STATISTICAL ANALYSIS PLAN

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

Phase 2b

PROTOCOL YKP3089C017 Amendment 2

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3 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

AE(s)	Adverse event(s)
AED	Antiepileptic drug
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ATC	Anatomical therapeutic chemical classification system
β-hCG	β-human chorionic gonadotropin
CBZ	Carbamazepine
CFR	Code of Federal Regulations
CNS	Central nervous system
CRO	Clinical Research Organization
CSR	Clinical study report
C-SSRS	Columbia Suicide Severity Rating Scale
CT	Computed tomography
DB	Double-Blind
ECG	Electrocardiogram
eCRF	Electronic case report form
EEG	Electroencephalograph
FDA	Food and Drug Administration
ICH	International Conference on Harmonisation
kg	Kilogram
LEV	Levetiracetam
LMD	Lacosamide
LTG	Lamotrigine
MedDRA	Medical Dictionary for Regulatory Activities Terminology
mg	Milligrams
mg/day	Milligrams per Day
mg/day/week	Milligrams per Day per Week
mg/week	Milligrams per Week
MIC	Minimally Important Change
MRI	Magnetic resonance imaging
OL	Open-Label
OLE	Open-Label Extension
OTC	Over the Counter
OXC	Oxcarbazepine
QC	Quality Control
QDS	Quality Data Services
RBC	Red Blood Cell
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Standard deviation
SE	Safety evaluable
SKLSI	SK Life Science Inc.

SOC	System Organ Class
TEAE	Treatment Emergent Adverse Event
TLF	Table, listing, figure
TPM	Topiramate
VPA	Valproic acid (divalproex sodium)
WHO DD	World Health Organization Drug Dictionary

4 INTRODUCTION

This statistical analysis plan (SAP) describes the statistical methodology to be used for the reporting and statistical analysis of efficacy and safety clinical data as collected under SK Life Science clinical study protocol YKP3089C017 (amendment 2, 20 March 2015) during open-label extension (OLE) phase of the protocol.

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

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

Table, listing and figure templates (TLFs) for the open-label extension of this phase 2b study are presented in a separate document.

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

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

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

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

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

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5 STUDY OBJECTIVES

The objectives of this study are:

- To determine the effective dose range of YKP3089 as adjunctive therapy for the treatment of partial seizures (primary objective).
- To evaluate the safety and tolerability of YKP3089 in the partial epilepsy population.

6 STUDY DESIGN AND VISIT SCHEDULE

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.

Approximately 400 randomized subjects with partial-onset seizures will be screened at approximately 100 study sites worldwide to achieve the required sample size of 400 subjects. Study sites were classified by geographic region prior to randomization. The geographic regions defined in the study are as follows: Region 1= USA, UK, Germany, France and Australia; Region 2 = Korea and Spain; and Region 3: Remaining countries.

Subjects who have experienced at least 8 partial seizures including only simple partial seizure with motor component, complex partial seizures or secondarily generalized 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.

Randomization was performed centrally, using an IWRS system. Randomization codes are based on a block randomization within study region.

Men and women 18 to 70 years of age, inclusive, in which subjects who meet inclusion/exclusion criteria (see study protocol) were permitted to enroll in this study.

Enrolled subjects are eligible to progress through the following study periods:

1. The Baseline/pre-treatment period consists of an 8-week prospective baseline period where pre-treatment seizure frequency information is collected. Subjects who have experienced at least 8 partial seizures during the baseline period without a seizure-free interval >25 days any time during the 8 week period may be randomized. Subjects must have at least 3 of these partial seizures during each of the two consecutive 4 week periods in

the baseline. A seizure diary check was performed by the CRO monitoring this protocol at Visit 3 (randomization) to confirm that these seizure frequency criteria were met during the 56 days prior to Visit 3.

2. The 18-week double-blind (DB) treatment period including:

   a. 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. During week 1, no dose reduction will be permitted. Subjects who had significant tolerability issues were to discontinue treatment with study drug. Subjects having tolerability issues for the first time during Weeks 2 to 6 will have their dose reduced by 50 or 100 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 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. Refer to Protocol Section 6.1.2.1 for details.

   b. Subjects will then enter a 12-week double-blind maintenance phase. The subjects were instructed to take their study medication once daily in the morning for 12 weeks. Those patients who withdraw prematurely will taper off the study drug.

   c. Subjects that did not participate in the optional open-label phase were to enter a 3 week, double blind taper period. The taper phase will last 3 weeks, followed by a final visit 14 days after the last dose of study drug. Refer to Protocol Section 6.1.2.3 for details on taper phase.

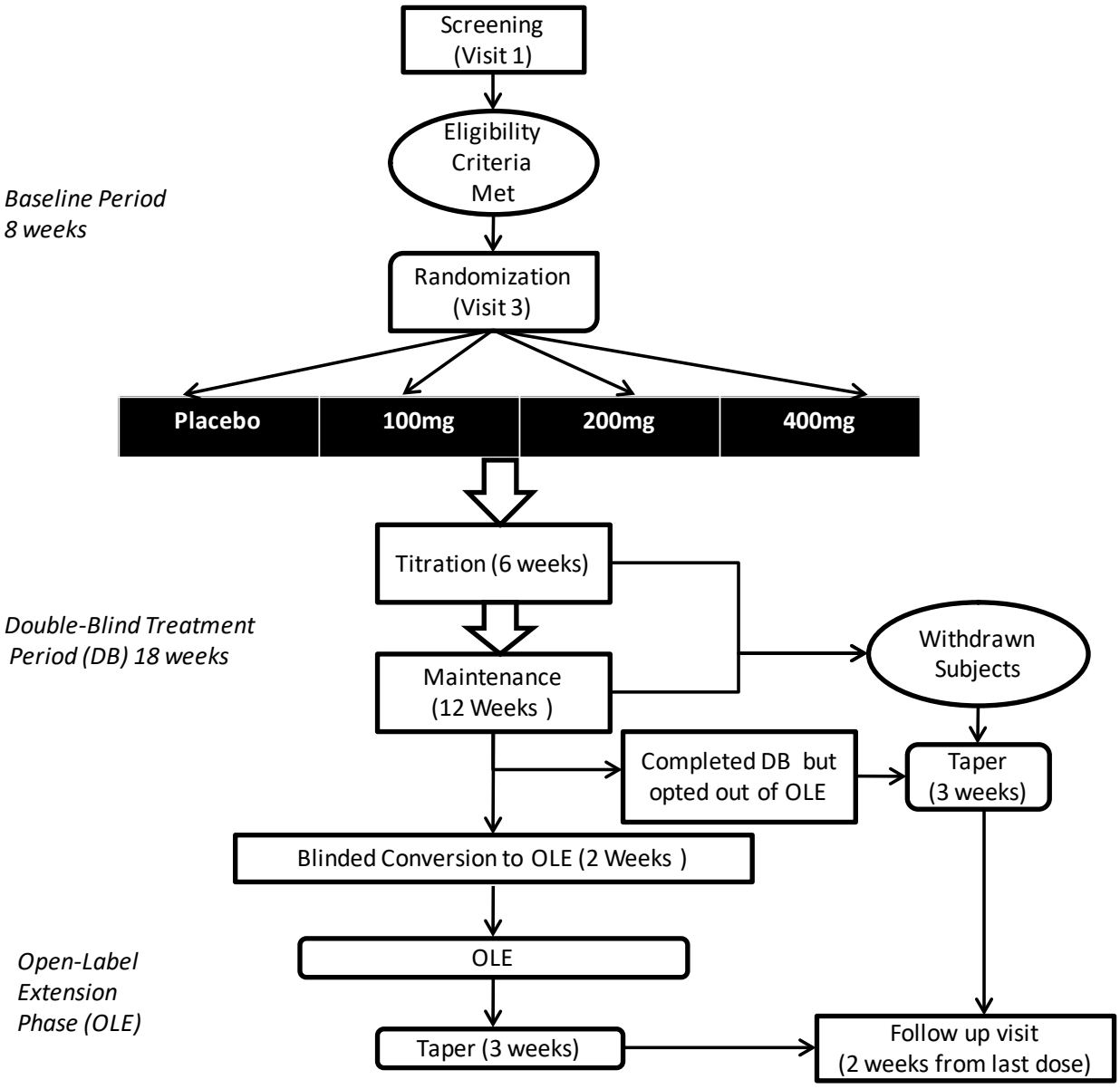
3. Only subjects who complete the double-blind maintenance phase will be given the option to continue treatment in an open-label extension phase. Refer to Protocol Section 6.1.4 for details. The open label extension includes:

   a. The blinded 2-week crossover period (for subjects participating in the open-label extension), during which all subjects will be converted to a target dose of 300 mg once daily, of open-label YKP3089. 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. 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.

b. The open-label extension period: Refer to section 6.1.4.2 of the protocol for details on the open label extension.

c. The taper period of 3 weeks with a final follow-up visit 2 weeks after the last dose of study drug. Refer to section 6.1.4.3 of the protocol for details and the table for taper period.

Figure 1 Study Flowchart



Study assessment chart for double-blind period is included in DB SAP. OLE SAP includes details for study assessment chart for OLE only.

Table 1 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.

7 ASSESSMENTS

7.1 Baseline Data and Prior Medications

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

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

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

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

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

All prescription and OTC medications taken by the subject during the 30 days before screening and up to the first dose of the study drug will be recorded on the Prior and Concomitant Medications eCRF. These data will include the verbatim medication name, indication for use, dose, route, frequency, start date, and end date or ongoing indication.

A full neurologic evaluation examination will also be made and recorded on the eCRF. If the subject has not had a recent CT or MRI, one will be performed and entered on the eCRF. An EEG may also be performed and entered on the eCRF.

Twelve-lead electrocardiograms (ECGs) will be collected at screening and will not be entered on an eCRF. Results will be returned electronically for inclusion in the clinical database.

Clinical laboratory evaluations will be will be collected at screening and results will be returned electronically for inclusion in the clinical database.

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

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

7.2 Efficacy Assessments

Daily seizure information regarding the date, type and number of individual seizures will be entered into a seizure diary. These values are recorded on a

daily basis throughout the OLE phase, and are the basis for deriving all endpoints involving seizure frequency.

7.3 Safety and Tolerability Measures

Adverse event (AE) assessments will be recorded on the Adverse Events eCRF. The term AE is used to include both serious and non-serious AEs. Treatment emergent AEs (TEAEs) occurring during the study treatment period from the first dose of study drug medication up to and including 30 days after the end of treatment (i.e., not present at baseline or worsened in severity following start of treatment) should be reported as AEs and summarized. These data will include the verbatim term for the AE, start date, end date or indication of ongoing, severity, indication of Serious AE, SAE criterion, relationship to study drug, action taken, and outcome. AEs will be coded using MedDRA.

Concomitant medications will be recorded on the Prior and Concomitant eCRF and used to identify prohibited medications.

Vital signs will be recorded on the Vital Signs eCRF. These data will include pulse, supine blood pressure, orthostatic blood pressure, oral temperature, and respiration rate.

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

Twelve-lead electrocardiograms (ECGs) will be collected and returned electronically and not entered on an eCRF.

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

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

Table 2 Clinical laboratory Evaluations

Category	Evaluation items
Hematology	red blood cell (RBC) count, platelet count, hematocrit, hemoglobin, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, mean corpuscular volume, red cell distribution width, reticulocyte count, white blood cell count and differential (basophils, eosinophils, lymphocytes, monocytes, and neutrophils) reported as absolute values
Chemistry	alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, bilirubin (total and direct), gamma-glutamyl transferase, blood urea nitrogen, creatinine, uric acid, sodium, potassium, chloride, carbon dioxide, albumin, calcium, glucose (fasting), and protein (total)
Urinalysis	pH, specific gravity, glucose, ketones, leukocyte esterase, nitrites, occult blood, protein, RBCs/hpf, white blood cells/hpf, bacteria, castes, epithelial cells, mucous threads, and crystals
Urine Pregnancy	β-HCG
Serology	Hepatitis B, Hepatitis C, and HIV antibody
Urine drug and alcohol	marijuana, opiates, cocaine metabolite, and amphetamines/methamphetamines, and alcohol

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

7.4 Study Compliance

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

End of study data will be recorded on the End of Study eCRF. These data will include completion status, date of completion or discontinuation, primary reason for discontinuation, adverse event id (if discontinued due to AE), lost to follow-up information.

Protocol deviations may be identified in two ways: 1) through programmatic checks or 2) through medical reviews. The protocol deviations may include:

1) Known protocol violations identified from the subject qualification eCRF and/or inclusion/exclusion entry criteria;

2) Exclusionary medical history or entry laboratory results;

3) Prior or concomitant medication deviations;

4) ECG deviations; and

5) Study drug dosing deviations.

Details about predefined protocol deviations are included in Appendix 1.

8 STUDY PATIENTS

8.1 Analysis Population

Open-Label Extension Safety Evaluable Population (OLE-SE): All subjects treated in DB who continued into OLE phase and took at least one dose of open-label study medication. All OLE safety analysesdescribed in this SAP will be performed using OLE-SE.

Open-Label Extension Efficacy Analysis Population(OLE-EA): All subjects who entered in OLE phase, took at least one dose of open-label medication and have any seizure data recorded in OLE seizure diary. All OLE efficacy analyses descried in this SAP will be performed by OLE-EA

Double-Blind and Open-Label Extension Safety Evaluable Population: All subjects who received at least one dose of study medication in either DB period only (ie, subjects treated in DB who did not continue in OLE phase) or in both DB and OLE (ie, subjects included in OLE-SE population). This analysis population will be considered when reporting protocol deviations.

OLE analysis summary results will be presented by the following treatment groups:

- All YKP3089 OLE
- YKP3089 100mg DB to YKP3089 OLE
- YKP3089 200mg DB to YKP3089 OLE
- YKP3089 400mg DB to YKP3089 OLE

- Placebo DB to YKP3089 OLE,

where YKP3089 100mg, 200mg, 400mg DB, and Placebo DB represent the randomized treatment group in double blind period and YKP3089 OLE represents the treatment given during OLE.

8.2 Subject Disposition

Subject disposition during OLE will be summarized using the number of subjects who opted for open-label extension as the denominator. Summary results will include, the number and percentage of subjects who completed the open-label extension, and the number and percentage of subjects who discontinued during the open-label extension along with the distribution of the reasons for discontinuation. Results will be summarized by OLE treatment groups.

For summary tables the reasons for termination/withdrawal recorded on the eCRF will be mapped as follows:

Reason for Termination/ Withdrawal on eCRF	Reason for Termination/ Withdrawal in Summary Table
Withdrew consent for reason other than adverse event	Withdrawal by Subject
Withdrew consent due to adverse event	Adverse Event
Terminated by PI for adverse event	Adverse Event
Terminated by Sponsor's medical monitor for adverse event	Adverse Event
Protocol violation	Protocol Violation
Lack of efficacy	Lack of efficacy
Pregnancy	Pregnancy
Lost to follow up	Lost to follow up
Death	Death
Other	Other

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

8.3 Protocol Deviations

Protocol deviations will be reviewed by clinical team on ongoing basis. All protocol deviations during DB and OLE will be listed for all subjects included in Double-Blind and Open-Label Extension Safety Evaluable Population.

8.4 Demographic and Baseline Characteristics

All demographic measurements such as age, gender, height, weight, and BMI (computed using baseline weight and height) will be summarized by OLE treatment groups. All baseline safety measurements, such as ECGs, vital signs, and clinical laboratory values, will be summarized by OLE treatment groups for OLE safety evaluable population.

The continuous variables (e.g., age [years], height, weight, BMI), will be summarized using mean, standard deviation, median, minimum, and maximum values. Categorical (nominal) variables (e.g., gender, ethnicity, and race), will be summarized using number and percentage of subjects.

Baseline measurement for weight, height, BMI will be the last measurement before the first dose in the DB period. Baseline seizure frequency will be computed as defined in Section 9.

By-subject listings of all baseline characteristics will be produced.

8.5 Drug Exposure and Compliance

The extent of exposure to study drug as recorded on eCRF will be provided in a listing by-subject and by study week.

The following parameters will be derived:

- Exposure (days) = date of the last dose in OLE – date of the first dose in OLE + 1
- Exposure (weeks) = (date of the last dose in OLE – date of the first dose in OLE + 1)/7
- Exposure (months) = (date of the last dose in OLE – date of the first dose in OLE + 1)/30.4
- Total subject years of exposure = sum of all subject total exposure days / 365.25.
- Modal daily dose defined as the dose taken the most days during OLE; in case of ties (i.e., 2 different dose levels taken the same number of days), modal dose will be defined as the highest dose between the two

Length of exposure (weeks and months) and modal dose will be summarized by OLE treatment groups using descriptive statistics.

The number and percentage of subjects for the following:

- exposure intervals: 0 to < 1 week,1 to < 2, 2 to < 4, 4 to < 12, 12 to < 24, 24 to < 48, 48 to < 96, 96 to < 144, 144 to < 192, 192 to < 240, 240 to < 288, 288 to <336, 336 to < 384, 384 to < 432, 432 to < 480, 480 to < 528, 528 to < 576, , >=576 weeks.

- exposure categories: >= 1 dose, >= 6, >= 12, >= 18, >= 24, >= 36, >= 48, >= 60, >= 72, >= 84, >= 96, >= 108, and >= 120 months.

Total subject years of exposure will be computed as sum of all subject total exposure days / 365.25 and reported in the summary table.

Drug accountability (tablets dispensed and tablets returned) will be listed by visit.

8.6 Prior and Concomitant Medications

Prior medications are defined as medications taken prior to the first dose of study drug medication and not ongoing at study visit 1 in DB.

Baseline antiepileptic drugs (AEDs) are AEDs that started prior to and are ongoing at the time of the first dose of study medication in double-blind period.

Concomitant AEDs/concomitant medications during OLE are identified as

- AEDs/medications with start date prior to the first dose date of study medication in OLE and end date on or after the first dose date of OLE study medication, OR
- AEDs/medications with start date prior to the first dose of study medication in OLE and ongoing at the end of OLE, OR
- AEDs/medications with a start date on or after the first dose of study medication in OLE.

Prior and concomitant AEDs/medications will be coded to a World Health Organization Drug Dictionary (WHO DD) Version 01Mar2013 term including ATC classification. A by-subject listing of prior AED, concomitant AED, and concomitant non-AED medications use will be produced.

The use of baseline and concomitant AED medications, prior medications, and concomitant non-AED medications will be summarized by OLE treatment group. The number and percentage of subjects taking each medication will be presented by ATC Classification.

In addition, the number of baseline AEDs per subject (mean, standard deviation, median, minimum, and maximum number of AED medications) will be included in the demographics and baseline characteristics summary table.

8.7 Seizure/Epilepsy History

Epilepsy classification and history of seizures by type will be summarized by OLE treatment group for OLE-SE population and will be included in a by-subject listing.

Duration of epilepsy diagnosis (years) will be estimated using year of diagnosis as collected on the CRF.

9 EFFICACY ENDPOINTS

During OLE subjects will records number of seizures by seizure type in the daily dairy. Data from OLE seizure diary will be used to assess percent reduction in seizure frequency over time in subjects with longer exposure to YKP3089.

Percent reduction in seizure frequency will be calculated over the entire OLE phase (overall) and by both 6-month intervals after the start of OLE and cumulative intervals with 6-month increment.

Definitions and Derivations:

- The baseline seizure frequency per 28-day will be based on the baseline seizure diary collected prior to the first dose date in the DB period. This will be calculated by counting the number of seizures over the baseline period, dividing by the number of days in the baseline period with non-missing seizure data, and then multiplying by 28.

- Overall seizure frequency per 28-day during OLE phase will be calculated by counting the number of seizures over the entire OLE phase, dividing by the number of days in the OLE phase with non-missing seizure data, and then multiplying by 28.

- Seizure frequency per 28-day by 6-month intervals during OLE phase will be calculated by counting the number of seizures reported during the respective 6-month interval, dividing by the number of days in the respective 6-month intervals with non-missing seizure data, and then multiplying by 28.

The following 6-months intervals will be defined for OLE seizure frequency per 28-day derivations:

6-Months Interval	OLE Phase Diary Study Days
1 – 6 Months	1 to 182
7 – 12 Months	183 to 365
13 – 18 Months	366 to 547
19 – 24 Months	548 to 730
25 – 30 Months	731 to 912
31 – 36 Months	913 to 1095

37 – 42 Months	1096 to 1277
43 – 48 Months	1278 to 1460
49 – 54 Months	1461 to 1642
55 – 60 Months	1643 to 1825
61 – 66 Months	1826 to 2007
67 – 72 Months	2008 to 2190
73 – 78 Months	2191 to 2372
79 – 84 months	2373 to 2555
85 – 90 months	2556 to 2737
91 – 96 months	2738 to 2920
97 – 102 months	2921 to 3102
103 – 108 months	3103 to 3285
109 – 114 months	3286 to 3467
115 – 120 months	3468 to 3650
>120 Months	>3650 (to last study day diary in OLE)

Study day 1 = day of the first dose in OLE phase.

- Seizure frequency per 28-day by cumulative intervals with 6-month increment during OLE phase will be calculated by counting the number of seizures reported during the respective cumulative intervals, dividing by the number of days in the respective cumulative intervals with non-missing seizure data, and then multiplying by 28.

The following cumulative intervals will be defined:

6-Months Interval	OLE Phase Diary Study Days
1 – 6 Months	1 to 182
1 – 12 Months	1 to 365
1 – 18 Months	1 to 547
1 – 24 Months	1 to 730
1 – 30 Months	1 to 912
1 – 36 Months	1 to 1095
1 – 42 Months	1 to 1277
1 – 48 Months	1 to 1460
1 – 54 Months	1 to 1642
1 – 60 Months	1 to 1825
1 – 66 Months	1 to 2007
1 – 72 Months	1 to 2190
1 – 78 Months	1 to 2372
1 – 84 Months	1 to 2555
1 – 90 Months	1 to 2737
1 – 96 Months	1 to 2920
1 – 102 Months	1 to 3102
1 – 108 Months	1 to 3285
1 – 114 Months	1 to 3467
1 – 120 Months	1 to 3650

Study day 1 = day of the first dose in OLE phase.

For both seizure frequency per 28-day by 6-month intervals during OLE phase and seizure frequency per 28-day by cumulative intervals with 6-month increment during OLE phase, percent change from baseline will be computed as [(OLE reporting interval seizure frequency per 28-day - baseline seizure frequency per 28-day) / baseline seizure frequency per 28-day] x 100.

10 SAFETY ENDPOINTS

10.1 Adverse Events

For open-label extension analyses, treatment-emergent AEs are defined as AEs with onset after the start of OLE study medication, up to last dose date of OLE study medication + 30 days, or onset before start of OLE study medication and worsened after starting OLE study medication, up to last dose date of OLE study medication + 30 days.

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

SAEs will be captured from the time of study drug administration in OLE to 30 days after the last dose of study drug, and will be monitored until resolution or stabilization.

10.2 Clinical Laboratory Evaluations

During OLE, laboratory assessments for hematology, serum chemistry, and urine pregnancy test will be performed Visit 9 (start of OLE), Visit 12, 14, 16, every 6 month after Visit 16, and 14 days after the last dose in OLE. Urinalysis will be performed at Visit 9 (start of OLE), Visit 14, 16, every 12 month after Visit 16, and 14 days after the last dose in OLE.

The following laboratory assessments will be performed in this study:

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

Serum Chemistry: BUN, calcium, chloride, creatinine, glucose, total bilirubin, direct bilirubin, alkaline phosphatase, AST, 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, microscopic examination.

Additional tests: serum pregnancy test.

10.3 Electrocardiograms

ECG parameters consist of heart rate (bpm), PR interval (msec), RR interval (msec), QRS-complex (msec), uncorrected QT interval (msec), and QTcF interval (msec). During OLE, ECG measurements will be performed at Visit 9 (start of OLE), Visit 12, 16, and every 12 months after Visit 16.

10.4 Vital Signs

Vital signs collected in this study are: blood pressure and heart rate (supine for 5 minutes followed by standing for 3 minutes); respiration rate and oral temperature in the supine position. During OLE, these will be collected at Visit 9 (start of OLE), Visits 11, 12, 13, 14, 15, 16, every 3 months after Visit 16, and 14 days after the last dose in OLE.

Weight will only be collected at Visit 9 (start of OLE), Visit 11, 15, 16, every 6 months after Visit 16, and 14 days after the last dose in OLE.

10.5 Physical and Neurologic Examination Results

During OLE, physical examinations will be performed at Visit 9 (start of OLE), Visit 16, and every 12 months after Visit 16.

Full neurological exam will be performed at Visit 9 (start of OLE, at Visit 16, and 14 days after the last dose in OLE. Brief neurological exam will be performed at Visits 11, 13, 15, and every 6 months after Visit 16.

10.6 Columbia Suicide Symptoms and Signs Rating Scale (CSSRS)

C-SSRS Ideation, Intensity and Behavior will be collected at the start of OLE (Visit 9) all visits during OLE: Visit 11, 12, 13, 14, 15, 16, every 3 months after Visit 16, and 14 days after the last dose in OLE.

11 STATISTICAL METHODS

11.1 General Methods

All analyses will be presented by the OLE treatment groups as described in Section 8.1. Categorical variables will be summarized using counts and percentages. Descriptive statistics for continuous variables will include mean, standard deviation, median, minimum, and maximum values. No inferential analysis will be performed for OLE analyses.

SAS® version 9.2 or later will be used for all statistical analyses.

11.2 Efficacy Analysis

11.2.1 Seizure Diary – Percent Change During OLE

The endpoint based on seizure diary is defined as: percent change (reduction) 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 seizure frequency over the entire OLE phase (overall) and by both 6-month intervals after the start of OLE and cumulative intervals. Endpoint definitions are included in Section 9.

Summary results (mean, SD, median, minimum, and maximum) will be presented by OLE treatment groups for OLE-EA population. Subjects in OLE-EA population with no seizure diary data for the reporting OLE interval will be counted under “missing” category.

There will be no hypothesis testing for efficacy endpoints during OLE. Results will be reported descriptively by OLE treatment groups.

11.3 Safety Analysis

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

Adverse events will be coded to a Medical Diction.ary for Regulatory Activities Terminology (MedDRA) version 18.1. Verbatim description and the MedDRA System Organ Class (SOC) and Preferred Term for all adverse events will be contained in the subject data listings.

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

All reported adverse events (regardless of treatment-emergent or not) will be included in a by- subject adverse event listing. Only OLE treatment-emergent adverse events will be included in summary tables. For this study, the AE reporting period is defined as 30 days following the last administration of study treatment; therefore, adverse events that occur up to 30 days following the subject's last dose in OLE are included as treatment-emergent events.

The incidence of treatment-emergent adverse events will be presented by the counts and percentages of subjects with adverse events. A subject will be counted only once in the incidence count for a MedDRA Preferred Term, although a subject may have multiple occurrences (start and stop) of an event associated with a specific MedDRA Preferred Term.

Severe adverse events and adverse events related to treatment (definitely, probably, possibly, or remotely) will be summarized OLE treatment group.

An adverse event is regarded as related to study medication if the relationship to study medication is definitely, probably, possibly or remotely related. Adverse events with missing relationship will be assumed to be treatment related. Adverse events with missing severity will be assumed to be severe in order to perform the most conservative statistical analysis.

Planned summary tables are listed below:

- Summary of treatment-emergent adverse events;
- Incidence of treatment-emergent adverse events by MedDRA System Organ Class and Preferred Term
- Incidence of treatment-emergent adverse events by MedDRA System Organ Class, Preferred Term, and maximum severity
- Incidence of treatment-emergent serious adverse events by MedDRA System Organ Class and Preferred Term

- Incidence of treatment-emergent adverse events leading to study drug discontinuation by MedDRA System Organ Class and Preferred Term
- Incidence of treatment-emergent adverse events leading to death by MedDRA System Organ Class and Preferred Term
- Incidence of treatment-emergent adverse events (all causality) by decreasing frequency in overall group reporting only preferred terms (no system organ class)

Deaths, serious adverse events, and adverse events leading to treatment discontinuation, will be listed including the OLE treatment group, start and stop dates of the adverse event, and onset day relative to the start of the OLE study drug. Details of listings that will be provided for the OLE-SE analysis population are as follows:

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

11.3.2 Analysis of Clinical Laboratory parameters

Laboratory results during open-label extension will be summarized by OLE treatment groups. For these summary tables, results will be reported using visit windows as defined in Appendix 14.2. Shift tables from baseline to each post-baseline OLE visit will be prepared for hematology and chemistry laboratory assessments based on the categories of Low, Normal, and High (for numerical results) or Abnormal and Normal (for categorical results). Baseline measurement is defined as the last available measurement prior to dosing in double-blind.

Laboratory results during OLE will be listed by subject.

11.3.3 Analysis of Electrocardiograms

All ECG results will be listed on a by-subject basis. ECG parameters consist of heart rate (bpm), PR interval (msec), RR interval (msec), QRS-complex (msec), uncorrected QT interval (msec), and QTcF interval (msec). Individual ECG values (parameters) will be listed by subject and visit. Baseline measurement is defined as the last available measurement prior to dosing in double-blind period.

For summary tables, the following rules will be applied to derive a single value corresponding for this visit:

- For all numerical values, the average of the 3 measurements will be computed
- For qualitative values (normal / abnormal):

- If 2 or more results are “abnormal”, visit 3 derived results will be “abnormal” (this rule applies for subjects with 3 or 2 measurements)

- Otherwise, visit 3 derived results will be “normal”.

For subjects with only one measurement collected at Visit 1 (DB baseline),

the collected value will be used as baseline value for summary results.

For the OLE-SE analysis population the following summary tables will be generated for the ECG data:

- Summary statistics (n, mean, standard deviation, median, minimum, and maximum) of the baseline value, the value at each scheduled post-baseline evaluation, and the corresponding change from baseline for each continuous ECG parameter,

- Count and percentage of subjects with QTcF absolute value > 450 msec, >480 msec, >500 msec, <360 msec, <340 msec, <320 msec, and <300 msec at each scheduled post-baseline evaluation,

- Count and percentage of subjects with a mean change from baseline in QTcF intervals >30 msec, >60 msec >90 msec, <30 msec, <60 msec, and <90 msec at each scheduled post-baseline evaluation,

- Count and percentage of subjects with absolute heart rate > 100 bpm at each scheduled post-baseline evaluation,

- Count and percentage of subjects with heart rate change from baseline >10 bpm, >20 bpm, and >30 bpm at each scheduled post-baseline evaluation,

For these summary tables, results will be reported using visit windows as defined in Appendix 14.1.

ECG results during OLE will be listed by subject.

11.3.4 Analysis of Vital Signs

All Vital Signs will be listed on a by-subject basis. Baseline measurement is defined as the last available measurement prior to dosing in double-blind period. Vital signs result during open-label phase will be summarized by OLE treatment groups. For these summary tables, results will be reported using visit windows as defined in Appendix 14.3.

11.3.5 Analysis of Physical and Neurologic Examination Results

Physical and neurological examination results during OLE will be included in by-subject listings only.

11.3.6 Columbia Suicide Symptoms and Signs Rating Scale (CSSRS)

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

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

For OLE, C-SSRS results will be included in by-subject listings only.

12 GENERAL PROGRAMMING SPECIFICATIONS

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

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

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

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

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

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

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

(e) Dates will be reported in SAS DATE9. format (e.g., 29MAR2007). Missing portions of dates should be represented on subject listings as dashes (--MAR2007). Dates that are missing because they are not applicable for the subject should be listed as “N/A”, unless otherwise specified.

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

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

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

13 APPENDIX 1: PROTOCOL DEVIATIONS

The following are predefined protocol deviations:

Code	Description	Comment
A	**Entrance criteria not met**	
A1	Inclusion criteria not met	
A1.1	Male or Female, 18 to 70 years of age inclusive.	Inclusion criterion 1
A1.2	Weight at least 40 kg.	Inclusion criterion 2
A1.3	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	Inclusion criterion 6
A2	Important exclusion criteria met	
A2.1	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.	Exclusion criterion 1
A2.2	A history of nonepileptic or psychogenic seizures	Exclusion criterion 2
A2.3	Presence of only nonmotor simple partial seizures or primary generalized epilepsies).	Exclusion criterion 3
A2.4	Presence or previous history of Lennox-Gastaut syndrome.	Exclusion criterion 5
A2.5	Pregnancy or lactation	Exclusion criterion 6

A2.6	Any clinically significant laboratory abnormality that in the opinion of the Investigator would exclude the subject from the study	Exclusion criterion 8
A2.7	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	Exclusion criterion 9
A2.8	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	Exclusion criterion 10
A2.9	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	Exclusion criterion 12
A2.5	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	Exclusion criterion 13
A2.6	History of alcoholism, drug abuse, or drug addiction within the past 2 years	Exclusion criterion 14
A2.7	Current use of felbamate with less than 18 months of continuous exposure	Exclusion criterion 15
A2.8	Current use of diazepam, phenytoin, phenobarbital, or metabolites of these drugs (within 1 month of Visit 1)	Exclusion criterion 16
A2.9	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	Exclusion criterion 17
A2.10	History of status epilepticus within 3 months of Visit 1	Exclusion criterion 18
A2.11	History of 1 serious drug-induced hypersensitivity reaction (including but not limited to Stevens Johnson syndrome, toxic epidermal necrolysis, drug reaction	Exclusion criterion 19

	with eosinophilia and systemic symptoms) or any drug-related rash requiring hospitalization	
A2.12	Creatinine clearance less than 50 mL/min, as calculated by the Cockcroft-Gault equation	Exclusion criterion 21
A2.13	Absolute neutrophil count less than 1500/μL	Exclusion criterion 22
A2.14	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 (QTc_F less than 340 msec or greater than 450 msec in males and greater than 470 msec in females)	Exclusion criterion 23
A2.15	Platelet counts lower than 80,000/μL in subjects treated with VPA	Exclusion criterion 24
A2.16	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.	Exclusion criterion 25
A2.17	More than 1 lifetime suicide attempt	Exclusion criterion 26
A2.18	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	Exclusion criterion 28
A2.19	History of positive antibody/antigen test for hepatitis B, hepatitis C, or HIV	Exclusion criterion 29
A2.20	Presence of congenital short QT syndrome	Exclusion criterion 30
B	Informed consent	
B1	Informed consent not available	
B2	Informed consent signed and dated after first study related activity	
C	**Trial medication & randomization**	
C1	Incorrect medication dose taken	

C2	Randomization not followed	
C3	Non-compliance	e.g., compliance rate < 80%
D	**Concomitant medication**	
D1	Use of prohibited concomitant medications	

14 APPENDIX 2: VISIT WINDOWS

14.1 ECG

The following visit windows will be applied for reporting **ECG** results open-label extension results:

Analysis Timepoint	C017 OLE	
	Target Study Day [1]	Window [2] Study Days
Baseline	1	<= 1
Start of OLE [3] – Visit 9	127	>= 113 to <= 141
Visit 12	155	>=142 to <= 323
Visit 16	491	>=324 to <=659
Visit 20	827	>=660 to <= 995
Visit 24	1163	>=996 to <=1306
Visit 28	1499	>=1307 to <=1642
Visit 32	1835	>=1643 to <= 2003
Visit 36	2171	>= 2004 to <=2339
Visit 40	2507	>= 2340 to <= 2675
Visit 44 [4]	2843	>=2676

OLE=Open-label Extension

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

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

[3] This window should include the study day when the first dose of OLE study medication was given.

[4] Expected timepoint C017 OLE.

14.2 Clinical Laboratory Assessments

The following visit windows will be applied for reporting **clinical laboratory** open-label extension results:

Analysis Timepoint	C017 OLE	
	Target Study Day [1]	Window [2] Study Days
Baseline	1	<= 1
Start of OLE [3] – Visit 9	127	>= 113 to <= 141
Visit 12	155	>=142 to <= 239
Visit 14	323	>=240 to <=407
Visit 16	491	>=408 to <= 575
Visit 18	659	>=576 to <=743
Visit 20	827	>=744 to <=911
Visit 22	995	>=912 to <=1079
Visit 24	1163	>= 1080 to <=1247
Visit 26	1331	>= 1248 to <=1415
Visit 28	1499	>=1416 to <=1583
Visit 30	1667	>=1584 to <=1751
Visit 32	1835	>=1752 to <=1919
Visit 34	2003	>=1920 to <=2087
Visit 36	2171	>=2088 to <=2255
Visit 38	2339	>=2256 to <=2423
Visit 40	2507	>=2424 to <=2591

Visit 42	2675	>=2592 to <=2756
Visit 44 [4]	2843	>=2760

OLE=Open-label Extension

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

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

[3] This window should include the study day when the first dose of OLE study medication was given.

[4] Expected timepoint C017 OLE.

14.3 Vital Sign Assessments

The following visit windows will be applied for reporting **vital signs** open-label extension results:

Analysis Timepoint	C017 OLE	
	Target Study Day [1]	Window [2] Study Days
Baseline	1	<= 1
Start of OLE [3] – Visit 9	127	>= 120 to <=134
Visit 11	141	>=135 to <=148
Visit 12	155	>=149 to <=197
Visit 13	239	>=198 to <=281
Visit 14	323	>=282 to <=365
Visit 15	407	>=366 to <=449
Visit 16	491	>=450 to <=533
Visit 17	575	>=534 to <=617
Visit 18	659	>=618 to <=701
Visit 19	743	>=702 to <=785
Visit 20	827	>=786 to <=869
Visit 21	911	>=870 to <=953
Visit 22	995	>=954 to <=1037
Visit 23	1079	>=1038 to <=1121
Visit 24	1163	>=1122 to <=1205
Visit 25	1247	>=1206 to <=1289

Visit 26	1331	>=1290 to <=1373
Visit 27	1415	>=1374 to <=1457
Visit 28	1499	>=1458 to <=1541
Visit 29	1583	>=1542 to <=1625
Visit 30	1667	>=1626 to <=1709
Visit 31	1751	>=1710 to <=1793
Visit 32	1835	>=1794 to <=1877
Visit 33	1919	>=1878 to <=1961
Visit 34	2003	>=1962 to <=2045
Visit 35	2087	>=2046 to <=2129
Visit 36	2171	>=2130 ro <=2213
Visit 37	2255	>=2214 to <=2297
Visit 38	2339	>=2298 to <=2381
Visit 39	2423	>=2382 to <=2465
Visit 40	2507	>=2466 to <=2549
Visit 41	2591	>=2550 to <=2633
Visit 42	2675	>=2634 to <=2717
Visit 43	2759	>=2718 to <=2801
Visit 44 [4]	2843	>=2802

OLE=Open-label Extension

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

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

[3] This window should include the study day when the first dose of OLE study medication was given.

[4] Expected timepoint C017 OLE.

15 REFERENCES

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