STATISTICAL ANALYSIS PLAN

Study: EP0091

Product: Padsevonil (UCB0942)

ARISE: pAdsevonil in drug-ResIStant Epilepsy

A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, DOSE FINDING STUDY TO EVALUATE THE EFFICACY AND SAFETY OF PADSEVONIL AS ADJUNCTIVE TREATMENT OF FOCAL-ONSET SEIZURES IN ADULT SUBJECTS WITH DRUG-RESISTANT EPILEPSY

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Amendment 3	12 Feb 2020

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LIST OF ABBREVIATIONS

AE	adverse event
AED	antiepileptic drug
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANCOVA	analysis of variance
AST	aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
bid	twice daily
BRV	brivaracetam
CI	confidence interval
CIWA-B	Clinical Institute Withdrawal Assessment-Benzodiazepines
CSR	Clinical Study Report
C-SSRS	Columbia-Suicide Severity Rating Scale
DBP	diastolic blood pressure
DMC	Data Monitoring Committee
DNA	deoxyribonucleic acid
ECG	electrocardiogram
EEG	electroencephalogram
eCRF	electronic Case Report form
EDV	Early Discontinuation Visit
EMA	European Medicines Agency
ES	Enrolled Set
FAS	Full Analysis Set
FDA	Food and Drug Administration
HADS	Hospital Anxiety and Depression Scale
HRU	healthcare resource utilization
ICF	Informed Consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ILAE	International League Against Epilepsy
IMP	investigational medicinal product
IRT	interactive response technology
LEV	levetiracetam

LOCF	Last observation carried forward
IPD	Important protocol deviation
LS	least squares
MedDRA®	Medical Dictionary for Regulatory Activities®
MMRM	Mixed Model Repeated Measures
MRI	magnetic resonance imaging
NRI	non-responder imputation
OLE	open-label extension
PDILI	potential drug-induced liver injury
PK	pharmacokinetic
PK-PPS	Pharmacokinetic Per-Protocol Set
PMDA	Pharmaceuticals and Medical Devices Agency
PPS	Per-Protocol Set
PSL	Padsevonil
PT	Preferred Term
QOLIE-31-P	Quality of Life Inventory in Epilepsy-31-P
QTcB	QT interval corrected for heart rate using Bazett's formula
QTcF	QT interval corrected for heart rate using Fridericia's formula
RS	Randomized Set
RNA	ribonucleic acid
RS	Randomized Set
SAE	serious adverse event
SAP	Statistical Analysis Plan
SBP	systolic blood pressure
SD	standard deviation
SFU	Safety Follow Up
SOC	System Organ Class
SOP	Standard Operating Procedure
SSG	Seizure Severity Global Item
SS	Safety Set
SV2A	synaptic vesicle 2A
TEAE	treatment-emergent adverse event
ULN	upper limit of normal
VAMS	volumetric absorptive microsampling

VNS	vagus nerve stimulation
WHO	World Health Organization
WHO DD	World Health Organization Drug Dictionary

1 INTRODUCTION

This statistical analysis plan (SAP) defines the scope of statistical analyses and provides a detailed description of statistical methodology for the statistical analyses to support the final clinical study report (CSR). The SAP is based on the following study document: Protocol EP0091 Amendment 2, 12 October 2018. All references to study protocol hereafter refer to this version of the protocol. Unless otherwise specified, the study will be analyzed as described in the most recent version of the protocol (EudraCT-Number: 2017-003200-48; IND number 135622). If a future protocol amendment necessitates a substantial change to the statistical analysis of the study data, or if analysis definitions must be modified or updated, this SAP will be amended accordingly. The content of this SAP is compatible with the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH)/Food and Drug Administration (FDA) E9 Guidance documents (ICH E9, 1998).

2 PROTOCOL SUMMARY

2.1 Study objective(s)

2.1.1 Primary objective(s)

The primary objectives of this study are to characterize the dose-response relationship with respect to efficacy of padsevonil (PSL) administered concomitantly with up to 3 antiepileptic drugs (AEDs) for treatment of observable focal-onset seizures in subjects with drug-resistant epilepsy and to evaluate the efficacy of the 4 selected dose regimens of PSL compared with placebo.

2.1.2 Secondary objective(s)

The secondary objective of the study is to assess the safety and tolerability of all doses of PSL in relation to placebo.

2.1.3 Other Objectives

2.1.3.1 Other Efficacy Objectives

The other efficacy objective is to:

- Assess the healthcare resource utilization (HRU) and quality of life.

2.1.3.2 Pharmacokinetic Objectives

The pharmacokinetic (PK) objectives are to:

- Evaluate the steady-state PK profiles of PSL and the exposure-response relationship
- Evaluate the impact of enzyme-inducing concomitant AEDs on PSL exposure
- Evaluate concomitant AED (and/or relevant metabolites) plasma concentrations

2.1.3.3 Exploratory nonhereditary pharmacogenomics and pharmacogenetic objectives

The other nonhereditary pharmacogenomics and pharmacogenetics objectives are to:

- Identify genetic polymorphisms, gene expression patterns, plasma proteins, plasma metabolites, plasma lipids, or other plasma and serum substances that predict or are associated with disease etiology, drug response, or tolerability.

2.2 Study variables

2.3 Efficacy variables

Seizure frequency refers to 28-day adjusted frequency. Observable focal-onset seizures refer to Type IA1, IB, and IC (ILAE Classification of Epileptic Seizures, 1981). Focal-onset seizures include all Type I seizures.

Seizure-free status and seizure-free days include all (Types I, II, and III) seizure types.

2.3.1 Primary efficacy variable

2.3.1.1 Primary efficacy variable for the US FDA, PMDA, and other regulatory authorities not specified in Section 4.1.1.2

The primary efficacy variable is the change in log-transformed observable focal-onset seizure frequency from Baseline, over the 12-week Maintenance Period.

2.3.1.2 Primary efficacy variable for EMA and regulatory authorities who reference EMA

The primary efficacy variable is the 75% responder rate, where a responder is a subject experiencing a ≥75% reduction in observable focal-onset seizure frequency from Baseline, over the 12-week Maintenance Period.

2.3.2 Secondary efficacy variables

2.3.2.1 Secondary efficacy variables for the US FDA, PMDA, and other regulatory authorities not specified in Section 4.1.1.2

The secondary efficacy variables are as follows:

- The 75% responder rate, where a responder is a subject experiencing a ≥75% reduction in observable focal-onset seizure frequency from Baseline, over the 12-week Maintenance Period
- The 50% responder rate, where a responder is a subject experiencing a ≥50% reduction in observable focal-onset seizure frequency from Baseline, over the 12-week Maintenance Period
- Percent reduction in observable focal-onset seizure frequency from Baseline, over the 12-week Maintenance Period

2.3.2.2 Secondary efficacy variables for EMA and regulatory authorities who reference EMA

The secondary efficacy variables are as follows:

- The change in log-transformed observable focal-onset seizure frequency from Baseline, over the 12-week Maintenance Period

- The 50% responder rate, where a responder is a subject experiencing a ≥50% reduction in observable focal-onset seizure frequency from Baseline, over the 12-week Maintenance Period
- Percent reduction in observable focal-onset seizure frequency from Baseline, over the 12-week Maintenance Period

2.3.3 Other efficacy variables (This list applies for all regulatory authorities)

The other efficacy variables are as follows:

- Change from Baseline in log-transformed observable focal-onset seizure frequency over the first 4 weeks, second 4 weeks, and third 4 weeks of the 12-week Maintenance Period
- Change from Baseline in log-transformed observable focal-onset seizure frequency over the 16-week Treatment Period
- The 50% responder rate, where a responder is a subject experiencing a ≥50% reduction in observable focal-onset seizure frequency from Baseline, over the 16-week Treatment Period
- The 75% responder rate, where a responder is a subject experiencing a ≥75% reduction in observable focal-onset seizure frequency from Baseline, over the 16-week Treatment Period
- The 90% responder rate, where a responder is a subject experiencing a ≥90% reduction in observable focal-onset seizure frequency from Baseline, over the 12-week Maintenance Period
- Percent reduction in observable focal-onset seizure frequency from Baseline, over the 16-week Treatment Period
- Change from Baseline in log-transformed focal-onset (Type I) seizure frequency over the 12-week Maintenance Period
- The 50% responder rate, where a responder is a subject experiencing a ≥50% reduction in focal-onset (Type I) seizure frequency from Baseline, over the 12-week Maintenance Period
- The 75% responder rate, where a responder is a subject experiencing as a ≥75% reduction in focal-onset (Type I) seizure frequency from Baseline, over the 12-week Maintenance Period
- The 90% responder rate, where a responder is a subject experiencing a ≥90% reduction in focal-onset (Type I) seizure frequency from Baseline, over the 12-week Maintenance Period
- Percent reduction in focal-onset (Type I) seizure frequency from Baseline, over the 12-week Maintenance Period and the 16-week Treatment Period
- Seizure-freedom status (yes/no) during the 12-week Maintenance and the 16-week Treatment Period
- Percentage of seizure-free days during the 12-week Maintenance Period and the 16-week Treatment Period
- Cumulative responder rate during the 16-week Treatment Period

- Change in the Seizure Severity Global Item (SSG) scores from Baseline to Week 4 during the Maintenance Period (Visit 4) and the end of the 16-week Treatment Period (Visit 7)
- Change in Quality of Life Inventory in Epilepsy-31-P (QOLIE-31-P) scores from Baseline to Week 4 during the Maintenance Period (Visit 4) and the end of the 16-week Treatment Period (Visit 7)
- Change in HADS scores from Baseline to Week 4 during the Maintenance Period (Visit 4) and to the end of the 16-week Treatment Period (Visit 7)
- Time to return to baseline 28-day observable focal-onset seizure count during the 12-week Maintenance Period
- Use of health-related outcomes and HRU, including healthcare provider consultations not foreseen by protocol, caregiver support, concurrent medical procedures, concomitant medications and hospitalizations

2.4 Safety variables

2.4.1 Primary safety variables

The safety variables are as follows:

- Incidence of TEAEs reported by the subject and/or caregiver or observed by the Investigator during the entire study
- Incidence of TEAEs leading to study withdrawal
- Incidence of treatment-emergent serious adverse events (SAEs) during the entire study

2.4.2 Other safety variables

Other safety variables are as follows:

- Incidence of TEAEs reported by the subject and/or caregiver or observed by the Investigator during the following periods: 16-week Treatment Period, 12-week Maintenance Period, 4-week Titration/Stabilization Period, and 3-week Taper Period
- Number of and reason for subjects requiring premature tapering due to TEAEs
- Number of and reason for subjects requiring a dose reduction during the Stabilization Period due to TEAEs
- Incidence of treatment-emergent SAEs during the following periods: 16-week Treatment Period, 12-week Maintenance Period, 4-week Titration/Stabilization Period
- Changes in clinical laboratory test parameters (including hematology, blood chemistry, and urinalysis)
- Changes in vital sign parameters (including pulse rate, systolic BP, diastolic BP, and respiratory rate)
- Changes in 12-lead ECG parameters
- Physical examination (including body weight) and neurological examination findings

- Changes in Psychiatric and Mental Status
- Occurrence of valvular abnormalities or pericardial effusion changes or other significant abnormalities as identified by 2-dimensional Doppler echocardiogram at each assessment by central reader
- Changes in withdrawal symptoms using Clinical Institute Withdrawal Assessment-Benzodiazepines (CIWA-B) from the End of Treatment Visit (Visit 7) to end of the Taper Period (Visit 8) and end of the SFU Period (Visit 9 [30 days after the last IMP intake]).

2.5 Other variables

2.5.1 Pharmacokinetic variables

Blood concentrations of PSL and metabolites will be determined from samples obtained in the study during the Titration and Maintenance Periods in order to investigate the following variables:

- The population PK profiles of PSL and active metabolite
- The exposure-response relationship for PSL and active metabolite

Blood concentrations of PSL and active [redacted] will be used to derive PK-population parameters (using population-PK analysis). Subjects will be asked to provide these samples whenever possible.

Blood concentrations of concomitantly administered AEDs will also be evaluated for evidence of drug-drug interaction with PSL at steady state.

2.5.2 Exploratory nonhereditary pharmacogenomics variables

Where local regulations permit, blood samples will be collected at time points specified in Table 2-1 and stored for up to 20 years to allow for potential exploratory analyses of RNA, proteins, lipids, and metabolites biomarkers. Candidate serum biomarkers may also be explored.

These samples will be used to support biomarker strategies related to epilepsy and drug response (including safety, efficacy, and tolerability of PSL and concomitant therapies).

2.5.3 Exploratory pharmacogenetic variables

Additional blood samples will be collected at specific time points (Table 2-1) from subjects who consent to participate in the pharmacogenetic substudy to measure DNA biomarkers in order to assess:

- Pharmacogenetic variants associated with drug-resistant epilepsy or AED resistance and drug response

The samples may be used for further genetic analyses to understand drug-resistant epilepsy, AED resistance, and PK. The samples will be stored up to 20 years for the research purposes stated in this protocol.

2.5.4 Exploratory pharmacokinetic evaluation

Comparison will be made of blood concentration data of PSL and [redacted] derived from either conventional venous sampling or from the volumetric absorptive microsampling (VAMS) MITRA® technology.

- Additionally, evaluation of PSL and major metabolites in plasma will be undertaken from trough samples. The collection of plasma samples for this comparison may cease during the course of the study based on periodic review of the data.

2.6 Study Design and Conduct

2.6.1 Study description

EP0091 is a multicenter, randomized, double-blind, placebo-controlled, parallel-group dose-finding study in adults (≥18 years of age) with drug-resistant epilepsy who continue to have uncontrolled focal-onset seizures despite treatment with at least 4 tolerated, appropriately chosen and used prior AEDs, including current AEDs (Kwan et al, 2010). All eligible subjects will have an epilepsy diagnosis and at least 4 observable focal-onset seizures per 28 days despite treatment with at least 1 to 3 AEDs with or without neurostimulation devices.

Subjects should be educated to complete their diary entries accurately as per instruction.

The study is composed of 4 periods (see Figure 2–1) for a schematic diagram):

Baseline Period (4 weeks)

During the Screening Visit (Visit 1, Week -4), subjects will sign a written Informed Consent form (ICF) prior to the conduct of any study-related procedure or pre-treatment assessments, and the subject's eligibility will be determined on the basis of the inclusion/exclusion criteria. Subject eligibility related to seizure frequency will be evaluated based on Investigator assessment of the subject report on historical seizure count during the 8 weeks prior to the Screening Visit (Visit 1) for the retrospective seizure baseline. Eligible subjects will be given a diary and receive instructions to further document seizures during the 4-week Baseline Period for a prospective seizure baseline. All subjects must have been on a stable dose of their present AEDs during the 8-week period prior to the Screening Visit (Visit 1). For the neurostimulation device (if applicable), the settings should be stable for 12 weeks prior to Screening Visit (Visit 1). Both should be stable throughout the study until the end of Treatment Period. The Investigator will be asked to send documentation of video-electroencephalogram (EEG) report as per instruction to the UCB Study Physician or representative for confirmation of eligibility before randomization of the subject.

Treatment Period (16 weeks)

The 16-week Treatment Period includes a 3-week Titration Period followed by a 1-week Stabilization Period and a 12-week Maintenance Period. Four weeks after the Screening Visit (Visit 1), subjects will return to the clinic for the Baseline Visit (Visit 2, Day 1). Subjects who continue to fulfill the inclusion and exclusion criteria will be randomized to 1 of the 5 treatment arms in a 1:1:1:1:1 ratio (random permuted blocks) to ensure the balance to 1 of the 5 treatment arms. Randomization will be stratified by current use of AEDs with binding to SV2A proteins

(LEV or brivaracetam) (Yes or No) and by region (North America, Europe, and Asia) at the time of randomization.

After the Baseline Visit (Visit 2), subjects will return to the clinic for regular visits for the remainder of the Titration Phase. Investigational medicinal product will be increased approximately every 3 to 7 days depending on treatment arms. Subjects will be instructed to take the IMP in 2 equally divided doses, approximately 12 hours apart in the morning and evening.

During the entire 16-week Treatment Period, the dose of concomitant AEDs and the settings for neurostimulation devices must remain stable. The dose of IMP should remain stable during the Maintenance Period.

Subjects who cannot tolerate IMP prior to Week 3 will be withdrawn from the study. For subjects with tolerability issues experienced at their target dose, one fallback option to a predefined dose based on the randomized dose will be allowed during the Stabilization Period and at least 2 days prior to start of maintenance (Visit 4). The Study Physician or delegate should be consulted prior to use of the fallback option and the date as well as the reason for fallback will be recorded in the source documents and in the electronic Case Report form (eCRF).

Fallback may be managed via an unscheduled visit. Fallback IMP packs will be allocated via the Interactive Response Technology (IRT). After fallback, the dose will be kept stable for the rest of the Maintenance Period. Further dose changes (ie, titration) are not allowed. Subjects, who are not able to tolerate the IMP during titration and after the fallback, will be tapered off IMP in a blinded fashion and will be withdrawn from the study.

At Visit 4 (at the end of the Stabilization Period), subjects will enter a 12-week Maintenance Period during which they will receive their target dose (or their fallback dose, if applicable). During the entire 12-week Maintenance Period, the dose of IMP (target dose or fallback dose) and concomitant AEDs must remain stable. Subjects must return to the clinic for scheduled visits as outlined in Table 2-1.

Subjects who complete the Maintenance Period will return for an End of Treatment Visit. Subjects who discontinue early from the study will return for an Early Discontinuation Visit (EDV). Subjects completing the Maintenance Period will have the opportunity to enroll into the OLE study, EP0093. They will be converted to the entry dose of the EP0093 study, 400mg/day. Subjects withdrawing from the study or deciding not to participate in the OLE study (EP0093) will be progressively tapered off the IMP.

For subjects discontinuing the study:

Taper Period (4 weeks)

The 4-week Taper Period will be required for subjects who choose not to enroll in the OLE study or who discontinue prior to the end of the Maintenance Period. Subjects participating in the 4-week Taper Period should be gradually tapered off the IMP over a 3-week period followed by 1-week drug-free period. A faster or slower taper schedule than the suggested 3 weeks may be implemented, if medically necessary, as per the Investigator's medical judgement. Subjects will start their taper at the EDV/End-of-Treatment (Visit 7) and will return 1 week after last intake of IMP for the End-of-Taper Visit at Visit 8. Changes to concomitant AED(s) are not allowed

during the taper of PSL unless they are medically necessary as per the Investigator's medical judgement to treat rebound seizures.

Safety Follow-Up Period

Safety follow up for subjects not entering the OLE will consist of 1 required visit, 30 days after the last IMP intake (Week 23 or sooner in case of early discontinuation) including an echocardiogram. An additional follow-up echocardiogram will be performed at 6 months (±1 month) after the last IMP intake only for subjects exposed to IMP for more than 3 weeks.

For subjects continuing to the OLE study:

Conversion Period (3 weeks)

The 3-week Conversion Period will be required for subjects who choose to enroll in the OLE study at the end of the Maintenance Period. Doses for subjects participating in the 3-week Conversion Period will be gradually adapted (increased or decreased) in a blinded way to reach the entry dose for the OLE. Subjects who took placebo during the maintenance phase will progressively receive PSL.

2.6.2 Study duration per subject

The total duration of study per subject will be up to 27 weeks with a maximum of 19 weeks exposure to PSL. An additional follow-up echocardiogram will be performed at 6 months (±1 month) after the last IMP intake only for subjects exposed to IMP for more than 3 weeks and either discontinuing the study or not entering the OLE.

The end of the study is defined as the date of the last SFU Visit (30-days after the last IMP intake) of the last subject in the study. Additionally, the reporting of SAEs will continue until the 6-month follow-up echocardiogram.

2.6.3 Treatments to be administered

All IMP will be administered in a double-blind manner.

All subjects will be instructed to take 5 or 6 tablets containing either PSL or placebo bid, approximately 12h apart. The IMP should be dosed within 30 minutes after food when practically feasible.

Subjects will be allocated to 1 of the following 5 treatment arms using the IRT system at the Randomization Visit (Visit 2):

- Padsevonil 100mg/day (or 50mg bid)
- Padsevonil 200mg/day (or 100mg bid)
- Padsevonil 400mg/day (or 200mg bid)
- Padsevonil 800mg/day (or 400mg bid)
- Placebo

Table 2-1: Schedule of assessments

		BL Period (4 Wk)	Treatment Period (16 Wk ±1 week from Visit 2)								Taper/Conversion Period (3 to 4 Wk ±1 week) [a]		SFU (30 days after IMP intake)	
			Titration Period (3 Wk ±1 week) (±3 days per week)			Stab (1 Wk ±3 days)	Maintenance Period (12 Wk ±1 week) (±3 days per week)							
	Visits	V1	V2 BL	TC	V3	TC	V4	V5	V6	V7 (EDV/EOT)	TC	V8	V9	Unsch Visit [b]
Assessments	Start of Week x	Wk -4	D 1	Wk 1	Wk 2	Wk 3	Wk 4	Wk 8	Wk 12	Wk 16		Wk 19/20	Wk 23	
Written informed consent		X												
Call IRT to obtain subject number and dispensation of Subject Trial Card		X												
Demographic data		X												
Verification of inclusion/exclusion criteria		X	X											
Verification of withdrawal criteria			X	X	X		X	X	X	X				
General medical/procedures history		X												
Epilepsy history including etiology, diagnosis, surgery, and seizure history		X												
Documentation of MRI (within 10 years)		X												
Documentation of video-EEG		X												
AED history		X												
Habits and lifestyle		X												
Randomization (IRT)			X											
C-SSRS Baseline [c]		X												

Table 2-1: Schedule of assessments

		BL Period (4 Wk)	Treatment Period (16 Wk ±1 week from Visit 2)								Taper/Conversion Period (3 to 4 Wk ±1 week) [a]		SFU (30 days after IMP intake)	
			Titration Period (3 Wk ±1 week) (±3 days per week)			Stab (1 Wk ±3 days)	Maintenance Period (12 Wk ±1 week) (±3 days per week)							
	Visits	V1	V2 BL	TC	V3	TC	V4	V5	V6	V7 (EDV/EOT)	TC	V8	V9	Unsch Visit [b]
Assessments	Start of Week x	Wk -4	D 1	Wk 1	Wk 2	Wk 3	Wk 4	Wk 8	Wk 12	Wk 16		Wk 19/20	Wk 23	
C-SSRS since last visit [c d]			X		X		X	X	X	X		X	X	
HADS [c]			X				X			X			X	
SSG [c]			X				X			X			X	
QOLIE-31-P [c]			X				X			X			X	
CIWA-B [c]										X		X	X	
Vital signs [e]		X	X		X		X	X	X	X		X	X	
Body weight and height [f]		X	X				X	X	X	X		X	X	
Physical examination [g] (XF = Full – XB = Brief)		XF	XB				XB			XF		XF	XB	
Neurological examination [h] (XF = Full – XB = Brief)		XF	XB				XB			XF		XF	XB	
Psychiatric and Mental Status			X		X		X	X	X	X		X	X	
12-lead ECG [i]		X	X		X		X	X		X		X	X	
Echocardiogram [j]		X							X				X [k]	
Blood/urine sample for clinical laboratory analyses		X	X				X		X	X		X	X	
Blood sample for concomitant AED assay [lm]		X	X						X	X				
Blood sample for PSL PK analysis [nm]					X		X	X	X	X				

Table 2-1: Schedule of assessments

		BL Period (4 Wk)	Treatment Period (16 Wk ±1 week from Visit 2)								Taper/Conversion Period (3 to 4 Wk ±1 week) [a]		SFU (30 days after IMP intake)	
			Titration Period (3 Wk ±1 week) (±3 days per week)			Stab (1 Wk ±3 days)	Maintenance Period (12 Wk ±1 week) (±3 days per week)							
	Visits	V1	V2 BL	TC	V3	TC	V4	V5	V6	V7 (EDV/EOT)	TC	V8	V9	Unsch Visit [b]
Assessments	Start of Week x	Wk -4	D 1	Wk 1	Wk 2	Wk 3	Wk 4	Wk 8	Wk 12	Wk 16		Wk 19/20	Wk 23	
Blood sample for DNA			X											
Blood sample for RNA			X				X			X				
Blood sample for proteins/lipids/metabolites			X				X			X				
Pregnancy test [o]		X	X		X		X	X	X	X		X	X	
Seizure evaluation (count & type) [p]			X	X	X	X	X	X	X	X	X	X	X	
Concomitant medications (AEDs and non-AEDs) and procedures		X	X	X	X	X	X	X	X	X	X	X	X	
Recording of adverse events		X	X	X	X	X	X	X	X	X	X	X	X	
Health-related outcomes and HRU		X	X		X		X	X	X	X		X	X	
IMP dispensing (IRT)			X		X		X	X	X	X				
IMP accountability and return [q]					X		X	X	X	X		X		
Entry and exit personal outcome interview [r]		X							X					
Study termination												X	X [s]	

AED=antiepileptic drug; BL=Baseline; BP=blood pressure; CIWA-B=Clinical Institute Withdrawal Assessment-Benzodiazepines; C-SSRS=Columbia-Suicide Severity Rating Scale; DNA=deoxyribonucleic acid; ECG=electrocardiogram; EDV=Early discontinuation Visit; EEG=electroencephalogram; ; HADS=Hospital Anxiety and Depression Scale; HRU=healthcare resource utilization; IMP=investigative medicinal product; IRT=interactive response technology; MRI=magnetic resonance imaging; OLE=open-label extension; PK=pharmacokinetic; PSL=padsevonil; QOLIE-31-P=Quality of Life Inventory in Epilepsy-31-P; RNA= ribonucleic acid; SFU=Safety Follow-Up; SSG=Seizure Severity Global Item; Stab=Stabilization Period; TC=telephone call; Unsch=unscheduled; V=visit; Wk=Week

[a] Taper Period, for subjects who choose to not enter OLE study EP0093, will last for 3 weeks plus 1 week of drug-free period. Conversion Period, for subjects who choose to enter OLE study EP0093, will last for 3 weeks.
[b] At any time, the subject may have an additional study visit if the Investigator or the subject and/or legal representative deem it necessary. Appropriate assessments will be conducted in relation to the reason for the visit.
[c] Questionnaires to be completed by all subjects prior to any other study procedures at the visit, when possible.
[d] If an unscheduled visit is conducted due to safety or efficacy reasons, a C-SSRS assessment will be performed with the subject during the visit. If an unscheduled visit is conducted for reasons other than safety or efficacy concerns (eg, replacement of lost medication, repeated collection of a laboratory specimen due to collection, or analysis issues), a C-SSRS will not be required at these visits.
[e] Vital signs measured in supine position after 5 minutes of rest include pulse rate, respiratory rate, systolic BP, and diastolic BP.
[f] Height will only be measured at Visit 1.
[g] Full physical examinations will assess cardiac and respiratory function via auscultation and review of the following body systems: general appearance; ear, nose, and throat; eyes; hair and skin; respiratory; cardiovascular; gastrointestinal; musculoskeletal; hepatic; neurological; and mental status. Brief physical examinations will include a review of the following body systems: general appearance (including mental status); skin; respiratory; cardiovascular; gastrointestinal; and hepatic.
[h] Brief neurological examination will include a general assessment and evaluation of reflexes, muscle strength and coordination, and cerebellar function. Full neurological examinations will include in addition, evaluation of cranial nerves, motor system (general muscle strength and tone), sensations in upper/lower extremities.
[i] Baseline ECG has to be scheduled and results received before Visit 2. An ECG at the SFU Visit will be performed only if abnormal at end of treatment or premature discontinuation visit. All ECG recordings will be performed with the subject resting in the supine position for at least 5 minutes.
[j] The echocardiogram will be conducted at Visit 1. Echocardiograms will be repeated at Visit 6 for subjects continuing the OLE study. Subjects discontinuing will have an echocardiogram 30 days after last IMP intake at the SFU Visit (except if performed at Visit 6). A repeat echocardiogram will be performed for subjects with a new finding, Grade 2 (moderate severity), or Grade 3 (severe severity).
[k] An echocardiogram will also be performed 6 months after last IMP intake for subjects exposed to >3 weeks to IMP and discontinuing the study (but not for subjects with <3 weeks exposure).
[l] AED samples will ideally be taken immediately prior to dose of concomitant medication on each occasion. If this is not possible, then the sample may be taken at any time after dose and the timing of sample in relation to dose should be kept the same (±1 hour) on each occasion for each subject. Therefore, the timing of visits for each subject when AED samples are collected should be scheduled approximately at the same time whenever possible. Assay of parent PSL and metabolites may be included in the AED panel of tests at Visits 6 and 7.
[m] On Visits 6 and 7, unless the concomitant AED sample is within ±5 minutes of a scheduled MITRA sample for PSL assay, a separate, additional MITRA sample will be taken at same time as the concomitant AED blood sample.
[n] Subjects are requested to provide blood samples for measurement of PSL and metabolites whenever possible. On Visits 3, 5, and 6, site personnel should obtain blood samples for measurement of random PSL concentrations at any time between IMP intake and record accurately the time of last IMP intake and the time of sample collection. On Visits 4 and 7, blood samples for measurement of sparse PK profiles will be collected as follows: immediately before IMP intake

(maximum 15 minutes before intake) and then 3 times after (between 30 minutes and 3 hours after IMP intake), taken at least 30 minutes apart. All samples may be taken either at home or in the site or partly at home and partly at the site.

[o] For all female subjects, serum pregnancy test at Visits 1 and 7 (in case the subject enters into the OLE study) and where applicable. Urine pregnancy test will be used at other visits for female subjects of childbearing potential.

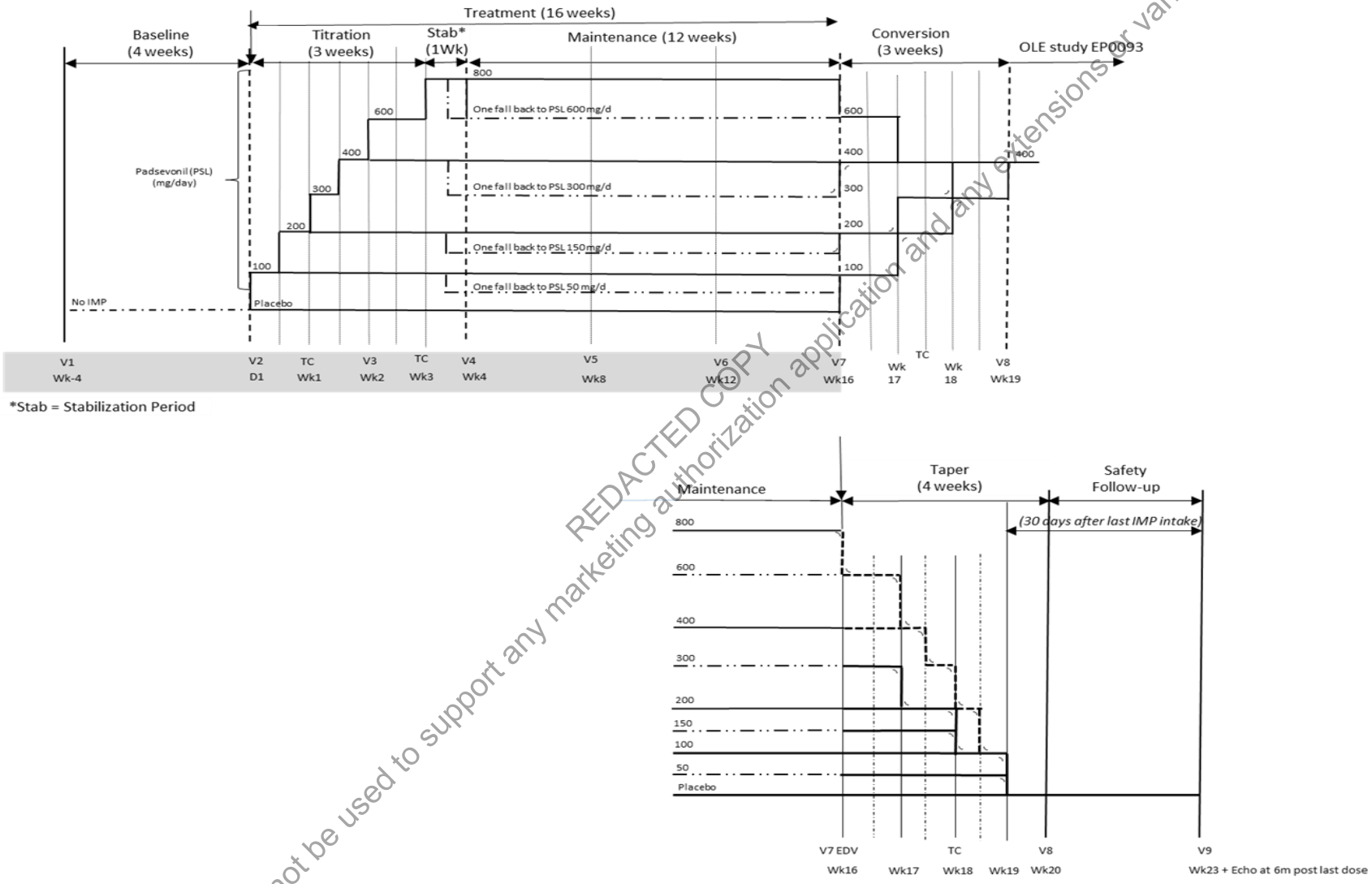
[p] Seizure counts are collected on the subject's daily record card on a daily basis.

[q] At each visit following an IMP dispensation, IMP should be presented to check for compliance.

[r] Subject entry interview will be performed on a voluntary basis either at Visit 1 or Visit 2. Subject/caregiver exit interview/survey will be performed on a voluntary basis either at Visit 6 or Visit 7.

[s] The SFU Visit will be performed only for subjects who do not enter EP0093.

Figure 2–1: Study design



2.7 Determination of sample size

The sample size was calculated based on achieving 90% power to observe a statistically significant result for either the 400mg bid and 200mg bid or 200mg bid and 100mg bid doses when compared to placebo, for a change from Baseline of the log-transformed (ln x +1) 28-day adjusted seizure frequency. Multiplicity is controlled for using the Hochberg step up procedure.

The log-reduction from Baseline in seizure frequency was assumed to be 0.195 for placebo and 0.492, 0.670, 0.754, and 0.780 for the 50mg bid, 100mg bid, 200mg bid, and 400mg bid doses of PSL, respectively. A common SD of 0.985 was assumed. These estimates are based on prior experience in epilepsy together with the EP0069 study results.

With power of 90%, a 2-sided Type-1 error of 5%, and all dose groups of the same size, 80 subjects are required per arm, giving a total of 400 subjects.

Assuming a screening failure rate of approximately 20%, it is anticipated to enroll around 500 subjects and randomize 400 subjects in this study.

The study is also powered to give over 80% power to observe a statistically significant result for the 75% response rate. For the 75% responder rate, assumptions were a 0.121 responder rate for placebo and corresponding responder rates of 0.233, 0.301, 0.332, and 0.342 for the 50mg bid, 100mg bid, 200mg bid, and 400mg bid doses of PSL, respectively.

3 DATA ANALYSIS CONSIDERATIONS

3.1 General presentation of summaries and analyses

Statistical analysis and generation of tables, figures, subject data listings, and statistical output will be performed using SAS Version 9.3 or higher. All tables and listings will use Courier New font size 9.

Descriptive statistics will be displayed to provide an overview of the study results. For categorical variables, the number and percentage of subjects in each category will be presented. Unless otherwise noted, all percentages will be displayed to 1 decimal place. No percentage will be displayed for zero counts, and no decimal will be presented when the percentage is 100%. For continuous variables, descriptive statistics will include number of subjects with available measurements (n), mean, SD, median, minimum, and maximum.

Decimal places for descriptive statistics will always apply the following rules:

- "n" will be an integer
- Mean, SD, and median will use one additional decimal place compared to the original data
- Minimum and maximum will have the same number of decimal places as the original value.

Unless otherwise specified, statistical tests of efficacy variables will be presented as two-sided p values rounded to three decimal places. P-values less than 0.001 will be presented as "<0.001" and p-values greater than 0.999 will be presented as ">0.999." Statistical comparisons will be two-sided and will be performed at the 0.05 level of significance.

A complete set of data listings containing all documented data as well as calculated data (e.g., change from Baseline), as applicable, will be generated.

Treatment groups will be displayed as: Placebo, PSL 50 mg bid, PSL 100mg bid, PSL 200mg bid, and PSL 400mg bid.

Log-transformation is based on natural logarithm. For analyses on log-transformed values, model estimates will be back-transformed to anti-log space for table presentation. See Section 8.1.1 for details.

Data collected at scheduled visits will be included the by-visit summary. Data collected at unscheduled visits will not be included in the by-visit summary, but will be considered when determining the Last Visit, minimum, and maximum post-Baseline values during the Treatment Period. Data collected on Visit 8 will be summarized separately for subjects in the Conversion Period versus the Taper and Safety FU Period.

In general, all CRF data will be presented in the subject listings.

3.2 General study level definitions

3.2.1 Initial processing of diary data for seizure frequency

Subjects are instructed to record in their diary all types of seizures that occur, after each seizure or at least once a day. The investigator will assess and confirm the seizures according to the ILAE codes (ILAE Classification of Epileptic Seizures, 1981) and record the seizure types and frequency in the eCRF/diary. With regard to cluster seizures, investigators are to report the number of cluster episodes rather than reporting the estimated number of individual seizures.

3.2.2 Analysis time points

3.2.2.1 Relative day

Study day for each subject is calculated relative to the date of the first administration of study drug. The date format in the study is dd-MMM-yyyy. Relative day is calculated as the current date in the study minus the date of first dose of study drug for days prior to the first dose of study drug, and the current date minus the date of first dose of study drug plus 1 for days on or after the day of first dose of study drug and prior to or on the day of last study drug dose (e.g., the day of first dose will be Day 1 and the day prior to first dose will be Day -1). For days after the last dose of study drug, relative day will be calculated as the current date minus the date of last dose of study drug and including a "+" to denote posttreatment days (e.g., the day after the last dose will be Day +1).

Similarly, relative days for an event or measurement occurring before a reference date (generally the date of the first dose of study drug) are calculated as follows:

- Relative Day = (Event Date-Reference Date)

Relative days for an event or measurement occurring on or after the reference date to the last day of dose administration are calculated as follows:

- Relative Day = (Event Date-Reference Date) + 1

For events or measurements occurring after the date of last dose of study drug (as defined above), the relative day will be calculated with the date of last dose administration as reference. Relative day in this case will be prefixed with '+' in the data listings and will be calculated as follows:

- Relative Day = + (Event Date-Reference Date)

3.2.2.2 End of the 16-week treatment period

The end of the 16-week overall treatment period will be either the date of Visit 7 for subjects completing the Treatment Period, or the date of the early discontinuation visit (EDV), for subjects who discontinued during the Treatment Period. If a subject does not have a Visit 7/EDV, then the date of the final contact will define the end date of the Treatment Period.

3.2.3 Analysis periods

The start and end dates of each analysis period (following the study design) are used for the classification of efficacy and safety data. The exact start and end of each of these periods is described for calculation purposes in Table 3–1. Note that measurements obtained from diaries returned on the start date of the Titration and Stabilization Period would be included in the Baseline Period calculations. Refer to Section 3.3.1. Similarly, measurements from diaries returned on the start date of a subsequent period would be included in calculations for the previous period.

Table 3–1: Start and end of EP0091 analysis periods

Analysis Period			Details
Description	**Start**	**End**	
Baseline (Week -4)	Date of informed consent at Visit 1	Date of the day before the date of Visit 2.	This is an approximate 28-day period for calculation of Baseline seizure frequencies. Study drug is dispensed, and first dose is generally taken the day of the Baseline Visit (Visit 2, Day 1). Note the pre-dose assessments will also be included in the Baseline Period.
Titration and Stabilization*	The date of the Baseline Visit, (Visit 2, Day 1).	The date of the day before Visit 4 or the end of the treatment period if the subject has discontinued prior to Visit 4.	For evaluation purposes, if results are presented by analysis period, the Titration and the Stabilization interval will be considered together (approximately 4 weeks in total). Titration is a period of dose increases to reach the protocol specified dose. Stabilization is an approximate week-long interval to stabilize at the target dose level. During stabilization the dose may be adjusted once (i.e. to a fallback dose).
Maintenance*	The date of Visit 4.	The date of Visit 7 or the end of the treatment period if the subject has discontinued prior to Visit 7.	This is a 12-week period where the subject remains on the randomized target dose (or fallback dose, if applicable).
16-week Treatment Period*	The date of the Baseline visit (Visit 2)	The date of Visit 7 or the end of the treatment period if the subject has discontinued prior to Visit 7.	Titration and Stabilization Period and Maintenance Period combined.
Conversion	The date of the day after Visit 7	The date of Visit 8.	This is a 3-week period of dose conversion to enable the subjects to enroll into the OLE study EP0093.
Taper and Safety Follow-up	The date of the day after Visit 7/EDV or the date of day after Visit 8 if the subject tapered after conversion	The date of final contact.	Subjects who withdraw from the study or decide not to participate in the OLE study will be tapered off the IMP during a 3-week period followed by a 1-week drug-free period. A SFU visit will be performed 30 days after the last IMP intake.

OLE=open-label extension; SFU=Safety Follow Up

* Only seizure data prior to and on the date of last dose of study medication will be included in the analysis.

3.2.4 Mapping of assessments performed at early discontinuation

Unlike other scheduled visits, an early discontinuation visit (EDV) doesn't have a predetermined visit window and can occur at any days during the study. If an EDV occurs at the day of a scheduled visit, assessments (in-clinic safety assessments such as vital signs, ECGs, and blood collection for clinical laboratory assessments) should correspond to that scheduled visit. Assessments at an EDV that occurs on a day between two scheduled visits will be assigned to the next scheduled visit. All other assessments (such as questionnaire and PK samples) collected on an EDV will not be mapped.

In the by-visit summary tables, only nominal (scheduled) visits where the assessment is scheduled will be included. For example, if a subject had an EDV after Visit 4 and before Visit 5, the applicable assessments will be mapped to Visit 5 (ie, the next scheduled visit). Vital signs and ECGs collected at the EDV will be summarized under Visit 5 in the by-visit summary tables. However, Visit 5 will not be included in the by-visit summary tables for the clinical laboratory assessments as lab assessments are not scheduled on Visit 5. Unscheduled visits will not be mapped to scheduled visits. In the subject listing, data will be presented under the actual visits, including EDV and unscheduled visits.

Seizure data collected by diary are associated with periods defined within the study and as such need no mapping to visits. If a subject withdraws between visits an effort is made to recover all diary records for use in calculation of seizure frequencies.

3.2.5 Last Visit during the Treatment Period

The Last Visit for an assessment is the last non-missing assessment during the Treatment Period. All scheduled and unscheduled assessments within the Treatment Period will be considered. Last Visit will be determined separately each study assessment. Last Visit during the Treatment Period will be included in the by-visit summary unless noted otherwise.

3.3 Definition of Baseline values

3.3.1 Baseline for variables based on seizure count

Baseline values for seizure frequency variables will be derived from diary data recorded by the subject during the 4-week Baseline Period. This diary is collected at the Baseline Visit (Visit 2, Day 1). The Baseline value will be the seizure frequency per 28 days during the Baseline Period and is defined as the number of seizures standardized to a 28-day baseline period. It is computed for each subject as the number of seizures recorded over the subject's baseline diary period, divided by the subject's total number of non-missing days in that period, multiplied by 28. See details for calculation of seizure frequency in Section 8.1.1.1.

3.3.2 Baseline for other variables

Unless otherwise specified, the last valid measurement before the first study medication administration will be used as the Baseline value, including the pre-dose assessments on the day of Visit 2. Unless otherwise stated, if a Baseline visit measurement is missing, and a Screening visit measurement is available, the most recent Screening value will be utilized as Baseline. Both scheduled and unscheduled Screening visits will be considered. If a scheduled Baseline assessment is taken on the same day as first administration of study medication and no time is collected, it will be assumed to have been taken prior to study medication. The time point used

for Baseline will be determined separately for each variable. An exception is blood pressure, where a complete set of both systolic and diastolic blood pressure should be selected for baseline. Baseline values for PK evaluations included in this SAP is defined in Section 9.

3.4 Protocol deviations

Important protocol deviations (IPD) are those deviations from the protocol identified by the study team as important which will be summarized in the clinical report, in accordance with ICH E3. The criteria for identifying important protocol deviations will be defined within the appropriate protocol-specific document at study start. All protocol deviations will be reviewed periodically through the study as part of the ongoing data cleaning process and those identified as important will be documented prior to unblinding and integrated into the clinical database.

3.5 Analysis sets

Primary and secondary efficacy endpoints will be analyzed using the Full Analysis Set (FAS). Sensitivity analysis on the primary endpoints will be performed using the Per Protocol Set (PPS). Safety variables will be analyzed using the Safety Set (SS). Pharmacokinetic data summaries will use the PK Per Protocol Set (PK-PPS) or AED PK Per Protocol Set (AED-PK-PPS).

These analysis sets are described below.

3.5.1 Enrolled Set

The Enrolled Set (ES) consists of all subjects who have given informed consent.

3.5.2 Randomized Set

The Randomized Set (RS) consists of all subjects randomized into the study; this includes all subjects who have a randomization number issued by the IRT, even if misrandomized.

3.5.3 Safety Set

The SS consists of all subjects who were administered at least 1 dose or a partial dose of IMP, based on the first dose date from the First Administration of Study Medication CRF. The SS will be used to summarize and analyze all safety variables. In case of dosing administration error, summaries and analyses using the SS will be conducted according to actual treatment administered.

3.5.4 Full Analysis Set

The Full Analysis Set (FAS) consists of all subjects in the RS who were administered at least 1 dose or a partial dose of IMP and have Baseline and at least 1 post-Baseline seizure frequency data during the Treatment Period. In case of dosing administration error, or change in treatment dose, summaries and analyses will be conducted according to randomized treatment and not the actual treatment received. The FAS will be the primary analysis set for all efficacy summaries and analyses.

3.5.5 Per Protocol Set

The Per Protocol Set (PPS) is a subset of the FAS, consisting of those subjects who had at least 1 post-Baseline efficacy measurement and who had no major protocol deviation affecting the primary efficacy variable, as confirmed during a pre-analysis data review meeting, conducted prior to study unblinding. Criteria will be developed and documented (in a separate document)

prior to study unblinding to identify subjects with major protocol deviations so that they may be excluded from the PPS. The PPS will be used for sensitivity analyses of selected efficacy endpoints as described later in the SAP.

3.5.6 Completer Set

The Completer Set is a subset of the FAS, consisting of those subjects who completed the 16-week treatment period.

3.5.7 Other analysis sets

3.5.7.1 Pharmacokinetic Set

The Pharmacokinetic Set (PKS) consists of those subjects who provide at least 1 PSL plasma concentration measurement. Note that it is possible for a subject in the PK-Set to have missing data for some evaluations (such as of the primary [redacted]).

3.5.7.2 Pharmacokinetic Per-Protocol Set (PK-PPS)

A PK Per Protocol Set (PK-PPS) will be a subset of the PKS and identified for active treatment groups, which would exclude subjects or PK sample data points with major deviations that could impact PK evaluations e.g. when there is evidence that the sample collected is not at steady-state due to missing doses, dose alterations or interacting concomitant medications, etc. Subjects or PK sample data points to be excluded from this PK-PPS, will be identified during a pre-analysis data review.

3.5.7.3 AED Pharmacokinetic Per-Protocol Set (AED-PK-PPS)

An AED PK Per Protocol Set (AED-PK-PPS) will be identified, which would exclude subjects or AED PK sample data points with major deviations that could impact AED PK evaluations. Subjects or AED PK sample data points to be excluded from this AED-PK-PPS, will be identified during a pre-analysis data review.

3.6 Treatment assignment and treatment groups

At Baseline, eligible subjects will be randomly assigned to treatment regimens as described in Section 2.3. Prior to unblinding, the study team should identify and review all cases in which subjects received an incorrect study drug (dosing errors resulting in treatment crossover). Note that while dispensing errors can be identified prior to unblinding, actual treatment crossovers can only be identified via IRT report (only identifying the subject number), or after unblinding.

The FAS will be the primary analysis set for all efficacy summaries and analyses. Treatment crossover Subjects (including any subjects with dosing errors) will be analyzed for efficacy according to their randomized treatment assignment and not the actual treatment received.

Safety analyses will be based on the SS. It is expected that subjects will receive the randomized treatment and be analyzed according to that assigned treatment. However, if a subject were to experience a dosing error resulting in treatment crossover, incorrectly treated subjects will be evaluated during the blinded data evaluation meetings to assess the potential impact of such cases and any special considerations for statistical analyses.

3.7 Sites pooling strategy

Since "site" per se is not considered as a factor in the planned analyses there is no strategy in place for pooling data from sites with low number of patients to another particular site. Data will be combined across all sites within region, according to the specified analysis. To ensure at least 5 subjects in each region in the FAS at each treatment group, Japan will be pooled with North America to form a non-Europe region for the efficacy analyses.

3.8 Coding dictionaries

All prior and concomitant medications other than study drug will be classified by World Health Organization WHO Anatomical Therapeutic Chemical (ATC) Classification, presenting Anatomical Main Group (ATC Level 1), Pharmacological Subgroup (ATC level 3), and preferred term, using Version SEP/2015 or higher of the World Health Organization Drug Dictionary (WHO-DD). Coding will be performed in accordance with UCB standard operating procedures (SOP).

Medical history and AEs will be coded by primary system organ class (SOC), high level term (HLT) and preferred term (PT) using version 19.0 or higher of Medical Dictionary for Regulatory Activities (MedDRA®) according to UCB Standard Operating Procedures (SOP).

3.9 Changes to protocol-defined analyses

Not applicable; there have not been any changed to protocol defined analyses.

4 STATISTICAL/ANALYTICAL ISSUES

General statistical and analytical issues are provided in the following sections.

4.1 Adjustments for covariates

The primary and selected efficacy analyses will be adjusted for baseline log-transformed seizure frequency and for the stratification factors:

- Current use of AEDs with binding to SV2A proteins (LEV and/or brivaracetam): Yes or No
- Geographical Region: Investigative sites have been identified in the following regions and countries at the time of this SAP amendment. More regions and/or countries may be identified and will be included in the analyses in accordance to the randomization strata:
  - Europe (Australia, Belgium, Bulgaria, Czech Republic, France, Germany, Hungary, Italy, Lithuania, Poland, Portugal, Slovakia, Spain, Turkey, and United Kingdom)
  - North America (Canada, Mexico, and United States)
  - Asia (Japan)

To ensure at least 5 subjects in each region in the FAS at each treatment group, Japan will be pooled with North America to form a non-Europe region for the efficacy analyses.

4.2 Handling of dropouts or missing data

4.2.1 Handling of missing data in seizure frequency

Unless noted otherwise, the imputation described below will be applied to seizure frequency. The responder status will be determined based on the imputed seizure frequency data. Sensitivity analyses for missing data are described in Section 8.1.2 for the primary efficacy variable.

4.2.1.1 Missing data caused by missing seizure diary

Seizure frequency will be computed over non-missing diary days. Diary compliance evaluation is described in Section 7.2. Subjects with diary data deemed unacceptably incomplete (during blinded data review) for the primary efficacy variable will be excluded from the PPS.
If seizure type is known but the number of seizures is unknown, the number of seizures will be imputed using the median for the same seizure type (daily seizure number > 0) during the same analysis period (baseline or treatment period). Otherwise, the missing seizure number will be imputed using the count of next higher level of seizure type.

4.2.1.2 Missing seizure data caused by discontinuation

- Seizure frequency by analysis period:

For subjects who prematurely discontinued during the Treatment Period, the calculation of 28-day adjusted seizure frequency over the Treatment Period will be based on available seizure diary up to the end of the Treatment Period.

If a subject had less than 14 days of seizure data during the Titration and Stabilization Period, seizure frequency during the Treatment Period will be calculated based on the last 28 days with seizure data, including the data in the Baseline Period. For subjects who prematurely discontinued the study, the following methods will be applied to obtain a seizure frequency estimate for the Maintenance Period:

- Subjects who discontinued during the Titration and Stabilization Period: If a subject had at least 14 days of seizure data, seizure frequency will be calculated using all available data in the Titration and Stabilization Period and carry forward for the Maintenance Period. If a subject had less than 14 days of seizure data, seizure frequency will be calculated based on the last 28 days with seizure data, including the data in the Baseline Period and carry forward for the Maintenance Period.
- Subjects discontinued during the Maintenance Period: If a subject had at least 28 days of seizure data during the Maintenance Period, seizure frequency will be calculated using all available data in the Maintenance Period. If a subject had less than 28 days of seizure data during the Maintenance Period, seizure frequency will be calculated based on the last 28 days with seizure data, including the data in the Titration and Stabilization Period.

- Seizure frequency by 4-week interval

Seizure frequency by 4-week interval will be calculated for the sensitivity analyses (Section 8.1.2.2) and secondary efficacy analyses (Section 8.3.2.1). Seizure frequency during a 4-week interval will be calculated as long as seizure data are available for at least 1 day in the given interval. No imputation will be applied for discontinuations.

4.2.2 Handling of missing data for adverse events and concomitant medications

For analyses of AEs and concomitant medication usage, a complete date must be established to correctly identify the AE or medication as occurring during treatment or not. In the event of completely missing dates, or if ambiguity or incomplete data makes it impossible to determine whether a medication was concomitant, or an adverse event was treatment emergent, the medication will be considered as concomitant or the adverse event will be considered treatment emergent.

For purposes of imputing missing components of partially-reported start and stop dates for AEs and for medication use, the algorithms listed below will be followed. Start and stop dates of AEs or concomitant medication will be displayed as reported in the subject data listings (i.e., no imputed values will be displayed in data listings).

Partial AE and concomitant medication start dates will be imputed as described in the following sections.

4.2.2.1 Imputation of Partial Start Dates

- If only the month and year are specified and the month and year of first dose of IMP is not the same as the month and year of the start date, then use the 1st of the month
- If only the month and year are specified and the month and year of first dose of IMP is the same as the month and year of the start date, then use the date of first dose of IMP
- If only the year is specified, and the year of first dose of IMP is not the same as the year of the start date, then use the 1st of January of the year of the start date
- If only the year is specified, and the year of first dose of IMP is the same as the year of the start date, then use the date of first dose
- If the start date is completely unknown and the stop date is unknown or not prior to the date of first dose of IMP, then use the date of first dose of IMP.
- If the imputed start date is after the known stop date, set the start date to be the same as the stop date.

4.2.2.2 Imputation of Partial Stop Dates

- If only the month and year are specified, then use the last day of the month
- If only the year is specified, then use December 31st of that year
- If the stop date is completely unknown, do not impute the stop date

4.2.3 Handling of missing data for history of epileptic seizures and diagnosis of epilepsy

4.2.3.1 Incomplete dates for first epileptic seizure

To calculate the time since the first seizure relative to the date of Visit 1 or age at onset of first seizure, January 1st of the year will be imputed for the date of birth, as only year of birth is collected on CRF. And a complete date will be imputed for partially missing first seizure date as following:

- Missing the day, but month and year present, then assign the 1st day of the month.
- Missing the day and month, but year present, then assign January 1st of the year.
- Completely missing, no imputation will be done.

4.2.3.2 Incomplete dates for last epileptic seizure

To calculate the time since last seizure relative to the date of Visit 1, a complete date will be imputed for partially missing last seizure date as following:

- Missing the day, but month and year present, then assign the 1st day of the month.
- Missing the day and month, but year present, then assign January 1st of the year or Visit 1, whichever is later in the year.
- Completely missing, no imputation will be done.

4.2.3.3 Incomplete dates for first epilepsy diagnosis

Month and year of the first epilepsy diagnosis are collected on the CRF. To calculate the duration of epilepsy derived from the date of first diagnosis relative to the date of Visit 1, or age at epilepsy diagnosis, January 1st of the year will be imputed for the date of birth, as only year of birth is collected on CRF. And a complete date will be imputed for partially missing date of the first epilepsy diagnosis as following:

- Month and year present, then assign the 1st day of the month or the date of the first seizure, whichever is later in the month.
- Missing the month, but year present, then assign January 1st of the year or the date of the first seizure, whichever is later in the year.
- Both month and year are missing, no imputation will be done.

4.3 Interim analyses and data monitoring

There is no formal interim analysis planned for the study.

A Data Monitoring Committee (DMC) will be formed to monitor the ongoing safety of the study through periodic review of data summaries. The general scope of DMC activities is presented in the protocol and will be described in detail in a separate DMC Charter. Preparation of data summaries for review by the DMC will be described in a separate DMC SAP.

4.4 Multicenter studies

In general, efficacy and safety summaries and analyses will be presented across investigative sites, countries and regions. When applicable, analyses will include adjustment for region, which is one of the stratification factors.

4.5 Multiple comparisons/multiplicity

For the primary efficacy variables, statistical testing will be based on the comparison of 400mg bid, 200mg bid and 100mg bid PSL groups versus placebo. Type 1 error will be controlled by the Hochberg step-up procedure within SAS® Proc Multtest. Hochberg procedure orders the p-values from the largest to the smallest. The significance level for the k-th step is given by 0.05/k. More specifically, the largest p-value will be compared to 0.05. If it is smaller than 0.05, we will stop the testing and conclude significance for all 3 comparisons; otherwise we will move to the

second highest p-value. The second largest p value will be compared to 0.025 (=0.05/2). If it is smaller than 0.025, we will stop and conclude significance for this comparison and the subsequent one that produced p-values smaller than the current one; otherwise we will move to the smallest p-value. The smallest p-value will be compared to 0.0167 (0.05/3). If it is smaller than 0.0167, we will conclude a significant difference between the dose and the placebo; otherwise, stop and no comparison is significant.

If the 3 higher doses are all statistically different from the placebo, the 50mg bid PSL group will be compared to placebo. Because this follows a gatekeeping procedure, testing will be conducted at the 0.05 level (2-sides). If the p-value is smaller than 0.05, we will conclude 50mg bid is also significantly different from the placebo.

4.6 Use of an efficacy subset of subjects

The FAS will be used as the primary analysis set for all efficacy analyses. Analyses using the PPS will also be performed for the FDA and European agency primary efficacy variables. The PPS analyses will provide additional information on efficacy evaluations and will describe findings in a subset of subjects who adhered more closely to the study protocol. No other efficacy subsets are defined for statistical analyses.

4.7 Active-control studies intended to show equivalence

This study is not an active controlled study intended to show equivalence.

4.8 Examination of subgroups

The primary efficacy variable will be evaluated for subgroups of interest including:

- Age (18 to <65 years, ≥65 years): less than 5 subjects in ≥65 years subgroup in the FAS at each treatment group, therefore the subgroup analysis will be omitted.
- Gender
- Region (Europe, North America, and Asia): To ensure at least 5 subjects in each region in the FAS at each treatment group, Asia (Japan) will be pooled with North America. The subgroup analyses will be performed for Europe vs non-Europe.
- Use of AEDs with binding to synaptic vesicle 2A (SV2A) proteins (levetiracetam [LEV] or brivaracetam [BRV], Y/N).

These evaluations will be descriptive; no statistical testing of treatment-by-subgroup interactions nor statistical testing of treatment effects within subgroups will be carried out. No subgroup evaluations are planned for safety variables.

5 STUDY POPULATION CHARACTERISTICS

5.1 Subject disposition

Screen failure data of screened subjects who did not meet study eligibility criteria are collected on the Study Termination Screen Failure CRF (dates of screen failure and last contact and reason for screen failure).

Disposition data of randomized subjects are obtained from the Study Termination CRF. Variables include date of last administration of study medication, date of premature study

termination, date of final contact with subject, subject status at study termination, primary reason for premature study termination (as listed on the CRF), and if the study blind was broken (Y/N and date, if applicable).

Disposition of subjects (ES) will be listed by region, country and investigative site. A listing will also be provided for study discontinuation (RS), and for study visit dates (RS).

Summaries of the numbers of screened subjects and reasons for screen failures will be produced overall for the ES.

The disposition of the ES will be summarized overall and by region, country and site presenting the dates of first subject in (first enrolled) and last subject out, number of subjects screened, and number of subjects included in the each of the RS, FAS, SS, PPS, and PK-PPS.

The disposition of the SS will be presented as the number and percentage of subjects who completed the study and of subjects who discontinued the study, including a breakdown of the primary reason for discontinuation. Of note, the corresponding table is required for data transparency reporting. Subjects who enrolled into EP0093 will also be summarized. The number of subjects completing and discontinuing with associated reasons for discontinuation at each visit of the Titration and Maintenance Periods will be displayed for the SS.

In addition, the numbers and percentages of subjects (SS) entering and completing each of the following analysis periods: (Titration and Stabilization Period, Maintenance Period, Conversion Period, and Taper and SFU Period) will be summarized by treatment group and overall. The same summary will be repeated by region.

The number and percentage of subjects in the SS who discontinued due to AE categorized by serious fatal, non-fatal, and non-serious fatal AE incidence will also be presented by treatment group and overall. Of note, the corresponding table is required for data transparency reporting.

5.2 Protocol deviations

All IPDs (defined in Section 3.4) will be listed by treatment group and subject, and will include at a minimum, deviation type (as collected under the important deviation collection plan), deviation number, and deviation description.

A summary of number and percentage of subjects with an IPD will be produced by treatment group and overall for the RS. The summary will be overall (any IPD) and by type of deviation.

As described in Section 3.5, subjects may be excluded from the PPS based on major protocol deviations determined to have a potential effect on primary efficacy variables. Similarly, subjects with certain major protocol deviations may be excluded from the PK-PPS. Criteria for exclusion of subjects from the PPS or PK-PPS will be defined in a separate document developed in conjunction with a formal data review plan. To the extent feasible, rules for identifying major protocol deviations will be defined without review of the data and without consideration of the frequency of occurrence of such deviations. Important protocol deviations will be reviewed as part of the ongoing data cleaning process prior to database lock to identify those that are major and confirm exclusion from analysis sets. After all data have been verified/entered into a database and prior to database lock, a final data evaluation meeting will take place. The PPS will be confirmed at this time.

A by-subject listing of subjects excluded from each of the analysis datasets (for SS, FAS, PPS, and PK-PPS) will be prepared for the RS. The listing will include the categorized reason for exclusion as well as the specific reason.

6 DEMOGRAPHICS AND OTHER BASELINE CHARACTERISTICS

By-subject listing will be produced for the ES for the demographics and for the RS for other baseline characteristics. All demographic and Baseline characteristics will be summarized descriptively for the FAS by treatment group and overall unless noted otherwise. The summary tables in Section 6 will be repeated by region.

6.1 Demographics

Data collected on the Demographic CRF at the Screening Visit or at Baseline, include the date of birth, age (in years), sex (male, female), race (all categories on the CRF), ethnicity (Hispanic or Latino, not Hispanic or Latino), ethnic sub-group (Japanese, not Japanese), height (in cm), and weight (in kg). Demographics will be summarized for the RS, SS, and FAS.

Descriptive statistics presentation will adhere to the guidelines in Section 3.1. In addition, the following age categories will be summarized:

- ≤18, 19 - <65, and ≥65 years
- 18 - <65, 65 - <85, and ≥ 85 years

Body mass index (BMI) and BMI categories (<18.5, 18.5 to <25, 25 to <30, 30 to <40, ≥40kg/m2) will also be summarized.

Of note, the demographic table is required for data transparency reporting. The age categories are also required for the data transparency reporting.

6.2 Other Baseline characteristics

- Randomization is stratified by region (Europe, North America, and Asia), and by current use of AEDs with binding to SV2A proteins, such as LEV and/or BRV (yes or no). The percentages of subjects in each stratum for each stratification factor will be summarized for the RS.
- Lifestyle information (alcohol and illicit drug use) obtained at the Screening Visit (Lifestyle CRF) will be listed for the RS. These variables will be summarized descriptively (number and percent of subjects in each category) for the SS.

6.3 Medical history and concomitant diseases

6.3.1 Medical history and ongoing medical conditions

Medical history and ongoing medical conditions will be listed and summarized for the SS by MedDRA system organ class (SOC) and preferred term (PT). The start date (month and year only) and end date (or ongoing if applicable) will be included in the listing. Epilepsy history will not be included in these tables. Procedure history will be listed separately by the procedure reported term.

6.3.2 Procedure history

Procedures or surgeries prior to study entry will not be summarized and will only be provided in subject data listing.

6.3.3 Medical history of epilepsy

The history of epilepsy data will be listed for all subjects in the RS. The following summaries will be produced by treatment group and overall using the FAS unless otherwise specified:

6.3.3.1 Etiology of epilepsy

The number and percentage of subjects with each type of etiology as specified in the Etiology of Epilepsy CRF will be presented.

6.3.3.2 Epilepsy surgery status

Epilepsy surgery status parameters are collected on the Epilepsy Surgery Status CRF. The number and percentage of subjects who are evaluated for epilepsy surgery and in each of the outcome category will be presented.

6.3.3.3 Epileptic seizure profile

Epileptic seizure profile is based on the historical seizure types reported by the subject on the ILAE Seizure Classification History form. The number and percentage of subjects experiencing each seizure type at any time in the past will be summarized.

6.3.3.4 Focus localization

The number and percentage of subjects with each category of focus localization (unknown, frontal, temporal, parietal, occipital) will be summarized. Subjects may be counted in more than one category of focal localization.

6.3.3.5 History of epileptic seizures and diagnosis of epilepsy

History of epileptic seizures are collected on the History of Epileptic Seizures CRF. The summary will present the number and percentage of subjects with a history of status epilepticus, the number and percentage of subjects with a history of withdrawal seizures, and quantitative summaries of time since the first seizure relative to the date of Visit 1, time since last seizure relative to the date of Visit 1, and age at onset of first seizure.

The date of diagnosis of epilepsy is collected on Diagnosis of Epilepsy CRF. The duration of epilepsy will be derived from the date of first diagnosis relative to the date of Visit 1. The duration of epilepsy and age at epilepsy diagnosis will be summarized descriptively.

6.3.3.6 Historical seizure count and cluster count

The Historical Seizure Count and Historical Cluster Count CRF records the number of seizures and clusters experienced by the subject during the past 2 months prior to the Screening Visit. The number of seizures and clusters will be summarized by seizure type and month.

6.3.3.7 Seizure types experienced during the Baseline Period

The number and percentage of subjects experiencing each seizure type during the Baseline Period will be summarized based on data from Seizure Count CRF.

6.3.3.8 Baseline focal seizure frequency

The 28-day adjusted frequency of observable focal-onset seizures (Types IA1, IB, and IC) and of all Type I focal-onset seizures during the Baseline Period will be summarized. Seizure counts are collected by diary; calculation of the Baseline 28-day adjusted frequency is provided in Section 3.3.1.

6.3.3.9 Brain magnetic resonance imaging (MRI)

MRI data will be provided in the subject listing.

6.4 Prior and concomitant medications

In this study, AED medications are collected separately from prior and concomitant non-AED medications. Handling of AED and non-AED medication is described in the following sections. AED medications will be summarized for the FAS, non-AED medications will be summarized for the SS.

6.4.1 AED medications

Each concomitant medication will be classified as either an AED or a non-AED medication. AED medication taken and stopped prior to the Visit 1 will be reported on the History of Previous Antiepileptic Drug Treatment CRF. AED mediation that started prior to Visit 1 and which is ongoing/or AED medication prescribed during the study will be recorded on the AED Medication CRF.

- Previous AEDs are AEDs taken and stopped prior to the Visit 1. Previous AEDs are reported on History of Previous Antiepileptic Drug Treatment CRF.
- AEDs taken at study entry are reported on AED CRF and if:
  - (start date of medication) < (the date of Visit 1) and (stop date of medication) ≥ (the date of Visit 1) or ongoing
- Prior AEDs include both previous AEDs and AEDs taken at study entry
- Concomitant AEDs are reported on AED CRF and if:
  - (start date of medication) ≤ (stop date of IMP) and (stop date of medication) ≥ (start date of IMP) or ongoing
  - start date of medication is unknown but (stop date of medication) ≥ (start date of study drug) or ongoing.

The number and percentage of subjects taking AED medications will be summarized by chemical/therapeutic/pharmacological subgroup (ATC classification level 4), and preferred drug name. The following summaries of AED medications will be produced for the FAS by treatment group and overall:

- Previous AEDs from the History of Previous Antiepileptic Drug Treatment CRF
- Number of previous AEDs taken: <4, 4-5, 6-7, 8-10,>10 AEDs.

- Previous AEDs by reason for AED discontinuation: The number and percentage of subjects by reason for discontinuation of previous AEDs will be summarized. Percentages for each reason for discontinuation will be relative to the number of subjects taking each AED.
- AEDs taken at study entry
- Number of AEDs taken at study entry: 1, 2, 3, and >3AEDs
- Prior AEDs
- Number of prior AEDs: <4, 4-5, 6-7, 8-10,>10 AEDs.
- Concomitant AEDs

6.4.2 Use of vagus nerve stimulation

Vagus Nerve Stimulation (VNS) status at Screening (VNS Status at Screening CRF) will be summarized as the number and percent of subjects with VNS at screening and as number and percent of subjects with VNS turned on. Subjects with VNS at screening and setting changed during treatment period will also be summarized. All other VNS data will be provided in subject data listings and will not be summarized for the FAS.

6.4.3 Prior and Concomitant non-AED medications

Medications recorded on the Prior and Concomitant Medication CRF should not include AEDs. Non-AED medications will be analyzed separately from AED medications.

- A prior non-AED medication if:
  - (start date of medication) < (start date of IMP)
  - start date of medication is unknown but (stop date of medication) < (start date of IMP)
- A concomitant non-AED medication if:
  - (start date of medication) ≤ (stop date of IMP) and (stop date of medication) ≥ (start date of IMP) or ongoing
  - start date of medication is unknown but (stop date of medication) ≥ (start date of study drug) or ongoing.

The number and percentage of subjects taking non-AED medications will be summarized by anatomical main group (Anatomical Therapeutic Chemical [ATC] classification level 1), therapeutic subgroup (ATC classification level 2), and preferred drug name. The following summaries of non-AED medications will be produced for the SS by treatment group and overall:

- Prior non-AED
- Concomitant non-AED

7 MEASUREMENTS OF COMPLIANCE

7.1 Treatment compliance

The IMP will be provided in blister-packed treatment cards, each providing 3, 4, or 7 days' treatment of active or placebo (plus some reserve tablets in case of unexpected event). At each

visit after IMP is dispensed and at the end of the Taper/Conversion Period, subjects must return all unused IMP and empty IMP containers. IMP is dispensed at Visits 2, 3, 4, 5, 6, and 7. IMP return and IMP accountability evaluation occurs at Visits 3, 4, 5, 6, 7 and 8. Drug accountability is recorded on the Drug Accountability form.

Measurement of treatment compliance with the dosage schedule will be based on dispensed and returned pill counts. Drug accountability data will be listed (SS) by treatment group and study visit. The listing will include dispense date and number of pills dispensed; return date and number of pills returned.

Subjects are instructed to take medication bid, approximately 12 hours apart. Based on the PSL tablet mg amounts provided, subjects will take 10 tablets per day (some containing PSL, some placebo) during the Titration and Taper (subjects not entering the EP0093 OLE) periods. They will take 12 tablets per day (some containing PSL, some placebo) during the Stabilization, Maintenance, and Conversion (subjects entering the EP0093 OLE) periods. Compliance during the entire 16-week Treatment Period, Titration and Stabilization Period, and the Maintenance Period will be calculated as 100 times the actual number of tablets taken over the evaluation period (based on the Study Medication Administration CRF), and dividing this quantity by the number of tablets that should have been taken during this period of time.

The number of tablets expected (that should be taken) during the periods of interest are:

- 16-week Treatment Period: 10 × duration of Titration Period (days) + 12 × duration of Stabilization Period and Maintenance Period (days)
- Maintenance Period: 12 × duration of the Maintenance Period (days)
- Titration and Stabilization Period: 10 × duration of Titration Period (days) + 12 × duration of Stabilization Period (days)

Duration of an analysis period in days will be calculated as date of the last dose of IMP in a period - date of the first dose at the specific period +1. Compliance is only computed for actual time of participation in the study up to the last dose of IMP during the Treatment Period. If a subject didn't enter an analysis period, the compliance for the analysis period will not be calculated.

Percent compliance will be summarized for the FAS using descriptive statistics for each treatment group and overall. In addition, the number and percentage of subjects with compliance <75%, 75% to 125%, and >125% will be summarized.

7.2 Diary compliance

Primary and secondary, and other efficacy variables are based on diary-collected seizure frequencies, and as such, diary compliance will be evaluated along with treatment compliance. Subjects are instructed to complete their diary entries at least once a day during the study. A dairy day will be considered missing for compliance if the seizure count field is checked as 'not done'. Diary compliance will be evaluated during the Baseline Period, during the entire 16-week Treatment Period, and during the Maintenance Period.

Diary compliance will be calculated as 100 times the number diary days (days with dairy completed) during the period and dividing this quantity by the expected number of diary days that should have been completed during this period of time. Compliance is only computed for

actual time of participation in the study up to the end of the Treatment Period. Only data prior to and on the date of last dose of study medication will be included in the compliance calculation. If a subject didn't enter an analysis period, the diary compliance for the analysis period will not be calculated.

Diary compliance data will be listed by subject. Percent diary compliance will be summarized for the FAS, by period using descriptive statistics for each treatment group and overall. In addition, the number and percentage of subjects with compliance ≤80% and > 80% will be summarized.

8 EFFICACY ANALYSES

Unless noted otherwise, analyses of efficacy endpoints will be performed on the FAS. Additional analyses of selected efficacy endpoints will be performed using the PPS as described in the sections below. For the efficacy variables described below, seizure frequency refers to a 28-day adjusted frequency; observable focal-onset seizures refer to Type IA1, IB, and IC (ILAE Classification of Epileptic Seizures, 1981); focal-onset seizures include all Type I seizures; and seizure-free status and seizure-free days include all seizure types (Types I, II, and III). Only seizure data prior to and on the date of last dose of study medication will be included in the analysis. Unless noted otherwise, all efficacy tables will be presented by treatment group.

As listed in Section 2.3.1, separate primary and secondary seizure frequency efficacy variables have been designated for submission to FDA and submission to European regulatory agencies along with other seizure frequency efficacy variables used for both submissions. A summary of seizure frequency variables and status as primary or secondary is presented in Table 8-1.

Table 8–1: Summary of seizure frequency variables

Variable	12-Week Maintenance Period			16-Week Treatment Period		
	Observable Focal Onset (IA1, IB and IC)	Focal Onset (All Type I)	All Seizures (Type I, II and III)	Observable Focal Onset (IA1, IB and IC)	Focal Onset (All Type I)	All Seizures (Type I, II and III)
Change in log-SF	X [a][c]	X		X		
75% RR	X [b][c]	X		X		
50% RR	X [c]	X		X		
Percent Reduction in SF	X [c]	X		X	X	
90% RR	X	X				
100% RR	X	X				
Change in log-SF (4-week intervals)	X					
Seizure Freedom			X			X
Number of seizure-free days			X			X
Cumulative RR				X	X	

Table 8–1: Summary of seizure frequency variables

Variable	12-Week Maintenance Period			16-Week Treatment Period		
	Observable Focal Onset (IA1, IB and IC)	Focal Onset (All Type I)	All Seizures (Type I, II and III)	Observable Focal Onset (IA1, IB and IC)	Focal Onset (All Type I)	All Seizures (Type I, II and III)
Change from baseline in seizure frequency	X	X		X	X	

RR=Responder Rate. SF=Seizure Frequency.
(a) Primary endpoint for FDA, PMDA and other Regulatory agencies not referencing EMA
(b) Primary endpoint EMA
(c) Secondary Endpoint

8.1 Statistical analysis of the primary efficacy variables

8.1.1 Derivations of primary efficacy variables

8.1.1.1 Seizure frequency

Seizure frequency (SF) refers to the 28-day adjusted seizure frequency. The 28-day adjusted seizure frequency is defined as: SF = (Number of Seizures) x (28 / D). The number of seizures is the total number of seizures during an analysis period or time interval. For cluster seizures, the number of cluster episodes will be included. D corresponds to the number of days for which the diary was available during the analysis period or time interval.

8.1.1.2 Change in log-transformed seizure frequency from Baseline

The 28-day adjusted seizure frequency value will be log-transformed using the function ln(x+1), where ln represents the natural logarithm function. The change in the log-transformed seizure frequency from Baseline is calculated as: Ln (SFT+1) – Ln (SFB+1), where SFT corresponds to the seizure frequency during an analysis period and SFB corresponds to the Baseline period seizure frequency.

For the primary efficacy variable for the FDA, SFT and SFB are the observable focal-onset seizure frequency during the 12-week Maintenance Period and Baseline Period, respectively.

8.1.1.3 Percent reduction in seizure frequency from Baseline

The percent reduction in seizure frequency (PRD) from the Baseline is defined as: PRD = [(SFB – SFT) / SFB] x 100, where SFT corresponds to the 28-day adjusted seizure frequency during an analysis period and SFB corresponds to the Baseline seizure frequency. A negative PRD indicates an increase in seizure frequency from Baseline.

8.1.1.4 75% Responder

Responder status (yes or no) for a subject is determined by the percent reduction in seizure frequency (PRD) from Baseline. A subject is defined as a 75% responder if s/he has a reduction in seizure frequency (PRD) of at least 75% from the Baseline. The 75% responder rate (RR) will be calculated as the proportion of 75% responders. For the primary efficacy variable for the

EMA, 75% responder status is calculated based on the percent reduction (PRD) from the Baseline in observable focal-onset seizure frequency during the 12-week Maintenance Period.

8.1.2 Analysis of the primary efficacy variables

8.1.2.1 Primary variable for submission to the US FDA, PMDA, and other regulatory authorities not referencing EMA

The primary efficacy variable for the US FDA/PMDA is the change in log-transformed observable focal onset seizure frequency from Baseline, over the 12-week Maintenance Period. Analyses of the primary variable for the FDA will be performed on the FAS as described below.

Change from Baseline in observable focal-onset seizure frequency (using the log-transformed data) will be analyzed for the FAS using analysis of covariance (ANCOVA) with treatment group (PSL 400mg bid, 200mg bid, 100mg bid, 50mg bid, and placebo) as the main factor, Baseline log-transformed seizure frequency as a continuous covariate, Baseline SV2A use (Yes or No), and Region (Europe or Non-Europe) as factors. Pairwise contrasts will be constructed to compute estimated effects of each dose from placebo.

Treatment effects will be characterized using treatment differences based on back-transformation of least squares (LS) means obtained from the above ANCOVA model. Percent reduction over placebo will be calculated as 100*(1-exp(diff)), where diff is the model estimate of the log ratio between each PSL group and placebo group. Similarly, estimates for the upper and lower bounds of the 95% confidence interval (CI) will be back-transformed for table presentation as exp(lower) and exp(upper), respectively, where upper and lower correspond to the 95% CI of the log ratio. If there are issues with convergence, covariates will be dropped sequentially in the order of Region, and then Baseline SV2A use (Yes or No) if further needed.

Pairwise comparisons of the 400mg bid, 200mg bid, and 100mg bid PSL dose groups versus placebo will be carried out using the analysis model described above. Type 1 error will be controlled using the Hochberg step-up procedure (Section 4.5) within SAS® Proc Multtest. If all the results of the 3 pairwise comparisons are statistically significant, then the 50mg bid dose group will be compared to placebo, too. Both multiplicity-adjusted and unadjusted p-values will be presented.

8.1.2.2 Supportive and sensitivity analyses for the primary variable for submission to the US FDA, PMDA, and other regulatory authorities not referencing EMA

8.1.2.2.1 Sensitivity analysis 1: PPS

The primary analysis of change from Baseline in observable focal-onset seizure frequency for submission the FDA described in Section 8.1.2.1 will be repeated for the PPS.

8.1.2.2.2 Sensitivity analysis 2: multiple imputation

Multiple imputations will be used to assess the robustness of the primary efficacy analysis results. Multiple imputation will be performed based on log (28-day adjusted seizure frequency +1) by 4-week visit interval over the 16-week Treatment Period. Seizure frequency during a 4-week interval will be calculated as long as seizure data are available for at least 1 day in the given interval.

Imputation for intermediate missing

Chances of intermittent missing due to completely missing seizure diary during a 4-week interval are low. The intermittent missing seizure frequency before the last 4-week visit interval will be assumed as missing at random (MAR). The intermittent missing data will be filled in using MCMC method with 30 iterations. The imputation model will include treatment groups, log-transformed baseline seizure frequency, baseline SV2A use (Yes or No), region (Europe or Non-Europe), and outcome from each visit interval (in chronological order). Seed=57832.

8.1.2.2.2.1 Sensitivity Analysis 2.1: Missing at random MI

After the intermittent missing data are imputed, the pattern of the missing data will be monotone. To complete the imputation assuming MAR for each treatment group separately, a regression method using PROC MI statement MONOTONE REG will be used. The imputation model will include explanatory variables for log-transformed baseline seizure frequency, baseline SV2A use (Yes or No), region (Europe or Non-Europe), and outcome from each visit interval (in chronological order). Seed=57832.

Log-transformed seizure frequency during the Maintenance Period will then be computed by taking the average of the data in the three 4-week visit intervals during the Maintenance Period. Multiple imputed datasets will be analyzed using the same ANCOVA model as in the primary analysis. If there are issues with model convergence, covariates will be dropped sequentially in the order of Region, and then Baseline SV2A use (Yes or No) if further needed. The result of the 30 imputed datasets will be combined for overall inference using SAS PROC MIANALYZE.

8.1.2.2.2.2 Sensitivity Analysis 2.2: Control-based MI

The control-based imputation method used the data from the subjects randomized in the placebo group to impute the missing value for the subjects in the PSL treatment groups. This assumes the subjects on PSL treatment groups will have their efficacy trend toward that of the subjects in the placebo group after the treatment discontinuation. Missing data for the first visit interval are imputed, then missing data for the second visit interval are imputed using observed data and missing data just imputed for the first interval; and so on to the final interval. The imputation will be performed via the sequential regression method using PROC MI statement MONOTONE REG. Multiple imputed datasets will be analyzed using the same ANCOVA model as in the primary analysis. If there are issues with model convergence, covariates will be dropped sequentially in the order of Region, and then Baseline SV2A use (Yes or No) if further needed. Seed=14823.

8.1.2.2.2.3 Sensitivity Analysis 2.3 Tipping point MI

Following the National Research Council (NRC) report on missing data (NRC, 2010), a sensitivity analysis using tipping point method to stress-test the result of MAR by imposing a succession of δ adjustments, each one more severe, in the PSL Groups until they are no longer statistically significant. This Delta (δ) will be applied just once, at the first visit that has missing frequency seizure data for each subject in the PSL groups who discontinued before the end of treatment period and hence have missing records for "seizure frequencies". Use nimpute = 30, seed = 56432.
The tipping point report (table) for each pairwise comparison will include values for the LSmeans, the 95% CI, and the p-value for each of the delta value (including 0, until p-values are

no longer statistically significant. Only 8 delta values will be tabulated in the report including δ=0 until δ=xx.x% shift the p-value to larger than multiplicity adjusted alpha level.

8.1.2.3 Primary variable for submission to the EMA and regulatory authorities who reference EMA

The primary efficacy available for the EMA is the 75% responder rate over the 12-week Maintenance Period. Analyses of the primary variable for the EMA submission will be done on the FAS as described below.

The analysis of 75% responder rate will be based on a logistic regression model with factors for treatment group (PSL 400mg bid, 200mg bid, 100mg bid, 50mg bid and placebo), Region (Europe or Non-Europe), Baseline SV2A use (Yes or No) and log-transformed Baseline seizure frequency as a continuous covariate. If there are issues with convergence, covariates will be dropped sequentially in the order of Region, and then Baseline SV2A use (Yes or No) if further needed. Odds Ratios of PSL dose to placebo will be obtained and tested for difference from unity (2-sided) for the dose groups 400mg bid, 200mg bid, and 100mg bid. The evaluation of statistical significance will be based on the Hochberg procedure as described in Section 4.5. If all 3 Odd's Ratios of PSL dose relative to placebo are statistically significant, then the 50mg bid dose group will be compared to placebo by testing the Odds Ratio for difference from unity, too. Both multiplicity adjusted p-values and unadjusted p-value will be presented.
If there is <2 responders in a treatment group, results will also be provided for an exact conditional logistic regression model where treatment group is included in the model and Region (Europe or Non-Europe) and Baseline SV2A use (Yes or No) are included as strata.

8.1.2.4 Supportive and sensitivity analyses for the primary variable for submission to the EMA and regulatory authorities who reference EMA

8.1.2.4.1 Sensitivity analysis 1: PPS

The primary analysis (75% responder rate) for submission to the European regulatory agency as described in Section 8.1.2.3 will be repeated using the PPS.

8.1.2.4.2 Sensitivity analysis 2: non-responder imputation

A sensitivity analysis of the 75% responder rate will be performed in which subjects who discontinued prior to the end of the Maintenance Period will be treated as non-responders. The primary analysis in Section 8.1.2.3 will be repeated.

8.1.2.4.3 Sensitivity analysis 3: multiple imputation

After the multiple imputation process described in Section 8.1.2.2.2, seizure frequency during the Maintenance Period will be calculated as [exp (log-transformed seizure frequency) -1] and the 75% responder status will be derived. Multiple imputed datasets will be analyzed using the same logistic regression model as in the primary analysis for the MAR imputation and control-based imputation respectively. If there are issues with model convergence, covariates will be dropped sequentially in the order of Region, and then Baseline SV2A use (Yes or No) if further needed. The tipping point analysis based on MAR multiple imputation will be repeated until

none of the PSL treatment group is significantly different from placebo based on the logistic regression model.

8.1.2.5 The log of the odds ratio estimates from the logistic regression model are used when combining into a single inference using SAS PROC MIANALYZE. Subgroup analyses for the primary variables

The analyses described in Section 8.1.2.1 and 8.1.2.3 will be repeated for the subgroups described in Section 4.8. In the subgroup analyses by region and Baseline SV2A use, the corresponding stratification factor will be removed from the model. These evaluations will be descriptive, and the model estimates and 95% CIs will be presented.

8.2 Statistical analysis of the secondary efficacy variables

Separate secondary efficacy variables have been designated for submission to US FDA/PMDA and submission to EMA.

8.2.1 Analysis of the secondary efficacy variables for submission to the US FDA, PMDA, and other regulatory authorities not referencing EMA

8.2.1.1 75% Responder Rate over the 12-week Maintenance Period

75% responder rate is the secondary efficacy variable for the US FDA and primary efficacy variable for the EMA. The analyses are described in Section 8.1.2.3.

8.2.1.2 50% Responder Rate over the 12-week Maintenance Period

Subjects with at least a 50% reduction in seizure frequency will be categorized as a 50% responder. The same methodology described in Section 8.1.2.3 will be used for 50% responder rate during the 12-week Maintenance Period. No multiplicity adjustment will be applied and tests will be carried out at a nominal two-sided 0.05 significance level.

8.2.1.3 Percent reduction from Baseline in observable focal-onset seizure frequency over the 12-week Maintenance Period

The third secondary efficacy variable is percent reduction from Baseline in observable focal-onset seizure frequency, over the 12-week Maintenance Period. The calculation of percent reduction from Baseline in seizure frequency is described in Section 8.1.1.2. The percent reduction in seizure frequency will be summarized descriptively.

Statistical comparisons between each PSL dose group and placebo will be performed on the FAS using the Wilcoxon-Mann-Whitney test. No multiplicity adjustment will be applied and tests will be carried out at a nominal two-sided 0.05 significance level. The Hodges-Lehmann nonparametric estimator will be used to estimate the median difference between each PSL dose group versus placebo, along with the corresponding 95% CI of the estimate.

In addition, the number and percentage of subjects within each of the following categories of percent reduction from Baseline will be summarized: <-25%, -25% to <25%, 25% to <50%, 50% to <75%, 75% to <100%, and 100%.

8.2.2 Analysis of the secondary efficacy variables for submission to EMA and regulatory authorities who reference EMA

8.2.2.1 The change in log-transformed observable focal onset seizure frequency from Baseline, over the 12-week Maintenance Period

The analysis described in Section 8.1.2.2 (for US FDA, PMDA, and other regulatory authorities not referencing EMA) of the change in log-transformed observable focal-onset seizure frequency from Baseline, over the 12-week Maintenance Period, serves as the key secondary variable for submission to EMA.

8.2.2.2 50% Responder Rate status over the 12-week Maintenance Period

This variable is also a secondary variable for FDA submission and is described in Section 8.2.1.2.

8.2.2.3 Percent reduction in observable focal-onset seizure frequency from Baseline, over the 12-week Maintenance Period

This variable is also a secondary variable for FDA submission and is described in Section 8.2.1.3.

8.3 Analysis of other efficacy variables

Other efficacy variables are listed in Section 2.2.1.3. These variables are the same for all regulatory agencies.

8.3.1 Derivations of other efficacy variables

For other efficacy variables based on seizure frequencies (observable focal-onset (Types IA1, IB, IC) and all Type I focal-onset seizures the frequencies), log-transformations, changes from Baseline, percent reduction from Baseline and Responder Rates during the evaluation period of interest are calculated similarly as described in Section 8.1.1, using the appropriate analysis period and responder criterion.

8.3.1.1 Seizure-freedom status (Yes/No)

A subject is defined as seizure free (ie, seizure-freedom status=Yes) during a specific evaluation period if they meet all of the following criteria:

1. The subject completed the specific time period.

2. The subject did not have any missing diary days over the time period. Missing diary day refers to no diary available at all for that day. If the diary for the day is present and 'no seizures' is checked then the diary day is not missing.

3. The subject did not report any seizure of any type over the time period.

8.3.1.2 Seizure-free days

The number of seizure-free days will be the total number of days within an interval for which daily diary data was available and indicated that no seizures occurred. The percentage of seizure-free days will be computed as 100 times the number of seizure-free days divided by the number of days for which daily diary data was available. Days without the corresponding daily diary data will not be used in these computations.

8.3.1.3 Seizure Severity Global Item (SSG) variables

The SSG consists of 1 item at baseline or 2 items during follow up from the Seizure Severity Questionnaire and asks the subjects to evaluate the severity of their seizures for the last 4 weeks and/or since the Baseline. The subject describes all seizure types when answering the questions.

The SSG is completed according to the schedule of study procedures in Table 2-2 (Visits 2, 4, 7 and 9) and is provided to each subject at the beginning of the visit. The SSG data are collected on 2 separate CRFs. On the "Seizure Severity Global Item – Baseline", seizure-intensity during the last 4 weeks is collected on a 7-point scale with 7 = very severe; On the "Seizure Severity Global Item – Follow-up" CRF, seizure-intensity during last 4 weeks is collected on a 7-point scale with 7 as very severe. Assessment of change since starting IMP, is also collected on a 7-point scale with 7 = much worse.

8.3.1.4 QOLIE-31-P variables

The QOLIE-31-P assesses subject functioning and health-related quality of life. The QOLIE-31-P (Cramer et al, 2003) is an adaptation of the original QOLIE-31 instrument (Cramer et al, 1998) that includes 31 items grouped into 7 multi item subscales (Seizure Worry [5 items], Overall Quality of Life [2 items], Emotional Well-being [5 items], Energy/Fatigue [4 items], Cognitive Functioning [6 items], Medication Effects [3 items], and Daily Activities/Social Functioning [5 items]) and 1 health status item.

In addition to the 31 items of the QOLIE-31, the QOLIE-31-P contains 7 items assessing the degree of "distress" associated with the topic of each subscale (ie, distress items) and 1 item asking about the relative importance of each subscale topic (ie, prioritization item).

The QOLIE-31-P will be completed according to the schedule of study procedures in Table 2-2 (Visits 2, 4, 7 and 9) and is provided to each subject at the beginning of the visit. The subject completes the questionnaire on his/her own. The Investigator or designee will verify that all questions have been answered. Further details about the QOLIE-31-P are provided in the scoring manual.

8.3.1.5 Hospital Anxiety and Depression Scale (HADS) score variables

The HADS is administered at Visits 2, 4, 7 and 9. The HADS scores for anxiety and for depression range from 0-21 with higher scores indicating a worse state. A score below 8 is considered to be normal (Zigmond and Snaith, 1983). HADS subscale scores will be determined by summing the scores of the 7 items belonging to each of the two subscales, i.e. anxiety (odd numbered questions) and depression (even numbered questions). The following rules will be applied for the computation of the subscale scores: 1) Missing items values will be set to the mean score of the subscale to which the item belongs, provided 50% or more of the items within the subscale are present. 2) The subscale scores will be calculated if 50% or more of the items within a subscale are present.

8.3.2 Analysis of other efficacy variables

Other efficacy variables and tests will be carried out at a nominal two-sided 0.05 significance level and no multiplicity adjustments will be applied.

8.3.2.1 Change from Baseline in log-transformed observable focal-onset seizure frequency over the first 4 weeks, second 4 weeks, and third 4 weeks of the 12-week Maintenance Period

The 28-day adjusted seizure frequencies during the Treatment Period will be computed using observed diary records for the following 4-week intervals: Visit 2 to Visit 4, Visit 4 to Visit 5, Visit 5 to Visit 6, and Visit 6 to Visit 7. The 28-day adjusted seizure frequency during the Treatment Period and change from baseline based on the observed data will be summarized descriptively by the 4-week interval.

The change from Baseline in log-transformed observable focal-onset seizure frequency by 4-week interval will be analyzed using a Mixed Model Repeated Measures (MMRM) model, including Baseline log-transformed seizure frequency as a continuous fixed effect covariate, and treatment, Region (Europeor Non-Europe), Baseline SV2A use (Yes or No), and visit as fixed effect factors, and Baseline × visit and treatment × visit interactions. MMRM assumes that missing data are missing at random and estimates the mean outcome at each time interval by treatment group. An unstructured covariance structure will be used. If the model does not converge, an appropriate covariance structure will be used instead. Estimates of effects and comparison contrasts and CI will be back-transformed for display in tables as described in Section 8.1.2.1.

8.3.2.2 Change from Baseline in log-transformed observable focal-onset seizure frequency over the16-week Treatment Period

The analyses of the change from Baseline in observable focal-onset seizure frequency during the entire 16-week Treatment Period will be analyzed for the FAS using the ANCOVA model on the log-transformed data, as specified for the primary efficacy analysis (Section 8.1.2).

8.3.2.3 The 50% responder rate over the 16-week Treatment Period

Analysis of the 50% responder rate during the entire 16-week Treatment Period will be analyzed, for the FAS, using the same logistic regression model as specified in Section 8.1.2.3.

8.3.2.4 The 75% responder rate over the 16-week Treatment Period

Analysis of the 75% responder rate during the entire 16-week Treatment Period will be analyzed, for the FAS, using the same logistic regression model as specified in Section 8.1.2.3.

8.3.2.5 The 90% and 100% responder rates over the 12-week Maintenance Period

Analysis of the 90% and 100% responder rates during the 12-week Maintenance Period will be analyzed for the FAS, using an exact conditional logistic regression model where treatment group is included in the model and region and Baseline SV2A use are included as strata.

8.3.2.6 Percent reduction in observable focal-onset seizure frequency from Baseline, over the 16-week Treatment Period

The same methodology described in Section 8.2.1.3 will be applied.

8.3.2.7 Change from Baseline in log-transformed focal-onset (Type I) seizure frequency over the 12-week Maintenance Period

The same ANCOVA model described in Section 8.1.2.1 will be applied.

8.3.2.8 The 50% responder rate status for focal-onset (Type I) seizures over the 12-week Maintenance Period

Analysis of the 50% responder rate for Type I focal-onset seizures during the 12-week Maintenance Period will be analyzed for the FAS, using the same logistic regression model as specified in Section 8.1.2.3).

8.3.2.9 The 75% responder rate for focal onset (Type I) seizures over the 12-week Maintenance Period

Analysis of the 75% responder rate for Type I focal-onset seizures during the 12-week Maintenance Period will be analyzed for the FAS, using the same logistic regression model as specified in Section 8.1.2.3.

8.3.2.10 The 90% and 100% responder rates for focal-onset (Type I) seizures over the 12-week Maintenance Period

Analysis of the 90% and 100% responder rates for Type I focal-onset seizures during the 12-week Maintenance Period will be analyzed for the FAS, using an exact conditional logistic regression model where treatment group is included in the model and region and Baseline SV2A use are included as strata.

8.3.2.11 Percent reduction in focal-onset (Type I) seizure frequency from Baseline, over the 12-week Maintenance Period and the 16-week Treatment Period

The same methodology described in Section 8.2.2.3 will be applied.

8.3.2.12 Change from Baseline in log-transformed Type IA1, IB, or IC seizure frequency over the12-week Maintenance Period

The change from Baseline in Type IA1, IB, or IC seizure frequency during the12-week Maintenance Period by each seizure type separately will be analyzed for the FAS using the ANCOVA model on the log-transformed data, as specified for the primary efficacy analysis (Section 8.1.2).

8.3.2.13 The 50% responder rate for Type IA1, IB, or IC seizure over the 12-week Maintenance Period

50% responder rate in Type IA1, IB, or IC seizure over the 12-week Maintenance Period by each seizure type separately will be analyzed for the FAS, using the same logistic regression model as specified in Section 8.1.2.3.

8.3.2.14 The 75% responder rate for Type IA1, IB, or IC seizure over the 12-week Maintenance Period

50% responder rate in Type IA1, IB, or IC seizure over the 12-week Maintenance Period by each seizure type separately will be analyzed for the FAS, using the same logistic regression model as specified in Section 8.1.2.3.

8.3.2.15 Percent reduction in Type IA1, IB, or IC seizure frequency from Baseline, over the 12-week Maintenance Period and the 16-week Treatment Period

The same methodology described in Section 8.2.2.3 will be applied. Analysis will be done by each seizure type separately.

8.3.2.16 Seizure-freedom status (yes/no) during the 12-week Maintenance and the 16-week Treatment Period

Seizure freedom status will be evaluated for each treatment by summarizing the percentage of seizure-free subjects as a response rate during the 12-week Maintenance Period and during the entire 16-week Treatment Period. The seizure freedom rate will be calculated based on the Completer Set. The seizure freedom rate for each of these periods will be analyzed using an exact conditional logistic regression model where treatment group is included in the model and region and Baseline SV2A use are included as strata.

8.3.2.17 Percentage of seizure-free days during the 12-week Maintenance Period and the 16-week Treatment Period

The percentage of seizure-free days during the Maintenance Period and Treatment Period will be summarized using descriptive statistics. The change in the percentage of seizure-free days from the Baseline Period to the Maintenance Period and Treatment Period will also be summarized.

The percentage of seizure-free days during the 12-week Maintenance Period and during the 16-week Treatment Period will each be analyzed using ANCOVA with treatment group as the main factor, Baseline percentage of seizure-free days as a continuous covariate, and the categorical factors Region (Europe or Non-Europe) and Baseline SV2A use (Yes or No). The 95% CI will be presented for estimates.

8.3.2.18 Cumulative responder rate during the 16-week Treatment Period

Cumulative responder rate curve will be generated by treatment group for the observable focal-onset seizures. The percent reduction in seizure frequency ranging from -25% to 100% will be shown on the X-axis and the percentage of responders experiencing at least the particular percent reduction will be shown on the Y-axis.

8.3.2.19 Change in the SSG score

The numbers and percentages of subjects in each severity category will be summarized descriptively for Baseline and at each scheduled assessment visit along with the numbers and percentages of subjects in each of the 7 categories of change (much better through much worse). Summary will be provided for Visit 2, Visit 4, Visit 7, and the Last Visit during the Treatment Period. All data will be listed by subject.

8.3.2.20 Change in the QOLIE-31-P score

The scoring algorithm for QOLIE-31-P is described in Section 8.3.1.3. Observed values and change from Baseline for QOLIE-31-P total score and subscale scores for Seizure Worry, Daily Activities/Social Function, Energy/Fatigue, Emotional Well-Being, Cognitive Function, Medication Effects, Overall Quality of Life, Health Status will be summarized descriptively for Visit 2, Visit 4, Visit 7, and the Last Visit during the Treatment Period. All data will be listed by subject.

8.3.2.21 Change in Hospital Anxiety and Depression Scale (HADS) score

The HADS observed scores and changes from Baseline for depression and anxiety will be summarized descriptively for Visit 2, Visit 4, Visit 7, and the Last Visit during the Treatment Period. All data will be listed by subject.

8.3.2.22 Time to return to the Baseline 28-day adjusted observable focal-onset seizure count

Time to return to the Baseline 28-day adjusted observable focal-onset seizure count during the 12-week Maintenance Period will be evaluated using Kaplan-Meier methods (French et al, 2015). The event date is the earliest date when the total number of seizures since the start of the Maintenance Period is equal or greater than the Baseline 28-day adjusted seizure count (ie, Baseline seizure frequency per 28-days described in Section 3.3.1). The time to event in days will be calculated as (the event date – start date of the Maintenance Period + 1). If the time to event is more than 28 days for a subject, it would indicate that during the Maintenance Period, it takes longer time for the subject to experience as many seizures as during the Baseline Period in 28 days, which is the result of reduced seizure frequency during the Maintenance Period. If the total number of seizures during the Maintenance Period is less than the Baseline 28-day adjusted seizure count, the subject will be censored as of the last day with non-missing seizure data during the Maintenance Period. Subjects who discontinued during the Titration and Stabilization Period will be censored as of Day 1. The median time to event and the associated 95% CI will be estimated using Kaplan-Meier methods. The log-rank test will be used to compare differences between each PSL dose group and placebo. The KM curves will be presented by treatment group.

8.3.2.23 Change from baseline in seizure frequency

The 28-day adjusted seizure frequency and change from baseline will be summarized descriptively by the treatment group in Titration and Stabilization, Maintenance, and Treatment Periods for observable focal-onset seizures and Type I seizures. The imputation rule described in Section 4.2.1 will be applied.

8.3.2.24 Additional figures for efficacy variables

The following figures will be generated using the FAS: median percent reduction in seizure frequency, 75% RR, and 50% RR in observable focal-onset seizures will be displayed for the 16-week Treatment Period and the 12-week Maintenance Period by treatment group.

8.3.2.25 Use of health-related outcomes and HRU

Health-related outcomes data and HRU data will be listed for the RS and summarized descriptively for the SS. Hospital and ER Visits will be listed for SS.

- Socio-professional status

Socio-professional status data are collected at Visit 1 and Visit 7/EDV. Variables include highest level of education, housing status, current professional status, current unemployed status, need for regular assistance due to epilepsy, and ability to drive. The number and percentages of subjects in each category will be summarized for Visit 1, Visit 7, and the Last Visit during the Treatment Period.

- Healthcare provider consultations not foreseen by the protocol

The number of health care provider consultations per subject with onset during the Treatment Period will be summarized as a continuous variable as well as in the following categories: 0, 1, 2, 3, 4, and 5 or more. Additionally, the number and percentage of consultations by type of provider (general practitioner, specialist physician, nurse, and other) will be presented for the Treatment Period.

- Hospital and ER visits

The number of hospitalizations per subject will be summarized as a continuous variable and categorical variable for the Treatment Period. ER visits will be extracted from the Hospitalization/ER Visit CRF page (if the initial entry point is ER). The number of ER visits will be summarized in the same manner as hospitalizations. Additionally, the number and percentage of subjects with each of the following categories of duration of hospital stay will be summarized: 0 days, 1-5 days, 6-10 days, 11-15 days, and >15 days.

- Caregiver assistance

Caregiver assistance data is collected on the CRFs "Caregiver Assistance Screening" and "Caregiver Assistance Follow-up". The number and percentages of subjects having a caregiver will be summarized by visit.

- Concomitant medical procedures

The number of concomitant medical procedures per subject during the Treatment Period will be summarized using the categories 0, 1, 2, and 3 or more.

- Number of school or working days lost

Number of school/working days lost data are collected on the CRFs "School and Workdays Lost Screening" and "School and Workdays Lost Follow-up". The number and percentages of subjects who lose school or work days as a result of epilepsy will be summarized by visit.

The percentage of days lost will be summarized by visit for subjects who have more than zero total number of school or work days. The percentage of days lost will be calculated as:

100 × (end date of absence – start date of absence +1)/ (3 × 30 + 1) for the screening visit. If the end date of absence is missing or after Visit 1 date, the end date of absence will be set to Visit 1; if the start date of absence is missing or prior to Visit 1-90, the start date of absence will be set to Visit 1-90.

100 × (end date of absence – start date of absence +1)/ (visit date of current visit – visit date of previous visit) for the later visits. If the end date of absence is missing or after the current visit date, the end date of absence will be set to the current visit date; if the start date of absence is missing or prior to the previous visit+1, the start date of absence will be set to the previous visit date+1.

If multiple absences are reported at a given visit, the sum of the duration of all absences will be used in the numerator.

9 PHARMACOKINETICS

9.1 Plasma concentrations of PSL and its major metabolites

Concentrations of PSL and its major metabolites will be determined from blood samples obtained during the Titration and Stabilization and Maintenance Periods (Visits 3, 4, 5, 6 and 7). Individual concentrations of PSL, [redacted] (from venous conventional sampling and dried blood (MITRA) sampling) and [redacted] (from venous conventional sampling) will be listed for subjects in PSL treatment groups for the PK-Set and will include visit, actual daily dose (mg), date and time of the most recent administration, scheduled sampling time per the CRF, actual date and time of sampling, time interval between plasma sample and the most recent administration (in hours with 2 decimal places). Samples excluded from the PK-PPS will be marked in the listing.

Values below the limit of quantification (LOQ) will be reported as BLQ (below the limit of quantification).

Concentrations of PSL and its [redacted] metabolite will be summarized by sampling method (venous, dried blood MITRA), PSL dose group, visit, and sampling times for the PK-PPS using the following descriptive statistics: number of observations, geometric mean, 95% CI of the geometric mean, geometric coefficient of variation, arithmetic mean, SD, median, and minimum and maximum values. Measured values below the LOQ will be excluded for the calculation of descriptive statistics but listed. Concentrations for [redacted] (only in venous blood) will also be summarized similarly. Only PSL samples taken up to the (date of the last dose of study medication +1) will be included in the summary.

Of note, geometric mean is calculated as: exp (arithmetic mean of log-transformed concentrations); upper and lower bounds of the 95% confidence interval (CI) of the geometric mean are calculated as exp (upper) and exp(lower) of the 95% CI of the arithmetic mean of log-transformed concentrations; geometric coefficient of variation is calculated as: 100 × sqrt [exp (variance of log-transformed concentrations)-1].

The PK samples will be summarized based on the actual time since the most recent dose using the following time categories:

- >0 to <45 min after dosage: 0.5h (30min)
- 45 to <75 min after dosage: 1h (60min)
- 75 to <105 min after dosage: 1.5h (90min)
- 105 to <150 min after dosage: 2h (120min)
- 150 to <210 min after dosage: 3h (180min)
- 4h: 3.5h to <4.5h
- 5h: 4.5 to <5.5h
- 6h: 5.5 to <6.5h
- 8h: 6.5 to <9h
- 10h: 9h to <11h or >-3h to <-1h

- 12h: 11h to <14h or >=-1h to <=0 (time points for the trough concentration,)

The geometric mean and associated 95% CI for the trough concentrations of PSL and [redacted] from MITRA will be presented by PSL treatment group and visit using semi-log plots.

9.2 Plasma concentrations of concomitant AEDs

Blood samples for measurement of concomitant AED concentrations are collected at Visits 1, 2, 6, and 7. The concomitant AED concentrations will be summarized by visit and treatment group using the same descriptive statistics above (<LOQ values will be excluded) for the AED-PK-PPS. Only AED PK samples taken up to the (date of the last dose of study medication +1) will be included in the summary.

The AEDs investigated with mixed models will be those with data available for at least 10 evaluable subjects in one of the treatment groups (subset of AED-PK-PPS). An evaluable subject is defined as a subject:

- with at least one AED measure (>LOQ) at baseline and at least one AED assessment (>LOQ) during the maintenance period
- who received constant dose of AED for at least 14 days prior to the AED samples

Plasma concentration data for concomitantly administered AEDs (values <LOQ will be excluded) will be assessed by evaluating ratios of steady state levels during the Maintenance Period vs baseline levels. The baseline concentration is defined as the arithmetic mean concentration (if multiple concentrations are available at Visits 1 and 2) or the single concentration (if only 1 concentration is available at Visit 1 or Visit 2). Difference between log-transformed AED concentration at Visits 6 and 7 and baseline will be assessed using Mixed Model Repeated Measures (MMRM). The model will include log-transformed baseline concentration, visit, treatment, and treatment-by-visit interaction as fixed effects. An unstructured covariance structure will be used. If the model does not converge, an appropriate covariance structure will be used instead. Geometric least-squares (LS) means ratios and associated 90% CIs for each visit, by treatment group and PSL total will be calculated by exponentiation of the log-transformed data. Changes in AED concentration during the Maintenance Period and baseline will be considered clinically relevant if the respective 90% CIs fall entirely outside the conventional 0.80-1.25 limits. Forest plots will be provided on these (LS) means ratios and associated 90% CIs.

9.3 Other PK analyses/variables

Other PK analyses, including population PK analyses and exploratory PK analyses will be described in a separate PK Data Analysis Plan and will be reported separately.

10 SAFETY ANALYSES

The SS will be used to summarize and analyze all safety variables. In case of dosing administration error, summaries and analyses using the SS will be conducted according to actual treatment administered according to the rule described in Section 3.6. Safety data will be summarized for each treatment group and the PSL total group.

10.1 Extent of exposure

Extent of exposure will be based on the SS. The date of first dose is reported on First Administration of Study Medication CRF. The date of last dose is reported on the Study Termination CRF. If the date of last dose is missing due to lost to follow-up, the date of the last scheduled or unscheduled visit will be used.

The duration of study drug exposure for the Treatment Period will be calculated as the date of the last dose of study drug during the 16-week Treatment Period minus the date of first dose of study drug plus 1 day. Date of the last dose of study drug during the 16-week Treatment Period is defined as the overall study last dose date or the end date of the 16-week Treatment Period, whichever is earlier.

Exposure (in days) will be summarized as a continuous variable for the 16-week treatment period. The number and percentage of subjects with the following categories of durations of exposure for the Treatment Period will also be summarized: >0 weeks, >=4 weeks, >=8 weeks, >=12 weeks, >=16 weeks. The same summaries will be repeated for the subjects who received dose reduction during the Stabilization Period.

10.2 Adverse events

Adverse events are recorded on the AE CRF as they occur, from the time informed consent is granted until study completion or study termination (end of the SFU period 30 days after the last IMP intake). All AEs will be coded using the latest available version of MedDRA.

A treatment-emergent adverse event (TEAE) is defined as any event not present prior to the initiation of the first dose of study treatment or any unresolved event already present before initiation of the first dose that worsens in intensity following exposure to the treatment. The number and percentage of subjects who experience TEAEs at any time during the study will be summarized by SOC and PT. The following tabular summaries will be presented for the SS:

- Incidence of pre-treatment AEs. Pre-treatment AEs are AEs with start dates prior to the date of first dose of IMP.
- Incidence of TEAEs during the Treatment Period – Overview. Of note, the corresponding table is required for data transparency reporting.
- Incidence of TEAEs by period (Treatment Period, Titration and Stabilization Period, Maintenance Period, Conversion Period, and Taper and SFU Period)
- Incidence of Serious TEAEs by period (Treatment Period, Titration and Stabilization Period, and Maintenance Period)
- Incidence of TEAEs leading to discontinuation by period (Treatment Period, Titration and Stabilization Period, and Maintenance Period)
- Incidence of TEAEs leading to dose reduction during the Stabilization Period

The following will be presented for TEAEs during the overall Treatment Period:

- Subject numbers for TEAEs
- Incidence of TEAEs occurring in at least 5% of subjects in any treatment group

- Incidence of TEAEs occurring in at least 2% of subjects in any PSL group and greater than placebo group
- Incidence of TEAEs by Relationship
- Incidence of TEAEs by Maximum Intensity
- Incidence of TEAEs of special interest
- Incidence of SAEs by Relationship. Of note, the corresponding table is required for data transparency reporting.
- Incidence of Fatal TEAEs by Relationship. Of note, the corresponding table is required for data transparency reporting.
- Incidence of Non-Serious TEAEs above the threshold of 5% of subjects in any treatment group. Of note, the corresponding table is required for data transparency reporting.
- Summary of the duration in days per event for the following TEAEs: somnolence, dizziness, fatigue, irritability and headache. In this analysis, if an AE is ongoing, the duration will be calculated till the date of final contact.

Summaries will be presented based on standard Sponsor AE table formats and considering formats used for the PSL program.

Where dates are missing or partially missing, AEs will be assumed to be treatment-emergent, unless there is unmistakable evidence (through comparison of partial dates, see Section 4.2) to suggest that the AE started prior to the first dose of study treatment. Summary tables will contain counts of subjects, percentages of subjects in parentheses and the number of events where applicable. A subject who has multiple events in the same MedDRA category (SOC or PT) will be counted only once in the subject count for that category, however all events will be included in the event count for the category. In summaries including relationship to study treatment, the following relationships will be summarized: 'Not related', 'Related'. A subject may be counted more than once according to the relationship to study treatment. Events with missing relationship will be considered as 'Related' to the last given study product for summary purposes but recorded as missing in the listings. In summaries of the maximum intensity, the following intensity categories will be summarized: 'Mild', 'Moderate', 'Severe'. Subjects who experience the same event multiple times, with differing severities, will be included in the most severe category. Events with missing intensity will be considered as 'Severe' events for summary purposes but recorded as missing in the listings. The main reasons for treatment discontinuation will be listed by subject. The daily dose of study medication corresponding to the AE onset date will be included in the listing. Daily dose will be derived from 'Study Medication Administration' CRF.

Adverse event summaries will be ordered in terms of decreasing frequency for SOC, and PT within SOC, within the PSL total group column.

10.3 Clinical laboratory evaluations

Clinical laboratory hematology, chemistry and urinalysis measurements obtained from blood/urine samples collected throughout the study are presented in Table 10-1.

During the study, non-protocol-specified lab parameters (unplanned) may be collected. Summaries of lab parameters will only include planned parameters as specified in the protocol. All lab parameter values will be listed and summarized using international units.

The observed value and change from Baseline will be summarized descriptively by treatment group and PSL total group and scheduled study visit. The Last Visit, minimum, and maximum post-baseline values during the Treatment Period will also be included. These summaries will be organized by lab function panel and parameter.

Shift from Baseline to the maximum and minimal values during the Treatment Period based on normal range (Low, Normal, High) will be provided for hematology and blood chemistry parameters in Table 10-1.

Possibly clinically significant treatment-emergent (PCST) criteria have been developed based on FDA Division of Neuropharmacologic Drug Products guidelines with some UCB-defined additions and are provided in Appendix 13.1. For lab parameters with PCST criteria, the number and percentage of subjects with a PCST value at any time (scheduled and unscheduled visits) during the Treatment Period will be summarized by treatment group and PSL total group. . Treatment-emergent values are those occurring any time on or after the first dose of study medication in EP0091. Subject numbers for those meeting the PCST criteria will also be presented.

Table 10–1: Laboratory measurements

Hematology	Chemistry	Urinalysis
Basophils	ALP	Glucose
Eosinophils	ALT	pH
Hematocrit	AST	RBC
Hemoglobin	Bilirubin	Total protein
Lymphocytes	BUN or urea	WBC
MCH	Calcium	Microscopy (WBC, RBC, casts, crystals, bacteria) [a]
MCHC	Chloride	**Other**
MCV	Creatinine	FSH[b]
Monocytes	Glucose	
Neutrophils	HDL	
Platelet count	LDH	
RBC count	LDL	
WBC count	Magnesium	
	Potassium	
	Sodium	
	Total bilirubin	
	Total cholesterol	

ALP=alkaline phosphatase; ALT=alanine aminotransferase; AST=aspartate aminotransferase; BUN=blood urea nitrogen; HDL=high density lipoprotein; FSH=follicle stimulating hormone; LDH=lactate dehydrogenase; LDL=low density lipoprotein; MCH=mean corpuscular hemoglobin; MCHC=mean corpuscular hemoglobin concentration; MCV=mean corpuscular volume; RBC=red blood cell; WBC=white blood cell

[a] Microscopy will be performed only in case of abnormalities.

[b] Only applicable to postmenopausal women

10.3.1 Subjects with potential drug-induced liver injury (PDILI)

There are specific criteria described in the protocol Section 11 to evaluate subjects for potential drug-induced liver injury (PDILI). The evaluations required by protocol for PDILI subjects are collected on the following CRFs:

- Most Recent Study Medication Administration, for PDILI
- Laboratory Tests DILI
- Vital Signs DILI
- Hepatic Event Supplemental Medical History for PDILI
- Potential Hepato-Toxic Medications Inquiry for PDILI

- Symptoms of Hepatitis and Hypersensitivity for PDILI
- Lifestyle PDILI
- Family Medical History for PDILI

Listings will be prepared presenting subjects with PDILI data. A summary of number and percent of subjects meeting PDILI criteria (ALT, AST, total bilirubin, ALP, and presence of symptoms) during the Treatment Period (scheduled and unscheduled visits) will be provided following the UCB standard table shell for PDILI Data. Subjects who met these criteria will be listed.

ALT Criteria	AST Criteria	Total Bilirubin Criteria	ALP Criteria	Presence of Symptoms
≥3xULN	≥3xULN	≥2xULN	≥2xULN	NA
≥8xULN	≥8xULN	NA		NA
≥3xULN	≥3xULN	NA		Y
≥3xULN -<5xULN and ≥2x Baseline	≥3xULN -<5xULN and ≥2xBaseline	<2xULN		N
≥5xULN -<8xULN and ≥2x Baseline	≥5xULN -<8xULN and ≥2xBaseline	<2xULN		N
≥5xULN and ≥2xBaseline	≥5xULN and ≥2xBaseline	<2xULN		N

N=No; NA=Not Applicable; ULN= upper limit of normal; Y=Yes.

A summary table highlighting the potential cases of Hy's Law, within each treatment group will be presented. Hy's Law is defined as:

- AST ≥3xULN or ALT ≥3xULN and
- Total Bilirubin ≥2xULN

In order to meet the above criteria, a subject must experience the elevation in bilirubin and ALT or AST at the same visit. For example, a subject who experiences a >=2 x ULN elevation of bilirubin at one visit and a 3 x ULN elevation in ALT (or AST) at a subsequent visit has not fulfilled the Hy's law criteria.

10.4 Vital signs, physical findings, and other observations related to safety

10.4.1 Vital Signs

Vital measurements (including SBP, DBP, PR, RR and weight) are generally collected in standard units. If any measurements are collected in international units, they will be converted to standard units for summaries. Subject Listings will be prepared for vitals variables.

The observed value and change from Baseline will be summarized descriptively by treatment group and scheduled study visit. In the same table, the observed value and change from Baseline

will be summarized by treatment for all scheduled visits. The Last Visit, minimum, and maximum post-baseline values during the Treatment Period will also be included.

The number and percentages of subjects with abnormal vital signs and body weight during the Treatment Period will be presented by treatment group and PSL total group. The abnormal vital sign and body weight criteria are provided in Appendix 13.2. Subject numbers for those meeting abnormal criteria will also be presented.

10.4.2 Electrocardiograms

ECG parameters include heart rate, PR interval, QRS duration, QT interval, QTcB [QT corrected for heart rate using Bazett's formula], and QTcF [QT corrected for heart rate using Fridericia's formula].

The observed ECG parameter values and their change from Baseline will be summarized (SS) descriptively by treatment group and PSL total group for each scheduled assessment visit. The Last Visit, minimum, and maximum post-baseline values during the Treatment Period will also be included. In addition, the number and percentage of subjects with QTc (Bazett and Fridericia corrected) classifications of <450ms, 450 to <480ms, 480 to <500ms, and ≥500ms and change from baseline of <30ms, 30 to <60ms, and ≥60ms will be presented for each visit.

For each ECG, the overall ECG result, is also collected, categorized as one of: no abnormality, an abnormal but not clinically significant finding, or a clinically significant finding. The number and percentage of subjects with no abnormality, an abnormal but not clinically significant finding, and a clinically significant finding will be summarized for each of the scheduled assessment visits. Percentages for the visit will be relative to the number of subjects with an ECG result for the visit.

The number and percentages of subjects with abnormal ECG during the Treatment Period will be presented by treatment group and PSL total group. The abnormal ECG criteria are provided in Appendix 13.3. Subject numbers for those meeting abnormal criteria will also be presented.

10.4.3 Echocardiograms

Echocardiogram data are collected at Visit 1, Visit 6, and Visit 9. Depending on the availability of data, echocardiogram abnormalities (Left Ventricle, Left Atrium, Right Ventricle, Right Atrium, Pericardium, Pulmonary Artery Systolic Pressure and overall assessment) will be summarized by treatment group and PSL total group and scheduled visit as the number and percentage of subjects with an abnormality. In addition, Echocardiogram Valvular abnormality grade (Aortic Valve, Mitral Valve, Tricuspid Valve, Pulmonary Valve) described in Appendix 13.4 will be summarized descriptively. Valvular abnormality grade equal or larger than grade 2 is corresponding to valvular abnormal. Subject numbers with abnormality for any assessment will be provided.

10.4.4 Other safety variable(s)

10.4.4.1 Physical Examination

Data from the Physical Examination are only provided in subject data listings presented by treatment group, subject and visit, displaying all data collected for all subjects. No summaries will be provided. Findings that are considered clinically significant will be reported AEs.

10.4.4.2 Neurologic Examination Data

Data from the Neurological Examination are collected on the Neurological Examination Complete and Neurological Examination Brief CRFs and are not summarized. Data from the Neurological Examination are only provided in subject data listings presented by treatment group, subject and visit, displaying all data collected for all subjects. No summaries will be provided. Findings that are considered clinically significant will be reported as AEs.

10.4.4.3 Psychiatric and Mental Status Data

The Psychiatric and Mental Status assessment is performed at Baseline and all scheduled visits. These data are collected on the Psychiatric and Mental Status CRF. Assessment of specific domains of psychiatric and cognitive symptoms will be performed by a staff member trained in the identification of psychiatric symptoms. The parameters that evaluated are orientation, attention, memory, mood, and calculus. These parameters will be assessed as normal or abnormal and then determined whether clinically significant. The presence of psychiatric symptoms, mental impairment, or behavioral problems are also assessed and evaluated as normal or abnormal, and whether they are clinically significant.

For each of these assessments, the number and percentage of subjects with an abnormal result, and the number and percentage with an abnormal result considered clinically significant, will be summarized at each scheduled visit.

10.4.4.4 The Columbia-Suicide Severity Rating Scale (C-SSRS)

The C-SSRS questionnaire is self-administered by the subject and assessed by trained study personnel. This scale is used to assess suicidal ideation and behavior at Baseline (Visit 1), and at each subsequent study visit. C-SSRS data will be provided in subject listing for subjects with suicidal ideation and suicide behavior.

10.4.4.5 Clinical Institute Withdrawal Assessment-Benzodiazepines (CIWA-B)

Subjects not entering the open label extension study (OLE) are tapered off study medication after completing the Maintenance Period (or if discontinued from the study). As part of monitoring of subjects for withdrawal symptoms during the Taper Period, the CIWA-B evaluation is performed at the end of the Maintenance Period (Visit7), at the end of the Taper Period (Visit 8), and at the Safety follow-up visit (Visit 9). The CIWA-B questionnaire contains 22 questions, which are utilized to determine the type and the severity of withdrawal symptoms, ranging from mild, moderate, severe and very severe withdrawal symptoms (Busto et al, 1989). Subscores of each of the first 20 questions (scores from 0-4) are summed up to a total score:

Total score	Interpretation
1-20	Mild withdrawal
21-40	Moderate withdrawal
41-60	Severe withdrawal
61-80	Very severe withdrawal

In case of a missing subscore the total score is set to missing. The remaining two items of the 22 ask for sleeping duration and time to fall asleep. A by-subject listing will be provided, presenting the response values to all assessment parameters as well as the CIWA-B scores. In addition, a descriptive summary table will be prepared for total CIWA-B scores at scheduled visits.

11 OTHER ANALYSIS

Analyses for the exploratory nonhereditary pharmacogenomics and pharmacogenetics variables will be described in separate documents.

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13 APPENDICES

13.1 PCST Criteria for Hematology, Serum Chemistry and Urinalysis Parameters

13.1.1 Hematology

PARAMETER	*AGE RANGE*	*UNIT (conventional)*	*ABNORMALITY CRITERIA (conventional)*	*UNIT (standard)*	*ABNORMALITY CRITERIA (standard)*
Hematocrit	<2y	%	≤27 >45	%	≤27 >45
	2y - <18y		≤29 >47		≤29 >47
	≥18y		≤85% of LLN ≥115% of ULN)		≤85% of LLN ≥115% of ULN
Hemoglobin	<2y	g/dL	≤9.0 >15.0	g/L	≤90 >150
	2y - <18y		≤9.5 >16.0		≤95 >160
	≥18y		≤85% of LLN ≥115% of ULN		≤85% of LLN ≥115% of ULN
WBC/Leukocytes	<12y	10^9/L	<3.5 >15.0	G/L	<3.5 >15.0
	≥12y		<3.0 >12.0		<3.0 >12.0
Neutrophils Absolute	>1m	10^9/L	<1.5	G/L	<1.5
Lymphocytes	<6m	%	≤30.0	%	≤30.0
	6m - <6y		≤22.0		≤22.0
	6y - ≤18y		≤12.0 ≥80.0		≤12.0 ≥80.0
	≥18y		≤10.0 ≥80.0		≤10.0 ≥80.0

PARAMETER	*AGE RANGE*	*UNIT (conventional)*	*ABNORMALITY CRITERIA (conventional)*	*UNIT (standard)*	*ABNORMALITY CRITERIA (standard)*
Basophils	>1m	%	≥3.0	%	≥3.0
Eosinophils	>1m	%	≥10.0	%	≥10.0
Monocytes	>1m	%	≥20.0	%	≥20.0
Platelets	>1m	10^9/L	≤100 >600	G/L	≤100 >600
RBC/ Erythrocytes	<2y	10^{12}/L	<3.0	T/L	<3.0
	≥2y		<3.5		<3.5

Abbreviations: F=female; M=male; m=month; y= year. A month is defined as 30 days; a year is defined as 365.25 days.

13.1.2 Serum Chemistry

PARAMETER	*AGE RANGE*	*UNIT (conventional)*	*ABNORMALITY CRITERIA (conventional)*	*UNIT (standard)*	*ABNORMALITY CRITERIA (standard)*
AST (SGOT)	<14y	U/L	>180	U/L	>180
	≥14y		>144		>144
ALT (SGPT)	1y - <18y	U/L	>90	U/L	>90
	≥18y		>123		>123
Alkaline Phosphatase	<4y	U/L	>690	U/L	>690
	4y - <10y		>834		>834
	10y - <18y		>1174		>1174
	≥18y		>432 (F) >933 (M)		>432 (F) >933 (M)
GGT	<6m	U/L	>522	U/L	>522
	6m - <1y		>279		>279
	1y - <13y		>66		>66
	13y - <18y		>126		>126
	≥18y		>255		>255
Total Bilirubin	>1m	mg/dL	≥1.5	umol/L	≥25.656
Total Protein	2m-<1y	g/dL	<3.0 >10.0	g/L	<30 >100

PARAMETER	*AGE RANGE*	*UNIT (conventional)*	*ABNORMALITY CRITERIA (conventional)*	*UNIT (standard)*	*ABNORMALITY CRITERIA (standard)*
	≥1y		<4.3 >10.0		<43 >100
Albumin	<1y	g/dL	<1.6 >6.0	g/L	<16 >60
	≥1y		<2.4 >7.0		<24 >70
BUN	<1y	mg/dL	>21	mmol/L	>7.497
	≥1y		>30		>10.71
Urea	<1y	mg/dL	>42	mmol/L	>7.014
	≥1y		>60		>10.02
Creatinine	1y - <10y	mg/dL	>0.9	umol/L	>79.56
	10y - <16y		>1.4		>123.76
	≥16y		>1.6		>141.44
Creatinine Clearance*	All	mL/min	<70	mL/s	<1.169
Calcium	<1y	mg/dL	<6.9 >12.2	mmol/L	<1.725 >3.05
	1y - <18y		<7.4 >11.7		<1.85 >2.925
	≥18y		<7.9 >11.1		≤1.975 ≥2.775
Phosphorous	<1y	mg/dL	<1.8 >8.2	mmol/L	<0.5814 >2.6486
	≥1y		<1.8 >7.4		<0.5814 >2.3902

PARAMETER	*AGE RANGE*	*UNIT (conventional)*	*ABNORMALITY CRITERIA (conventional)*	*UNIT (standard)*	*ABNORMALITY CRITERIA (standard)*
Potassium	<1y	mEq/L	<3.0 >6.5	mmol/L	<3.0 >6.5
	≥1y		<3.0 >5.8		<3.0 >5.8
Sodium	>1m	mEq/L	≤130 ≥150	mmol/L	≤130 ≥150
Glucose	>1m	mg/dL	<50 >180	mmol/L	<2.775 >9.99
Total Cholesterol	1y - <18y	mg/dL	>250	mmol/L	>6.475
	≥18y		>300		>7.77
LDL (calculated)	1y - <18y	mg/dL	>140	mmol/L	>3.626
	≥18y		>200		>5.18
HDL	≤2y	mg/dL	<10	mmol/L	<0.259
	>2y		<20		<0.518
Triglycerides	<1y	mg/dL	>750	mmol/L	>8.475
	≥1y		>250		>2.825

PARAMETER	*AGE RANGE*	*UNIT (conventional)*	*ABNORMALITY CRITERIA (conventional)*	*UNIT (standard)*	*ABNORMALITY CRITERIA (standard)*
Uric Acid	<1y	mg/dL	>7.7	umol/L	>457.996
	1y - <13y		>6.5		>386.62
	13y - <18y		>8.6		>511.528
	≥18y		>6.8 (F) >9.6 (M)		>404.464 (F) >571.008 (M)
Thyroxine (T4)	<1y	ug/dL	≤4.3 ≥18.4	nmol/L	≤55.3453 ≥236.8264
	≥1y		≤3.8 ≥13.5		≤48.9098 ≥173.7585
Globulin	<1y	g/dL	<1.0 >3.8	g/L	<10 >38
	≥1y		<1.2 >4.4		<12 >44

Abbreviations: ALT= alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; dL = deciliter; F=female; GGT: gamma-glutamyltransferase; HDL = high density lipoprotein; LDL = low density lipoprotein; L = liter; M=male; m = month (a month is defined as 30 days) mg = milligram; mmol = millimoles; µg = microgram; U = unit; ULN = upper limit of normal; y = years (a year is defined as 365.25 days)
*Schwartz equation (patients <12y): Cr Cl ml/min = [Height (cm) * 0.55] / serum creatinine Cockroft equation (patients ≥12y): Male: Cr Cl ml/min = [(140-age) x body weight (kg)] / (72 x serum creatinine); Female: Cr Cl ml/min = [(140-age) x body weight (kg)] / (72 x serum creatinine)] x 0.85

13.1.3 Urinalysis

Qualitative urine parameters are generally reported by a descriptive score, which differs among laboratories. For data analysis purpose, a four-point scale is used. Five-point, six- point, or seven-point scales will be collapsed into a four-point scale first. A value is considered possibly clinically significant treatment emergent abnormal if an upward shift of at least 2 degrees from the baseline occurs under investigational treatment. To collapse the results in a five-point scale into a four-point scale, the lowest two positive results will be combined (see example below). For results reported with a scale of more than five-point, please consult your study physician for how to collapse into four-point scale.

Original Five-point Scale	**Four-point Scale**
Negative/None	Negative/None
Trace/Rare/Mild/A Few	Trace/1+/Rare/Mild/A Few
1+	
2+/Mod	2+/Mod
3+/Sev	3+/Sev

13.2 Abnormal Criteria for Vital Sign and Body Weight Parameters

Abnormality criteria to be applied in the assessment of vital signs parameter values are given below.

PARAMETER	*AGE RANGE*	*ABNORMALITY CRITERIA*
Pulse Rate (beats/minute)	<6m	<100 >180
	6m - <3y	<90 >150
	3y - <12y	<60 >130
	12y - <17y	<50 >120
	≥17y	<50 and a decrease from Baseline of ≥15 >120 and an increase from Baseline of ≥15
Systolic Blood Pressure (mmHg)	<6m	<60 >100
	6m - <3y	<70 >120
	3y - <12y	<80 >140
	12y - <17y	<90 >160
	≥17y	≤ 90 and a decrease from Baseline of ≥20 ≥ 180 and an increase from Baseline of ≥20
Diastolic Blood Pressure (mmHg)	<6m	<40 >65
	6m - <3y	<45 >75
	3y - <12y	<50 >80
	12y - <17y	<50 >105
	≥17y	<50 and a decrease from Baseline of ≥15 >105 and an increase from Baseline of ≥ 15
Respiratory Rate (breaths/minute)	<6m	<25 >55
	6m - <3y	<20 >45
	3y - <12y	<15 >35
	≥12y	<10 >25

PARAMETER	*AGE RANGE*	*ABNORMALITY CRITERIA*
Temperature	>1m	>101 ^{0}F (38.3^{0}C)
Body Weight	1m - <17y	<3% or 97% of the normal body weight growth curve ranges based on gender and the age of subject on date of weight assessment[a]
	≥17y	≥ 10% change from Baseline (an increase or a decrease)[a]

Abbreviations: m = month, y = year. A month is defined as 30 days; a year is defined as 365.25 days. [a]source: http://www.cdc.gov/growthcharts/

13.3 Abnormal Criteria for ECG

Abnormality criteria to be applied in the assessment of ECG parameter values are given below:

Parameter	Age	Abnormality Criteria
QT interval (ms)	1m-<12y	>500
	>12y	>500 or ≥60ms increase from Baseline
QTc(F) (ms)	<6m	>490, or >15% increase from Baseline
	6m-<3y	>440, or >15% increase from Baseline
	3y-<12y	>440, or >15% increase from Baseline
	>12y- <17y	>440, or >15% increase from Baseline
	≥17y	>500 or ≥60ms increase from Baseline
QTc(B) (ms)	<6m	>490, or >15% increase from Baseline
	6m-<3y	>450, or >15% increase from Baseline
	3m-<12y	>450, or >15% increase from Baseline
	>12y- <17y	>450, or >15% increase from Baseline
	≥17y	>500 or ≥60ms increase from Baseline
PR interval (ms)	<6m	>150, or >25% increase from Baseline
	6m-<3y	>170, or >25% increase from Baseline
	3y-<12y	>180, or >25% increase from Baseline
	>12y - <17y	>200, or >25% increase from Baseline
	≥17y	Treatment-emergent value >200, >220, >250
QRS interval (ms)	<6m	>90, or >25% increase from Baseline
	6m-<3y	>90, or >25% increase from Baseline
	3y-<12y	>100, or >25% increase from Baseline
	>12y - <17y	>110, or >25% increase from Baseline
	≥17y	Treatment-emergent value >100, >120, >140
Heart rate (bpm)	<6m	<100, >180
	6m-<3y	<90, >150
	3y-<12y	<60, >130
	≥12y	<50, >120

Abbreviations: bpm = beats per minute; m = months; ms = milliseconds; QTc = corrected QT interval; y = years. A month is defined as 30 days; a year is defined as 365.25 days.
Note: Treatment-emergent is defined as meeting the criteria at any post-Baseline visit during the Treatment Period (including unscheduled visits) and not meeting the same criteria during Baseline

13.4 Echocardiogram Valvular Abnormality Grading Criteria

Echocardiogram Valvular Abnormality	Severity / Description	Potential Cardiovascular Signs/Symptoms	Action
Grade 0	Absent: no regurgitation, no stenosis	None reported	None
Grade 1	Mild: trace or barely detected regurgitation/stenosis	Minimal to none	None; continued observation
Grade 2	Moderate: regurgitation/stenosis with intermediate values	Symptoms[a]: Shortness of breath on exertion or at rest; palpitation; syncope; anginal or pericarditic chest pain; fatigue or weakness	For a Grade 2/moderate severity, a decision to discontinue is based on severity of clinical signs/symptoms; if accompanied with moderate to severe signs/symptoms this results in subject discontinuation.
Grade 3	Severe: regurgitation/stenosis in the extreme range, often accompanied by other symptoms (eg, pulmonary congestion)	Signs: Pulmonary arterial pressure ≥40mm Hg and rise of ≥10mmHg; pulmonary edema; peripheral edema or ascites; atrial fibrillation or malignant arrhythmia; hypotension	Discontinuation of subject. For a Grade 3 of severe, subject should be discontinued regardless of accompanying clinical symptoms.
Grade increase by 2 levels	Increasing from: Grade 0 to 2 or Grade 1 to 3	Rapid onset of above signs/symptoms	A jump of 2 grades to Grade 2/moderate accompanied with moderate to severe signs/symptoms results in subject discontinuation. A jump of 2 grades to Grade 3/severe (with/without symptoms) will result in subject discontinuation.

[a]Note: Based on the New York Heart Association Classification of symptoms. Other echocardiogram measurements are described in the study Echocardiogram Manual.

14 AMENDMENT(S) TO THE SAP

14.1 Amendment 1

Rationale for the amendment

The primary purpose of this amendment is to remove Multiple Comparison Procedures – Modeling (MCP-Mod) analyses in accordance with Protocol Amendment 2 and to add sensitivity analyses to evaluate the impact of missing data on the primary efficacy variable.

Modifications and changes

Global Changes

Section 2 Protocol Summary has been updated to use the same order and text as in the Protocol Amendment 2. Selected texts in other sections have been modified to minimize repetitions and provide clarifications and additional details to the planned analyses.

Major specific changes

Change #1

Table 3-1 Start and end of EP0091 study periods

Period	Start of Period	End of Period	Details
Baseline (Week -4)	Date of informed consent at Visit 1	Date of the day before the date of Visit 2.	This is an approximate 28-day period for calculation of Baseline seizure frequencies. Study drug is dispensed, and first dose is generally taken the day of the Baseline Visit (Visit 2, Day 1).
Dose Titration plus Stabilization	The date of the Baseline Visit, (Visit 2, Day 1).	The date of the day before Visit 4.	For evaluation purposes, if results are presented by study period, the Dose Titration and the Stabilization interval will be considered together (approximately 4 weeks in total). Dose Titration is a period of dose increases to reach the protocol specified dose. Stabilization is an approximate week-long interval to stabilize at the target dose level. During stabilization the dose may be adjusted once (i.e. to a fallback dose). Note that seizure counts collected from the diary returned on Day 1 are included in the baseline period seizure counts.
Maintenance	The date of Visit 4.	The date of Visit 7	This is a 12-week period where the subject remains on the protocol-specified dose. Note that seizure counts collected from the diary returned at Visit 4 are included in the previous period seizure counts.
16-week Treatment Period	The date of the Baseline visit (Visit 2)	The date of Visit 7	
Taper/Conversion	The date of the day after Visit 7	The date of Visit 8	This is a 3- to 4-week period of dose tapering or dose conversion to enable the subjects to end the study, or enroll into the OLE study EP0093, respectively.
Safety Follow-up	The date of the day after Visit 8	Date of Visit 9 for subjects not entering OLE EP0093	Only subjects not entering the OLE Study EP0093 return for the SFU visit. Subjects not entering OLE will have an additional ECHO at 6 months after the SFU visit. SAEs will be collected until the 6-month echo.

OLE=open-label extension; SFU=Safety Follow Up

Has been changed to:

Period	Start of Period	End of Period	Details
Baseline (Week -4)	Date of informed consent at Visit 1	Date of the day before the date of Visit 2.	This is an approximate 28-day period for calculation of Baseline seizure frequencies. Study drug is dispensed, and first dose is generally taken the day of the Baseline Visit (Visit 2, Day 1). Note the pre-dose assessments on the date of Visit 2 will also be included in the Baseline Period.
Titration and Stabilization	The date of the Baseline Visit, (Visit 2, Day 1).	The date of the day before Visit 4 or the end of the treatment period if the subject has discontinued prior to Visit 4.	For evaluation purposes, if results are presented by analysis period, the Titration and the Stabilization interval will be considered together (approximately 4 weeks in total). Titration is a period of dose increases to reach the protocol specified dose. Stabilization is an approximate week-long interval to stabilize at the target dose level. During stabilization the dose may be adjusted once (i.e. to a fallback dose).
Maintenance	The date of Visit 4.	The date of Visit 7 or the end of the treatment period if the subject has discontinued prior to Visit 7.	This is a 12-week period where the subject remains on the randomized target dose (or fallback dose, if applicable).
16-week Treatment Period	The date of the Baseline visit (Visit 2)	The date of Visit 7 or the end of the treatment period if the subject has discontinued prior to Visit 7.	Titration and Stabilization Period and Maintenance Period combined.
Conversion	The date of the day after Visit 7	The date of Visit 8.	This is a 3- -week period of dose conversion to enable the subjects to enroll into the OLE study EP0093.
Taper and Safety Follow-up	The date of the day after Visit 7/EDV	The date of final contact.	Subjects who withdraw from the study or decide not to participate in the OLE study will be tapered off the IMP during a 3-week period followed by a 1-week drug-free period. A SFU visit will be performed 30 days after the last IMP intake.

OLE=open-label extension; SFU=Safety Follow Up

Change #2

The following has been added:

3.2.5 Last Visit during the Treatment Period

The Last Visit for an assessment is the last non-missing assessment during the Treatment Period. All scheduled and unscheduled assessments within the Treatment Period will be considered. Last

Visit will be determined separately each study assessment. Last visit during the Treatment Period will be included in the by-visit summary unless noted otherwise.

Change #3

Section 3.5.4 Full Analysis Set

The Full Analysis Set (FAS) consists of all subjects in the RS who were administered at least 1 dose or a partial dose of IMP and have at least 1 post-Baseline visit during the Treatment Period. In case of dosing administration error, or change in treatment dose, summaries and analyses using the FAS will be conducted according to randomized treatment. The FAS will be the primary analysis set for all efficacy summaries and analyses.

Has been changed to:

The Full Analysis Set (FAS) consists of all subjects in the RS who were administered at least 1 dose or a partial dose of IMP and have Baseline and at least 1 post-Baseline seizure frequency data during the Treatment Period. In case of dosing administration error, or change in treatment dose, summaries and analyses using the FAS will be conducted according to randomized treatment. The FAS will be the primary analysis set for all efficacy summaries and analyses.

Change #4

Section 3.5.6.2 Pharmacokinetic Per-Protocol Set

A PK Per Protocol Set (PK-PPS) may be identified for active treatment groups, which would exclude subjects with major deviations that could impact PK evaluations. Subjects to be excluded from this PK-PPS, for example, those with values that are BLQ, will be identified during a pre-analysis data review meeting of PK variables.

Has been changed to:

A PK Per Protocol Set (PK-PPS) will be identified for active treatment groups, which would exclude subjects or PK sample data points with major deviations that could impact PK evaluations. Subjects or PK sample data points to be excluded from this PK-PPS, will be identified during a pre-analysis data review.

Change #5

Section 3.6

Treatment crossover Subjects (including any subjects with dosing errors) will be analyzed for efficacy according to their randomized treatment assignment and not the actual treatment received.

Safety analyses will be based on the SS. It is expected that subjects will receive the randomized treatment and be analyzed according to that assigned treatment. However, if a subject were to experience a dosing error resulting in treatment crossover, the subject will be analyzed as follows. If, after unblinding, it is determined that a subject randomized to placebo received PSL at any time, then for safety analyses the subject will be reallocated to the appropriate PSL dose group. If the dosing error exposes the subject to more than one dose level, the subject will be reallocated to the treatment arm for the lowest dose level. If a subject is randomized to PSL but experiences a dosing error resulting treatment with placebo, that subject will only be reallocated to the placebo treatment group if the subject never received a dose of PSL.

Has been changed to:

The FAS will be the primary analysis set for all efficacy summaries and analyses. Treatment crossover Subjects (including any subjects with dosing errors) will be analyzed for efficacy according to their randomized treatment assignment and not the actual treatment received.

Safety analyses will be based on the SS. It is expected that subjects will receive the randomized treatment and be analyzed according to that assigned treatment. However, if a subject were to experience a dosing error resulting in treatment crossover, incorrectly treated subjects will be evaluated during the blinded data evaluation meetings to assess the potential impact of such cases and any special considerations for statistical analyses.

Change #6

The following has been added in Section 4.1:

Investigative sites have been identified in the following regions and countries at the time of this SAP amendment. More regions and/or countries may be identified and will be included in the analyses in accordance to the randomization strata:

- Europe (Australia, Belgium, Bulgaria, Czech Republic, France, Germany, Hungary, Italy, Lithuania, Poland, Portugal, Slovakia, Spain, Turkey, and United Kingdom)
- North America (Canada, Mexico, and United States)
- Asia (Japan)

Change #7

Section 4.2.1 Handling of missing data for efficacy variables based on diary-collected seizure frequency

Seizure frequency will be computed over non-missing diary days. Calculation of seizure frequency is described in Section 8.1.1. Missing seizure diary days will not be considered in the calculation of seizure frequency. For subjects who prematurely discontinue, or otherwise have missing diary days, the calculation of the seizure frequency over a specified period will be based on available seizure diary up to the last diary entry of the period. This effectively imputes the unobserved seizures after discontinuation with the seizure frequency observed prior to discontinuation. Generally, compliance with the daily seizure diary is expected to be high in a refractory population and, therefore, the impact of missing diary data is expected to be minimal. However, the impact of missing diary data cannot be ruled out, and missing data will be assessed as part of the database pre-lock meeting to ensure an acceptable level of compliance with the seizure diary across the study population. Diary compliance evaluation is described in Section 7.2. Subjects with diary data deemed unacceptably incomplete (during blinded data review) for the primary endpoint may be excluded from the PPS supportive analyses.

- Efficacy analyses of changes from Baseline, Percent reduction from Baseline, and seizure-free days
  - Continuous variables of change from Baseline, percent reduction from Baseline in seizure frequency over the 12-week Maintenance Period, changes from Baseline to successive 4 week intervals within the Maintenance Period, and number of seizure-free days within the 12-week Maintenance Period:

The specified primary period of evaluation for changes in 28-day adjusted seizure frequency is during the 12-week Maintenance Period. For certain other efficacy variables, the period of evaluation is the entire 16-week Treatment Period, or during 3 successive 4-week intervals within then Maintenance Period. If a subject completes all or part of the 12 week Maintenance Period but has no seizure diary records at all during the period, such that seizure frequency cannot be calculated, then the 28-day adjusted seizure frequency will be imputed using the diary data from the most recent study period available (starting with the Stabilization Period if available, and using the Dose Titration Period data if no data from the Stabilization Period are available). There will be no use of Baseline diary data to compute any post-Baseline seizure frequencies.

- Continuous variables of change from Baseline and percent reduction from Baseline in seizure count over the entire 16-week Treatment Period

Since the calculation of the seizure frequency over a specified period will be based on available seizure diary from the start of the Treatment Period up to the last diary entry, for FAS (subjects must have at least one post-baseline visit), if at least one diary day entry is returned, missing data (unobserved seizures) during the Treatment period are effectively imputed. If there are any subjects in the FAS who do not return any seizure diary data at all, those dropouts will not be included in the analysis.

- Seizure clusters

Investigator sites are to report the number of cluster episodes rather than reporting the estimated number of individual seizures. No imputation will be applied for any seizure counts corresponding to reports of cluster seizures.

- Responder Analyses

For the main analyses of responder rates (RR), including seizure-free status rates, observed data will be used, with no imputation of missing status. However, a sensitivity analysis of the 75% and 50% RR may be performed in which missing data will be handled using non-responder imputation (NRI). That is, subjects who have missing data at the time point or interval of evaluation will be treated as though they did not respond to the treatment.

Has been changed to:

4.2.1 Handling of missing data in seizure frequency

Unless noted otherwise, the imputation described below will be applied to seizure frequency. The responder status will be determined based on the imputed seizure frequency. Sensitivity analyses for missing data are described in Section 8.1.2 for the primary efficacy variable.

4.2.1.1 Missing data caused by missing seizure diary

Seizure frequency will be computed over non-missing diary days. Diary compliance evaluation is described in Section 7.2. Subjects with diary data deemed unacceptably incomplete (during blinded data review) for the primary efficacy variable will be excluded from the PPS.

4.2.1.2 Missing seizure data caused by discontinuation

For subjects who prematurely discontinued during the Treatment Period, the calculation of 28-day adjusted POS frequency over the Treatment Period will be based on available seizure diary up to the end of the Treatment Period.

For subjects who prematurely discontinued the study, the last observation carried forward (LOCF) method will be applied to obtain a seizure frequency estimate for the Maintenance Period:

- Subjects who discontinued during the Titration and Stabilization Period: seizure frequency will be calculated using all available data in the Titration and Stabilization Period and carry forward for the Maintenance Period.
- Subjects discontinued during the Maintenance Period: seizure frequency will be calculated using all available data in the Maintenance Period.

Change #8

Section 4.5 Multiple comparisons/multiplicity

Change during the Maintenance Period in log-transformed observable focal-onset seizure frequency from Baseline is the primary efficacy variable for FDA submission and the key secondary endpoint for submission to European regulatory agencies. For these analyses, the dose-response relationship for change from Baseline in observable focal-onset seizure frequency across 4 doses of PSL and placebo will be evaluated using Multiple Comparison Procedure-Modeling (MCP-Mod) methodology (Bretz et al, 2005) to test monotonic dose-response trends and controlling the overall Type 1 error rate at 0.05 (2-sided testing), as described in Section 8.1.2.1. Assuming at least 1 statistically significant result is obtained from the primary MCP-Mod analysis, then pairwise comparisons of each of the 400mg (800mg/day), 200mg (400 mg/day) and 100mg (200 mg/day) dose groups versus placebo will be carried out using the ANCOVA analysis model described in Section 8.1.2.1. Type 1 error will be controlled by the Hochberg step-up procedure within SAS® Proc Multtest. If all the results of the pairwise comparisons are statistically significant, then the 50mg (100mg/day) dose group will be compared to placebo.

A similar strategy for Type 1 error control will be used for the primary variable for the EMA submission. Analysis details are provided in Section 8.

Has been changed to:

For the primary efficacy variables, statistical testing will be based on the comparison of 400mg bid, 200mg bid and 100mg bid PSL groups versus placebo. Type 1 error will be controlled by the Hochberg step-up procedure within SAS® Proc Multtest. Hochberg procedure orders the p-values from the largest to the smallest. The significance level for the k-th step is given by 0.05/k. More specifically, the largest p-value will be compared to 0.05. If it is smaller than 0.05, we will stop the testing and conclude significance for all 3 comparisons; otherwise we will move to the second highest p-value. The second largest p value will be compared to 0.025 (=0.05/2). If it is smaller than 0.025, we will stop and conclude significance for this comparison and the subsequent one that produced p-values smaller than the current one; otherwise we will move to the smallest p-value. The smallest p-value will be compared to 0.0167 (0.05/3). If it is smaller than 0.0167, we will conclude a significant difference between the dose and the placebo; otherwise, stop and no comparison is significant.

If the 3 higher doses are all statistically different from the placebo, the 50mg bid PSL group will be compared to placebo. Because this follows a gatekeeping procedure, testing will be conducted at the 0.05 level (2-sides). If the p-value is smaller than 0.05, we will conclude 50mg bid is also significantly different from the placebo.

Change #9

Section 5.1 Subject disposition

Screen failure data of screened subjects who did not meet study eligibility criteria are collected on the Study Termination Screen Failure CRF (dates of screen failure and last contact and reason for screen failure).

Disposition data of randomized subjects are obtained from the Study Termination CRF. Variables include date of last administration of study medication, date of premature study termination, date of final contact with subject, subject status at study termination, primary reason for premature study termination (as listed on the CRF), and if the study blind was broken (Y/N and date, if applicable).

Disposition of subjects (ES) will be listed by region, country and investigative site. A listing will also be provided for study discontinuation (RS), and for study visit dates (RS).

The date of first subject first visit (earliest Visit 1), date of last subject last visit (latest scheduled or unscheduled visit), and the number of screened subjects will be summarized for all study sites and by study site using the ES.

Summaries of the numbers of screened subjects and reasons for screen failures will be produced overall and by region, country and site for the ES.

The disposition of the ES will be summarized overall and by region, country and site presenting the dates of first subject in (first enrolled) and last subject out, number of subjects screened, the number randomized to each treatment group, and number of subjects included in the each of the RS, FAS, SS, and PK Sets.

The disposition of subjects into treatments groups and analysis sets (RS, FAS, SS, and PK Set) will also be summarized for the RS, overall and by region.

The disposition of the RS will be presented as the number and percentage of subjects who discontinued treatment and of subjects who discontinued the study, including a breakdown of the primary reason for discontinuation. Only 1 primary reason for discontinuation should have been reported. If more than 1 reason is specified in the clinical database, both reasons will be summarized, and a footnote will be added to the summary table to indicate that at least 1 subject is counted for multiple reasons for discontinuation. This will also be provided for the FAS and SS.

In addition, the numbers and percentages of subjects (FAS) entering and completing each of the following study periods: (Dose Titration plus Stabilization Period, Maintenance Period, and the Taper/Conversion Period) will be summarized overall and by treatment group within region.

The number and percentage of randomized subjects completing each scheduled study visit will be summarized overall and by treatment group. Early discontinuation visits (EDV) that correspond to scheduled visits will be included in the counts for the scheduled visits to which they correspond.

Has been changed to:

Screen failure data of screened subjects who did not meet study eligibility criteria are collected on the Study Termination Screen Failure CRF (dates of screen failure and last contact and reason for screen failure).

Disposition data of randomized subjects are obtained from the Study Termination CRF. Variables include date of last administration of study medication, date of premature study termination, date of final contact with subject, subject status at study termination, primary reason for premature study termination (as listed on the CRF), and if the study blind was broken (Y/N and date, if applicable).

Disposition of subjects (ES) will be listed by region, country and investigative site. A listing will also be provided for study discontinuation (RS), and for study visit dates (RS).

Summaries of the numbers of screened subjects and reasons for screen failures will be produced overall for the ES.

The disposition of the ES will be summarized overall and by region, country and site presenting the dates of first subject in (first enrolled) and last subject out, number of subjects screened, and number of subjects included in the each of the RS, FAS, SS, PPS, and PK-PPS.

The disposition of the SS will be presented as the number and percentage of subjects who completed the study and of subjects who discontinued the study, including a breakdown of the primary reason for discontinuation. Of note, the corresponding table is required for data transparency reporting.

In addition, the numbers and percentages of subjects (SS) entering and completing each of the following analysis periods: (Titration and Stabilization Period, Maintenance Period, Conversion Period, and Taper and SFU Period) will be summarized by treatment group and overall. The same summary will be repeated by region.

The number and percentage of subjects in the SS who discontinued due to AE categorized by serious fatal, non-fatal, and non-serious fatal AE incidence will also be presented by treatment group and overall. Of note, the corresponding table is required for data transparency reporting.

Change #10

Section 8.1.1 Derivations of primary efficacy variables

8.1.1.1 Primary efficacy variable for submission to the FDA, PMDA, and other regulatory authorities not referencing EMA

The primary efficacy variable is the change from Baseline in the log-transformed observable focal-onset seizure frequency from Baseline over the 12-week Maintenance Period.

- Calculation of seizure frequency:

The total number of observable focal-onset seizures (Types IA1, IB, and IC) will be calculated for each subject across all diary records during the study period being evaluated. For the primary variable, this is the 12-week Maintenance Period. The diary days for this period, which are collected onto the Seizure Count eCRF, are obtained from the diaries returned at Maintenance Period Visits 5, 6, and 7, which document daily seizure counts since Visit 4 (start of Maintenance).

The patient's 28-day adjusted seizure frequency of observable focal-onset seizures (Types IA1, IB, and IC) during the 12-week Maintenance Period will be calculated by dividing the number of seizures in the Maintenance Period by the number of days for which the diary was completed in the period and multiplying the resulting value by 28. The corresponding Baseline 28-day adjusted seizure frequency for the endpoint is calculated similarly, as described in Section 3.3.

The 28-day adjusted seizure frequency value for Baseline and the Maintenance Period will be log-transformed using the function ln(x+1), where ln represents the natural logarithm function.

- Calculation of Change in seizure frequency from Baseline:

In the calculation below the 28-day adjusted seizure frequency refers to the log-transformed value.

The change from Baseline is calculated for each subject by subtracting the 28-day adjusted seizure frequency during the 12-week Maintenance Period from the 28-day adjusted seizure frequency during the 4-week Baseline period as follows:

(log-transformed focal-onset seizure frequency during Maintenance) - (log-transformed focal-onset seizure frequency during Baseline), where seizure frequency refers to the 28-day adjusted frequency for the period.

Seizure frequency estimates obtained using log-transformed values, i.e. ln(x+1), will be back-transformed for table presentation: table_estimate=exp(ln_estimate)-1. Differences relative to placebo will be back-transformed as 100*(1-exp(diff)), where diff is the model estimate of the log ratio. Similarly, estimates for the upper and lower bounds of the 95% CI will be back-transformed for table presentation as exp(upper) and exp(lower), respectively, where upper and lower are the estimates from the model performed on log-transformed values. As applicable for a presentation, the difference may be expressed as percent difference relative to placebo.

8.1.1.2 Primary efficacy variable for submission the EMA and regulatory authorities who reference EMA

The primary efficacy variable will be the 75% responder rate status, defined as a ≥75% reduction in observable focal-onset seizure frequency from Baseline, over the 12-week Maintenance Period.

- Responder Rate for reduction in seizure frequency

A subject is defined as a 75% responder in the evaluation period if s/he has a reduction in seizure frequency of at least 75% (≥ 75%) from the Baseline seizure frequency.

The Responder rate will be calculated as follows:

$$\frac{\text{Count of responders during the 12-week Maintenance Period}}{\text{Responder count + Non-responder count during the Maintenance Period}} \times 100$$

Has been changed to:

8.1.1.1 Seizure frequency

Seizure frequency (SF) refers to the 28-day adjusted seizure frequency. The 28-day adjusted seizure frequency is defined as: SF = (Number of Seizures) x (28 / D). The number of seizures is the total number of seizures during an analysis period or time interval. For cluster seizures, the

number of cluster episodes will be included. D corresponds to the number of days for which the diary was available during the analysis period or time interval.

8.1.1.2 Change in log-transformed seizure frequency from Baseline

The 28-day adjusted seizure frequency value will be log-transformed using the function ln(x+1), where ln represents the natural logarithm function. The change in the log-transformed seizure frequency from Baseline is calculated as: Ln (SFT+1) – Ln (SFB+1), where SFT corresponds to the seizure frequency during an analysis period and SFB corresponds to the Baseline period seizure frequency.

For the primary efficacy variable for the FDA, SFT and SFB are the observable focal-onset seizure frequency during the 12-week Maintenance Period and Baseline Period, respectively.

8.1.1.3 Percent reduction in seizure frequency from Baseline

The percent reduction in seizure frequency (PRD) from the Baseline is defined as: PRD = [(SFB – SFT) / SFB] x 100, where SFT corresponds to the 28-day adjusted seizure frequency during an analysis period and SFB corresponds to the Baseline seizure frequency. A negative PRD indicates an increase in seizure frequency from Baseline.

8.1.1.4 75% Responder

Responder status (yes or no) of a subject is determined by the percent reduction in seizure frequency (PRD) from Baseline. A subject is defined as a 75% responder if s/he has a reduction in seizure frequency (PRD) of at least 75% from the Baseline. The 75% responder rate (RR) will be calculated as the proportion of 75% responders. For the primary efficacy variable for the EMA, 75% responder status is calculated based on the percent reduction (PRD) from the Baseline in observable focal-onset seizure frequency during the 12-week Maintenance Period.

Change #11

Section 8.1.2 Analysis of the primary efficacy variables

8.1.2.1 Primary variable for submission to the FDA, PMDA, and other regulatory authorities not referencing EMA

Analyses of the primary variable for FDA/PMDA submission will be done on the FAS as described below.

1. Dose Response Relationship

The first step for analyzing the primary variable is to assess the monotonic dose-response relationship for change from Baseline in observable focal-onset seizure frequency across 4 doses of PSL and placebo using the Multiple Comparison Procedure-Modeling (MCP-Mod) methodology (Bretz et al, 2005). MCP-Mod is a testing and model selection approach for clinical dose finding studies. During testing, contrasts of dose group means are derived from candidate dose response models and a multiple-comparison procedure is applied that controls the alpha level for the family of null hypotheses associated with the contrasts. Provided at least one contrast is significant, a corresponding set of candidate models is identified.

The study design evaluates five doses: 0 (placebo), 50, 100, 200 and 400 mg, all administered BID. The primary efficacy variable is log change from Baseline in Seizure frequency. The candidate models will include adjustments for Baseline log-transformed seizure frequency

(continuous covariate), and Baseline SV2A use (Yes or No) and Region (Asia, Europe or North America) as categorical factors. Monotonic dose-response trends will be tested using the appropriate contrasts as determined by the MCP-Mod methodology such that the overall Type 1 error rate is controlled at 0.05 (2-sided testing).

Candidate Models and Corresponding Contrasts

Four different dose-response models ("candidate models") were identified:

1. Sigmoidal Emax
2. Emax
3. Log-linear
4. Logistic

Four families of models were considered in the candidate set for representing the expected response μ_d at dose d:

Sigmoidal Emax: $\mu_d = E_0 + E_{max} * \frac{d^h}{ED_{50}^h + d^h}$,

parameters to estimate: E_0(placebo effect), E_{max} (asymptotic maximum effect) , ED_{50} (Dose giving half of the asymptotic maximum effect) and h (Hill parameter, detremining the steepness of the model at the ED_{50}).

Emax: $\mu_d = E_0 + E_{max} * \frac{d}{ED_{50} + d}$,

parameters to estimate: E_0, E_{max} and ED_{50}.

Linear in log: $\mu_d = E_0 + \delta * \log(d + off)$,

parameters to estimate: E_0 and δ(slope parameter=1 for standardized model)

Logistic: $\mu_d = E_0 + E_{max}/\{1 + \exp[(ED_{50} - d)/\delta]\}$,

parameters to estimate:
E_0, E_{max}(asymptotic maximum effect), ED_{50}(dose giving half of the asymptotic maximum effect) and δ(parameter controlling the steepness of the curve)

The specified candidate models for MCD-mod were:

Sigmoidal Emax: $\mu_d = 0.195 + 0.780 * \frac{d^2}{50^2 + d^2}$,

Emax: $\mu_d = 0.195 + 0.780 * \frac{d}{75 + d}$

Linear in log: $\mu_d = 0.195 + 480 * \log(d + 1)$,

Logistic: $\mu_d = 0.195 + 0.780/\{1 + \exp[(150 - d)/75]\}$,

Optimal contrasts:

Dose	linlog	emax	sigEmax	logistic
0	-0.845	-0.772	-0.792	-0.485
50	-0.008	-0.164	-0.178	-0.357
100	0.138	0.096	0.190	-0.171
200	0.284	0.333	0.363	0.289
400	0.431	0.507	0.417	0.724

The contrasts are used to calculate the test statistics and multiplicity adjusted p-values. The covariance matrix chosen will be the identity matrix unless the data indicate otherwise, in which case a compound symmetry or unstructured covariance matrix may be used instead. If at least one model is significant, there is an indication for evidence of a dose-response effect.

2. Initial Pairwise Comparisons

Assuming at least 1 statistically significant result is obtained from the MCP-mod analysis, described in (1) above, then pairwise comparisons of the 400mg (800mg/day), 200mg (400mg/day) and 100mg (200mg/day) dose groups versus placebo will be carried out using the analysis model described below. Type 1 error will be controlled using the Hochberg step-up procedure within SAS® Proc Multtest.

Change from Baseline in observable focal-onset seizure frequency (using the log-transformed data) will be analyzed for the FAS using analysis of covariance (ANCOVA) with treatment group as the main factor, Baseline log-transformed seizure frequency as a continuous covariate, and Baseline SV2A use (Yes or No) and Region (Asia, Europe or North America) as categorical factors. Pairwise contrasts will be constructed to compute estimated effects of each dose from placebo.

Treatment effects will be characterized using treatment differences based on back-transformation of least squares (LS) means obtained for each treatment group from the above ANCOVA model. Two-sided 95% confidence intervals for comparisons will also be obtained using the above ANCOVA model. Estimates of effects and comparison contrasts and CI will be back-transformed for display in tables as described in Section 8.1.1.1.

3. Additional Comparison

If all the results of the 3 pairwise comparisons described in (2) above are statistically significant, then the 50mg dose group (100mg/day) will be compared to placebo.

8.1.2.2 Supportive and sensitivity analyses for the primary variable for submission to the FDA, PMDA, and other regulatory authorities not referencing EMA

The primary analysis of change from Baseline in observable focal-onset seizure frequency for submission the FDA described in Section 8.1.2.1 will be repeated using the PPS.

In addition, a sensitivity analysis of the continuous primary efficacy variable will be carried out using a Mixed Model Repeated Measures (MMRM) analysis on the FAS. The observable focal-onset seizure frequency (using the log-transformed data) will be analyzed with treatment group

as the main factor, Baseline log-transformed seizure frequency as a continuous covariate, and with Region (Asia, Europe or North America), and Baseline SV2A use (Yes or No) as fixed effects. For the MMRM analysis the 28-day adjusted seizure frequencies will be computed using diary records for the following visit intervals: Maintenance Period intervals from Visit 4 to Visit 5, from Visit 5 to Visit 6 and from Visit 6 to Visit 7. These will be utilized as the repeated measures (random effect) for the analysis. MMRM estimates the mean outcome at each measurement time by treatment arm. An unstructured covariance structure will be used. If the model does not converge, an appropriate covariance structure will be used instead. The variance of the outcome measure at each observed time and the covariance between each of the repeated measures are all estimated based on the data, without assumption.

Estimates of effects and comparison contrasts and CI will be back-transformed for display in tables as described in Section 8.1.1.1.

8.1.2.3 Primary variable for submission to the EMA and regulatory authorities who reference EMA

Analyses of the primary variable for EMA submission will be done on the FAS as described below.

1. Dose response relationship

As done for the FDA/PMDA primary variable analysis, the first step for analyzing the primary variable for EMA is to assess the dose-response relationship across 4 doses of PSL and placebo using the MCP-Mod methodology. This will be done for the primary EMA submission variable, which is the 75% RR binary endpoint. The As described in Section 8.1.2.1, monotonic dose-response trends will be tested using the appropriate contrasts as determined by the MCP Mod methodology such that the overall Type I error rate is controlled at 0.05 (2-sided testing). The candidate models will include adjustments for Baseline log-transformed seizure frequency (continuous covariate), and Baseline SV2A use (Yes or No) and Region (Asia, Europe or North America) as categorical factors. Because the same assumptions for the candidate models' parameters are used, the optimal contrasts are the same as those presented in Section 8.1.2.1.

2. Initial Pairwise Comparisons

The primary efficacy variable is the 75% responder rate (RR) status during the Maintenance Period. Assuming at least 1 statistically significant result is obtained from the MCP-Mod analysis, then pairwise comparisons of the 75% RR, for each of the 400mg (800mg/day), 200mg (400mg/day) and 100mg (200mg/day) dose groups versus placebo, will be carried out using a logistic regression model on the 75% RR, with factors for treatment group (each PSL dose group referenced to the placebo group), Region (Asia, Europe or North America), Baseline SV2A use (0, 1) and log-transformed Baseline seizure frequency as a continuous covariate. If there are issues with convergence, Baseline SV2A use will be dropped. Odd's Ratios of PSL dose to Placebo will be obtained and tested for difference from unity (2-sided) for the dose groups 400mg (800mg/day), 200mg (400mg/day) and 100mg (200mg/day).

3. Additional Comparison

If all 3 Odd's Ratios of PSL dose relative to Placebo are statistically significant, then the 50mg (100mg/day) dose group will be compared to placebo by testing the Odd's Ratio for difference from unity.

8.1.2.4 Supportive and sensitivity analyses for the primary variable for submission to the EMA and regulatory authorities who reference EMA

The primary analysis (75% responder rate) for submission to the European regulatory agency as described in Section 8.1.2.3 will be repeated using the PPS.

In addition, a sensitivity analysis of the 75% and 50% RR may be performed in which missing data will be handled using non-responder imputation (NRI). That is, subjects who have missing data at the time point or interval of evaluation are to will be treated as though they did not respond to the treatment.

Has been changed to:

8.1.2.1 Primary variable for submission to the US FDA, PMDA, and other regulatory authorities not referencing EMA

The primary efficacy variable for the US FDA/PMDA is the change in log-transformed observable focal onset seizure frequency from Baseline, over the 12-week Maintenance Period. Analyses of the primary variable for the FDA will be performed on the FAS as described below.

Change from Baseline in observable focal-onset seizure frequency (using the log-transformed data) will be analyzed for the FAS using analysis of covariance (ANCOVA) with treatment group (PSL 400mg bid, 200mg bid, 100mg bid, 50mg bid, and placebo) as the main factor, Baseline log-transformed seizure frequency as a continuous covariate, Baseline SV2A use (Yes or No), and Region (Europe, North America, or Asia) as categorical factors. Pairwise contrasts will be constructed to compute estimated effects of each dose from placebo.

Treatment effects will be characterized using treatment differences based on back-transformation of least squares (LS) means obtained from the above ANCOVA model. Percent reduction over placebo will be calculated as 100*(1-exp(diff)), where diff is the model estimate of the log ratio between each PSL group and placebo group. Similarly, estimates for the upper and lower bounds of the 95% confidence interval (CI) will be back-transformed for table presentation as exp(lower) and exp(upper), respectively, where upper and lower correspond to the 95% CI of the log ratio.

Pairwise comparisons of the 400mg bid, 200mg bid, and 100mg bid PSL dose groups versus placebo will be carried out using the analysis model described above. Type 1 error will be controlled using the Hochberg step-up procedure (Section 4.5) within SAS® Proc Multtest. If all the results of the 3 pairwise comparisons are statistically significant, then the 50mg bid dose group will be compared to placebo, too. Both multiplicity-adjusted and unadjusted p-values will be presented.

8.1.2.2 Supportive and sensitivity analyses for the primary variable for submission to the US FDA, PMDA, and other regulatory authorities not referencing EMA

8.1.2.2.1 Sensitivity analysis 1: PPS

The primary analysis of change from Baseline in observable focal-onset seizure frequency for submission the FDA described in Section 8.1.2.1 will be repeated for the PPS.

8.1.2.2.2 Sensitivity analysis 2: “worst case” imputation

A "worst case" imputation will be performed to assess the impact of missing data. For subjects who discontinued during the Titration and Stabilization, if the seizure frequency during the Titration and Stabilization Period is less than the Baseline, the seizure frequency during the Maintenance Period will be imputed using the Baseline seizure frequency. For other subjects who discontinued early, seizure frequency during the Maintenance Period will be imputed using the LOCF methods described in Section 4.2.1.2.

The primary analysis in Section 8.1.2.1 will be repeated following the "worst case" imputation.

8.1.2.3 Primary variable for submission to the EMA and regulatory authorities who reference EMA

The primary efficacy available for the EMA is the 75% responder rate over the 12-week Maintenance Period. Analyses of the primary variable for the EMA submission will be done on the FAS as described below.

The analysis of 75% responder rate will be based on a logistic regression model with factors for treatment group (PSL 400mg bid, 200mg bid, 100mg bid, 50mg bid and placebo), Region (Europe, North America, or Asia), Baseline SV2A use (Yes or No) and log-transformed Baseline seizure frequency as a continuous covariate. If there are issues with convergence, Baseline SV2A use will be dropped. Odd's Ratios of PSL dose to placebo will be obtained and tested for difference from unity (2-sided) for the dose groups 400mg bid, 200mg bid, and 100mg bid. The evaluation of statistical significance will be based on the Hochberg procedure as described in Section 4.5. If all 3 Odd's Ratios of PSL dose relative to placebo are statistically significant, then the 50mg bid dose group will be compared to placebo by testing the Odd's Ratio for difference from unity, too. Both multiplicity adjusted p-values and unadjusted p-value will be presented.

8.1.2.4 Supportive and sensitivity analyses for the primary variable for submission to the EMA and regulatory authorities who reference EMA

8.1.2.4.1 Sensitivity analysis 1: PPS

The primary analysis (75% responder rate) for submission to the European regulatory agency as described in Section 8.1.2.3 will be repeated using the PPS.

8.1.2.4.2 Sensitivity analysis 2: non-responder imputation

A sensitivity analysis of the 75% responder rate will be performed in which subjects who discontinued prior to the end of the Maintenance Period will be treated as non-responders. The primary analysis in Section 8.1.2.3 will be repeated.

8.1.2.5 Subgroup analyses for the primary variables

The analyses described in Section 8.1.2.1 and 8.1.2.3 will be repeated for the subgroups described in Section 4.8. In the subgroup analyses by region and Baseline SV2A use, the corresponding stratification factor will be removed from the model. These evaluations will be descriptive and the model estimates and 95% CIs will be presented.

Change #12

Section 8.2 Statistical analysis of the secondary efficacy variables

Separate secondary efficacy variables have been designated for submission to FDA and submission to European regulatory agencies.

8.2.1 Derivations of secondary efficacy variables

This section describes variable derivations and calculation of population statistics to be used for analyses.

8.2.1.1 Secondary variables for submission to the FDA, PMDA, and other regulatory authorities not referencing EMA

The secondary endpoint variables described in Section 8.2.2 are based on evaluation of the 12 week Maintenance Period. Calculations for these endpoint variables are as follows:

- Responder Rates for reduction in seizure frequency

The 75% and 50% Responder Rates will be calculated for evaluation as secondary efficacy variables for FDA/PMDA submissions. The 90% Responder Rate is considered as one of the other efficacy variable (Section 8.3) and will also be calculated. A subject is defined as a XX% responder in the evaluation period (where XX refers to 75 or 50) if s/he has a reduction in seizure frequency of at least XX% (≥ XX%) from the Baseline seizure frequency.

Responder rates will be calculated as follows:

$$\frac{\text{Count of responders during the 12-week Maintenance Period}}{\text{Responder count + Non-responder count during the Maintenance Period}} \times 100$$

- The percent reduction from Baseline in the frequency of observable focal onset seizures over the 12-week Maintenance Period will be calculated for each subject as:

$$\frac{\text{Change from Baseline in the 28-day adjusted seizure frequency during Maintenance}}{\text{28-day adjusted seizure frequency during the Baseline Period}} \times 100$$

8.2.1.2 Secondary variables for submission to EMA and regulatory authorities who reference EMA

The derivations for log-transformed observable focal onset seizure frequency from Baseline, over the 12-week Maintenance Period, which is also the primary variable for FDA submission, is described in Section 8.1.1.1.

The calculation of 50% responder rate status, defined as a ≥50% reduction in observable focal-onset seizure frequency from Baseline, over the 12-week Maintenance Period is described in Section 8.2.1.1.

The derivations for the percent reduction from Baseline in the frequency of observable focal onset seizures over the 12-week Maintenance Period are described in Section 8.2.1.1.

8.2.2 Analysis of the secondary efficacy variables for submission to the FDA, PMDA, and other regulatory authorities not referencing EMA

8.2.2.1 75% Responder Rate status over the 12-week Maintenance Period

The secondary efficacy variable, 75% responder rate status, is defined as a ≥75% reduction in observable focal-onset seizure frequency from Baseline, over the 12-week Maintenance Period. The 75% responder rate status will be analyzed for the FAS using a logistic regression model,

with factors for treatment group (each PSL dose group referenced to the placebo group), Region (Asia, Europe or North America), Baseline SV2A use (0, 1) and log-transformed Baseline seizure frequency as a continuous covariate. If there are issues with convergence, Baseline SV2A use will be dropped. Odd's Ratios of each PSL dose to Placebo will be obtained and tested for difference from unity (2-sided). The 95% confidence intervals will be presented for each estimate. This analysis will be repeated using the PPS.

8.2.2.2 50% Responder Rate status over the 12-week Maintenance Period

The secondary efficacy variable, 50% responder rate status, is defined as a ≥50% reduction in observable focal-onset seizure frequency from Baseline, over the 12-week Maintenance Period. The 50% responder rate status will also be analyzed for the FAS using a logistic regression model, with factors for treatment group (each PSL dose group referenced to the placebo group), Region (Asia, Europe or North America), Baseline SV2A use (0, 1) and log-transformed Baseline seizure frequency as a continuous covariate. If there are issues with convergence, Baseline SV2A use will be dropped. Odd's Ratios of each PSL dose to Placebo will be obtained and tested for difference from unity (2-sided). The 95% confidence intervals will be presented for each estimate. The analysis will be repeated using the PPS.

8.2.2.3 Percent reduction from Baseline in observable focal-onset seizure frequency over the 12-week Maintenance Period

The third secondary efficacy variable is percent reduction from Baseline in observable focal-onset seizure frequency, over the 12-week Maintenance Period. Analyses of the percent change in seizure reduction endpoints will be performed on the FAS using the Wilcoxon-Mann-Whitney test. The Hodges-Lehmann nonparametric estimator will be used to estimate the median difference between groups in percent reduction in seizures, along with the corresponding 95% confidence interval (CI) of the estimate. The Hodges-Lehmann estimator is the median of all possible differences (ordered) among subjects in the 2 groups being compared.

Essentially, for each comparison of a given dose to placebo, a dataset must be created merging all responses for the dose and all responses for placebo (using proc SQL) to obtain all possible differences in response. These are ordered, and the median is obtained. A detailed method for calculating the estimator and distribution-free CI are described in Decker, C., Calculating a nonparametric estimate and confidence interval using SAS software. If available, Proc StatXact™ 4 for SAS users may be used to calculate the Hodges-Lehmann estimate and distribution-free CI. This analysis will be repeated using the PPS.

8.2.3 Analysis of the secondary efficacy variables for submission to EMA and regulatory authorities who reference EMA

8.2.3.1 Change from Baseline in observable focal-onset seizure frequency

The analysis described in Section 8.1.2.2 (for FDA, PMDA, and other regulatory authorities not referencing EMA) of the change in log-transformed observable focal-onset seizure frequency from Baseline, over the 12 week Maintenance Period, serves as the key secondary variable for submission to EMA. To reiterate, Type 1 error will be controlled by the Hochberg step-up procedure within SAS® Proc Multtest. If the results of all pairwise comparisons are statistically significant, then the 50mg dose group will also be compared to placebo.

8.2.3.2 50% Responder Rate status over the 12-week Maintenance Period

This variable is also a secondary variable for FDA submission and is described in Section 8.2.2.2.

8.2.3.3 Percent reduction in observable focal-onset seizure frequency from Baseline, over the 12-week Maintenance Period

This variable is also a secondary variable for FDA submission and is described in Section 8.2.2.3.

Has been changed to:

Separate secondary efficacy variables have been designated for submission to US FDA/PMDA and submission to EMA.

8.2.1 Analysis of the secondary efficacy variables for submission to the US FDA, PMDA, and other regulatory authorities not referencing EMA

8.2.1.1 75% Responder Rate over the 12-week Maintenance Period

75% responder rate is the secondary efficacy variable for the US FDA and primary efficacy variable for the EMA. The analyses are described in Section 8.1.2.3.

8.2.1.2 50% Responder Rate over the 12-week Maintenance Period

Subjects with at least a 50% reduction in seizure frequency will be categorized as a 50% responder. The same methodology described in Section 8.1.2.3 will be used for 50% responder rate during the 12-week Maintenance Period. No multiplicity adjustment will be applied and tests will be carried out at a nominal two-sided 0.05 significance level.

8.2.1.3 Percent reduction from Baseline in observable focal-onset seizure frequency over the 12-week Maintenance Period

The third secondary efficacy variable is percent reduction from Baseline in observable focal-onset seizure frequency, over the 12-week Maintenance Period. The calculation of percent reduction from Baseline in seizure frequency is described in Section 8.1.1.2. The percent reduction in seizure frequency will be summarized descriptively.

Statistical comparisons between each PSL dose group and placebo will be performed on the FAS using the Wilcoxon-Mann-Whitney test. No multiplicity adjustment will be applied and tests will be carried out at a nominal two-sided 0.05 significance level. The Hodges-Lehmann nonparametric estimator will be used to estimate the median difference between each PSL dose group versus placebo, along with the corresponding 95% CI of the estimate.

In addition, the number and percentage of subjects within each of the following categories of percent reduction from Baseline will be summarized: <-25%, -25% to <25%, 25% to <50%, 50% to <75%, 75% to <100%, and 100%.

8.2.2 Analysis of the secondary efficacy variables for submission to EMA and regulatory authorities who reference EMA

8.2.2.1 The change in log-transformed observable focal onset seizure frequency from Baseline, over the 12-week Maintenance Period

The analysis described in Section 8.1.2.2 (for US FDA, PMDA, and other regulatory authorities not referencing EMA) of the change in log-transformed observable focal-onset seizure frequency

from Baseline, over the 12-week Maintenance Period, serves as the key secondary variable for submission to EMA.

8.2.2.2 50% Responder Rate status over the 12-week Maintenance Period

This variable is also a secondary variable for FDA submission and is described in Section 8.2.1.2.

8.2.2.3 Percent reduction in observable focal-onset seizure frequency from Baseline, over the 12-week Maintenance Period

This variable is also a secondary variable for FDA submission and is described in Section 8.2.1.3.

Change #13

The following text has been added in Section 8.3.2:

8.3.2.21 Use of health-related outcomes and HRU

Health-related outcomes data and HRU data will be listed for the RS and summarized descriptively for the SS.

- Socio-professional status

Socio-professional status data are collected at Visit 1 and Visit 7/EDV. Variables include highest level of education, housing status, current professional status, current unemployed status, need for regular assistance due to epilepsy, and ability to drive. The number and percentages of subjects in each category will be summarized for Visit 1, Visit 7, and the Last Visit during the Treatment Period.

- Healthcare provider consultations not foreseen by the protocol

The number of health care provider consultations per subject with onset during the Treatment Period will be summarized as a continuous variable as well as in the following categories: 0, 1, 2, 3, 4, and 5 or more. Additionally, the number and percentage of consultations by type of provider (general practitioner, specialist physician, nurse, and other) will be presented for the Treatment Period.

- Hospital and ER visits

The number of hospitalization per subject will be summarized as a continuous variable and categorical variable for the Treatment Period. ER visits will be extracted from the Hospitalization/ER Visit CRF page (if the initial entry point is ER). The number of ER visits will be summarized in the same manner as hospitalizations. Additionally, the number and percentage of subjects with each of the following categories of duration of hospital stay will be summarized: 0 days, 1-5 days, 6-10 days, 11-15 days, and >15 days.

- Caregiver assistance

Caregiver assistance data is collected on the CRFs “Caregiver Assistance Screening” and “Caregiver Assistance Follow-up”. The number and percentages of subjects having a caregiver will be summarized by visit.

- Concomitant medical procedures

The number of concomitant medical procedures per subject during the Treatment Period will be summarized using the categories 0, 1, 2, and 3 or more.

- Number of school or working days lost

Number of school/working days lost data are collected on the CRFs "School and Workdays Lost Screening" and "School and Workdays Lost Follow-up". The number and percentages of subjects who lose school or work days as a result of epilepsy will be summarized by visit.

The percentage of days lost will be summarized by visit for subjects who have more than zero total number of school or work days. The percentage of days lost will be calculated as:

100 × (end date of absence – start date of absence +1)/total number of school or work days

If a subject didn't have days lost, the percentage of days lost will be zero.

Change #14

Section 9.1 Pharmacokinetics

Plasma concentrations of PSL and its major metabolite will be determined from blood samples obtained during the Dose Titration and Maintenance Periods (Visits 3, 4, 5, 6 and 7) in order to investigate the population PK of PSL and its [redacted]). Individual concentrations of PSL will be listed by treatment group for the PK-Set and will include the actual and nominal sampling times and the deviation between them. All deviations will be calculated relative to the IMP administration. Concentrations will be summarized by treatment group and sampling times for the PK-PPS. Geometric means and associated 95% CI of plasma concentrations will be tabulated and may be presented graphically for each treatment (dose) group by visit.

Blood samples for measurement of concomitant AED concentrations are collected at Visits 1 (Screening) and 2 (Baseline). Steady state plasma concentrations of concomitantly administered AEDs will be listed by treatment group and will be assessed by evaluating ratios of steady state concentrations while on maintenance PSL vs. Baseline (pre-PSL) concentrations. If the Visit 2 Baseline sample is not available, then the Visit 1 sample may be used. On Visits 6 and 7, unless the concomitant AED sample is within ±5 minutes of a scheduled MITRA sample for PSL assay, a separate, additional MITRA sample will be taken at same time as the concomitant AED blood sample. Subjects are requested to provide blood samples for measurement of PSL and the [redacted]) whenever possible. On Visits 3, 5, and 6, site personnel should obtain blood samples for measurement of random PSL concentrations at any time between IMP intake and record accurately the time of last IMP intake and the time of sample collection. On Visits 4 and 7, blood samples for measurement of sparse PK profiles will be collected as follows: immediately before IMP intake (maximum 15 minute before intake) and then 3 times after (between 30 minutes and 3 hours after IMP intake), taken at least 30 minutes apart. All samples may be taken either at home or in the site or partly at home and partly at the site.

Other PK analyses, including population PK analyses and exploratory PK analyses (such as exploratory comparisons of PSL blood concentrations derived from the MITRA sampler with conventional venous sampling) will be described in a separate PK Data Analyses Plan (PK DAP). An exploratory evaluation of the PSL [redacted] will also be undertaken. The evaluations described in the PK DAP will be reported separately.

Has been changed to:

9.1 Plasma concentrations of PSL and its major metabolite

Plasma concentrations of PSL and its major metabolite will be determined from blood samples obtained during the Titration and Stabilization and Maintenance Periods (Visits 3, 4, 5, 6 and 7). Individual concentrations of PSL and its [redacted] (from venous conventional sampling and dried blood (MITRA) sampling) will be listed for subjects in PSL treatment groups for the PK-Set and will include the actual and nominal sampling times and the deviation between them. All deviations will be calculated relative to the IMP administration. Values below the LLOQ will be reported with a clear sign indicating that they were below the LLOQ.

Concentrations of PSL and its [redacted] will be summarized by sampling method (venous, dried blood MITRA), PSL dose group, visit, and sampling times for the PK-PPS using the following descriptive statistics: number of observations, geometric mean, geometric coefficient of variation, arithmetic mean, SD, median, and minimum and maximum values. Measured values below the limit of quantification (LOQ) will be set LOQ/2 for the calculation.

Descriptive statistics of concentrations will be calculated if at least 2/3rd of the individual data points are quantifiable (≥LLOQ).

Of note, geometric mean is calculated as: exp (arithmetic mean of log-transformed concentrations); geometric coefficient of variation is calculated as: 100 × sqrt [exp (variance of log-transformed concentrations)-1].

The PK samples will be summarized using the following nominal time points based on the time since last dose:

- 15 to <45 min after dosage: 0.5h (30min)
- 45 to <75 min after dosage: 1h (60min)
- 75 to <105 min after dosage: 1.5h (90min)
- 105 to <150 min after dosage: 2h (120min)
- 150 to <210 min after dosage: 3h (180min)
- 4h: 3.5h to <4.5h
- 5h: 4.5 to <5.5h
- 6h: 5.5 to <6.5h
- 8h: 6.5 to <9h
- 10h: 9h to <11h
- 12h: 11h to <12h (this window will contain the blood sample pre-dose)

9.2 Plasma concentrations of concomitant AEDs

Blood samples for measurement of concomitant AED concentrations are collected at Visits 1, 2, 6, and 7. The concomitant AED concentrations will be summarized by visit and treatment group using the same descriptive statistics above for the PK-Set for AED.

The AEDs investigated with mixed models will be those with data available for at least 10 subjects in one of the treatment groups (subset of PK-Set).

Plasma concentration data for concomitantly administered AEDs will be assessed by evaluating ratios of steady state levels during the Maintenance Period vs baseline levels. The baseline concentration is defined as the arithmetic mean concentration (if multiple concentrations are available at Visits 1 and 2) or the single concentration (if only 1 concentration is available at Visit 1 or Visit 2). Difference between log-transformed AED concentration at Visits 6 and 7 and baseline will be assessed using Mixed Model Repeated Measures (MMRM). The model will include log-transformed baseline concentration, visit, treatment, and treatment-by-visit interaction as fixed effects. An unstructured covariance structure will be used. If the model does not converge, an appropriate covariance structure will be used instead. Geometric least-squares (LS) means ratios and associated 90% CIs for each visit, by treatment group and PSL total will be calculated by exponentiation of the log-transformed data. Changes in AED concentration during the Maintenance Period and baseline will be considered clinically relevant if the respective 90% CIs fall entirely outside the conventional 0.80-1.25 limits. Forest plots will be provided on these (LS) means ratios and associated 90% CIs.

9.3 Other PK variables

Other PK analyses, including population PK analyses and exploratory PK analyses will be described in a separate PK Data Analyses Plan.

Change #15:

Section 10.2 Adverse events

Adverse events are recorded on the AE CRF as they occur, from the time informed consent is granted until study completion or study termination (end of the SFU period 30 days after the last IMP intake). All AEs will be coded using the latest available version of MedDRA and will be categorized by intensity (mild/moderate/severe). The following subject data listings may be provided to the DMC in masked unblinded fashion for the closed session: SAEs, AEs leading to dose reduction, AEs leading to withdrawal, and AEs leading to death. Listings will be organized by treatment group using the SS. No other AE data listings will be prepared for the DMC.

A treatment-emergent adverse event (TEAE) is defined as any event not present prior to the initiation of the first dose of study treatment or any unresolved event already present before initiation of the first dose that worsens in intensity following exposure to the treatment. The number and percentage of subjects who experience TEAEs at any time during the study will be summarized (using the SS) for each treatment group, for combined PSL groups, and overall (combined treatments) by SOC and PT. In the same table, the number and percentage of subjects will be summarized by the following treatment periods as defined in Section 2.3.1: Overall, Dose Titration plus Stabilization, Maintenance, and Conversion/Taper. The following tabular summaries will be presented for the SS:

- Incidence of AEs – Overview
  - During the entire study
- Incidence of TEAEs

  - During the following periods: the entire study, the 16-week Treatment Period, the 12-week Maintenance Period, the 4-week Titration/Stabilization Period, and the 3-week Conversion/Taper Period

- Incidence of Serious TEAEs

During the following periods: the entire study, the 16-week Treatment Period, the 12-week Maintenance Period, the 4-week Titration/Stabilization Period, and the 3-week Conversion/Taper Period

- Incidence of TEAEs by Relationship
  - During the entire study
- Incidence of SAEs by Relationship
  - During the entire study
- Incidence of Fatal TEAEs by Relationship
  - During the entire study
- Incidence of TEAEs by Maximum Relationship
  - During the entire study
- Incidence of TEAEs by Maximum Intensity
  - During the entire study
- Incidence of TEAEs (subjects and events) leading to Dose Reduction
  - During the Stabilization Period (fall-back option due to a TEAE)
- Incidence of TEAEs leading to Withdrawal
  - During the entire study

The following 2 summary tables will be produced to support results disclosure activities.

- Incidence of Non-Serious TEAEs above the Threshold of 5% of Subjects
- Incidence of Non-Serious TEAEs above the Threshold of 5% of Subjects by Relationship

Summaries will be presented based on standard Sponsor AE table formats and considering formats used for the PSL program.

Where dates are missing or partially missing, AEs will be assumed to be treatment-emergent, unless there is unmistakable evidence (through comparison of partial dates, see Section 4.2) to suggest that the AE started prior to the first dose of study treatment. Summary tables will contain counts of subjects, percentages of subjects in parentheses and the number of events where applicable. A subject who has multiple events in the same MedDRA category (SOC or PT) will be counted only once in the subject count for that category, however all events will be included in the event count for the category. In summaries including relationship to study treatment, the following relationships will be summarized: ‘Not related’, ‘Related’. Subjects who experience the same event multiple times will be included in the most related category (i.e. a subject experiencing both a ‘not related’ and a ‘related’ event in the same MedDRA category will be counted as related). Events with missing relationship will be considered as ‘Related’ to the last

given study product for summary purposes but recorded as missing in the listings. In summaries including intensity, the following intensity categories will be summarized: 'Mild', 'Moderate', 'Severe'. Subjects who experience the same event multiple times, with differing severities, will be included in the most severe category. Events with missing intensity will be considered as 'Severe' events for summary purposes but recorded as missing in the listings.

Adverse event summaries will be ordered in terms of decreasing frequency for SOC, and PT within SOC, within the combined treatment group column.

Illustrative graphs may be prepared of the most frequent AE preferred terms (>=2%) and for SAE. Graphs will present percentage of subjects with the AE (for each severity level) by treatment group to visually assess the dose-response relationship. This may also be done for percentage of subjects with an SAE. Graphic formats may be adjusted for better illustration based on observed frequencies.

The relationship between somnolence and dose and between fatigue and dose will be explored graphically with an event chart presenting subjects on the y-axis (ascending dose group) with events charted horizontally over time. Events will be plotted to indicate start and end and will be flagged if related to study drug and if severe.

Has been changed to:

Adverse events are recorded on the AE CRF as they occur, from the time informed consent is granted until study completion or study termination (end of the SFU period 30 days after the last IMP intake). All AEs will be coded using the latest available version of MedDRA.

A treatment-emergent adverse event (TEAE) is defined as any event not present prior to the initiation of the first dose of study treatment or any unresolved event already present before initiation of the first dose that worsens in intensity following exposure to the treatment. The number and percentage of subjects who experience TEAEs at any time during the study will be summarized by SOC and PT. The following tabular summaries will be presented for the SS:

- Incidence of pre-treatment AEs. Pre-treatment AEs are AEs with start dates prior to the date of first dose of IMP.
- Incidence of TEAEs during the Treatment Period – Overview. Of note, the corresponding table is required for data transparency reporting.
- Incidence of TEAEs by period (Treatment Period, Titration and Stabilization Period, Maintenance Period, Conversion Period, and Taper and SFU Period)
- Incidence of Serious TEAEs by period (Treatment Period, Titration and Stabilization Period, and Maintenance Period)
- Incidence of TEAEs leading to discontinuation by period (Treatment Period, Titration and Stabilization Period, and Maintenance Period)
- Incidence of TEAEs leading to dose reduction during the Stabilization Period

The following will be presented for TEAEs during the overall Treatment Period:

- Subject numbers for TEAEs
- Incidence of TEAEs occurring in at least 5% of subjects in any treatment group

- Incidence of TEAEs by Relationship
- Incidence of TEAEs by Maximum Intensity
- Incidence of SAEs by Relationship. Of note, the corresponding table is required for data transparency reporting.
- Incidence of Fatal TEAEs by Relationship. Of note, the corresponding table is required for data transparency reporting.
- Incidence of Non-Serious TEAEs above the threshold of 5% of subjects in any treatment group. Of note, the corresponding table is required for data transparency reporting.
- Summary of the duration in days per event for the following TEAEs: somnolence, dizziness, fatigue, irritability and headache.

Summaries will be presented based on standard Sponsor AE table formats and considering formats used for the PSL program.

Where dates are missing or partially missing, AEs will be assumed to be treatment-emergent, unless there is unmistakable evidence (through comparison of partial dates, see Section 4.2) to suggest that the AE started prior to the first dose of study treatment. Summary tables will contain counts of subjects, percentages of subjects in parentheses and the number of events where applicable. A subject who has multiple events in the same MedDRA category (SOC or PT) will be counted only once in the subject count for that category, however all events will be included in the event count for the category. In summaries including relationship to study treatment, the following relationships will be summarized: 'Not related', 'Related'. A subject may be counted more than once according to the relationship to study treatment. Events with missing relationship will be considered as 'Related' to the last given study product for summary purposes but recorded as missing in the listings. In summaries of the maximum intensity, the following intensity categories will be summarized: 'Mild', 'Moderate', 'Severe'. Subjects who experience the same event multiple times, with differing severities, will be included in the most severe category. Events with missing intensity will be considered as 'Severe' events for summary purposes but recorded as missing in the listings. The main reasons for treatment discontinuation will be listed by subject.

Adverse event summaries will be ordered in terms of decreasing frequency for SOC, and PT within SOC, within the PSL total group column.

14.2 Amendment 2

Rationale for the amendment

The primary purpose of this amendment is adding additional sensitivity analyses to evaluate the impact of missing data on the primary efficacy variable and update appendices 13.1, 13.2, and 13.3 with the latest UCB standards.

Modifications and changes

Major specific changes

Change #1

The following has been added:

3.5.6.3 AED Pharmacokinetic Per-Protocol Set (AED-PK-PPS)

An AED PK Per Protocol Set (AED-PK-PPS) will be identified, which would exclude subjects or AED PK sample data points with major deviations that could impact AED PK evaluations. Subjects or AED PK sample data points to be excluded from this AED-PK-PPS, will be identified during a pre-analysis data review.

Change #2

The following has been added:

4.1 Adjustments for covariates

To ensure at least 5 subjects in each region in the FAS at each treatment group, Japan will be pooled with North America to form a non-Europe region for the efficacy analyses.

Change #3

4.2.1.2 Missing seizure data caused by discontinuation

For subjects who prematurely discontinued during the Treatment Period, the calculation of 28-day adjusted POS frequency over the Treatment Period will be based on available seizure diary up to the end of the Treatment Period.

For subjects who prematurely discontinued the study, the last observation carried forward (LOCF) method will be applied to obtain a seizure frequency estimate for the Maintenance Period:

- Subjects who discontinued during the Titration and Stabilization Period: seizure frequency will be calculated using all available data in the Titration and Stabilization Period and carry forward for the Maintenance Period.
- Subjects discontinued during the Maintenance Period: seizure frequency will be calculated using all available data in the Maintenance Period.

Has been changed to:

4.2.1.2 Missing seizure data caused by discontinuation

Seizure frequency by analysis period:

For subjects who prematurely discontinued during the Treatment Period, the calculation of 28-day adjusted seizure frequency over the Treatment Period will be based on available seizure diary up to the end of the Treatment Period. If a subject had less than 14 days of seizure data during the Titration and Stabilization Period, seizure frequency during the Treatment Period will be calculated based on the last 28 days with seizure data, including the data in the Baseline Period.

For subjects who prematurely discontinued the study, the following methods will be applied to obtain a seizure frequency estimate for the Maintenance Period:

- Subjects who discontinued during the Titration and Stabilization Period: If a subject had at least 14 days of seizure data, seizure frequency will be calculated using all available data in the Titration and Stabilization Period and carry forward for the Maintenance Period. If a subject had less than 14 days of seizure data, seizure frequency will be calculated based on the last 28 days with seizure data, including the data in the Baseline Period and carry forward for the Maintenance Period.
- Subjects discontinued during the Maintenance Period: If a subject had at least 28 days of seizure data during the Maintenance Period, seizure frequency will be calculated using all available data in the Maintenance Period. If a subject had less than 28 days of seizure data during the Maintenance Period, seizure frequency will be calculated based on the last 28 days with seizure data, including the data in the Titration and Stabilization Period.

Seizure frequency by 4-week interval

Seizure frequency by 4-week interval will be calculated for the sensitivity analyses (Section 8.1.2.2) and secondary efficacy analyses (Section 8.3.2.1). Seizure frequency during a 4-week interval will be calculated as long as seizure data are available for at least 1 day in the given interval. No imputation will be applied for discontinuations.

Change #4

The following has been added:

4.2.3 Handling of missing data for history of epileptic seizures and diagnosis of epilepsy
4.2.3.1 Incomplete dates for first epileptic seizure
To calculate the time since the first seizure relative to the date of Visit 1 or age at onset of first seizure, January 1st of the year will be imputed for the date of birth, as only year of birth is collected on CRF. And a complete date will be imputed for partially missing first seizure date as following:
• Missing the day, but month and year present
Assign the 1st day of the month.
• Missing the day and month, but year present
Assign January 1st of the year.
• Completely missing
No imputation will be done.
4.2.3.2 Incomplete dates for last epileptic seizure
To calculate the time since last seizure relative to the date of Visit 1, a complete date will be imputed for partially missing last seizure date as following:
• Missing the day, but month and year present
Assign the 1st day of the month.

- Missing the day and month, but year present

Assign January 1st of the year or Visit 1, whichever is later in the year.

- Completely missing

No imputation will be done.

4.2.3.3 Incomplete dates for first epilepsy diagnosis

Month and year of the first epilepsy diagnosis are collected on the CRF. To calculate the duration of epilepsy derived from the date of first diagnosis relative to the date of Visit 1, or age at epilepsy diagnosis, January 1st of the year will be imputed for the date of birth, as only year of birth is collected on CRF. And a complete date will be imputed for partially missing date of the first epilepsy diagnosis as following:

- Month and year present

Assign the 1st day of the month or the date of the first seizure, whichever is later in the month.

- Missing the month, but year present

Assign January 1st of the year or the date of the first seizure, whichever is later in the year.

- Both month and year are missing

No imputation will be done.

Change #5

4.8 Examination of subgroups

The primary efficacy variable will be evaluated for subgroups of interest including:

- Age (18 to <65 years, ≥65 years)
- Gender
- Region (Europe, North America, and Asia)
- Use of AEDs with binding to synaptic vesicle 2A (SV2A) proteins (levetiracetam [LEV] or brivaracetam [BRV], Y/N).

These evaluations will be descriptive; no statistical testing of treatment-by-subgroup interactions nor statistical testing of treatment effects within subgroups will be carried out. No subgroup evaluations are planned for safety variables.

Has been changed to:

The primary efficacy variable will be evaluated for subgroups of interest including:

- Age (18 to <65 years, ≥65 years): less than 5 subjects in ≥65 years subgroup in the FAS at each treatment group, therefore the subgroup analysis will be omitted.
- Gender
- Region (Europe, North America, and Asia): To ensure at least 5 subjects in each region in the FAS at each treatment group, Asia (Japan) will be pooled with North America. The subgroup analyses will be performed for Europe vs non-Europe.
- Use of AEDs with binding to synaptic vesicle 2A (SV2A) proteins (levetiracetam [LEV] or brivaracetam [BRV], Y/N).

These evaluations will be descriptive; no statistical testing of treatment-by-subgroup interactions nor statistical testing of treatment effects within subgroups will be carried out. No subgroup evaluations are planned for safety variables.

Change #6

6.4.3 Use of vagal nerve stimulation at study entry

Vagal Nerve Stimulation (VNS) status at Screening (VNS Status at Screening CRF) will be summarized as the number and percent of subjects with VNS at screening and as number and percent of subjects with VNS turned on. All other VNS data will be provided in subject data listings and will not be summarized for the SS.

Has been changed to:

6.4.3 Use of vagus nerve stimulation

Vagus Nerve Stimulation (VNS) status at Screening (VNS Status at Screening CRF) will be summarized as the number and percent of subjects with VNS at screening and as number and percent of subjects with VNS turned on. Subjects with VNS at screening and setting changed during treatment period will also be summarized. All other VNS data will be provided in subject data listings and will not be summarized for the FAS.

Change #7

7.1 Treatment compliance

Percent compliance will be summarized for the SS using descriptive statistics for each treatment group and overall. In addition, the number and percentage of subjects with compliance <80%, 80% to 120%, and >120% will be summarized.

Has been changed to:

Percent compliance will be summarized for the FAS using descriptive statistics for each treatment group and overall. In addition, the number and percentage of subjects with compliance <75%, 75% to125%, and >125% will be summarized.

Change #8

The following has been removed:

8.1.2.2.2 Sensitivity analysis 2: "worst case" imputation

A "worst case" imputation will be performed to assess the impact of missing data. For subjects who discontinued during the Titration and Stabilization, if the seizure frequency during the Titration and Stabilization Period is less than the Baseline, the seizure frequency during the Maintenance Period will be imputed using the Baseline seizure frequency. For other subjects who discontinued early, seizure frequency during the Maintenance Period will be imputed using the LOCF methods described in Section 4.2.1.2.

The primary analysis in Section 8.1.2.1 will be repeated following the "worst case" imputation.

The following has been added:

8.1.2.2.2 Sensitivity analysis 2: multiple imputation

Multiple imputations will be used to assess the robustness of the primary efficacy analysis results. Multiple imputation will be performed based on log (28-day adjusted seizure frequency +1) by 4-week visit interval over the 16-week Treatment Period. Seizure frequency during a 4-week interval will be calculated as long as seizure data are available for at least 1 day in the given interval.

Imputation for intermediate missing

Chances of intermittent missing due to completely missing seizure diary during a 4-week interval are low. For subjects with intermittent missing, the last observation carried forward (LOCF)

method will be applied to impute the missing seizure frequency during a 4-week interval from a previous 4-week interval.

Sensitivity analysis 2.1: Missing at random MI

After the intermittent missing data are imputed, the rest of the missing data will be monotone. The first MI analysis assumes MAR for each treatment group separately. Regression method using PROC MI statement MONOTONE REG will be used. The imputation model will include explanatory variables for log-transformed baseline seizure frequency, baseline SV2A use (Yes or No), region (Europe or Non-Europe), and outcome from each visit interval (in chronological order). Seed=57832.

Log-transformed seizure frequency during the Maintenance Period will then be computed by taking the average of the data in the three 4-week visit intervals during the Maintenance Period. Multiple imputed datasets will be analyzed using the same ANCOVA model as in the primary analysis. If there are issues with model convergence, covariates will be dropped sequentially in the order of Region, and then Baseline SV2A use (Yes or No) if further needed. The result of the 100 imputed datasets will be combined for overall inference using SAS PROC MIANALYZE.

8.1.2.2.2.1 Sensitivity Analysis 2.2: Control-based MI

The control-based imputation method used the data from the subjects randomized in the placebo group to impute the missing value for the subjects in the PSL treatment groups. This assumes the subjects on PSL treatment groups will have their efficacy trend toward that of the subjects in the placebo group after the treatment discontinuation. Missing data for the first visit interval are imputed, then missing data for the second visit interval are imputed using observed data and missing data just imputed for the first interval; and so on to the final interval. The imputation will be performed via the sequential regression method using PROC MI statement MONOTONE REG. Multiple imputed datasets will be analyzed using the same ANCOVA model as in the primary analysis. If there are issues with model convergence, covariates will be dropped sequentially in the order of Region, and then Baseline SV2A use (Yes or No) if further needed. Seed=14823

8.1.2.2.3.2 Sensitivity Analysis 2.3 Tipping point MI

In the tipping point analysis, the missing seizure frequencies imputed in the PSL groups using MAR will be adjusted repeatedly by a small increment until none of the PSL treatment groups is significantly different from placebo. The seed used will be 56432.

8.1.2.4.3 Sensitivity analysis 3: multiple imputation

After the multiple imputation process described in Section 8.1.2.2.2, seizure frequency during the Maintenance Period will be calculated as [exp (log-transformed seizure frequency) -1] and the 75% responder status will be derived. Multiple imputed datasets will be analyzed using the same logistic regression model as in the primary analysis for the MAR imputation and control based imputation respectively. If there are issues with model convergence, covariates will be dropped sequentially in the order of Region, and then Baseline SV2A use (Yes or No) if further needed. The tipping point analysis based on MAR multiple imputation will be repeated until none of the PSL treatment group is significantly different from placebo based on the logistic regression model.

The log of the odds ratio estimates from the logistic regression model are used when combining into a single inference using SAS PROC MIANALYZE.

Change #9

9.1 Plasma concentrations of PSL and its major metabolite

Plasma concentrations of PSL and its major metabolite will be determined from blood samples obtained during the Titration and Stabilization and Maintenance Periods (Visits 3, 4, 5, 6 and 7). Individual concentrations of PSL and its [redacted] metabolite (from venous conventional sampling and dried blood (MITRA) sampling) will be listed for subjects in PSL treatment groups for the PK-Set and will include visit, actual daily dose (mg), date and time of the most recent administration, scheduled sampling time per the CRF, actual date and time of sampling, time interval between plasma sample and the most recent administration (in hours). Samples excluded from the PK-PPS will be marked in the listing.will include the actual and nominal sampling times and the deviation between them. All deviations will be calculated relative to the IMP administration. Values below the LLOQ will be reported with a clear sign indicating that they were below the LLOQ.

Concentrations of PSL and its [redacted] will be summarized by sampling method (venous, dried blood MITRA), PSL dose group, visit, and sampling times for the PK-PPS using the following descriptive statistics: number of observations, geometric mean, geometric coefficient of variation, arithmetic mean, SD, median, and minimum and maximum values. Measured values below the limit of quantification (LOQ) will be set LOQ/2 for the calculation.

Descriptive statistics of concentrations will be calculated if at least 2/3rd of the individual data points are quantifiable (≥LLOQ).

Of note, geometric mean is calculated as: exp (arithmetic mean of log-transformed concentrations); geometric coefficient of variation is calculated as: 100 × sqrt [exp (variance of log-transformed concentrations)-1].

The PK samples will be summarized using the following nominal time points based on the time since last dose:

- 15 to <45 min after dosage: 0.5h (30min)
- 45 to <75 min after dosage: 1h (60min)
- 75 to <105 min after dosage: 1.5h (90min)
- 105 to <150 min after dosage: 2h (120min)
- 150 to <210 min after dosage: 3h (180min)
- 4h: 3.5h to <4.5h
- 5h: 4.5 to <5.5h
- 6h: 5.5 to <6.5h
- 8h: 6.5 to <9h
- 10h: 9h to <11h
- 12h: 11h to <14h (time points for the trough concentration,)

Has been changed to:

9.1 Plasma concentrations of PSL and its major metabolites

Plasma concentrations of PSL and its major metabolites will be determined from blood samples obtained during the Titration and Stabilization and Maintenance Periods (Visits 3, 4, 5, 6 and 7). Individual concentrations of PSL and its [redacted] (from venous conventional sampling and dried blood (MITRA) sampling) and concentrations for the [redacted] will be listed for subjects in PSL treatment groups for the PK-Set and will include visit, actual daily dose (mg), date and time of the most recent administration, scheduled sampling time per the CRF, actual date and time of sampling, time interval between plasma sample and the most recent administration (in hours with 2 decimal places). Samples excluded from the PK-PPS will be marked in the listing.

. Values below the limit of quantification (LOQ) will be reported as BLQ (below the limit of quantification).

Concentrations of PSL and its [redacted] will be summarized by sampling method (venous, dried blood MITRA), PSL dose group, visit, and sampling times for the PK-PPS using the following descriptive statistics: number of observations, geometric mean, 95% CI of the geometric mean, geometric coefficient of variation, arithmetic mean, SD, median, and minimum and maximum values. Measured values below the LOQ will be set LOQ/2 for the calculation. Concentrations for [redacted] (only in venous blood) will also be summarized similarly.

Descriptive statistics of concentrations will be calculated if at least 2/3rd of the individual data points are quantifiable (≥LOQ).

Of note, geometric mean is calculated as: exp (arithmetic mean of log-transformed concentrations); upper and lower bounds of the 95% confidence interval (CI) of the geometric mean are calculated as exp (upper) and exp(lower) of the 95% CI of the arithmetic mean of log-transformed concentrations; geometric coefficient of variation is calculated as: 100 × sqrt [exp (variance of log-transformed concentrations)-1].

The PK samples will be summarized based on the actual time since the most recent dose using the following time categories:

- >0 to <45 min after dosage: 0.5h (30min)
- 45 to <75 min after dosage: 1h (60min)
- 75 to <105 min after dosage: 1.5h (90min)
- 105 to <150 min after dosage: 2h (120min)
- 150 to <210 min after dosage: 3h (180min)
- 4h: 3.5h to <4.5h
- 5h: 4.5 to <5.5h
- 6h: 5.5 to <6.5h
- 8h: 6.5 to <9h
- 10h: 9h to <11h or >-3h to <-1h

- 12h: 11h to <14h or >=-1h to <=0 (time points for the trough concentration,)

The geometric mean and associated 95% CI for the trough concentrations of PSL and [redacted] MITRA will be presented by PSL treatment group and visit using semi-log plots.

14.3 Amendment 3

Rationale for the amendment

The primary purpose of this amendment is to clarify details in the planned analyses.

Modifications and changes

Major specific changes

Change #1

The following has been added:

3.2.3 Analysis periods

Table 3–1: Start and end of EP0091 analysis periods

Only seizure data prior to and on the date of last dose of study medication will be included in the analysis.

Change #2

The following has been added:

3.5.6 Completer Set

The Completer Set is a subset of the FAS, consisting of those subjects who completed the 16-week treatment period.

3.5.7.2 Pharmacokinetic Per-Protocol Set (PK-PPS)
e.g. when there is evidence that the sample collected is not at steady-state due to missing doses, dose alterations or interacting concomitant medications, etc.

Change #3

The following has been added:

4.2.1.1 Missing data caused by missing seizure diary
If seizure type is known but the number of seizures is unknown, the number of seizures will be imputed using the median for the same seizure type (daily seizure number > 0) during the same analysis period (baseline or treatment period) by subject. Otherwise, the missing seizure number will be imputed using the count of next higher level of seizure type.

Change #4

The following has been added:

5.1 Subject disposition

Subjects who enrolled into EP0093 will also be summarized.

Change #5

6.4.1 Definitions

Previous AEDs are AEDs taken previously and which has stopped prior to the Visit 1. Previous AEDs are reported on History of Previous Antiepileptic Drug Treatment CRF.

Prior and concomitant medications will be defined for medications reported on AED Medication CRF and Prior and Concomitant Medication CRF. Prior medications include any medications that started prior to the date of first dose of IMP. Concomitant medications are medications taken at least one day in common with the IMP. Medications may be both prior and concomitant.

- A prior medication if:

- (start date of medication) < (start date of IMP)

- start date of medication is unknown but (stop date of medication) < (start date of IMP)

- A concomitant medication if:

- (start date of medication) ≤ (stop date of IMP) and (stop date of medication) ≥ (start date of IMP) or ongoing

- start date of medication is unknown but (stop date of medication) ≥ (start date of study drug) or ongoing.

- A medication at study entry if:

- (start date of medication) ≤ (the date of Visit 1) and (stop date of medication) > (the date of Visit 1) or ongoing

6.4.2 AED medications

Each concomitant medication will be classified as either an AED or a non-AED medication. AED medication taken previously and which has stopped prior to the Visit 1 will be reported on the History of Previous Antiepileptic Drug Treatment CRF. AED mediation that started prior to Visit 1 and which is ongoing/or AED medication prescribed during the study will be recorded on the AED Medication CRF.

The number and percentage of subjects taking AED medications will be summarized by chemical/therapeutic/pharmacological subgroup (ATC classification level 4), and preferred drug name. The following summaries of AED medications will be produced for the SS by treatment group and overall:

- Previous AEDs from the History of Previous Antiepileptic Drug Treatment CRF
- Number of previous AEDs taken: <4, 4-5, 6-7, 8-10,>10 AEDs.
- Previous AEDs by reason for AED discontinuation: The number and percentage of subjects by reason for discontinuation of previous AEDs will be summarized. Percentages for each reason for discontinuation will be relative to the number of subjects taking each AED.
- Prior AEDs
- AEDs taken at study entry
- Number of AEDs taken at study entry: 1, 2, 3, and >3, 4, 5, >5 AEDs

- Number of lifetime AEDs: <4, 4-5, 6-7, 8-10,>10 AEDs. Lifetime AEDs is defined as AEDs with the start date prior to study entry including prior AEDs on AED medication CRF and previous AEDs on History of Previous Antiepileptic Drug Treatment CRF.
- Concomitant AEDs

6.4.4 Prior and Concomitant non-AED medications

Medications recorded on the Prior and Concomitant Medication CRF should not include AEDs. Non-AED medications will be analyzed separately from AED medications.

The number and percentage of subjects taking non-AED medications will be summarized by anatomical main group (Anatomical Therapeutic Chemical [ATC] classification level 1), therapeutic subgroup (ATC classification level 2), and preferred drug name. The following summaries of non-AED medications will be produced for the SS by treatment group and overall:

- Prior non-AED
- Concomitant non-AED

Has been changed to:

6.4.1 AED medications

Each concomitant medication will be classified as either an AED or a non-AED medication. AED medication taken previously and which has stopped prior to the Visit 1 will be reported on the History of Previous Antiepileptic Drug Treatment CRF. AED mediation that started prior to Visit 1 and which is ongoing/or AED medication prescribed during the study will be recorded on the AED Medication CRF.

- Previous AEDs are AEDs taken and stopped prior to the Visit 1. Previous AEDs are reported on History of Previous Antiepileptic Drug Treatment CRF.
- AEDs taken at study entry are reported on AED CRF and if:

- (start date of medication) < (the date of Visit 1) and (stop date of medication) ≥ (the date of Visit 1) or ongoing

- Prior AEDs include both previous AEDs and AEDs taken at study entry
- Concomitant AEDs are reported on AED CRF and if:

- (start date of medication) ≤ (stop date of IMP) and (stop date of medication) ≥ (start date of IMP) or ongoing

- start date of medication is unknown but (stop date of medication) ≥ (start date of study drug) or ongoing.

The number and percentage of subjects taking AED medications will be summarized by chemical/therapeutic/pharmacological subgroup (ATC classification level 4), and preferred drug name. The following summaries of AED medications will be produced for the SS FAS by treatment group and overall:

- Previous AEDs from the History of Previous Antiepileptic Drug Treatment CRF
- Number of previous AEDs taken: <4, 4-5, 6-7, 8-10,>10 AEDs.

• Previous AEDs by reason for AED discontinuation: The number and percentage of subjects by reason for discontinuation of previous AEDs will be summarized. Percentages for each reason for discontinuation will be relative to the number of subjects taking each AED.

• AEDs taken at study entry

• Number of AEDs taken at study entry: 1, 2, 3, and >3AEDs

• Prior AEDs

• Number of prior AEDs: <4, 4-5, 6-7, 8-10,>10 AEDs.

• AEDs taken at study entry

• Number of AEDs taken at study entry: 1, 2, 3, and >3AEDs

• Number of lifetime AEDs: <4, 4-5, 6-7, 8-10,>10 AEDs. Lifetime AEDs is defined as AEDs with the start date prior to study entry including prior AEDs on AED medication CRF and previous AEDs on History of Previous Antiepileptic Drug Treatment CRF.

• Concomitant AEDs

6.4.3 Prior and Concomitant non-AED medications

Medications recorded on the Prior and Concomitant Medication CRF should not include AEDs. Non-AED medications will be analyzed separately from AED medications.

• A prior non-AED medication if:

- (start date of medication) < (start date of IMP)

- start date of medication is unknown but (stop date of medication) < (start date of IMP)

• A concomitant non-AED medication if:

- (start date of medication) ≤ (stop date of IMP) and (stop date of medication) ≥ (start date of IMP) or ongoing

- start date of medication is unknown but (stop date of medication) ≥ (start date of study drug) or ongoing.

A medication at study entry if:

(start date of medication) ≤ (the date of Visit 1) and (stop date of medication) > (the date of Visit 1) or ongoing

The number and percentage of subjects taking non-AED medications will be summarized by anatomical main group (Anatomical Therapeutic Chemical [ATC] classification level 1), therapeutic subgroup (ATC classification level 2), and preferred drug name. The following summaries of non-AED medications will be produced for the SS by treatment group and overall:

• Prior non-AED

• Concomitant non-AED

Change #6

The following has been added:

7.2 Diary compliance

Only data prior to and on the date of last dose of study medication will be included in the compliance calculation.

Change #7

Table 8–1: Summary of seizure frequency variables

Variable	12-Week Maintenance Period		16-Week Treatment Period	
	Observable Focal Onset (IA1, IB and IC)	Focal Onset (All Type I)	Observable Focal Onset (IA1, IB and IC)	Focal Onset (All Type I)
Change in log-SF	X [(a)(c)]	X	X	
75% RR	X [(b)(c)]	X	X	
50% RR	X [(c)]	X	X	
Percent Reduction in SF	X [(c)]	X	X	X
90% RR	X	X		
Change in log-SF (4-week intervals)	X			
Seizure Freedom	X	X	X	X
Number of seizure-free days	X	X	X	X
Cumulative RR			X	X
Change from baseline in seizure frequency	X	X	X	X

Has been changed to:

Table 8–1: Summary of seizure frequency variables

Variable	12-Week Maintenance Period			16-Week Treatment Period		
	Observable Focal Onset (IA1, IB and IC)	Focal Onset (All Type I)	All Seizures (Type I, II and III)	Observable Focal Onset (IA1, IB and IC)	Focal Onset (All Type I)	All Seizures (Type I, II and III)
Change in log-SF	X [(a)(c)]	X		X		
75% RR	X [(b)(c)]	X		X		
50% RR	X [(c)]	X		X		
Percent Reduction in SF	X [(c)]	X		X	X	
90% RR	X	X				
100% RR	X	X				
Change in log-SF (4-week intervals)	X					
Seizure Freedom			X			X

Table 8–1: Summary of seizure frequency variables

Variable	12-Week Maintenance Period			16-Week Treatment Period		
	Observable Focal Onset (IA1, IB and IC)	Focal Onset (All Type I)	All Seizures (Type I, II and III)	Observable Focal Onset (IA1, IB and IC)	Focal Onset (All Type I)	All Seizures (Type I, II and III)
Number of seizure-free days			X			X
Cumulative RR				X	X	
Change from baseline in seizure frequency	X	X		X	X	

Change #8

8.1.2.2.2 Sensitivity analysis 2: multiple imputation

Imputation for intermediate missing

Chances of intermittent missing due to completely missing seizure diary during a 4-week interval are low. For subjects with intermittent missing, the last observation carried forward (LOCF) method will be applied to impute the missing seizure frequency during a 4-week interval from a previous 4-week interval.

8.1.2.2.2.3 Sensitivity Analysis 32.3 Tipping point MI

In the tipping point analysis, the missing seizure frequencies imputed in the PSL groups using MAR will be adjusted repeatedly by a small increment (eg, a small percentage of the mean of the log-transformed baseline seizure frequency in the Placebo group) until none of the PSL treatment groups is significantly different from placebo. The seed used will be 56432.

Has been changed to:

Imputation for intermediate missing

Chances of intermittent missing due to completely missing seizure diary during a 4-week interval are low. For subjects with intermittent missing, the last observation carried forward (LOCF) method will be applied to impute the missing seizure frequency during a 4-week interval from a previous 4-week interval. The intermittent missing seizure frequency before the last 4-week visit interval will be assumed as missing at random (MAR). The intermittent missing data will be filled in using MCMC method with 30 iterations. The imputation model will include treatment groups, log-transformed baseline seizure frequency, baseline SV2A use (Yes or No), region (Europe or Non-Europe), and outcome from each visit interval (in chronological order). After the intermittent missing data are imputed, the rest of the missing data will be monotone. Seed=57832.

8.1.2.2.2.3 Sensitivity Analysis 2.3 Tipping point MI

Following the National Research Council (NRC) report on missing data (NRC, 2010), a sensitivity analysis using tipping point method to stress-test the result of MAR by imposing a succession of δ adjustments, each one more severe, in the PSL Groups until they are no longer statistically significant. This Delta (δ) will be applied just once, at the first visit that has missing frequency seizure data for each subject in the PSL groups who discontinued before the end of treatment period and hence have missing records for "seizure frequencies". Use nimpute = 30, seed = 56432.

The tipping point report (table) for each pairwise comparison will include values for the LSmeans, the 95% CI, and the p-value for each of the delta value (including 0, until p-values are no longer statistically significant. Only 8 delta values will be tabulated in the report including δ=0 until δ=xx.x% shift the p-value to larger than multiplicity adjusted alpha level.

Change #9

The following has been added:

8.1.2.3 Primary variable for submission to the EMA and regulatory authorities who reference EMA

If there is <2 responders in a treatment group, results will also be provided for an exact conditional logistic regression model where treatment group is included in the model and Region (Europe or Non-Europe) and Baseline SV2A use (Yes or No) are included as strata.

Change #10

8.3.2.5 The 90% responder rate over the 12-week Maintenance Period

Analysis of the 90% responder rate during the 12-week Maintenance Period will be analyzed for the FAS, using the same logistic regression model as specified in Section 8.12.3.

8.3.2.10 The 90% responder rate for focal-onset (Type I) seizures over the 12-week Maintenance Period

Analysis of the 90% responder rate for Type I focal-onset seizures during the 12-week Maintenance Period will be analyzed for the FAS, using the same logistic regression model as in Section 8.1.2.3.

8.3.2.16 Seizure-freedom status (yes/no) during the 12-week Maintenance and the 16-week Treatment Period

Seizure freedom status will be evaluated for each treatment by summarizing the percentage of seizure-free subjects as a response rate during the 12-week Maintenance Period and during the entire 16-week Treatment Period. The seizure freedom rate for each of these periods will be analyzed using Fisher's Exact Test to compare differences between each PSL dose group and placebo.

Has been changed to:

8.3.2.5 The 90% and 100% responder rates over the 12-week Maintenance Period

Analysis of the 90% and 100% responder rates during the 12-week Maintenance Period will be analyzed for the FAS, using an exact conditional logistic regression model where treatment group is included in the model and region and Baseline SV2A use are included as strata.

8.3.2.10 The 90% and 100% responder rates for focal-onset (Type I) seizures over the 12-week Maintenance Period

Analysis of the 90% and 100% responder rates for Type I focal-onset seizures during the 12-week Maintenance Period will be analyzed for the FAS, using an exact conditional logistic regression model where treatment group is included in the model and region and Baseline SV2A use are included as strata.

8.3.2.16 Seizure-freedom status (yes/no) during the 12-week Maintenance and the 16-week Treatment Period

Seizure freedom status will be evaluated for each treatment by summarizing the percentage of seizure-free subjects as a response rate during the 12-week Maintenance Period and during the entire 16-week Treatment Period. The seizure freedom rate will be calculated based on the Completer Set. The seizure freedom rate for each of these periods will be analyzed using an exact conditional logistic regression model where treatment group is included in the model and region and Baseline SV2A use are included as strata.

Change #11

9.2 Plasma concentrations of concomitant AEDs

The AEDs investigated with mixed models will be those with data available for at least 10 subjects in one of the treatment groups (subset of AED-PK-PPS).

Has been changed to:

9.2 Plasma concentrations of concomitant AEDs

The AEDs investigated with mixed models will be those with data available for at least 10 evaluable subjects in one of the treatment groups (subset of AED-PK-PPS). An evaluable subject is defined as a subject:

- with at least one AED measure (>LOQ) at baseline and at least one AED assessment (>LOQ) during the maintenance period
- who received constant dose of AED for at least 14 days prior to the AED samples

15 ADDENDUM

All tables described in the SAP will be repeated for Japan and non-Japan subgroups for the purpose of Japan specific CSR.

STATISTICAL ANALYSIS PLAN SIGNATURE PAGE

This document has been reviewed and approved per the Review and Approval of Clinical Documents Standard Operating Procedures. Signatures indicate that the final version of the Statistical Analysis Plan (SAP) or amended SAP is released for execution.

Approval Signatures

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