STATISTICAL ANALYSIS PLAN

Study: EP0092

Product: Padsevonil (UCB0942)

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

PHASE 3

SAP/Amendment Number	Date
Final SAP	10 Dec 2018
Amendment 1	18 Aug 2020

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LIST OF ABBREVIATIONS

AE	adverse event
AED	antiepileptic drug
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
AST	aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
Bid	twice daily
BMI	body mass index
BRV	Brivaracetam
CFDA	Chinese FDA
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

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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

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WHO DD	World Health Organization Drug Dictionary

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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 EP0092 Amendment 1, 21 January 2020. 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: 2018-002303-33; 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 objective of this study is to evaluate the efficacy of the 3 selected dose regimens of padsevonil (PSL) administered concomitantly with up to 3 antiepileptic drugs (AEDs) compared with placebo for treatment of observable focal-onset seizures in subjects with drug-resistant epilepsy.

2.1.2 Secondary objective(s)

The secondary objective of the study is to assess the safety and tolerability 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
- Evaluate the impact of enzyme-inducing concomitant AEDs on PSL exposure
- Evaluate concomitant AED (and/or relevant metabolites) plasma levels

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2.2 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 include all (Types I, II, and III) seizure types.

2.2.1 Primary efficacy variable

2.2.1.1 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.

2.2.1.2 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.

2.2.2 Secondary efficacy variables

2.2.2.1 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

2.2.2.2 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

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

2.2.3 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
- Number of seizure-free days during the 12-week Maintenance Period and the 16-week Treatment Period

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- 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)
- Use of health-related outcomes and HRU, including healthcare provider consultations not foreseen by protocol, caregiver support, concurrent medical procedures, concomitant medications and hospitalizations

2.3 Safety variables

2.3.1 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

2.3.2 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

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- 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]).

2.4 Other variables

2.4.1 Pharmacokinetic variables

Blood concentrations of PSL will be determined from samples obtained in the study during the Treatment Period in order to investigate the following variables:

- The population PK profiles of PSL

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

Comparison may be made between blood concentration data of PSL and [redacted] metabolite derived from the volumetric absorptive microsampling MITRA® technology. Additionally, evaluation of PSL and [redacted] metabolite in plasma may 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.

2.5 Study Design and Conduct

2.5.1 Study description

EP0092 is a multicenter, randomized, double-blind, placebo-controlled, parallel-group 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 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 at stable regimens, with doses and settings individually optimized for efficacy and safety/tolerability.

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

The study is composed of 4 periods (see Figure 6–1) for a schematic diagram.

Baseline Period (4 weeks)

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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 4 treatment arms in a 1:1:1:1 ratio (random permuted blocks) to ensure the balance to 1 of the 4 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 Japan) at the time of randomization.

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.

After the Baseline Visit (Visit 2), subjects will return to the clinic for regular visits for the remainder of the Treatment Period.

Titration Period (3 weeks)

Subjects will be instructed to take the IMP in 2 equally divided dosed, approximately 12 hours apart in the morning and evening. Subjects who cannot tolerate IMP prior to Week 3 will be withdrawn from the study.

Stabilization Period and fallback (1 week)

For subjects with tolerability issues at their target dose, one fallback to a predefined dose based on the randomized dose will be allowed during the Stabilization Period and should occur at least 2 days prior to the start of the Maintenance Period (Visit 4) for subjects who experience tolerability issues during Week 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).

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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.

Maintenance Period (12 weeks)

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 **Error! Reference source not found.**.

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. 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 early or not enrolling in the OLE 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 the study. Subjects entering 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 (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 (1 month)

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

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the entry dose for the OLE. Subjects who took placebo during the Maintenance Period will receive PSL titrated to the target dose.

2.5.2 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.

2.5.3 Treatments to be administered

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

All subjects will be instructed to take 5 tablets during the Titration and Taper Periods or 6 tablets during the Stabilization, Maintenance, and Conversion Periods from the appropriate medication wallets containing either PSL or placebo bid, approximately 12 hours apart. The IMP should be dosed within 30 minutes after food when practically feasible.

Subjects will be allocated to 1 of the following 4 treatment arms using the IRT system at the Baseline Visit (Visit 2):

- Padsevonil 100mg bid
- Padsevonil 200mg bid
- Padsevonil 400mg bid
- Placebo

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Table 2–1: Schedule of assessments

Visit	BL Period (4 weeks)	Treatment Period (16 weeks)								Taper/Conversion Period (3 to 4 weeks) [a]			SFU Period (30 days after IMP intake)	Unsch Visit [b]	Setting (Required Onsite [t])
		Titration Period (3 weeks)			Stab Period (1 week)	Maintenance Period (12 weeks)									
Visit	**V1**	**V2 BL**	**TC**	**V3**	**TC**	**V4**	**V5**	**V6**	**V7 (EDV/EOT)**	**TC**	**V8 (Conversion)**	**V8 (Taper)**	**V9**		
Week Number	**Wk -4**	**D 1**	**Wk 1**	**Wk 2**	**Wk 3**	**Wk 4**	**Wk 8**	**Wk 12**	**Wk 16**		**Wk 19**	**Wk 20**	**Wk 23**		
Day Number	-28	1	7	14	21	28	56	84	112		133	140	161		
Visit Window (days)		±3	±3	±3	±3	±7	±7	±7	±7		±7		±7		
Assessments															
Written informed consent	X														NA – V1 always performed onsite
Call IRT to obtain subject number and dispensation of Subject Trial Card	X														NA – V1 always performed onsite
Demographic data	X														NA – V1 always performed onsite
Habits and lifestyle	X														NA – V1 always performed onsite

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Visit	**V1**	**V2 BL**	**TC**	**V3**	**TC**	**V4**	**V5**	**V6**	**V7 (EDV/EOT)**	**TC**	**V8 (Conversion)**	**V8 (Taper)**	**V9**		
Week Number	**Wk -4**	**D 1**	**Wk 1**	**Wk 2**	**Wk 3**	**Wk 4**	**Wk 8**	**Wk 12**	**Wk 16**		**Wk 19**	**Wk 20**	**Wk 23**		
Verification of inclusion/exclusion criteria	X	X													NA – V1/2 always performed onsite
Verification of withdrawal criteria		X	X	X		X	X	X	X						Partially required onsite
General medical/procedures history	X														NA – V1 always performed onsite
Epilepsy history including etiology, diagnosis, surgery, and seizure history	X														NA – V1 always performed onsite
Documentation of MRI (within 10 years)	X														NA – V1 always performed onsite
Documentation of video-EEG [c]	X														NA – V1 always performed onsite

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Visit	**V1**	**V2 BL**	**TC**	**V3**	**TC**	**V4**	**V5**	**V6**	**V7 (EDV/EOT)**	**TC**	**V8 (Conversion)**	**V8 (Taper)**	**V9**		
Week Number	**Wk -4**	**D 1**	**Wk 1**	**Wk 2**	**Wk 3**	**Wk 4**	**Wk 8**	**Wk 12**	**Wk 16**		**Wk 19**	**Wk 20**	**Wk 23**		
AED history	X														NA – V1 always performed onsite
Randomization (IRT)		X													NA – V2 always performed onsite
C-SSRS Baseline [d]	X														NA – V1 always performed onsite
C-SSRS since last visit **Error! Reference source not found.** [e]		X		X		X	X	X	X		X		X		no
HADS **Error! Reference source not found.**		X				X			X				X		no

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Week Number	**Wk -4**	**D 1**	**Wk 1**	**Wk 2**	**Wk 3**	**Wk 4**	**Wk 8**	**Wk 12**	**Wk 16**		**Wk 19**	**Wk 20**	**Wk 23**		
SSG **Error! Reference source not found.**		X				X			X				X		no
QOLIE-31-P **Error! Reference source not found.**		X				X			X				X		no
CIWA-B **Error! Reference source not found.**									X		X		X		no
TSQM-9 **Error! Reference source not found.**									X						no
Vital signs [f]	X	X		X		X	X	X	X		X		X		yes
Body weight and height [g]	X	X				X	X	X	X		X		X		no
Physical examination [h] (XF=Full; XB=Brief)	XF	XB				XB			XF		XF		XB		yes

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Week Number	**Wk -4**	**D 1**	**Wk 1**	**Wk 2**	**Wk 3**	**Wk 4**	**Wk 8**	**Wk 12**	**Wk 16**		**Wk 19**	**Wk 20**	**Wk 23**		
Neurological examination [i] (XF=Full; XB=Brief)	XF	XB				XB			XF		XF		XB		no
Psychiatric and Mental Status		X		X		X	X	X	X		X		X		no
12-lead ECG [j]	X	X		X		X	X		X		X		X		yes
Echocardiogram [k]	X							X					X [l]		yes
Blood/urine sample for clinical laboratory analyses	X	X				X		X	X		X		X		yes
Blood sample for concomitant AED assay [m n]	X	X						X	X						yes
Blood sample for PSL PK analysis [o] **Error! Reference source not found.**				X		X	X	X	X						yes
Pregnancy test [p]	X	X		X		X	X	X	X		X		X		yes

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Week Number	**Wk -4**	**D 1**	**Wk 1**	**Wk 2**	**Wk 3**	**Wk 4**	**Wk 8**	**Wk 12**	**Wk 16**		**Wk 19**	**Wk 20**	**Wk 23**		
Diary dispensing (provide instructions on proper completion)	X	X		X		X	X	X	X		X		X		no
Seizure evaluation (count & type) [q]		X	X	X	X	X	X	X	X	X	X		X		no
Concomitant medications (AEDs and non-AEDs) and procedures	X	X	X	X	X	X	X	X	X	X	X		X		no
Recording of adverse events	X	X	X	X	X	X	X	X	X	X	X		X		no
Health-related outcomes and HRU	X	X		X		X	X	X	X		X		X		no
IMP dispensing (IRT)		X		X		X	X	X	X						no
IMP accountability and return [r]				X		X	X	X	X		X				no
Study termination [s]											X		X		NA – this is not an assessment

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AED=antiepileptic drug; BL=Baseline; CIWA-B=Clinical Institute Withdrawal Assessment-Benzodiazepines; C-SSRS=Columbia-Suicide Severity Rating Scale; D=day; DBP=diastolic blood pressure; ECG=electrocardiogram; EDV=Early discontinuation Visit; EEG=electroencephalogram; EOT=End of Treatment; HADS=Hospital Anxiety and Depression Scale; HRU=healthcare resource utilization; IMP=investigational 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; SBP=systolic blood pressure; SFU=Safety Follow-Up; SSG=Seizure Severity Global Item; Stab=Stabilization Period; TC=telephone call; TSQM=Treatment Satisfaction Questionnaire for Medication; Unsch=unscheduled; V=visit; Wk=Week, NA=Not Applicable

Error! Reference source not found. Taper Period, for subjects who choose not to 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.

Error! Reference source not found. 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] Epileptic seizures must have been documented using video-EEG recording in the past (description or report must be available). The Investigator must consult with the UCB Study Physician or representative for confirmation of eligibility as per instructions in the Study Manual.

Error! Reference source not found. Questionnaires to be completed by all subjects prior to any other study procedures at the visit. The CIWA-B will only be completed by subjects tapering.

Error! Reference source not found. 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.

Error! Reference source not found. Vital signs measured in supine position after 5 minutes of rest include pulse rate, respiratory rate, SBP, and DBP.

Error! Reference source not found. Height will only be measured at Visit 1.

Error! Reference source not found. 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.

Error! Reference source not found. 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), and sensations in upper/lower extremities.

Error! Reference source not found. 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 the End of Treatment or Early Discontinuation Visit. All ECG recordings will be performed with the subject resting in the supine position for at least 5 minutes.

Error! Reference source not found. The echocardiogram will be conducted at Visit 1. Echocardiograms will be repeated at Visit 6 for subjects continuing into 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).

Error! Reference source not found. 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).

Error! Reference source not found. 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.

Error! Reference source not found. 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.

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Error! Reference source not found. Subjects are requested to provide blood samples for measurement of PSL PK whenever possible. On Visits 3, 5, and 6, site personnel should obtain blood samples, via MITRA microsampling, for measurement of random PSL levels at any time between IMP intakes and record accurately the time of last IMP intake and the time of sample collection. On Visits 4 and 7, blood samples, via MITRA microsampling, 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.

Error! Reference source not found. 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.

Error! Reference source not found. Seizure counts are collected on the subject's daily record card on a daily basis.

Error! Reference source not found. At each visit following an IMP dispensation, IMP should be presented to check for compliance.

Error! Reference source not found. Study termination will occur at Visit 8 only for subjects enrolling in OLE study, EP0093. The SFU Visit will be performed only for subjects who do not enter the OLE study, EP0093.

Error! Reference source not found. Data may be collected through phone or video calls for visits that do not require onsite assessment.

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Figure 6–1: Study design

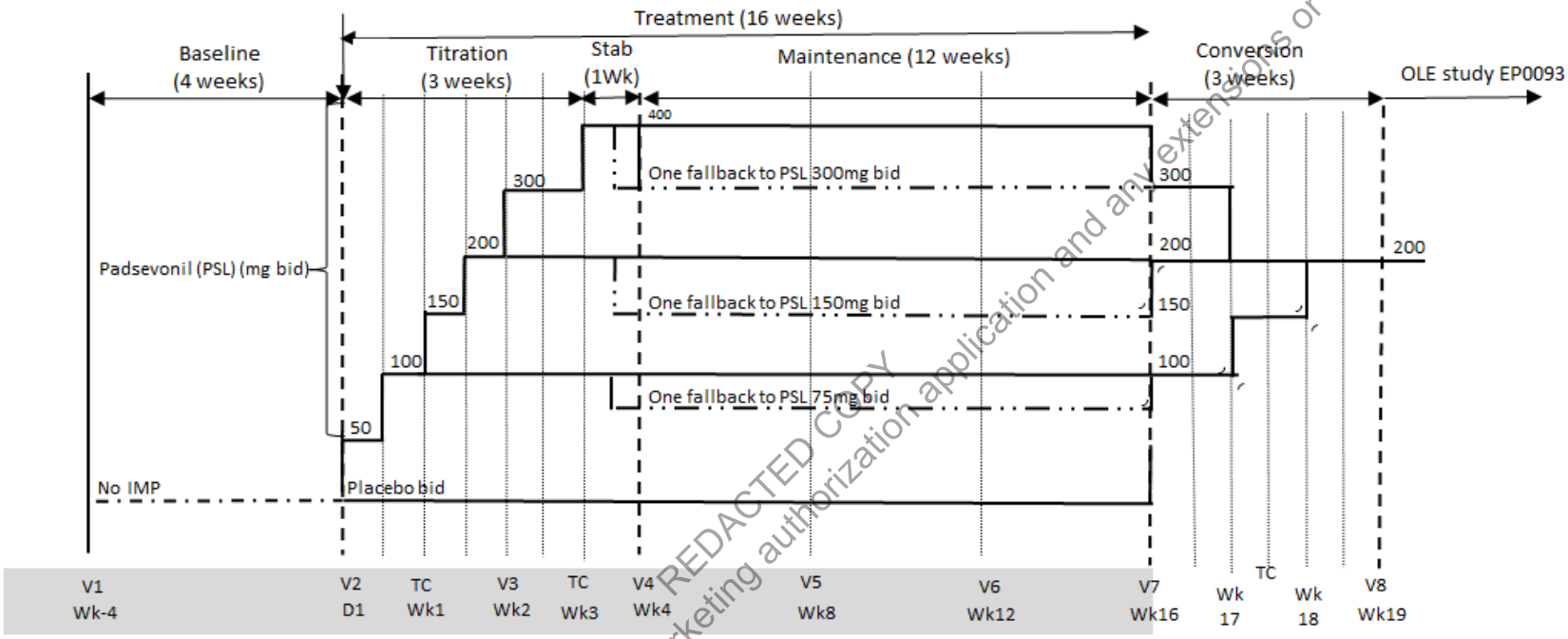

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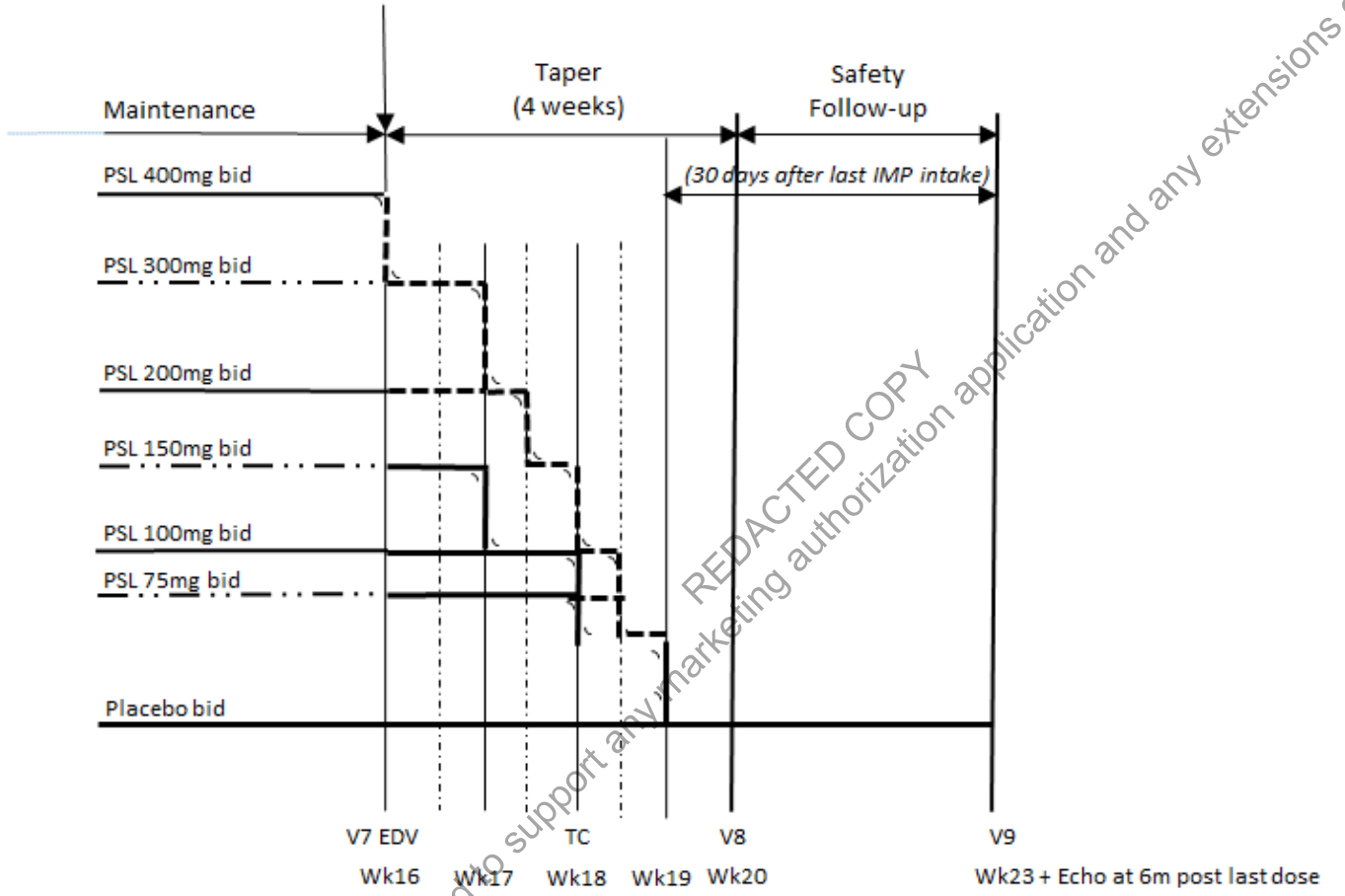
Figure 6–1: Study design (continued)



bid=twice daily; d=day; Echo=echocardiogram; EDV=Early Discontinuation Visit; IMP=investigational medicinal product; m=months; OLE=open-label extension; PSL=padsevonil; Stab=Stabilization Period; TC=telephone contact; V=Visit; Wk=Week

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2.6 Determination of sample size

In the event that 2 data analyses are conducted to accommodate an extended enrollment period in China, the initial data cut and analysis will be performed after all randomized non-Chinese subjects (approximately 400) have completed or terminated the study. The safety and efficacy analyses from this first data cut will serve as the basis for the European, North American, and Japanese submissions for marketing authorization. The power for this analysis is greater than 90%, at the 2-sided 5% significance level. Because of uncertainty regarding the time point when China will join the global program and the duration of recruitment in China, a second efficacy and safety analysis for all randomized subjects will also be performed: the power in this case remains greater than 90%, at the 2-sided 5% significance level. The safety and efficacy analyses from the second data cut will serve as the basis for submission for marketing authorization only for China.

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 PBO for both the primary variable for FDA/PMDA/CFDA, change from Baseline of the log transformed (ln x+1) 28-day adjusted seizure frequency, and the primary variable for EMA, the 75% responder rate. The log reduction from Baseline in seizure frequency was assumed to be 0.195 for PBO and 0.670, 0.754, and 0.780 for 100mg bid, 200mg bid, and 400mg bid doses of PSL, respectively. A common SD of 0.985 was assumed. For the 75% responder rate endpoint, assumptions were a 0.121 responder rate for PBO and corresponding responder rates of 0.301, 0.332, and 0.342 for the 100mg bid, 200mg bid, and 400mg bid doses of PSL, respectively. These estimates are based on prior experience in epilepsy together with the EP0069 study results. A significance level of 0.05 was chosen, and a 2-sided test assumed. With power of greater than 90%, a 2-sided Type-1 error of 5%, and all dose groups of the same size, 100 subjects are required per arm, giving a total of 400 subjects.

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

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- 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 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

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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 last 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: Start and end of EP0092 analysis periods. 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.

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Table 3–1: Start and end of EP0092 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.

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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

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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). Safety variables will be analyzed using the Safety Set (SS). Pharmacokinetic data listings will use the Pharmacokinetic Set (PKS).

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 Safety Set (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. The FAS will be the primary analysis set for all efficacy summaries and analyses.

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3.5.5 Per Protocol Set

Due to the early termination of the study, and the change in the , the, Per Protocol Set (PPS) will not be included in the study.

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] metabolite).

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

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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 22.1 or higher of Medical Dictionary for Regulatory Activities (MedDRA®) according to UCB Standard Operating Procedures (SOP).

3.9 Changes to protocol-defined analyses

Due to Covid-19 impact on site initiation and enrollment and due to early termination of the study, the following items in the protocol were updated in this SAP.

Section in this SAP	Description	Change from the protocol
2.2	Efficacy variables	Removed: Seizure-free days
2.2.3	Other efficacy variables	Removed: Time to return to baseline 28-day observable focal-onset seizure count during the 12 week Maintenance Period
Table 2-1:	Schedule of Assessments	Added Setting (Required Onsite) column to include data that may be collected through phone or video calls for visit, during the pandemic.
3.5.5	Per Protocol Set	Due to early termination of the study, PPS will not be included in the study. Removed: 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.
3.10	COVID-19 eCRF	Added, see section 3.10 for details

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4.3.1	Sequential Analyses	Removed all text associated with China region due to no patient enrollment and due to early termination of the study.
4.8	Examination of subgroups	Removed: subgroup by region, gender, age Added: Levetiracetam/Brivaracetam use at study entry (Y/N) based on AED medication CRF.
6.2	Other Baseline characteristics	Removed text associated with China region.
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	Removed text related to sensitivity analyses due to changed scope of the study.
8.1.2.4	Supportive and sensitivity analyses for the primary variable for submission to the EMA and regulatory authorities who reference EMA.	Removed text related to sensitivity analyses due to changed scope of the study.
8.1.3	Analysis of primary efficacy variable for submission to the CFDA	Removed text associated with China region.

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3.10 COVID-19 eCRF

A new COVID-19 eCRF, to evaluate the impact of global pandemic was created and implemented to collect the information on impacted visit, impact category, and relationship to COVID-19.

Summary and listing (see Section 12 for details) to describe the impact on the interpretability of efficacy and safety endpoints will be performed to assess the impact of the changes on the planned analyses due to COVID-19.

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, Austria, Belgium, Bosnia and Herzegovina, Bulgaria, Croatia, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Netherlands, Norway, Poland, Portugal, Romania, Serbia, Slovakia, Spain, Sweden, Switzerland, Turkey, and United Kingdom)
- North America (Canada, Mexico, and United States)
- 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.

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:

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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.

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

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- 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

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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

A Data Monitoring Committee (DMC) will be formed to monitor the ongoing safety of the study through periodic review of safety data. The general scope of DMC activities is presented in the protocol and will be described in detail in the DMC Charter. A DMC Statistical Analysis Plan will be prepared to describe all analysis / reports required for the execution of the DMC meeting.

4.3.1 Sequential Analyses for European/North American/Japanese regulatory submissions

Due to COVID-19 pandemic, subjects from the China region (100 in total) were not enrolled, hence this region will not be included in the sequential analyses - gatekeeping procedure mentioned in the protocol.

Once all subjects have completed or terminated the study, data will be locked and unblinded and no changes to these data are allowed after unblinding. Analysis for European/North American/Japanese regulatory submissions will be carried out at 0.05 alpha level (two-sided).

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

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than 0.0167, we will conclude a significant difference between the dose and the placebo; otherwise, stop and no comparison is significant.

4.6 Use of an efficacy subset of subjects

The FAS will be used for the primary efficacy analyses. 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:

- Use of AEDs with binding to synaptic vesicle 2A (SV2A) proteins (levetiracetam [LEV] or brivaracetam [BRV], Y/N) based on stratification CRF.
- Levetiracetam/Brivaracetam use at study entry (Y/N) based on AED medication CRF.

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, CS, SS , and PKS.

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

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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.

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.

A by-subject listing of subjects excluded from each of the analysis datasets (for SS, FAS) 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 (Chinese, Japanese, Non-Chinese, Non-

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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 Japan), 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.

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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.

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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 and 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.

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- 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.

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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.

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.

8 EFFICACY ANALYSES

Unless noted otherwise, analyses of efficacy endpoints will be performed on the FASFor the efficacy variables seizure frequency refers to a 28-day adjusted frequency; observable focal-

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onset seizures refer to Type IA1, IB, and IC (ILAE Classification of Epileptic Seizures, 1981); 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 2.2.1, 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				
Seizure Freedom			X			X
Number of seizure-free days			X			X
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

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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. Only subjects with > 0 seizure frequency at baseline will be included in the summary analysis.

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.

Only subjects with > 0 seizure frequency at baseline will be included in all percent reduction analysis.

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.

Only subjects with > 0 seizure frequency at baseline will be included in the analysis.

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, 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 difference 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

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the log difference. 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. 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, Chinese FDA and other regulatory authorities not referencing EMA

Due to early termination of the study and COVID-19 global pandemic, all sensitivity analyses will not be executed.

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 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. 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

Due to early termination of the study and COVID-19 global pandemic, all sensitivity analyses will not be executed.

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 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.

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8.1.3 Analysis of the primary efficacy variable for submission to the CFDA

Due to COVID-19 pandemic subjects (100 in total) from the China region were not enrolled

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.

Only subjects with > 0 seizure frequency at baseline will be included in the analysis.

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.

Only subjects with > 0 seizure frequency at baseline will be included in the analysis.

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.

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.

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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

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

The 50% responder rate during the entire 16-week Treatment Period will be listed, for the RS.

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

The 75% responder rate during the entire 16-week Treatment Period will be listed, for the RS.

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

The 90% and 100% responder rates during the 12-week Maintenance Period will be listed for the RS.

8.3.2.4 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.

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

The 50% responder rate for Type I focal-onset seizures during the 12-week Maintenance Period will be listed for the RS.

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

The 75% responder rate for Type I focal-onset seizures during the 12-week Maintenance Period will be listed for the RS.

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

The 90% and 100% responder rates for Type I focal-onset seizures during the 12-week Maintenance Period will be listed for the RS.

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

Percent reduction in focal-onset (Type I) seizure frequency from baseline over the 12-week Maintenance Period and the 16-week Treatment Period will be listed.

8.3.2.9 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 listed for the RS.

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

75% responder rate in Type IA1, IB, or IC seizure over the 12-week Maintenance Period by each seizure type separately will be listed for the RS.

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

Percent reduction in Type IA1, IB, or IC seizure frequency from baseline over the 12-week Maintenance Period and the 16-week Treatment Period will be listed.

8.3.2.12 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.

8.3.2.13 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 listed. The change in the percentage of seizure-free days from the Baseline Period to the Maintenance Period and Treatment Period will also be listed.

8.3.2.14 Change in the SSG score

All data will be listed by subject for Baseline and at each scheduled assessment visit for each of the 7 categories of change (much better through much worse).

8.3.2.15 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 listed by subject.

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

The HADS observed scores and changes from Baseline for depression and anxiety will be listed by subject.

8.3.2.17 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.

8.3.2.18 Use of health-related outcomes and HRU

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

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- 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..

- Healthcare provider consultations not foreseen by the protocol

The health care provider consultations by type of provider (general practitioner, specialist physician, nurse, and other) per subject will be listed.

- Hospital and ER visits

ER visits will be extracted from the Hospitalization/ER Visit CRF page (if the initial entry point is ER).

- Caregiver assistance

Caregiver assistance data is collected on the CRFs "Caregiver Assistance Screening" and "Caregiver Assistance Follow-up". Data will be listed per visit.

- 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 listed.

The percentage of days lost will be listed 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.

8.3.2.19 Treatment satisfaction

Treatment satisfaction will be collected at visit 7 or at Early Discontinuation Visit. The Treatment Satisfaction Questionnaire for Medication (TSQM)-9 is a 9-item questionnaire developed to provide a suitable measure of treatment satisfaction with medication (Bharmal et al, 2009). It has 5 to 7 Likert response options per item and consists of 3 subscales: effectiveness (3 items), convenience (3 items), and a global satisfaction scale (3 items). The TSQM-9 was

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developed from the TSQM 1.42, which has an additional subscale that measures side effects (3 items) (Atkinson et al, 2004). The estimated completion time for this questionnaire is less than 5 minutes. Scores range from 0 (worst) to 100 (best). Treatment satisfaction assessed by TSQM-9 will be listed.

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] metabolite (from venous conventional sampling and dried blood (MITRA) sampling) and [redacted] metabolite (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).

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

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 listed by visit and treatment group.

9.3 Other PK analyses/variables

Not applicable.

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

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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.

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 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 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.

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- 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.

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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 EP0092. 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

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- 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.

Potential Hy's Law, is defined as ≥3xULN ALT or AST with coexisting ≥2xULN total bilirubin in the absence of ≥2xULN ALP, with no alternative explanation for the biochemical abnormality.

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.

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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.

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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

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

In case of a missing sub score 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.

12 COVID-19 IMPACT

The impact of COVID-19 global pandemic on this study is detailed in section 3.10. COVID-19 impact will be summarized by impact category and impacted visit. The data including visit, date, relationship to COVID-19, impact category and narrative of event will be listed for the RS, if the subject has been impacted.

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13 REFERENCES

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14 APPENDICES

14.1 PCST Criteria for Hematology, Serum Chemistry and Urinalysis Parameters

14.1.1 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
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

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PARAMETER	AGE RANGE	UNIT (conventional)	ABNORMALITY CRITERIA (conventional)	UNIT (standard)	ABNORMALITY CRITERIA (standard)
	≥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.

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14.1.2 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
	≥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

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PARAMETER	AGE RANGE	UNIT (conventional)	ABNORMALITY CRITERIA (conventional)	UNIT (standard)	ABNORMALITY CRITERIA (standard)
	≥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
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

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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

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14.1.3 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

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14.2 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
	6m - <3y	<90
	3y - <12y	<60
	12y - <17y	<50
	≥17y	<50 and a decrease from Baseline of ≥15
Systolic Blood Pressure (mmHg)	<6m	<60
	6m - <3y	<70
	3y - <12y	<80
	12y - <17y	<90
	≥17y	<90 and a decrease from Baseline of ≥20
Diastolic Blood Pressure (mmHg)	<6m	<40
	6m - <3y	<45
	3y - <12y	<50
	12y - <17y	<50
	≥17y	<50 and a decrease from Baseline of ≥15
Respiratory Rate (breaths/minute)	<6m	<25
	6m - <3y	<20
	3y - <12y	<15
	≥12y	<10

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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/

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14.3 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.

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Echocardiogram Valvular Abnormality	Severity / Description	Potential Cardiovascular Signs/Symptoms	Action
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.

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14.4 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

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15 AMENDMENT(S) TO THE SAP

15.1 Amendment 1

Rationale for the amendment

The primary purpose of this amendment is to specify changes in the planned analyses due to early termination of the study and due to COVID-19 global pandemic impact.

Modifications and changes

Major specific changes

Change #1

The following has been changed:

2.2 Efficacy variables

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

Changed to:

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

Change #2

The following has been removed:

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

- Time to return to baseline 28-day observable focal-onset seizure count during the 12-week Maintenance Period

Change #3

The following has been added:

Table 2-1 Schedule of Assessments

Added Setting (Required Onsite) column to include data that may be collected through phone or video calls for visit, during the pandemia.

Change #4

The following has been added:

3.2.3 Analysis periods

Table 3–1: Start and end of EP0092 analysis periods

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

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Change #5

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.

Change #6

The following has been added:

3.7 Sites pooled strategy

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 #7

The following has been added:

3.9 Changes to protocol-defined analyses

Due to Covid-19 impact on site initiation and enrollment and due to early termination of the study, the following items in the protocol were updated in this SAP.

Section in this SAP	Description	Change from the protocol
2.2	Efficacy variables	Removed: Seizure-free days include all (Types I, II, and III) seizure types
2.2.3	Other efficacy variables	Removed: Time to return to baseline 28-day observable focal-onset seizure count during the 12 week Maintenance Period
Table 2-1:	Schedule of Assessments	Added Setting (Required Onsite) column to include data that may be collected through phone or video calls for visit, during the pandemia.

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3.5.5	Per Protocol Set	Due to early termination of the study, PPS will not be included in the study. Removed: 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.
3.10	COVID-19 eCRF	Added, see section 3.10 for details
4.3.1	Sequential Analyses	Removed all text associated with China region due to no patient enrollment and due to early termination of the study.
4.8	Examination of subgroups	Removed: subgroup by region, gender, age Added: Levetiracetam/Brivaracetam use at study entry (Y/N) based on AED medication CRF.
6.2	Other Baseline characteristics	Removed text associated with China region.
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	Removed text related to sensitivity analyses due to changed scope of the study.
8.1.2.4	Supportive and sensitivity analyses for the primary variable for submission to the EMA and regulatory authorities who reference EMA.	Removed text related to sensitivity analyses due to changed scope of the study.

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8.1.3	Analysis of primary efficacy variable for submission to the CFDA	Removed text associated with China region.

Change #7

The following has been added:

3.10 COVID-19 eCRF

A new COVID-19 eCRF, to evaluate the impact of global pandemic was created and implemented to collect the information on impacted visit, impact category, and relationship to COVID-19.

Summary and listing (see Section 12 for details) to describe the impact on the interpretability of efficacy and safety endpoints will be performed to assess the impact of the changes on the planned analyses due to COVID-19.

Change #9

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 #10

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 #11

The following has been changed:

4.3.1 Sequential Analyses for European/North American/Japanese/Chinese regulatory submissions

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In the event that enrollment is completed in China and Europe/North America/Japan at approximately the same time, a single analysis will be conducted including all randomized subjects for the submission to all regulatory agencies. If the enrollment period in China is extended to attain the target of approximately 100 subjects randomized in that country, then 2 analyses will be carried out in a sequential fashion with statistical significance required from the first analysis in order for the second analysis to take place. In the latter case, the first analysis for European/North American/Japanese regulatory submissions will be carried out when all randomized (approximately 400) non-Chinese subjects have completed or terminated the study. All data for the non-Chinese subjects will be locked and unblinded and no changes to these data are allowed after unblinding. Subjects in China will remain blinded and will not be included in the first analysis.

If the primary efficacy analysis for the US FDA/PMDA reaches statistical significance, the second analysis for Chinese regulatory submission will be performed when all randomized (approximately 100) Chinese subjects have completed or terminated the study. The second analysis will include all randomized subjects (approximately 500). All the analyses described in this SAP will be included in both first and second analyses.

Changed to:

Due to COVID-19 pandemic, subjects from the China region (100 in total) were not enrolled, hence this region will not be included in the sequential analyses - gatekeeping procedure mentioned in the protocol.

Only data from (approximately 400 randomized subjects) European/North American/Japanese regulatory submissions at 0.05 alpha level (two-sided) will be analyzed. This database will be after locked and unblinded and no further changes will be allowed.

Change #12

The following has been changed:

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 Japan)
- Use of AEDs with binding to synaptic vesicle 2A (SV2A) proteins (levetiracetam [LEV] or brivaracetam [BRV], Y/N)

Changed to:

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

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- Use of AEDs with binding to synaptic vesicle 2A (SV2A) proteins (levetiracetam [LEV] or brivaracetam [BRV], Y/N) based on stratification CRF.
- Levetiracetam/Brivaracetam use at study entry (Y/N) based on AED medication CRF.

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 #13

The following has been added:

5.1 Subject disposition

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.

Change #14

The following has been added:

6.1 Demographics

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.

Change #15

The following has been added:

6.4.1 Prior and concomitant medications

AED medications will be summarized for the FAS, non-AED medications will be summarized for the SS.

Change #16

The following has been changed:

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:

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- (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

6.4.3 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

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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.

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 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) ≤ (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

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- 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.

6.4.2 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

Change #17

The following has been added:

7.1 Treatment compliance

- Titration and Stabilization Period: 10 × duration of Titration Period (days) + 12 × duration of Stabilization Period (days)

Change #18

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The following has been removed:

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.

Change #19

The following has been removed:

7.2 Diary compliance

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.

Change #20

The following has been changed:

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:

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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)]					
50% RR	X [(c)]					
Percent Reduction in SF	X [(c)]			X		
Seizure Freedom			X			X
Change from baseline in seizure frequency	X					

Change #21

Added:

8.1.1.3 Percent reduction in seizure frequency from Baseline

Only subjects with > 0 seizure frequency at baseline will be included in all percent reduction analysis.

Change #22

The following has been added:

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.

Due to early termination of the study due to COVID-19 global pandemic, sensitivity analyses will not be executed.

Change #23

The following have been removed:

8.1.2.2.1 Sensitivity analyses 1: PPS

8.1.2.2.2 Sensitivity analyses 2: "worse case" imputation

Change #24

The following has been added:

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

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Due to early termination of the study due to COVID-19 global pandemic, all sensitivity analyses will not be executed.

Change #25

The following have been removed:

8.1.2.4.1 Sensitivity analyses 1: PPS

8.1.2.4.2 Sensitivity analyses 2: "worse case" imputation

Change #26

The following has been added:

8.1.2.5 Subgroup analyses for the primary variables

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 #27

The following has been added:

8.1.3 Analysis of the primary efficacy variable for submission to the CFDA

Due to COVID-19 pandemic subjects (100 in total) from the China region were not enrolled.

Removed the following:

If the enrollment period in China is extended, the analyses to support European/North American/Japanese regulatory submissions will be carried out when all randomized (approximately 400) non-Chinese subjects have completed or terminated the study. If the primary efficacy analyses described in Section 8.1.2.1 are statistically significant, a subsequent analysis will be carried out for all randomized (approximately 500) subjects when all Chinese subjects have completed or terminated the study to support the submission for China. The 2-step sequential analyses are described in Section 4.3. In the analyses for the Chinese FDA, the primary efficacy analyses described in Section 8.1.2.1 will be repeated, the treatment difference between a PSL dose group and placebo will be concluded statistically significant only if the difference is statistically significant in both the first and second analyses.

The consistency of the primary efficacy variables across regions will be evaluated based on the subgroup analyses described in Section 8.1.2.5. Consistent treatment effect is demonstrated if the estimated treatment effects across regions are in the same direction and the confidence intervals are overlapping.

Change #28

The following has been removed:

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

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%.

Change #29

The following sections have been removed:

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.

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

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

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

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

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

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

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

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

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

8.3.2.14 Cumulative responder rate during the 16-week Treatment Period

Change #30

The following has been removed:

8.3.2.4 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).

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Summary will be provided for Visit 2, Visit 4, Visit 7, and the Last Visit during the Treatment Period.

Change #31

The following has been removed:

8.3.2.5 Change in the QOLIE-31-P score

All data will be summarized descriptively for Visit 2, Visit 4, Visit 7, and the Last Visit during the Treatment Period.

Change #32

The following has been removed:

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

Data will be summarized descriptively for Visit 2, Visit 4, Visit 7, and the Last Visit during the Treatment Period.

Change #33

The following has been removed:

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

Change #34

The following has been removed:

8.3.2.20 Additional figures for efficacy variables

Change #35

The following has been changed:

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

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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.

Has been changed to:

8.3.2.8 Use of health-related outcomes and HRU

Health-related outcomes data and HRU data will be listed for RS.

- 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.

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- Healthcare provider consultations not foreseen by the protocol

The health care provider consultations by type of provider (general practitioner, specialist physician, nurse, and other) per subject will be listed.

- Hospital and ER visits

ER visits will be extracted from the Hospitalization/ER Visit CRF page (if the initial entry point is ER).

- Caregiver assistance

Caregiver assistance data is collected on the CRFs "Caregiver Assistance Screening" and "Caregiver Assistance Follow-up". Data will be listed per visit.

- 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".

Change #34

The following has been changed:

9.1 Plasma concentration of PSL and its major metabolites

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 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] 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, 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)

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- 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)

Has been changed to:

9.1 Plasma concentration 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] metabolite (from venous conventional sampling and dried blood (MITRA) sampling) and [redacted] metabolite (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).

Measured values below the LOQ will be listed.

Change #35

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

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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.

Has been changed to:

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 listed by visit and treatment group.

Change #36

The following has been removed:

10.1 Extent of exposure

The same summaries will be repeated for the subjects who received dose reduction during the Stabilization Period.

Change #37

The following have been removed:

10.2 Adverse events

- 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 of special interest

  The following has been **added:**
- Incidence of TEAEs occurring in at least 5% of subjects in any treatment group

Change #38

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

The following has been changed:

A summary table highlighting the potential cases of Hy’s Law, within each treatment group will

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be presented. Hy’s Law is defined as:

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

Has been changed to:

Potential Hy’s Law, is defined as ≥3xULN ALT or AST with coexisting ≥2xULN total bilirubin in the absence of ≥2xULN ALP, with no alternative explanation for the biochemical abnormality.

Change #39

The following has been changed:

10.4.1 Vital Signs

Possibly clinically significant (PCS) have been developed for the PSL program based on FDA Division of Neuropharmacologic Drug Products guidelines with some UCB-defined additions and are provided in Appendix 13.2. For vital sign parameters with PCS criteria, the number and percentage of subjects with a treatment-emergent PCS low or high value at any time during the Treatment Period will be summarized by treatment group and PSL total. Treatment-emergent PCS is defined as meeting a PCS criterion after receiving treatment but not meeting the same criterion during the Baseline Period. Subject numbers for those meeting the treatment-emergent PCS criteria will also be presented.

Has been changed to:

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.

Change #40

The following has been added:

10.4.2 Electrocardiograms

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.

Change #41

The following has been added:

10.4.3 Echocardiograms

In addition, Echocardiogram Valvular abnormality grade (Aortic Valve, Mitral Valve, Tricuspid Valve, Pulmonary Valve) described in Appendix 13.4 will be summarized descriptively.

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Valvular abnormality grade equal or larger than grade 2 is corresponding to valvular abnormal. Subject numbers with abnormality for any assessment will be provided.

Change #42

The following has been added:

12. COVID-19 IMPACT

The impact of COVID-19 global pandemic on this study is detailed in section 3.10. COVID-19 impact will be summarized by impact category and impacted visit. The data including visit, date, relationship to COVID-19, impact category and narrative of event will be listed for the RS, if the subject has been impacted.

Change #43

The following has been added:

8.2.1.1 75% Responder Rate over the 12-week Maintenance Period Only subjects with > 0 seizure frequency at baseline will be included in the analysis.

Change #44

The following has been added:

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

Only subjects with > 0 seizure frequency at baseline will be included in the analysis

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16 ADDENDUM

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

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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.

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Approval Signatures

Name: EP0092-SAP-Amend-1

Version: 1.0

Document Number: CLIN-000158296

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Document Approvals	
Approval Verdict: Approved	Name: [redacted] Capacity: Clinical Date of Signature: 18-Aug-2020 07:23:45 GMT+0000
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