizure" does not give our reviewer enough information. Be sure to specify if there is bilateral stiffening followed by bilateral shaking.

□ OTHER_____

PLEASE PRINT LEGIBLY

PROTOCOL: YKP3089C017 CONFIDENTIAL

Subject ID #:_____

Seizure Diary Code: _____

Description 3:_____

_____

_____

How long does the seizure last? _____

IS THERE LOSS OF AWARENESS DURING THE SEIZURE? □ yes □ no

Does the patient have a warning? □ yes □ no

If yes, describe: _____

Please check/tick the classification of the seizure described above.

□ SIMPLE PARTIAL SEIZURE WITHOUT MOTOR/OBSERVABLE COMPONENT

□ SIMPLE PARTIAL SEIZURE WITH MOTOR/OBSERVABLE COMPONENT

□ COMPLEX PARTIAL SEIZURE (ALTERATION OF AWARENESS OR DYSCOGNITIVE FEATURES)

□ PARTIAL SEIZURE CONSISTING OF OR ENDING IN A GENERALIZED TONIC CLONIC CONVULSION

Include all symptoms. Only reporting "a generalized tonic-clonic seizure" does not give our reviewer enough information. Be sure to specify if there is bilateral stiffening followed by bilateral shaking.

□ OTHER_____

Seizure Diary Code: _____

Description 4:_____

_____

_____

How long does the seizure last? _____

IS THERE LOSS OF AWARENESS DURING THE SEIZURE? □ yes □ no

Does the patient have a warning? □ yes □ no

If yes, describe: _____

Please check/tick the classification of the seizure described above.

□ SIMPLE PARTIAL SEIZURE WITHOUT MOTOR/OBSERVABLE COMPONENT

□ SIMPLE PARTIAL SEIZURE WITH MOTOR/OBSERVABLE COMPONENT

□ COMPLEX PARTIAL SEIZURE (ALTERATION OF AWARENESS OR DYSCOGNITIVE FEATURES)

□ PARTIAL SEIZURE CONSISTING OF OR ENDING IN A GENERALIZED TONIC CLONIC CONVULSION

Include all symptoms. Only reporting "a generalized tonic-clonic seizure" does not give our reviewer enough information. Be sure to specify if there is bilateral stiffening followed by bilateral shaking.

□ OTHER_____

ALL FORMS INCLUDING EEG AND IMAGING REPORTS MUST BE SENT BEFORE THIS FORM IS REVIEWED. APPROVAL WILL BE WITHELD UNTIL ALL DOCUMENTS ARE SUBMITTED.

PLEASE SEND THIS FORM BY FAX OR EMAIL TO BREE DIVENTURA
Fax: 1-646-478-9603 (USA) or 00-1-646-478-9603 (International) or to
Epilepsy.Consortium@gmail.com

DRF and SIF_Version 25Apr13 Page 6 of 6

APPENDIX E: 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

SUICIDAL IDEATION		
Ask questions 1 and 2. If both are negative, proceed to "Suicidal Behavior" section. If the answer to question 2 is "yes", ask questions 3, 4 and 5. If the answer to question 1 and/or 2 is "yes", complete "Intensity of Ideation" section below.	**Lifetime: Time He/She Felt Most Suicidal**	**Past __ Months**
1. Wish to be Dead Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up. ***Have you wished you were dead or wished you could go to sleep and not wake up?*** If yes, describe:	Yes ☐ No ☐	Yes ☐ No ☐
2. Non-Specific Active Suicidal Thoughts General non-specific thoughts of wanting to end one's life/commit suicide (e.g., *"I've thought about killing myself"*) without thoughts of ways to kill oneself/associated methods, intent, or plan during the assessment period. ***Have you actually had any thoughts of killing yourself?*** If yes, describe:	Yes ☐ No ☐	Yes ☐ No ☐
3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different than a specific plan with time, place or method details worked out (e.g. thought of method to kill self but not a specific plan). Includes person who would say, *"I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it…and I would never go through with it."* ***Have you been thinking about how you might do this?*** If yes, describe:	Yes ☐ No ☐	Yes ☐ No ☐
4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan Active suicidal thoughts of killing oneself and subject reports having some intent to act on such thoughts, as opposed to *"I have the thoughts but I definitely will not do anything about them."* ***Have you had these thoughts and had some intention of acting on them?*** If yes, describe:	Yes ☐ No ☐	Yes ☐ No ☐
5. Active Suicidal Ideation with Specific Plan and Intent Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out. ***Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?*** If yes, describe:	Yes ☐ No ☐	Yes ☐ No ☐
INTENSITY OF IDEATION		
The following features should be rated with respect to the most severe type of ideation (i.e., 1-5 from above, with 1 being the least severe and 5 being the most severe). Ask about time he/she was feeling the most suicidal. Lifetime - ***Most Severe Ideation:*** ***Type # (1-5)*** ***Description of Ideation*** Past X Months - ***Most Severe Ideation:*** ***Type # (1-5)*** ***Description of Ideation***	Most Severe	Most Severe
Frequency ***How many times have you had these thoughts?*** (1) Less than once a week (2) Once a week (3) 2-5 times in week (4) Daily or almost daily (5) Many times each day	____	____
Duration ***When you have the thoughts how long do they last?*** (1) Fleeting - few seconds or minutes (2) Less than 1 hour/some of the time (3) 1-4 hours/a lot of time (4) 4-8 hours/most of day (5) More than 8 hours/persistent or continuous	____	____
Controllability ***Could/can you stop thinking about killing yourself or wanting to die if you want to?*** (1) Easily able to control thoughts (2) Can control thoughts with little difficulty (3) Can control thoughts with some difficulty (4) Can control thoughts with a lot of difficulty (5) Unable to control thoughts (0) Does not attempt to control thoughts	____	____
Deterrents ***Are there things - anyone or anything (e.g., family, religion, pain of death) - that stopped you from wanting to die or acting on thoughts of committing suicide?*** (1) Deterrents definitely stopped you from attempting suicide (2) Deterrents probably stopped you (3) Uncertain that deterrents stopped you (4) Deterrents most likely did not stop you (5) Deterrents definitely did not stop you (0) Does not apply	____	____
Reasons for Ideation ***What sort of reasons did you have for thinking about wanting to die or killing yourself? Was it to end the pain or stop the way you were feeling (in other words you couldn't go on living with this pain or how you were feeling) or was it to get attention, revenge or a reaction from others? Or both?*** (1) Completely to get attention, revenge or a reaction from others (2) Mostly to get attention, revenge or a reaction from others (3) Equally to get attention, revenge or a reaction from others and to end/stop the pain (4) Mostly to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (5) Completely to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (0) Does not apply	____	____

SUICIDAL BEHAVIOR *(Check all that apply, so long as these are separate events; must ask about all types)*	**Lifetime**	**Past __ Years**
Actual Attempt: A potentially self-injurious act committed with at least some wish to die, *as a result of act.* Behavior was in part thought of as method to kill oneself. Intent does not have to be 100%. If there is ***any*** intent/desire to die associated with the act, then it can be considered an actual suicide attempt. ***There does not have to be any injury or harm***, just the potential for injury or harm. If person pulls trigger while gun is in mouth but gun is broken so no injury results, this is considered an attempt. Inferring Intent: Even if an individual denies intent/wish to die, it may be inferred clinically from the behavior or circumstances. For example, a highly lethal act that is clearly not an accident so no other intent but suicide can be inferred (e.g., gunshot to head, jumping from window of a high floor/story). Also, if someone denies intent to die, but they thought that what they did could be lethal, intent may be inferred. ***Have you made a suicide attempt?*** ***Have you done anything to harm yourself?*** ***Have you done anything dangerous where you could have died?*** ***What did you do?*** ***Did you_____ as a way to end your life?*** ***Did you want to die (even a little) when you_____?*** ***Were you trying to end your life when you _____?*** ***Or Did you think it was possible you could have died from_____?*** ***Or did you do it purely for other reasons / without ANY intention of killing yourself (like to relieve stress, feel better, get sympathy, or get something else to happen)?*** (Self-Injurious Behavior without suicidal intent) If yes, describe: **Has subject engaged in Non-Suicidal Self-Injurious Behavior?**	Yes ☐ No ☐ Total # of Attempts _____ Yes ☐ No ☐	Yes ☐ No ☐ Total # of Attempts _____ Yes ☐ No ☐
Interrupted Attempt: When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act *(if not for that, actual attempt would have occurred).* Overdose: Person has pills in hand but is stopped from ingesting. Once they ingest any pills, this becomes an attempt rather than an interrupted attempt. Shooting: Person has gun pointed toward self, gun is taken away by someone else, or is somehow prevented from pulling trigger. Once they pull the trigger, even if the gun fails to fire, it is an attempt. Jumping: Person is poised to jump, is grabbed and taken down from ledge. Hanging: Person has noose around neck but has not yet started to hang - is stopped from doing so. ***Has there been a time when you started to do something to end your life but someone or something stopped you before you actually did anything?*** If yes, describe:	Yes ☐ No ☐ Total # of interrupted _____	Yes ☐ No ☐ Total # of interrupted _____
Aborted Attempt: When person begins to take steps toward making a suicide attempt, but stops themselves before they actually have engaged in any self-destructive behavior. Examples are similar to interrupted attempts, except that the individual stops him/herself, instead of being stopped by something else. ***Has there been a time when you started to do something to try to end your life but you stopped yourself before you actually did anything?*** If yes, describe:	Yes ☐ No ☐ Total # of aborted _____	Yes ☐ No ☐ Total # of aborted _____
Preparatory Acts or Behavior: Acts or preparation towards imminently making a suicide attempt. This can include anything beyond a verbalization or thought, such as assembling a specific method (e.g., buying pills, purchasing a gun) or preparing for one's death by suicide (e.g., giving things away, writing a suicide note). ***Have you taken any steps towards making a suicide attempt or preparing to kill yourself (such as collecting pills, getting a gun, giving valuables away or writing a suicide note)?*** If yes, describe:	Yes ☐ No ☐	Yes ☐ No ☐
Suicidal Behavior: Suicidal behavior was present during the assessment period?	Yes ☐ No ☐	Yes ☐ No ☐

Answer for Actual Attempts Only	Most Recent Attempt Date:	Most Lethal Attempt Date:	Initial/First Attempt Date:
Actual Lethality/Medical Damage: 0. No physical damage or very minor physical damage (e.g., surface scratches). 1. Minor physical damage (e.g., lethargic speech; first-degree burns; mild bleeding; sprains). 2. Moderate physical damage; medical attention needed (e.g., conscious but sleepy, somewhat responsive; second-degree burns; bleeding of major vessel). 3. Moderately severe physical damage; *medical* hospitalization and likely intensive care required (e.g., comatose with reflexes intact; third-degree burns less than 20% of body; extensive blood loss but can recover; major fractures). 4. Severe physical damage; *medical* hospitalization with intensive care required (e.g., comatose without reflexes; third-degree burns over 20% of body; extensive blood loss with unstable vital signs; major damage to a vital area). 5. Death	*Enter Code* _____	*Enter Code* _____	*Enter Code* _____
Potential Lethality: Only Answer if Actual Lethality=0 Likely lethality of actual attempt if no medical damage (the following examples, while having no actual medical damage, had potential for very serious lethality: put gun in mouth and pulled the trigger but gun fails to fire so no medical damage; laying on train tracks with oncoming train but pulled away before run over). 0 = Behavior not likely to result in injury 1 = Behavior likely to result in injury but not likely to cause death 2 = Behavior likely to result in death despite available medical care	*Enter Code* _____	*Enter Code* _____	*Enter Code* _____

APPENDIX F: 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.)*

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

SUICIDAL IDEATION	
Ask questions 1 and 2. If both are negative, proceed to "Suicidal Behavior" section. If the answer to question 2 is "yes," ask questions 3, 4 and 5. If the answer to question 1 and/or 2 is "yes", complete "Intensity of Ideation" section below.	Since Last Visit
1. Wish to be Dead Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up. ***Have you wished you were dead or wished you could go to sleep and not wake up?*** If yes, describe:	**Yes** ☐ **No** ☐
2. Non-Specific Active Suicidal Thoughts General, non-specific thoughts of wanting to end one's life/commit suicide (e.g. *"I've thought about killing myself"*) without thoughts of ways to kill oneself/associated methods, intent, or plan during the assessment period. ***Have you actually had any thoughts of killing yourself?*** If yes, describe:	**Yes** ☐ **No** ☐
3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different than a specific plan with time, place or method details worked out (e.g. thought of method to kill self but not a specific plan). Includes person who would say, *"I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it…..and I would never go through with it".* ***Have you been thinking about how you might do this?*** If yes, describe:	**Yes** ☐ **No** ☐
4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan Active suicidal thoughts of killing oneself and subject reports having some intent to act on such thoughts, as opposed to *"I have the thoughts but I definitely will not do anything about them".* ***Have you had these thoughts and had some intention of acting on them?*** If yes, describe:	**Yes** ☐ **No** ☐
5. Active Suicidal Ideation with Specific Plan and Intent Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out. ***Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?*** If yes, describe:	**Yes** ☐ **No** ☐
INTENSITY OF IDEATION	
The following features should be rated with respect to the most severe type of ideation (i.e.,1-5 from above, with 1 being the least severe and 5 being the most severe). ***Most Severe Ideation:*** _____ _____ ***Type # (1-5)*** ***Description of Ideation***	Most Severe
Frequency ***How many times have you had these thoughts?*** (1) Less than once a week (2) Once a week (3) 2-5 times in week (4) Daily or almost daily (5) Many times each day	_____
Duration ***When you have the thoughts, how long do they last?*** (1) Fleeting - few seconds or minutes (2) Less than 1 hour/some of the time (3) 1-4 hours/a lot of time (4) 4-8 hours/most of day (5) More than 8 hours/persistent or continuous	_____
Controllability ***Could /can you stop thinking about killing yourself or wanting to die if you want to?*** (1) Easily able to control thoughts (2) Can control thoughts with little difficulty (3) Can control thoughts with some difficulty (4) Can control thoughts with a lot of difficulty (5) Unable to control thoughts (0) Does not attempt to control thoughts	_____
Deterrents ***Are there things - anyone or anything (e.g. family, religion, pain of death) - that stopped you from wanting to die or acting on thoughts of committing suicide?*** (1) Deterrents definitely stopped you from attempting suicide (2) Deterrents probably stopped you (3) Uncertain that deterrents stopped you (4) Deterrents most likely did not stop you (5) Deterrents definitely did not stop you (0) Does not apply	_____
Reasons for Ideation ***What sort of reasons did you have for thinking about wanting to die or killing yourself? Was it to end the pain or stop the way you were feeling (in other words you couldn't go on living with this pain or how you were feeling) or was it to get attention, revenge or a reaction from others? Or both?*** (1) Completely to get attention, revenge or a reaction from others. (2) Mostly to get attention, revenge or a reaction from others. (3) Equally to get attention, revenge or a reaction from others and to end/stop the pain. (4) Mostly to end or stop the pain (you couldn't go on living with the pain or how you were feeling). (5) Completely to end or stop the pain (you couldn't go on living with the pain or how you were feeling). (0) Does not apply	_____

Version 1/14/09

SUICIDAL BEHAVIOR *(Check all that apply, so long as these are separate events; must ask about all types)*	Since Last Visit
Actual Attempt: A potentially self-injurious act committed with at least some wish to die, *as a result of act.* Behavior was in part thought of as method to kill oneself. Intent does not have to be 100%. If there is ***any*** intent/desire to die associated with the act, then it can be considered an actual suicide attempt. ***There does not have to be any injury or harm***, just the potential for injury or harm. If person pulls trigger while gun is in mouth but gun is broken so no injury results, this is considered an attempt. Inferring Intent: Even if an individual denies intent/wish to die, it may be inferred clinically from the behavior or circumstances. For example, a highly lethal act that is clearly not an accident so no other intent but suicide can be inferred (e.g. gunshot to head, jumping from window of a high floor/story). Also, if someone denies intent to die, but they thought that what they did could be lethal, intent may be inferred. ***Have you made a suicide attempt?*** ***Have you done anything to harm yourself?*** ***Have you done anything dangerous where you could have died?*** ***What did you do?*** ***Did you_____ as a way to end your life?*** ***Did you want to die (even a little) when you_____?*** ***Were you trying to end your life when you _____?*** ***Or did you think it was possible you could have died from_____?*** ***Or did you do it purely for other reasons / without ANY intention of killing yourself (like to relieve stress, feel better, get sympathy, or get something else to happen)?*** (Self-Injurious Behavior without suicidal intent) If yes, describe: **Has subject engaged in Non-Suicidal Self-Injurious Behavior?**	**Yes** **No** ☐ ☐ Total # of Attempts _____ **Yes** **No** ☐ ☐
Interrupted Attempt: When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act *(if not for that, actual attempt would have occurred).* Overdose: Person has pills in hand but is stopped from ingesting. Once they ingest any pills, this becomes an attempt rather than an interrupted attempt. Shooting: Person has gun pointed toward self, gun is taken away by someone else, or is somehow prevented from pulling trigger. Once they pull the trigger, even if the gun fails to fire, it is an attempt. Jumping: Person is poised to jump, is grabbed and taken down from ledge. Hanging: Person has noose around neck but has not yet started to hang - is stopped from doing so. ***Has there been a time when you started to do something to end your life but someone or something stopped you before you actually did anything?*** If yes, describe:	**Yes** **No** ☐ ☐ Total # of interrupted _____
Aborted Attempt: When person begins to take steps toward making a suicide attempt, but stops themselves before they actually have engaged in any self-destructive behavior. Examples are similar to interrupted attempts, except that the individual stops him/herself, instead of being stopped by something else. ***Has there been a time when you started to do something to try to end your life but you stopped yourself before you actually did anything?*** If yes, describe:	**Yes** **No** ☐ ☐ Total # of aborted _____
Preparatory Acts or Behavior: Acts or preparation towards imminently making a suicide attempt. This can include anything beyond a verbalization or thought, such as assembling a specific method (e.g. buying pills, purchasing a gun) or preparing for one's death by suicide (e.g. giving things away, writing a suicide note). ***Have you taken any steps towards making a suicide attempt or preparing to kill yourself (such as collecting pills, getting a gun, giving valuables away or writing a suicide note)?*** If yes, describe:	**Yes** **No** ☐ ☐
Suicidal Behavior: Suicidal behavior was present during the assessment period?	**Yes** **No** ☐ ☐
Completed Suicide:	**Yes** **No** ☐ ☐
Answer for Actual Attempts Only	Most Lethal Attempt Date:
Actual Lethality/Medical Damage: 0. No physical damage or very minor physical damage (e.g. surface scratches). 1. Minor physical damage (e.g. lethargic speech; first-degree burns; mild bleeding; sprains). 2. Moderate physical damage; medical attention needed (e.g. conscious but sleepy, somewhat responsive; second-degree burns; bleeding of major vessel). 3. Moderately severe physical damage; *medical* hospitalization and likely intensive care required (e.g. comatose with reflexes intact; third-degree burns less than 20% of body; extensive blood loss but can recover; major fractures). 4. Severe physical damage; *medical* hospitalization with intensive care required (e.g. comatose without reflexes; third-degree burns over 20% of body; extensive blood loss with unstable vital signs; major damage to a vital area). 5. Death	*Enter Code* _____
Potential Lethality: Only Answer if Actual Lethality=0 Likely lethality of actual attempt if no medical damage (the following examples, while having no actual medical damage, had potential for very serious lethality: put gun in mouth and pulled the trigger but gun fails to fire so no medical damage; laying on train tracks with oncoming train but pulled away before run over). 0 = Behavior not likely to result in injury 1 = Behavior likely to result in injury but not likely to cause death 2 = Behavior likely to result in death despite available medical care	*Enter Code* _____

APPENDIX G: CLINICAL GLOBAL IMPRESSION OF CHANGE (CGIC)

Subject ID: Date:

Investigator Name: Protocol # YKP3089C017

Clinical Global Impression of Change (CGIC)

Instructions: *Circle the appropriate number after the following.*

Rate total improvement whether or not, in your judgment, it is due entirely to drug treatment. This assessment should take into account seizure frequency and severity, the occurrence of AEs, and overall functional status of the subject.

Compared to the subject's condition at baseline, how much has the subject changed?

1	Very much improved
2	Much improved
3	Minimally improved
4	No change
5	Minimally worse
6	Much worse
7	Very much worse

APPENDIX H: QUALITY OF LIFE IN EPILEPSY (QOLIE-31-P)

Quality of Life in Epilepsy-31-Problems (QOLIE-31-P)

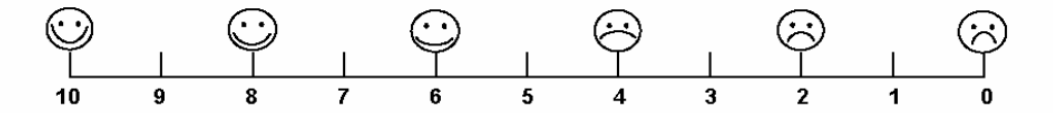
Patient Weighted Quality Of Life In Epilepsy: QOLIE-31-P (Version 2.0, US - English)

Today's Date: __ __ __ M D Y	**Visit Number:** __
Patient's Name (Patient's Initials): _____	**Gender:** ☐ Male ☐ Female
Patient's ID #: _____	**Date of birth:** __ __ __ M D Y

NOTE: ***If you experienced a simple or complex partial seizure within the previous four hours, or a generalized tonic-clonic seizure within the previous 24 hours, please delay completing this questionnaire***

INSTRUCTIONS:
This survey asks about your health and daily activities. **Answer every question** by circling the appropriate number (1, 2, 3…).
If you are unsure about how to answer a question, please give the best answer you can and write a comment or explanation in the margin. Please feel free to ask someone to assist you if you need help reading or marking the form.

1. Overall, how would you rate your quality of life?
(Circle one number on the scale below)



Quality of Life in Epilepsy-31-Problems (QOLIE-31-P)

Part A.

These questions are about how you have been FEELING during the past 4 weeks. For each question, please indicate the one answer that comes closest to the way you have been feeling.

How much of the time during the past 4 weeks…

(Circle one number on each line)

	All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	None of the time
2. Did you feel full of pep?	1	2	3	4	5	6
3. Did you have a lot of energy?	1	2	3	4	5	6
4. Did you feel worn out?	1	2	3	4	5	6
5. Did you feel tired?	1	2	3	4	5	6

*Reviewing only questions in **Part A**, consider the overall impact of these issues on your life **in the past 4 weeks**.*

(Circle one number)

	Not at all	Somewhat	Moderately	A lot	Very much
6. How much do the above problems and worries about <u>energy</u> **distress** you overall?	1	2	3	4	5

Quality of Life in Epilepsy-31-Problems (QOLIE-31-P)

Part B.

These questions are about how you have been FEELING during the past 4 weeks. For each question, please indicate the one answer that comes closest to the way you have been feeling.

How much of the time during the past 4 weeks…
(Circle one number on each line)

	All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	None of the time
7. Have you been a very nervous person?	1	2	3	4	5	6
8. Have you felt so down in the dumps that nothing could cheer you up?	1	2	3	4	5	6
9. Have you felt calm and peaceful?	1	2	3	4	5	6
10. Have you felt downhearted and blue?	1	2	3	4	5	6
11. Have you been a happy person?	1	2	3	4	5	6

*Reviewing only questions in **Part B**, consider the overall impact of these issues on your life **in the past 4 weeks.***

(Circle one number)

	Not at all	Somewhat	Moderately	A lot	Very much
12. How much do the above problems and worries about <u>emotions</u> **distress** you overall?	1	2	3	4	5

Quality of Life in Epilepsy-31-Problems (QOLIE-31-P)

Part C.

The following questions are about how you FEEL and about problems you may have with daily ACTIVITIES during the past 4 weeks. For each question, please indicate the one answer that comes closest to the way you have been feeling.

The following question asks about how you FEEL and how things have been going for you.

How much of the time during the past 4 weeks…

(Circle one number)

	All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	None of the time
13. Has your health limited your social activities (such as visiting with friends or close relatives)?	1	2	3	4	5	6

The following questions ask about problems you may have with certain ACTIVITIES.

How much of the time during the past 4 weeks your epilepsy or antiepileptic medication has caused trouble with…

(Circle one number on each line)

	A great deal	A lot	Somewhat	Only a little	Not at all
14. Leisure activities (such as hobbies, going out)	1	2	3	4	5
15. Driving (or transportation)	1	2	3	4	5

	Not at all bothersome				Extremely bothersome
16. How much do your work limitations bother you?	1	2	3	4	5
17. How much do your social limitations bother you?	1	2	3	4	5

*Reviewing only questions in **Part C**, consider the overall impact of these issues on your life **in the past 4 weeks**.*

(Circle one number)

	Not at all	Somewhat	Moderately	A lot	Very much
18. How much do the above problems and worries about daily activities **distress** you overall?	1	2	3	4	5

Quality of Life in Epilepsy-31-Problems (QOLIE-31-P)

Part D.

These questions are about thinking, reading, concentrating and memory problems you may have had during the past 4 weeks. For each question, please indicate the one answer that comes closest to the way you have been feeling.

How much of the time during the past 4 weeks…

(Circle one number)	All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	None of the time
19. Did you have difficulty reasoning and solving problems (such as making plans, making decisions, learning new things)?	1	2	3	4	5	6

	Yes, a great deal	Yes, somewhat	Only A little	No, not at all
20. In the past 4 weeks, have you had any trouble with your memory?	1	2	3	4

In the past 4 weeks, how often have you had…

(Circle one number on each line)	All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	None of the time
21. Trouble remembering things people tell you?	1	2	3	4	5	6
22. Trouble concentrating on reading?	1	2	3	4	5	6
23. Trouble concentrating on doing one thing at a time?	1	2	3	4	5	6

	Not at all bothersome				Extremely bothersome
24. How much do your memory difficulties bother you?	1	2	3	4	5

*Reviewing only questions in **Part D**, consider the overall impact of these issues on your life **in the past 4 weeks**.*

(Circle one number)

	Not at all	Somewhat	Moderately	A lot	Very much
25. How much do the above problems and worries about mental function **distress** you overall?	1	2	3	4	5

Quality of Life in Epilepsy-31-Problems (QOLIE-31-P)

Part E.

These questions are about problems you may have related to your epilepsy or antiepileptic medication.

During the past 4 weeks…

(Circle one number on each line)

	Not at all bothersome				Extremely bothersome
26. How much do physical effects of antiepileptic medication bother you?	1	2	3	4	5
27. How much do mental effects of antiepileptic medication bother you?	1	2	3	4	5

	Very worried	Somewhat worried	Not very worried	Not worried at all
28. How worried are you that medications you are taking will be bad for you if taken for a long time?	1	2	3	4

*Reviewing only questions in **Part E**, consider the overall impact of these issues on your life **in the past 4 weeks**.*

(Circle one number)

	Not at all	Somewhat	Moderately	A lot	Very much
29. How much do the above problems and worries about the effects of medication **distress** you overall?	1	2	3	4	5

Quality of Life in Epilepsy-31-Problems (QOLIE-31-P)

Part F.

These questions are about how you FEEL about your seizures during the past 4 weeks. For each question, please indicate the one answer that comes closest to the way you have been feeling.

How much of the time during the past 4 weeks…

(Circle one number)	All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	None of the time
30. Have you worried about having another seizure?	1	2	3	4	5	6

	Very fearful	Somewhat fearful	Not very fearful	Not fearful at all
31. How fearful are you of having a seizure during the next month?	1	2	3	4

	Worry a lot	Occasionally worry	Don't worry at all
32. Do you worry about hurting yourself during a seizure?	1	2	3

	Very worried	Somewhat worried	Not very worried	Not at all worried
33. How worried are you about embarrassment or other social problems resulting from having a seizure during the next month?	1	2	3	4

	Not at all bothersome				Extremely bothersome
34. How much do your seizures bother you?	1	2	3	4	5

*Reviewing only questions in **Part F**, consider the overall impact of these issues on your life **in the past 4 weeks**.*

(Circle one number)

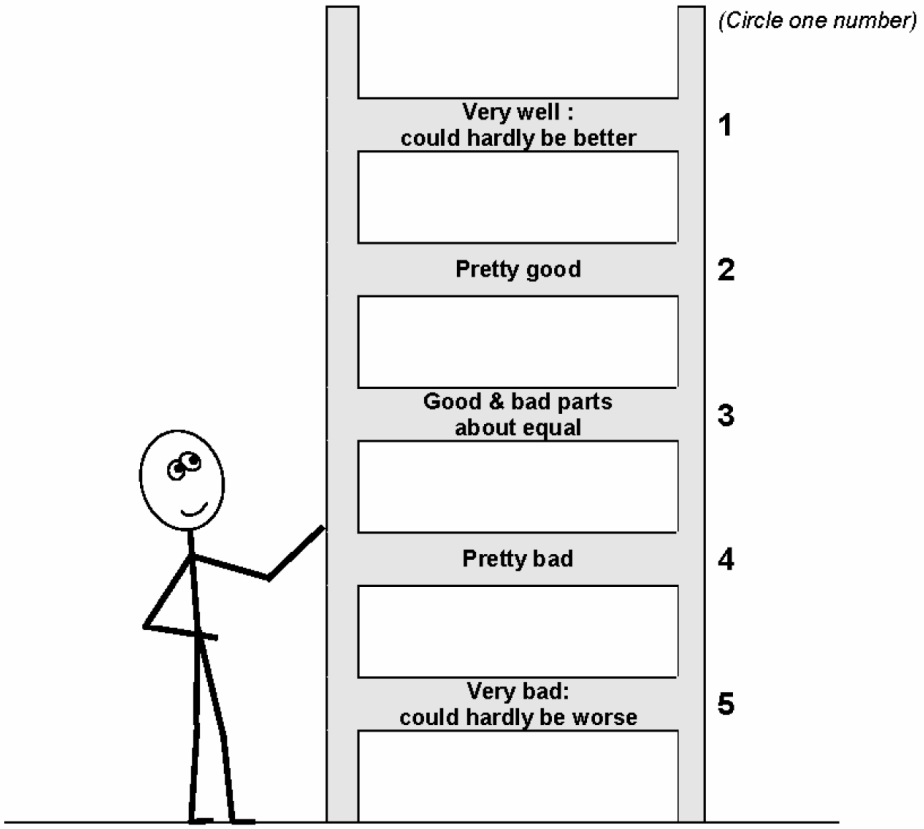
	Not at all	Somewhat	Moderately	A lot	Very much
35. How much do the above problems and worries about <u>seizures</u> **distress** you overall?	1	2	3	4	5

Quality of Life in Epilepsy-31-Problems (QOLIE-31-P)

Part G.

The following question asks about how you FEEL about your overall quality of life. Please indicate the one answer that comes closest to the way you have been feeling.

36. How has the **QUALITY OF YOUR LIFE** been during the **past 4 weeks** (that is, how have things been going for you)?



*Reviewing only questions 1 and 36 in **Part G** (on page 1 and this page), consider the overall impact of your quality of life **in the past 4 weeks**.*

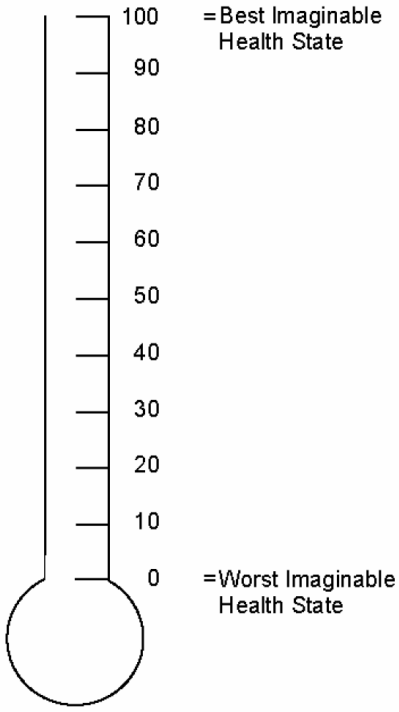
(Circle one number)

	Not at all	Somewhat	Moderately	A lot	Very much
37. How much does the state of your <u>quality of life</u> **distress** you overall?	1	2	3	4	5

Quality of Life in Epilepsy-31-Problems (QOLIE-31-P)

Part H.

38. How good or bad do you think your HEALTH is?
On the scale below, the best imaginable state of health is 100 and the worst imaginable state is zero (0). Please indicate how you feel about your health by circling one number on the scale. **Please consider your epilepsy as part of your health when you answer this question.**



Quality of Life in Epilepsy-31-Problems (QOLIE-31-P)

Part I.

*Considering **ALL** the questions you have answered, please **indicate the areas** related to your epilepsy that are most **IMPORTANT** to you **NOW.***

39. *Number the following topics from '1' to '7', with '1' corresponding to the very most important topic and '7' to the least important one. Please use each number only once.*

- ___ **A.** Energy (tiredness)
- ___ **B.** Emotions (mood)
- ___ **C.** Daily activities (work, driving, social)
- ___ **D.** Mental activity (thinking, concentrating, memory)
- ___ **E.** Medication effects (physical, mental)
- ___ **F.** Seizure worry (impact of seizures)
- ___ **G.** Overall quality of life

Please check to be sure you have answered every question on every page.

THANK YOU FOR COMPLETING THIS QUESTIONNAIRE ABOUT LIVING WITH EPILEPSY.

14 REFERENCES

1. World Health Organization. Epilepsy: aetiogy, epidemiology and prognosis. WHO Fact Sheet No. 165, February 2001.
2. Guidelines for the clinical evaluation of antiepileptic drugs. Epilepsia 1989;30:400-406.
3. European Agency for the Evaluation of Medicinal Products, Committee for Proprietary Medicinal Products. Note for guidance on clinical investigation of medicinal products in the treatment of epileptic disorders. CPMP/EWP/566/98 rev 1, 2000.
4. Food and Drug Administration, Guidelines for the clinical evaluation of antiepileptic drugs (adults and children). HHS (FDA) 81-3110, 1981.
5. Kwan P, Brodie MJ. Early identification of intractable epilepsy. N Engl J Med 2000;342:314-319