STATISTICAL ANALYSIS PLAN

Study: EP0093

Product: Padsevonil (UCB0942)

AN OPEN LABEL, MULTICENTER, EXTENSION STUDY TO EVALUATE THE SAFETY AND EFFICACY OF PADSEVONIL AS ADJUNCTIVE TREATMENT OF FOCAL-ONSET SEIZURES IN ADULT SUBJECTS WITH DRUG-RESISTANT EPILEPSY

PHASE 2/3

SAP	Date
Final SAP	18 Jan 2019
Amendment 1	25 SEP 2020

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LIST OF ABBREVIATIONS

AE	adverse event
AED	antiepileptic drug
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
bid	twice daily
BMI	body mass index
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
ECG	electrocardiogram
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
IPD	Important protocol deviation
MedDRA®	Medical Dictionary for Regulatory Activities®
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
SAE	serious adverse event
SAP	Statistical Analysis Plan
SBP	systolic blood pressure
SD	standard deviation
SFU	Safety Follow Up
SOC	System Organ Class
SOP	Standard Operating Procedure
SSG	Seizure Severity Global Item
SS	Safety Set
SV2A	synaptic vesicle 2A
TEAE	treatment-emergent adverse event
ULN	upper limit of normal
VAMS	volumetric absorptive microsampling
VNS	vagus nerve stimulation
WHO	World Health Organization
WHO DD	World Health Organization Drug Dictionary

1 INTRODUCTION

This statistical analysis plan (SAP) defines the scope of statistical analyses and provides a detailed description of statistical methodology for the statistical analyses to support the final

clinical study report (CSR). The SAP is based on the following study document: Protocol EP0093 Amendment 2, 4 February 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: 2017-003241-26; 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 objectives

2.1.1 Primary objective

The primary objective of this study is to evaluate the long-term safety and tolerability of Padsevonil (PSL) administered at individualized doses between 100mg/day and 800mg/day as adjunctive treatment for subjects with focal-onset seizures and drug-resistant epilepsy.

2.1.2 Secondary objective

The secondary objective is to evaluate the long-term efficacy of PSL as an adjunctive treatment for focal-onset seizures in adults with drug-resistant epilepsy.

2.1.3 Exploratory Objective

The exploratory objective is to assess the impact of PSL as an adjunctive treatment for subjects with focal-onset seizures and drug-resistant epilepsy on health-related outcomes and healthcare resources utilization (HRU).

2.2 Study variables

2.2.1 Safety variables

2.2.1.1 Primary safety variables

The primary safety variables are the following:

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

2.2.1.2 Other safety variables

Other safety variables are the following:

- Changes in laboratory tests (including hematology, blood chemistry, urinalysis)
- Changes in 12-lead electrocardiogram (ECG) parameters

- Changes in withdrawal symptoms using Clinical Institute Withdrawal Assessment Benzodiazepines (CIWA-B) from the End-of-Study (EOS) Visit, to the end of Taper Period and to the end of the Safety Follow-up (SFU) Period (30 days after last PSL intake)
- Changes in vital sign parameters (pulse rate, blood pressure [BP], and respiratory rate)
- Occurrence of a clinically significant valvular change or pericardial effusion or other clinically significant abnormalities as identified by 2-dimensional Doppler echocardiogram at each assessment by central reader
- Physical examination (including body weight) and neurological examination findings
- Changes in Psychiatric and Mental Status

2.2.2 Efficacy variables

Seizure frequency refers to 28-day adjusted frequency.

Observable focal-onset seizures refer to Type IA1, IB, and IC (according to the International League Against Epilepsy [ILAE] Classification of Epileptic Seizures, 1981). Focal-onset seizures include all Type I seizures. Seizure-free status and seizure-free days include all (Type I, II, and III) seizure types.

2.2.2.1 Primary efficacy variable

The primary efficacy variable will be the change from Baseline (from the respective parent study) in observable focal-onset seizure frequency over the Evaluation Period.

2.2.2.2 Other efficacy variables

The other efficacy variables are the following:

- Observable focal-onset seizure frequency per 28 days by 3-month intervals over the Evaluation Period
- Observable focal-onset seizure frequency per 28 days by seizure type and by 3-month intervals over the Evaluation Period
- The 50%, 75%, and 90% responder rate (RR) by 3-month intervals for observable focal-onset seizures over the Evaluation Period. A 50%, 75%, and 90% responder is defined as a subject with a ≥50%, ≥75%, or ≥90% reduction in the observable focal onset seizure frequency relative to the Baseline Period defined in the parent study.
- The 50%, 75%, and 90% RR by 3-month intervals for focal-onset seizures (Type I) over the Evaluation Period
- Percentage of seizure-free days (for all seizure types) by 3-month intervals over the Evaluation Period
- Seizure-freedom status for all seizure types by 3-month intervals over the Evaluation Period

- Time to Discontinuation
- Change from Baseline from parent study in the Seizure Severity Global Item (SSG) scores at each assessment
- Changes from Baseline from parent study in Quality of Life Inventory in Epilepsy-31-P (QOLIE-31-P) scores at each assessment
- Changes from Baseline from parent study in Hospital Anxiety and Depression Scale (HADS) scores at each assessment
- Use of health-related outcomes and HRU, including healthcare provider consultations not foreseen by protocol, caregiver support, concurrent medical procedures, concomitant medications, and hospitalizations.

2.2.2.3 Pharmacokinetic and pharmacodynamic variables

- No pharmacokinetic (PK) nor pharmacodynamic variables will be assessed in this study.

2.3 Study design and conduct

This is an open-label extension (OLE) study that will assess the safety, tolerability, and change in focal-onset seizure frequency associated with long term oral PSL as an adjunctive therapy in adult subjects with drug-resistant epilepsy. This study will enroll consenting subjects, or subjects whose legal representatives have given consent, and who have completed a PSL parent study (eg, EP0091 or subsequent PSL studies). The total study duration per subject will be up to approximately 2 years.

Evaluation Period

The Entry Visit (EV, Visit 1) will be done the same day as the last visit of the parent study. After the Entry Visit (EV, Visit 1), subjects will return to the clinic for visits as follows:

- Every 2 weeks during Month 1
- Every month during Month 2 and Month 3
- Every 3 months after Month 3 to the end of Year 2

Dose adjustment of PSL and/or concomitant AEDs and/or settings to neurostimulation devices is allowed at any time during the study, if seizure control is insufficient, or in case of safety or tolerability issue. Subjects who are not able to tolerate or who do not benefit from the PSL treatment may be tapered off PSL and withdrawn from the study.

Taper Period

Subjects who complete the study or who discontinue early will return for an End of Study (EOS) Visit or Early Discontinuation Visit (EDV), respectively, and will be progressively tapered off over 4 weeks and return to the site 1 week after the last PSL intake for an end of Taper Visit.

Safety Follow-up Period

Safety follow-up will consist of 1 required visit (SFU Visit) 30 days after the last PSL intake. A follow up echocardiogram will be required at approximately 1 month and 6 months after the last PSL intake.

Subjects must return to the clinic for scheduled visits as outlined in Table 2-1.

Table 2-1: Schedule of assessments

			Evaluation Period [a]								Taper Period (including 1 Wk drug free)	SFU (30 days after last PSL intake)	
		Entry Visit	Bi-weekly Visits		Monthly Visits		Visits every 3 M		EOS Visit	EDV Visit	End of Taper Visit	SFU Visit	Unsch Visit/TC
	Setting (Required Onsite [s])	V1 [b]	V2	V3	V4	V5	V6, V8, V10	V7, V9, V11	EOS [c]	EDV [c]			
Assessments		**Wk 0**	**Wk 2**	**Wk 4**	**M2**	**M3**	**M6, M12, M18**	**M9, M15, M21**	**M24**		**Up to 4 Wk**		
Written informed consent	NA – V1 as per UCB requirement had to be performed onsite	X											
Dispensation of Subject Trial card	NA – V1 as per UCB requirement had to be performed onsite	X											

Table 2-1: Schedule of assessments

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	Setting (Required Onsite [s])	V1 [b]	V2	V3	V4	V5	V6, V8, V10	V7, V9, V11	EOS [c]	EDV [c]			
Assessments		**Wk 0**	**Wk 2**	**Wk 4**	**M2**	**M3**	**M6, M12, M18**	**M9, M15, M21**	**M24**		**Up to 4 Wk**		
Demographic data	NA – V1 as per UCB requirement had to be performed onsite	X											
Verification of inclusion/exclusion criteria	NA – V1 as per UCB requirement had to be performed onsite	X											
Verification of withdrawal criteria	Partially required onsite		X	X	X	X	X	X		X			

Table 2-1: Schedule of assessments

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	Setting (Required Onsite [s])	V1 [b]	V2	V3	V4	V5	V6, V8, V10	V7, V9, V11	EOS [c]	EDV [c]			
Assessments		**Wk 0**	**Wk 2**	**Wk 4**	**M2**	**M3**	**M6, M12, M18**	**M9, M15, M21**	**M24**		**Up to 4 Wk**		
Medical history update	NA – V1 as per UCB requirement had to be performed onsite	X											
C-SSRS since last visit [d]	no	X*	X	X	X	X	X	X	X	X	X	X	
HADS [d]	no	X			X		X	X	X	X			
SSG	no	X				X	X	X	X	X			
QOLIE-31-P [d]	no						X		X	X			
CIWA-B [d]	no								X[e]	X	X	X	
TSQM-9 [d]	no								X	X			
Vital signs [f]	yes	X*	X	X	X	X	X	X	X	X	X	X	
Body weight	no	X*		X		X	X	X	X	X		X	

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	Setting (Required Onsite [s])	V1 [b]	V2	V3	V4	V5	V6, V8, V10	V7, V9, V11	EOS [c]	EDV [c]			
Assessments		**Wk 0**	**Wk 2**	**Wk 4**	**M2**	**M3**	**M6, M12, M18**	**M9, M15, M21**	**M24**		**Up to 4 Wk**		
Physical examination [g] (XF = Full – XB = Brief)	yes	XF*		XB		XB	XB	XB	XB	XB	XB	XB	
Neurological examination [h] (XF = Full – XB = Brief)	yes	XF*		XB		XB	XB	XB	XB	XB	XB	XB	
Psychiatric and Mental Status	no	X*		X		X	X	X	X	X	X	X	
Personal Outcomes assessment[i]	yes						X	X					
12-lead ECG [j]	yes	X*		X		X		X	X	X		X	
Echocardiogram [k]	yes		X			X	X	X	X [k]			X	
Blood/urine sample for clinical laboratory analysis	yes	X*		X	X	X	X	X	X	X			

Table 2-1: Schedule of assessments

			Evaluation Period [a]								Taper Period (including 1 Wk drug free)	SFU (30 days after last PSL intake)	
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	Setting (Required Onsite [s])	V1 [b]	V2	V3	V4	V5	V6, V8, V10	V7, V9, V11	EOS [c]	EDV [c]			
Assessments		**Wk 0**	**Wk 2**	**Wk 4**	**M2**	**M3**	**M6, M12, M18**	**M9, M15, M21**	**M24**		**Up to 4 Wk**		
Pregnancy test (female subjects only) [l]	yes	X*	X	X	X	X	X	X	X	X	X		
Seizure evaluation (count and type) [m]	no	X*	X	X	X	X	X	X	X	X	X	X	
Concomitant medications and procedures [n]	no	X*	X	X	X	X	X	X	X	X	X	X	
Recording of adverse events	no	X*	X	X	X	X	X	X	X	X	X	X	
Health-related outcomes and HRU	no	X*	X	X	X	X	X	X	X	X	X	X	
IRT call	no	X										X	
PSL dispensing (IRT)	no	X	X	X	X	X	X	X	X [p]	X			
PSL accountability and return [o]	no		X	X	X	X	X	X	X	X	X		

Table 2-1: Schedule of assessments

			Evaluation Period [a]								Taper Period (including 1 Wk drug free)	SFU (30 days after last PSL intake)	
		Entry Visit	Bi-weekly Visits		Monthly Visits		Visits every 3 M		EOS Visit	EDV Visit	End of Taper Visit	SFU Visit	Unsch Visit/TC
	Setting (Required Onsite [s])	V1 [b]	V2	V3	V4	V5	V6, V8, V10	V7, V9, V11	EOS [c]	EDV [c]			
Assessments		**Wk 0**	**Wk 2**	**Wk 4**	**M2**	**M3**	**M6, M12, M18**	**M9, M15, M21**	**M24**		**Up to 4 Wk**		
Study termination	NA – this is not an assessment								X [q]			X [r]	

AED=antiepileptic drug; BP=blood pressure; CIWA-B=Clinical Institute Withdrawal Assessment-Benzodiazepines; C-SSRS=Columbia-Suicide Severity Rating Scale; ECG=electrocardiogram; EDV=Early Discontinuation Visit; EOS=End of Study; HADS=Hospital Anxiety and Depression Scale; HRU=healthcare resource utilization; IRT=interactive response technology; M=month; PSL=padsevonil; QOLIE-31-P=Quality of Life Inventory in Epilepsy-31-P; SFU=Safety Follow-up; SSG=Seizure Severity Global Item; TC=telephone call; TSQM=Treatment Satisfaction Questionnaire for Medication; Unsch=unscheduled; V=visit; Wk=week, NA=Not Applicable

[a] At any point during the Evaluation Period, an unscheduled visit may be conducted due to safety or efficacy reasons. Appropriate assessments will be conducted in relation to the reason for the visit. 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.

[b] Entry Visit (Visit 1) will be done on the same day as the last visit of parent study. Data from parent study will be used (identified by *) and corresponding assessments will not be repeated.

[c] The Taper Period is only valid for subjects discontinuing the study or completing without continuation of the PSL treatment. This period will last for 3 weeks plus a 1-week drug-free period.

[d] Questionnaires to be completed by all subjects prior to any other study procedures at the visit, when possible.

[e] Assessment is only valid for subjects discontinuing PSL treatment.

[f] Vital signs measured in supine position after 5 minutes of rest include pulse rate, respiratory rate, systolic BP, and diastolic BP.

[g] Full physical examination will include assessment of cardiac and respiratory function via auscultation and review of the following body systems: general appearance; ear, nose, and throat; eyes; hair and skin; respiratory; cardiovascular; gastrointestinal; musculoskeletal; hepatic; neurological; and mental status. Brief physical examinations will include a review of the following body systems: general appearance (including mental status); skin; respiratory; cardiovascular; gastrointestinal; and hepatic.

[h] Brief neurological examination will include a general assessment and evaluation of reflexes, muscle strength and coordination and cerebellar function. Full neurological examination will include in addition, evaluation of cranial nerves, motor system (general muscle strength and tone), and sensations in upper/lower extremities.

[i] Personal outcome assessments will be completed at Visit 6 (Month 6) and Visit 11 (Month 21) (for subjects who agree to participate).

[j] An ECG at the SFU will be performed only if abnormal at the EOS or EDV Visit. All ECG recordings will be performed with the subject resting in supine position for at least 5 minutes.

[k] Only subjects who do not require tapering of PSL at M24 will have an echocardiogram at M24. All other subjects will have an echocardiogram at the SFU Visit and at 6 months after the last dose of PSL. A repeat echocardiogram will be performed for subjects with a new finding, Grade 2 severity (moderate), or Grade 3 severity (severe).

[l] Results of a serum pregnancy test performed during parent study will be used at Visit 1 together with a urine test performed at Visit 1. Urine pregnancy tests will be used at all other visits for female subjects of childbearing potential.

m Seizure counts are collected on the subject's daily record card on a daily basis.

n Assessment includes AED history.

o Medication should be presented at each visit for check on compliance.

p PSL will be dispensed at the EOS Visit only to subjects who will be tapered off PSL.

q The study termination assessment at the EOS visit is for subjects who will transfer into either a Managed Access Program or another PSL study.

r The study termination assessment at the SFU Visit is for subjects who withdraw early or who complete the study, but will not be transferred to either a Managed Access Program or another PSL study.

Error! Reference source not found. Data may be collected through phone or video calls for visits that do not require onsite assessment because of COVID-19 pandemic.

2.4 Determination of sample size

For this OLE study, no sample size calculation is needed. The sample size will depend upon recruitment into and completion of a PSL parent studies (eg, EP0091 or subsequent PSL studies). Approximately 1000 subjects with focal-onset seizures and drug resistant epilepsy may be included.

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.

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

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

Derived variables in general will display the mean, SD and median to 1 more decimal place than the variables used in the derivation. If the number of decimal places reported in the raw data is varied then use either the maximum raw number of reported decimal places or 3, whichever is the lowest, as a guide for the descriptive statistics.

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.

The total daily dose (mg/day) is presented in EP0093.

Unless otherwise stated, safety and efficacy summaries will be presented for all subjects. Selected summaries will also be presented by region.

In general, all data collected in the EP0093 clinical database and parent study data included in the analyses 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 electronic Case Report form (eCRF)/diary. Each seizure code in the clinical database will be mapped to exactly 1 of the following ILAE classification codes: I, IA, IA1, IA2,

IA3, IA4, IB, IB1, IB2, IC, II, IIA, IIB, IIC, IID, IIE, IIF, or III. 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 First and last dose of PSL

Unless otherwise noted, all references to the first dose of PSL in this SAP refer to the first dose of PSL during EP0093 (i.e. not the first dose of PSL from the parent studies in which subjects participated in prior to EP0093).

At the time of a clinical cutoff, for subjects who are ongoing and don't have the End of Taper Visit, the last dose of PSL will be set to the date of the clinical cutoff for the interim analyses. For subjects who are ongoing but had the End of Taper Visit at the time of a clinical cutoff, the last dose of PSL will be set to the last dosing date on the Study Medication Administration eCRF for the interim analyses.

3.2.2.2 Relative day

Relative days for an event or measurement occurring before the date of first dose of PSL in EP0093 will have a '-' prefix and will be calculated as follows:

Relative Day=−[(Event date-Date of first dose)]

Relative days for an event or measurement occurring on or after the date of first dose of PSL but not after the date of last dose of PSL in EP0093 will be calculated as follows:

- Relative Day = (Event date-Date of first dose) + 1

For events or measurements occurring after the date of last dose of PSL in EP0093, relative day in this case will be prefixed with '+' in the data listings and will be calculated as follows:

- Relative Day = + (Event date-Date of last dose)

All study level variables should be defined in subsections below. This includes analysis time points and definitions of study periods to be analyzed.

3.2.2.3 Study Entry visit

3.2.2.4 The Entry Visit (EV, Visit 1) will be done on the same day as the last visit of the parent study. End date of the Evaluation Period

The end date of the Evaluation Period will be either EOS at Month 24 or EDV for subjects who discontinue early. If a subject does not have an EOS or EDV Visit, then the final contact date will define the end date of the Evaluation Period. At the time of a clinical cutoff prior to the study completion, if a subject is ongoing and doesn't have the EDV, the end of the Evaluation Period is set to the clinical cutoff date.

3.2.3 Analysis periods

The start and end dates of each study period are used for the classification of seizure data and TEAEs for applicable summaries. The exact start and end of each of these periods is described for calculation purposes in Table 3–3.21. Measurements from diaries returned on the start date of a subsequent period would be included in calculations for the previous period.

Table 3–3.21: Start and end of EP0093 analysis periods

Description	Start	End	Details
Evaluation Period	Entry Visit (EV, Visit 1)	EOS or EDV or the last contact date if neither EOS or EDV visit is available. At the time of a clinical cutoff prior to the study completion, if a subject is ongoing and doesn't have the EDV, the end of the period is set to the clinical cutoff date.	The Entry Visit (EV, Visit 1) will be done on the same day as the last visit of the parent study. Subjects will return to clinic every 2 weeks during Month 1, every month during Month 2-3, every 3 months after Month 3 up to Month 24.
Taper Period/ Safety Follow-Up Period	1 day after end date of evaluation period.	The date of final contact. At the time of a clinical cutoff prior to the study completion, if a subject is ongoing, the end of the period is set to the clinical cutoff date.	Applies only to patients who discontinue the study or complete it without continuation of PSL treatment.
Exposure Period	Date of first dose of PSL	Date of last dose of PSL	Extends from the date of first dose until the last dose of PSL in EP0093. It may include the Evaluation and Taper Period. (Section 3.2.2.1).

At the time of a clinical cutoff prior to the study completion, subjects without the Study Termination eCRF will be classified as "ongoing." Only the data on or prior to the clinical cutoff date will be included in the analyses.

3.2.3.1 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, in-clinic safety assessments such as vital signs, ECGs, and blood collection for clinical laboratory assessments, should correspond to that scheduled visit. In-clinic safety assessments at an EDV that occurs on a day between two scheduled visits will be assigned to the next scheduled clinic visit. All other efficacy assessments and questionnaire 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. 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 there is no need to map them to visits. If a subject withdraws between visits an effort is made to recover all diary records for use in calculation of seizure frequencies.

3.2.4 Last visit during the Exposure Period

The Last Visit for an assessment is the last non-missing assessment prior to or on the date of last dose of PSL (Section 3.2.2.1). All scheduled and unscheduled will be considered. Last Visit will be determined separately for each study assessment. Last Visit during the Exposure Period will be included in the by-visit summary unless noted otherwise. Similarly, the minimum and maximum values are defined as the minimum and maximum values prior to or on the date of last dose of PSL.

3.2.5 Interval duration

A month is defined as 30 days and time intervals based on monthly durations are defined as a multiple of 30 days (eg, 12 months is defined as 360 days).

Interval Duration Definition:

- Months 0-3 Days 1-90
- Months >3-6 Days 91-180
- Months >6-9 Days 181-270
- Months >9-12 Days 271-360

Subsequent intervals are defined in a similar manner. For the analysis of seizure data during the Evaluation Period, 3-month intervals will be derived for the Evaluation Period. For the analysis of AEs and safety variables, 3-month intervals will be derived for the Exposure Period.

3.2.6 Number of completers by time interval

Each subject will be classified into one or more of the following intervals based on the duration of the Evaluation Period:

≥3 months = ≥90 days

≥6 months = ≥180 days

≥12 months = ≥360 days

≥18 months = ≥540 days

≥24 months = ≥720 days

The duration of the Evaluation Period is calculated as the date of the end of the Evaluation Period – EV +1. Selected efficacy variables will be analyzed for completers by time intervals. The number of completers by time interval is also defined as completer cohort.

3.3 Definition of Baseline values

Baseline refers to the baseline of the parent study unless noted otherwise.

3.3.1 Baseline for variables based on seizure count

The current study does not provide a baseline period. Baseline values for observable focal-onset seizures (Types IA1, IB, and IC) and for all Type I seizures will be derived from subject diary data collected during the 4-week Prospective Baseline Period of the parent studies.

[Definition from parent studies: The Baseline value will be the seizure frequency per 28 days prior to the day of the first dose of IMP 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.]

3.3.2 Baseline for other variables

Unless otherwise specified, Baseline values from the parent study will be used in the analysis which is defined as the last valid measurement before the first study medication administration, including the pre-dose assessments on the day of Visit 2. If a Baseline visit measurement is missing, and a Screening visit measurement is available, the most recent Screening value will be utilized. Both scheduled and unscheduled Screening visits will be considered.

If a scheduled Baseline assessment is taken on the same day as first administration of study medication and no time is collected, it will be assumed to have been taken prior to study medication. The time point used 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.

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 final database lock and integrated into the clinical database.

3.5 Analysis sets

Primary and other safety endpoints will be analyzed using the Safety Set (SS). Primary and other efficacy endpoints will be analyzed using the Full Analysis Set (FAS).

These analysis sets are described below.

3.5.1 Enrolled Set

The Enrolled Set (ES) will consist of all subjects who have signed the ICF.

3.5.2 Safety Set

The Safety Set (SS) will consist of all enrolled subjects who were administered at least 1 dose of PSL, based on the first dose date from the First Administration of Study Medication CRF.

3.5.3 Full Analysis Set

The Full Analysis Set (FAS) will consist of all enrolled subjects who were administered at least 1 dose of PSL or a partial dose of PSL and completed at least 1 seizure diary during the Evaluation Period.

3.6 Treatment assignment and treatment groups

The individual starting dose of each subject will be the one recommended at the end of the parent study. Further individual dose adjustments are allowed between 100mg/day up to a maximum of 800mg/day to the extent possible with combination of tablet strengths available (ie, 25mg, 100mg, and 200mg).

3.7 Sites pooling strategy

Pooling strategy is not planned for this study.

3.8 Coding dictionaries

All prior and concomitant medications other than study drug will be classified by World Health Organization WHO Anatomical Therapeutic Chemical (ATC) Classification, presenting Anatomical Main Group (ATC Level 1), Pharmacological Subgroup (ATC level 3), and preferred term, using Version SEP/2017 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 the COVID-19 impact on site initiation and enrollment as well as early termination of the study, the following items in the protocol were updated in the SAP

Section in this SAP	Description	Change from the protocol
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.

3.10	COVID-19 eCRF	Added, see section 3.10 for details
4.4	Examination of subgroups	Removed China as a region
10.2.1.8	Derivation of other efficacy variables	Removed: Drug Loads of AEDs Changes in drug load are captured by number of products and daily dose per given product recorded in the AED Medication CRF. Drug load will be assessed using ratio of actual daily dose and World Health Organization defined daily dose (DDD). "https://www.whocc.no/atc_ddd_index/?code=N03A&showdescription=no". The daily dose of the administered AED will be calculated at Entry Visit, Visit 8, and EOS. All AEDs which has the stop date at the visit (EV, Visit 8, EOS) or ongoing and the start date prior to the visit will considered administered at that specific visit. The drug load of all AEDs will be calculated as the sum of ratios of dose and DDD for each of the AEDs at the respective visit. The drug load of each AED class will be calculated as the sum of ratios of dose and DDD for each of the AEDs within the AED class. AED classes included in this analysis are: • SV2A: levetiracetam and brivaracetam • BZD: ATC code N05BA • sodium channel-blocking AED (SCB (+): carbamazepine, oxcarbazepine, eslicarbazepine, phenytoin and lamotrigine Ratio of dose and DDD, absolute change from EV in the ratio, and percent change from EV in the ratio will be summarized by all AEDs, AED drug class and by each of the AEDs. For two visits, the absolute change of a given AED drug load can be calculated if the product is administered at one of the visits; and the percent change can only be calculated if the AED is administered at EV. The change in number of all AEDs at Visit 8 and EOS relative to EV will also be summarized.
11	COVID-19	The impact of COVID-19 global pandemic on this study is detailed in section 3.10. COVID-19 impact will be listed by

	Impact	impacted visit, date, impact category, and relationship to COVID-19 (confirmed, suspected, general circumstances around COVID-19 without infection or other) for each subject in the ES.
15	Addendum	Added: All tables described in the SAP will be repeated for Japan and non-Japan subgroups.

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.

Listing and table (see Section 11 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 Handling of dropouts or missing data

4.1.1 Handling of missing data in seizure frequency

Seizure frequency will be calculated over non missing diary days during an analysis period or time interval. Days with missing seizure diary (ie, "Not Done" is ticked on the Seizure Count CRF) will not be considered in the calculation of seizure frequency or seizure free days. No imputation will be applied to missing seizure diary data. Seizure frequency during a time interval will be calculated if seizure data are available for at least 1 day during the interval.

4.1.2 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). Note that imputed times and dates should not be presented in the patient data listing.

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

4.1.2.1 Imputation of Partial Start Dates

- If only the month and year are specified and the month and year of first dose 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 is the same as the month and year of the start date, then use the date of first dose
- If only the year is specified, and the year of first dose 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 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, then use the date of first dose.
- If the imputed start date is after the known stop date, set the start date to be the same as the stop date.

4.1.2.2 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

4.1.3 Incomplete dates for first epileptic seizure

To calculate the time since the first seizure relative to the date of EV of EP0093 at onset of first seizure, a complete date will be imputed for partially missing first seizure date as following:

- Missing the day, but month and year present

  Assign the 1st day of the month.
- Missing the day and month, but year present

  Assign January 1st of the year.
- Completely missing

  No imputation will be done.

4.2 Interim analyses and data monitoring

No formal interim analysis is planned. However, data may be reported prior to the completion of this study to support annual reports, regulatory submissions, and publications.

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

4.3 Multicenter studies

In generally, efficacy and safety summaries and analyses will be presented across investigative sites, countries and regions.

4.4 Examination of subgroups

Selected summaries will be provided for the following subgroups:

- Region

Countries will be stratified to geographic regions as follows:

Geographic region	**country**
North America	Canada, US, Mexico
Europe	Australia, Austria, Belgium, Bosnia and Herzegovina, Bulgaria, Croatia, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Lithuania, Netherlands, Norway, Poland, Portugal, Romania, Serbia, Slovakia, Spain, Sweden, Switzerland, Turkey, United Kingdom.
Japan	Japan

Further sites in countries not yet included in this table are possible.

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 CRF (dates of screen failure and last contact and reason for screen failure).

Details on the last study visit are obtained from the Study Termination CRF. Variables include date of last administration of study medication, date of final contact with the subject, subject

status at study termination, date of premature study termination and primary reason for premature study termination (as listed on CRF).

The disposition of subjects will be summarized for the ES, and SS overall and by region, country as well as by investigator.

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

The disposition will also be presented as the number and percentage of subjects who started, completed or discontinued the study. Discontinuation of study includes a breakdown of primary reasons for discontinuation. These tables are presented overall and by region for the SS.

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 summarized for the SS. Of note, the corresponding table is required for data transparency reporting.

Listings will be provided for disposition, reason for discontinuation and visit dates.

5.2 Protocol deviations

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

Important protocol deviations will be reviewed as part of the ongoing data cleaning process prior to database lock. After all data have been verified/entered into a database and prior to database lock, a final data evaluation meeting will take place. Protocol deviations will not lead to exclusion from any analysis set.

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

6 DEMOGRAPHICS AND OTHER BASELINE CHARACTERISTICS

6.1 Demographics

Demographic variables are collected on the Demographics CRF. The following demographic variables will be summarized for the SS by region:

Based on data collected at EV of EP0093:

- Age (in years)
- The following age categories will be summarized in the same table: (i) ≤18 years, 19 - <65 years and ≥65 years; (ii) 18- <65 years, 65 - <85 years and ≥ 85 years

Based on data collected at study entry of the parent study:

- Sex (male, female)
- Race (all categories on the CRF)
- Ethnicity (Hispanic or Latino, not Hispanic or Latino)
- Ethnic sub-group (Japanese, non-Japanese)
- Height (in cm)
- Weight (in kg)
- Body mass index (BMI) (kg/m2) and BMI category (<18.5, 18.5 to <25, 25 to <30, 30 to <40, ≥40)
- Vagus Nerve Stimulation (Yes, No)
- Parent study (EP0091, EP0092)

6.2 Other baseline characteristics

The following data collected at the time of entry into the parent study will be summarized for the SS. The parameters derived in the parent will be directly used.

- Number of lifetime AEDs taken prior to the parent study: <4, 4 or 5, 6 or 7, 8 to 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 eCRF.
- Number of AEDs taken at the entry of the parent study: 1, 2, 3, and > 3 AEDs
- Current use of AEDs with binding to SV2A proteins (LEV and/or BRV): Yes or No

6.3 Medical history and concomitant diseases

6.3.1 Medical history

Medical history reported at the entry of the parent study and any medical history update will be summarized and listed 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.

A medical history update is done at the Entry Visit. Of note, medical history update CRF should only be used after the database of the parent study is already locked. All efforts will be taken to make sure medical history are completed in the database of the parent study.

6.3.2 Medical history of epilepsy

Selected medical history of epilepsy collected at the entry of the parent study will be summarized for the SS.

6.3.2.1 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.

6.3.2.2 History of epileptic seizures and diagnosis of epilepsy

History of epileptic seizures, including 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 first seizure relative to the Entry Visit of EP0093 (ie, Entry Visit of EP0093 minus the date of the first epileptic seizure plus 1 divided by 365.25) and the age at onset of first seizure will be summarized for the SS.

6.4 Concomitant medications

Concomitant AED and non-AED medication are collected on separate CRFs. These include the AED Medication CRF and the Concomitant medication CRF. All concomitant medication started in the parent studies and are ongoing at the time of Entry Visit in EP0093 are collected on separate CRFs (Prior and Concomitant Medications_Parent Study CRF, AED Medication_Parent Study CRF).

A medication will be included in a concomitant summary if:

- (Date of first dose of PSL in EP0093) ≤ (Start date of medication) ≤ (Date of last dose of PSL in EP0093); or
- Start date of medication is prior to the first dose of PSL in EP0093 or unknown, but medication is ongoing at study entry.

6.4.1 AED medication

The number and percentage of subjects taking concomitant AED medications will be summarized by chemical/therapeutic/pharmacological subgroup (ATC classification level 4), and preferred drug name.

6.4.2 Use of vagus nerve stimulation

The number and percentage of subjects with Vagus Nerve Stimulation (VNS) in Previous Study (collected at EV) will be summarized. Subjects with VNS setting changed during the Evaluation Period will also be summarized. All other VNS data will be provided in subject data listings and will not be summarized for the SS.

6.4.3 Non-AED medication

The number and percentage of subjects (SS) 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.

7 MEASUREMENTS OF TREATMENT COMPLIANCE

Information reported on the CRF regarding the number of tablets dispensed and returned and doses taken in the morning and evening will be reported in subject data listings. 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.

PSL treatment compliance will be evaluated through the review of important protocol deviations.

8 PHARMACOKINETICS AND PHARMACODYNAMICS

No pharmacokinetic or pharmacodynamic analyses will be conducted.

9 SAFETY ANALYSES

All safety analysis will be provided for the SS.

9.1 Extent of exposure

The overall duration of exposure of the study will be calculated as the date of last dose of PSL minus the date of first dose of PSL (Section 3.2.2.1) in EP0093 plus 1 day.

Modal daily dose of a subject will be calculated as the daily dose the subject received for the longest duration during EP0093. In the event of a tie, the modal dose will be set to the lower of the tied doses. Modal daily dose will be categorized as ≤200mg/day, >200mg/day to ≤400mg/day, >400mg/day to ≤600mg/day, and >600mg/day.

The duration of exposure will be summarized overall and by modal dose for the SS and by region:

- Cumulative months of exposure: duration of exposure in days will be summarized. Duration of exposure will also be categorized into the following cumulative months categories of exposure: >=3 months, >=6 months, >=9 months, >=12 months, >=18 months, and >=24 months.

Listings will include the study medication exposure per subject and the administration of study medication per dispense interval. Data collected on the Prescribed Padsevonil Dose CRF will be listed.

9.2 Adverse events

Adverse events are recorded on the Adverse Event 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). Also, adverse events ongoing at the Entry Visit in EP0093 will be recorded in the Adverse Event_Parent Study CRF.

A treatment-emergent adverse event (TEAE) is defined as any event not present prior to the initiation of the first dose of study treatment in this study or any unresolved event already present

before initiation of the first dose that worsens in intensity following exposure to the treatment. TEAEs are AEs with start dates on or after the date of first dose of PSL in EP0093. The number and percentage of subjects who experience TEAEs at any time during the study will be summarized (using the SS) by SOC and PT.

Unless noted otherwise, TEAEs during the study will be summarized. At the time of a clinical cutoff, TEAEs with onset date prior to or on the clinical cutoff date will be included. TEAEs are assigned into an analysis period or time interval based on the start date. Adverse event summaries will be ordered in terms of decreasing frequency for SOC, and PT within SOC. The following tabular summaries will be presented for the SS:

- Ongoing AEs at EP0093 study entry
- Incidence of TEAEs during the Study – Overview by Region
- Incidence of TEAEs by Region
- Incidence of TEAEs by 3-month time interval during the Exposure Period
- Incidence of Serious TEAEs
- Incidence of TEAEs by Relationship
- Incidence of SAEs by Relationship. Of note, this table is needed for data transparency reporting.
- Incidence of Fatal TEAEs by Relationship. Of note, this table is needed for data transparency reporting.
- Incidence of TEAEs by Maximum Intensity
- Incidence of TEAEs leading to discontinuation (ie, drop out)
- Incidence of TEAEs leading to dose reduction
- Incidence of TEAEs occurring in at least 5% of Subjects
- Incidence of TEAEs by Dose at Onset (≤ 200mg/day, >200mg/day to ≤400mg/day, >400mg/day to ≤600mg/day, and >600mg/day) during the Exposure Period.
- Incidence of Non-Serious TEAEs above the Threshold of 5% of Subjects. This table is needed for data transparency reporting.

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 SOC and PT will be counted only once in the subject counts, but all events will be included.

In summaries of relationship to study treatment per the investigator, the following relationships will be summarized: ‘Not related’, ‘Related’. Events with missing relationship will be considered as ‘Related’ for summary purposes but recorded as missing in the listings.

In summaries of maximum intensity, the following intensity categories will be summarized: ‘Mild’, ‘Moderate’, ‘Severe’. Subjects who experience the same event multiple times 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.

Listings will be provided for AEs, SAEs, AEs leading to discontinuation (ie, drop out), and AEs leading to death by subject for the SS.

9.3 Clinical laboratory evaluations

Clinical laboratory hematology, chemistry and urinalysis measurements obtained from blood/urine samples collected throughout the study are presented in Table 9-1.

Table 9-1: 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; FSH=Follicle Stimulating Hormone, HDL=high-density lipoprotein; 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 for postmenopausal women

A blood and urine sample for clinical laboratory analysis will be obtained at Entry Visit, Visit 3 up to EOS/EDV Visit. Samples are analyzed in a central laboratory. During the study, non-protocol-specified lab parameter values (unplanned) may be collected. Summaries of lab parameter values will only include those of planned visits as specified in the protocol. All lab parameter values will be listed and summarized using international units. Per-subject listings

include flag for possibly clinically significant treatment-emergent (PCST) result and calculated change from Baseline for each laboratory variable. If the subject had both scheduled sampling and unscheduled sampling at the same date/time, scheduled sample will be flagged as the analysis record. For the subjects with DILI event, lab tests are done locally for more rapid results, a concurrent sample should also be sent to the central laboratory. The central lab results will be flagged as the analysis record.

The observed value and change from Baseline will be summarized (SS) descriptively by scheduled study visit, as well as including Last Visit, maximum value, and minimal value. These summaries will also be organized by lab function panel and parameter. Data collected at unscheduled visits will not be summarized.

For hematology and blood chemistry parameters that are identified in Table 10-1, the shift from Baseline in category (relative to normal range: low, normal, high) to the maximum and minimal values during the exposure period will be presented. Categorical urinalysis results will be summarized by visit.

PCST criteria 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 12.1. For lab parameters with treatment emergent PCST criteria, the number and percentage of subjects with a PCST will be summarized for the overall and by 3-month interval during the Exposure Period. Subject numbers for those meeting the PCST will also be presented. Results of additional tests like the urine pregnancy test will be listed.

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

There are specific criteria described in the protocol Section 9.2.1 to evaluate subjects for PDILI. The evaluations required by protocol for PDILI subjects are collected on the following CRFs:

- Most Recent Study Medication Administration, for DILI
- Laboratory Tests DILI
- Physical Examination for DILI
- Vital Signs DILI
- Hepatic Event Supplemental Medical History for DILI
- Potential Hepato-Toxic Medications Inquiry for DILI
- Symptoms of Hepatitis and Hypersensitivity for DILI
- Lifestyle DILI
- Family Medical History for DILI

PDILI is suspected if potential Hy's Law applies. In order to meet potential Hy's Law, 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 potential Hy's law criteria (see protocol section 6.3.1 and 9.1.1.3 for further details).

Potential Hy's Law is defined as:

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

A summary of number and percent of subjects meeting PDILI criteria for potential Hy's Law will be provided by visit and for any visit. Additionally, a per-subject listing for subjects with PDILI by visit for the potential Hy's law criteria relevant lab values will be provided. Further CRF information regarding DILI and PDILI will be listed. Visits due to PDILI which cannot be mapped to any study visits will only be listed.

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

9.5.1 Vital signs

Vital measurements (including SBP, DBP, PR and RR) are taken at every scheduled visit. These measurements 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 including absolute change from Baseline and abnormality criteria flag.

The observed value and absolute change from Baseline will be summarized (SS) descriptively by scheduled study visit, as well as Last Visit, maximum value, and minimal value Data collected at unscheduled visits will not be included in the by-visit summary.

The number and percentage of subjects with abnormal vital signs described in Appendix 13.2 will be summarized for the overall and by 3-month interval during the Exposure Period. Subject numbers for those meeting the abnormal criteria will also be presented.

9.5.2 Electrocardiograms

The following ECG parameters will be recorded: heart rate, PR-interval, QRS-duration, QT-interval, QTcB [QT corrected for heart rate using Bazett's formula] or QTcF [QT corrected for heart rate using Fridericia's formula], and Investigator's conclusion on ECG profile.

The 12-Lead ECG results are collected at Entry Visit, Visit 3, Visit 5 and at visits every 6 months thereafter. An ECG at the SFU will be performed only if abnormal at EOS or EDV Visit.

For each ECG, the overall ECG result, is also collected, categorized by the investigator as one of: no abnormality, an abnormal but not clinically significant finding, or a clinically significant finding.

QTcB and QTcF will also be presented by following classification per visit:

- Observed results: <450ms, 450-<480ms, 480-<500ms and >=500ms
- Change from Baseline: <30ms, 30-<60ms, >=60ms

The observed ECG parameter values and their absolute change from Baseline will be summarized (SS) descriptively for each scheduled assessment visit, as well as Last Visit, maximum value, and minimal value.

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 percentage of subjects with an abnormal ECG value described in Appendix 13.3 will be summarized for the overall and by 3-month interval during the Exposure Period. Subject numbers for those meeting the abnormal criteria will also be presented.

All 12-Lead ECG parameters will be listed per visit, including the change from baseline and a abnormality criteria flag. In addition, the data from patients with at least one finding will be listed with the finding.

9.5.3 Echocardiogram

Echocardiogram data are collected at Visit 2, Visit 5 and then every 3 months and at the Safety Follow-Up Visit. Only subjects who will remain in the study will have an echocardiogram at Month 24. Subjects who will taper off PSL will have an echocardiogram at the SFU Visit and at 6 months after the last dose of PSL. The data of the follow-up echocardiogram after 6 months will be obtained after data base lock and therefore analyzed separately.

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 each scheduled visit and by the number and percentage of subjects with an abnormality. 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.

9.5.4 Other safety variables

9.5.4.1 Changes in CIWA-B

Subjects are tapered off study medication if they discontinue the study or complete it without continuation of PSL treatment. As part of monitoring of subjects for withdrawal symptoms during the Taper Period, the CIWA-B evaluation is performed at the EOS/EDV Visit, at the end of the Taper Period, and at the Safety Follow-Up Visit. The CIWA-B questionnaire contains 17 questions and 3 observations, 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). Sub scores of each of the first 20 questions/observations (scores from 0-4) are summed up to a total score:

Total score	Interpretation

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

In case there is any sub score missing, no total score can be calculated.

There are additional two items for sleeping duration and time to fall asleep, but both are not considered in the score.

Data listings will be provided.

9.5.4.2 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 Entry Visit, and at each subsequent study visit. C-SSRS data will be provided in subject listing for subjects with suicidal ideation and suicide behavior.

9.5.4.3 Physical Examination

At Entry Visit the full Physical Examination is performed. The brief Physical Examination including the body weight measurement is performed at Visit 3, Visit 5 and at each visit thereafter. The body weight is not collected at End of Taper Visit. Findings that are considered clinically-significant changes will be recorded as AEs.

Data from the Physical Examination are only provided in subject data listings displaying all data collected for all subjects by subject and visit. No summaries will be provided.

9.5.4.4 Neurologic Examination

At Entry Visit the full Neurological Examination is performed. The brief Neurological Examination is performed at Visit 3, Visit 5 and at each visit thereafter. Data from the Neurological Examination are collected on the Neurological Examination Complete and Neurological Examination Brief CRFs Findings that are considered clinically-significant changes will be recorded as AEs.

A brief neurological examination will include general assessment and the evaluation of reflexes, muscle strength and coordination, and cerebellar function.

Data from the Neurological Examination are only provided in subject data listings presented by subject and visit, displaying all data collected for all subjects. No summaries will be provided.

9.5.4.5 Changes in Psychiatric and Mental Status

The Psychiatric and Mental Status is performed at Entry Visit, Visit 3, Visit 5 and at each visit thereafter. 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 to be evaluated are orientation, attention, memory, mood, and calculus.

For each of these assessments, data is provided in subject data listings presented by subject and visit, displaying all data collected for all subjects

There are no derived outcomes for the Psychiatric and Mental Status evaluation and no imputation rules for missing response values and no date imputation rules are applicable.

10 EFFICACY ANALYSES

Analyses of efficacy endpoints will be performed on the FAS.

10.1 Statistical analysis of the primary efficacy variables

10.1.1 Derivations of primary efficacy variable

Seizure frequency (SF) refers to the 28-day adjusted seizure frequency, which is defined as:

SF = (Number of Seizures) x (28 / D)

- where Number of Seizures = total number of seizures during an analysis period or time interval. For cluster seizures, the number of cluster episodes will be included.
- D = number of days for which the diary was available during the analysis period or time interval.

Change from Baseline in seizure frequency will be calculated as seizure frequency during an analysis period or time interval minus the Baseline seizure frequency.

The primary efficacy variable is the change from Baseline in the observable focal-onset seizure frequency over the Evaluation Period.

10.1.2 Primary analysis of the primary efficacy variable

The observed and the absolute change in 28-day adjusted observable focal-onset seizure frequency will be summarized (FAS) for the overall Evaluation Period. The summary will be repeated for each region. A per-subject listing (FAS) will be provided with details of seizure diary including type of seizure, cluster, number of seizures per diary. No additional statistical testing or modelling will be performed.

10.2 Analysis of other efficacy variables

Other efficacy variables are listed in Section 2.2.2.2.

10.2.1 Derivations of other efficacy variables

This section describes variable derivation and calculation of descriptive statistics to be used for analyses.

10.2.1.1 Percent reduction in seizure frequency from Baseline of parent study

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 or time interval and SFB corresponds to the Baseline seizure frequency. A negative PRD indicates an increase in seizure frequency from Baseline of parent study.

10.2.1.2 50%, 75% and 90% Responder

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

10.2.1.3 Seizure-free status (Yes or No)

Subjects will be considered seizure-free for a given period or time interval if the subject, completes the period, reports zero seizures during the period, and has no more than 10% of days in the period for which seizure data is not available (ie, "Not Done" is reported on the Seizure Count CRF).

10.2.1.4 Number and percentage of Seizure-free days

The number of seizure-free days will be the total number of days within an analysis period or time 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.

10.2.1.5 Seizure Severity Global Item (SSG) variables

The SSG consists of 2 items from the Seizure Severity Questionnaire and asks the subjects to evaluate the severity of their seizures for the last 4 weeks. The subject describes all seizure types when answering the questions. Seizure Severity will be asked for Entry Visit, Visit 5, and every 3 months thereafter until EOS/EDV Visit at the beginning of each visit. The seizure-intensity during the last 4 weeks is collected on a 7-point scale with 7 = very severe and the assessment of change since starting IMP, is also collected on a 7-point scale with 7 = much worse.

10.2.1.6 QOLIE-31-P

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 at Visit 6 and 6 months thereafter. It 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.

10.2.1.7 Hospital Anxiety and Depression Scale (HADS) score variables

The HADS questionnaire is filled out by subjects at Visits 1, 4, and every 3 months until EOS Visit or Early Discontinuation Visit.

The HADS assessment consists of 14 items that are each scored on a 4-point scale ranging from 0 to 3, with a higher score corresponding to worse anxiety or depression. The depression and anxiety scores will be calculated by summing the scores for the items corresponding to each subscale, as described in the Hospital Anxiety and Depression Scale Manual (Snaith and Zigmond, 1994): the depression score is calculated as the sum of all even-numbered items; the anxiety score is calculated as the sum of all odd-numbered items. Scores for each subscale range from 0 to 21, with higher scores corresponding to a greater level of anxiety or depression.

Missing items will be replaced by the mean of non-missing items from the same subscale when calculating the above, provided at least 50% of the items (ie, at least 4 of 7 items) within the subscale are present. A subscale score will not be calculated if more than 50% of the items are missing within a subscale. This rule applies separately to the subscale scores for anxiety and depression; for example, it may be possible to calculate the depression score in cases where the anxiety score is not calculated due to non-response.

10.2.1.8 Time to Discontinuation to Treatment

Time to discontinuation of treatment is calculated by the date of the last PSL dose minus the date of first dose +1.

10.2.1.9 Treatment satisfaction

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 developed from the TSQM 1.42, which has an additional subscale that measures side effects (3 items) (Atkinson et al, 2004). Scores range from 0 (worst) to 100 (best). The questionnaire is administered at EOS or EDV Visit, respectively.

Effectiveness	**Responses**
1.How satisfied or dissatisfied are you with the ability of the medication to prevent or treat your condition?	1=Extremely dissatisfied to 7=extremely satisfied

2.How satisfied or dissatisfied are you with the way the medication relieves your symptoms?	1=extremely dissatisfied to 7=extremely satisfied
3.How satisfied or dissatisfied are you with the amount of time it takes the medication to start working?	1=extremely dissatisfied to 7=extremely satisfied
Convenience	
4.How easy or difficult is it to use the medication in its current form?	1=extremely difficult 7=extremely easy
5.How easy or difficult is it to plan when you will use the medication each time?	1=extremely difficult 7=extremely easy
6.How convenient or inconvenient is it to take the medication as instructed?	1=extremely inconvenient 7=extremely convenient
Global satisfaction	
7.Overall, how confident are you taking this medication is a good thing for you?	1=Not at all confident 5=extremely confident
8.How certain are you that the good things about your medication outweigh the bad things?	1=not at all certain 5=extremely certain
9.Taking all things into account, how satisfied or dissatisfied are you with this medication?	1=extremely dissatisfied 7=extremely satisfied

10.2.2 Analysis of other efficacy variables

All summaries and listings provided for the efficacy variables are calculated on FAS unless noted otherwise.

10.2.2.1 Seizure frequency by 3-month interval over the Evaluation Period

The observed and the absolute change in 28-day adjusted seizure frequency of observable focal-onset seizures by the 3-month intervals over the Evaluation Period will be summarized by region in descriptive tables. The same summary will be repeated for the completer cohorts.

The observed and change from baseline in seizure frequency of Type IA1, IB, and IC seizures will be summarized separately by seizure type. Summary will be provided for the overall and by 3-month interval during the Evaluation Period. Summary will also be provided by 3-month interval for each completer cohort. The same summary will also be provided for the all Type I seizures.

10.2.2.2 50%, 75% and 90% responder rates by 3-month interval for observable focal onset seizures over the Evaluation Period

Summaries and listings for the 50%, 75% and 90% responder rates for observable focal-onset seizures will be provided for the overall Evaluation Period and by 3-month interval. Summaries will also be provided by 3-month interval for each completer cohort.

10.2.2.3 50%, 75% and 90% responder rates for focal- onset seizures (all Type I) over the Evaluation Period

Summaries for the 50%, 75% and 90% responder rates for all Type I seizures will be provided for the overall Evaluation Period and by 3-month interval. Summaries will also be provided by 3-month interval for each completer cohort.

10.2.2.4 Seizure-freedom status for all seizure types by 3-month interval over the Evaluation Period

The number and percentage of subjects achieving a seizure-free status will be summarized by 3-month interval for each completer cohort. After the study completion, the same summary will be performed for the overall and by 3-month interval for the Evaluation Period.

10.2.2.5 Percentage of seizure-free days (for all seizure types) by 3-month interval over the Evaluation Period

The percentage of seizure-free days and change from baseline in percentage of seizure-free days will be summarized for the overall Evaluation Period and by 3-month interval. Summaries will also be provided by 3-month interval for each completer cohort.

10.2.2.6 Percentage of reduction in seizure frequency by 3-month interval over the Evaluation Period

The percentage of reduction in seizure frequency from baseline for observable focal-onset seizures and all Type I seizures will be summarized for the overall Evaluation Period and by 3-month interval. Summaries will also be provided by 3-month interval for each completer cohort.

10.2.2.7 Change in the SSG score

Data will be listed for each scheduled visit and the Last Visit during the Evaluation Period by subject.

10.2.2.8 Changes in the QOLIE-31-P score

Observed values 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, and Health Status will be listed for Visit 6, Visit 8, Visit 10 and EOS Visit.

For each time point, the change from baseline of the parent study will be listed by subject for total and subscales.

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

Changes in the HADS scores will be calculated from Baseline from parent study to Entry Visit, Visit 4, Visit 6 and to Visits every 3 months thereafter until EOS or EDV Visit. The observed scores and changes in the scores for depression and anxiety will be presented in a subject listing.

10.2.2.10 Health-related Outcomes and HRU

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

- Socio-professional status

Socio-professional status data are collected at Entry Visit and EOS/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

Healthcare consultations by type of provider (general practitioner, specialist physician, nurse, and other) will be listed for each subject during the study.

- 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".

- Number of school or working days lost

Number of school/working days lost data are collected on the CRFs "School and Workdays Lost". The number and percentages of subjects who lose school or work days as a result of epilepsy will be listed by visit. The percentage of days lost will be calculated as:

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

10.2.2.11 Time to Discontinuation to Treatment

Kaplan-Meier estimates of the percentage of subjects completing 3, 6, 12, 18, and 24 months of treatment will be provided for the SS. For subjects who discontinued from the study, the event date is set to the date of last dose of PSL and the time to event will be calculated as the date of

last dose minus the date of first dose of PSL in EP0093 plus 1. Subjects who completed the study will be censored as of the date of last dose of PSL in EP0093. At a clinical cutoff, subjects who are ongoing will be censored as of the date of last dose of PSL defined for the interim analyses (Section 3.2.2.1).

10.2.2.12 Treatment satisfaction

A per-subject listing will be provided with all subscale scores for FAS overall.

11 COVID-19 IMPACT

The impact of COVID-19 global pandemic on this study is detailed in section 3.10. COVID-19 impact will be listed by impacted visit, date, impact category, and relationship to COVID-19 (confirmed, suspected, general circumstances around COVID-19 without infection or other) in the ES. Impact of COVID-19 for any reason by country will be tabulated in the ES.

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13 APPENDICES

13.1 LABORATORY ASSESSMENTS – PCST

The following criteria will be applied in the determination of possibly clinically significant treatment emergent laboratory assessment values.

13.1.1 Hematology

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

PARAMETER	*AGE RANGE*	*UNIT (conventional)*	*ABNORMALITY CRITERIA (conventional)*	*UNIT (standard)*	*ABNORMALITY CRITERIA (standard)*
	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
	≥2y		<3.5		<3.5

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

13.1.2 Blood chemistry

PARAMETER	*AGE RANGE*	*UNIT (conventional)*	*ABNORMALITY CRITERIA*	*UNIT (standard)*	*ABNORMALITY CRITERIA*
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)		>432 (F)
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

PARAMETER	*AGE RANGE*	*UNIT (conventional)*	*ABNORMALITY CRITERIA*	*UNIT (standard)*	*ABNORMALITY CRITERIA*
Total Protein	2m-<1y	g/dL	<3.0	g/L	<30
	≥1y		<4.3		<43
Albumin	<1y	g/dL	<1.6	g/L	<16
	≥1y		<2.4		<24
BUN	<1y	mg/dL	>21	mmol/L	>7.497
	≥1y		>30		>10.71
Urea	<1y	mg/dL	>42	mmol/L	>7.014
	≥1y		>60		>10.02
Creatinine	1y - <10y	mg/dL	>0.9	umol/L	>79.56
	10y - <16y		>1.4		>123.76
	≥16y		>1.6		>141.44
Creatinine Clearance*	All	mL/min	<70	mL/s	<1.169
Calcium	<1y	mg/dL	<6.9	mmol/L	<1.725
	1y - <18y		<7.4		<1.85
	≥18y		<7.9 >11.1		≤1.975

PARAMETER	*AGE RANGE*	*UNIT (conventional)*	*ABNORMALITY CRITERIA*	*UNIT (standard)*	*ABNORMALITY CRITERIA*
Phosphorous	<1y	mg/dL	<1.8	mmol/L	<0.5814
	≥1y		<1.8		<0.5814
Potassium	<1y	mEq/L	<3.0	mmol/L	<3.0
	≥1y		<3.0		<3.0
Sodium	>1m	mEq/L	≤130	mmol/L	≤130
Glucose	>1m	mg/dL	<50	mmol/L	<2.775
Total Cholesterol	1y - <18y	mg/dL	>250	mmol/L	>6.475
	≥18y		>300		>7.77
LDL (calculated)	1y - <18y	mg/dL	>140	mmol/L	>3.626
	≥18y		>200		>5.18
HDL	≤2y	mg/dL	<10	mmol/L	<0.259
	>2y		<20		<0.518
Triglycerides	<1y	mg/dL	>750	mmol/L	>8.475
	≥1y		>250		>2.825

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

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

13.1.3 Urinalysis

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

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

13.2 VITAL SIGN ASSESSMENTS - ABNORMAL

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

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

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PARAMETER	*AGE RANGE*	*ABNORMALITY CRITERIA*
	≥17y	≥ 10% change from Baseline (an increase or a decrease)[a]

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

13.3 ELECTROCARDIOGRAM (ECG) – ABNORMAL

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 EP0093 (including unscheduled visits) and not meeting the same criteria during Baseline in the parent study.

13.4 Echocardiogram Valvular Abnormality Grading Criteria

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

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: Shortness of breath on exertion or at rest; palpitation; syncope; anginal or pericarditic chest pain; fatigue or weakness	For a Grade 2/moderate severity, a decision to discontinue is based on severity of clinical signs/symptoms; if accompanied with moderate to severe signs/symptoms this results in subject discontinuation.
Grade 3	Severe: regurgitation/stenosis in the extreme range, often accompanied by other symptoms (eg, pulmonary congestion)	Signs: Pulmonary arterial pressure >40mm Hg and rise of >10mmHg; pulmonary edema; peripheral edema or ascites; atrial fibrillation or malignant arrhythmia; hypotension	Discontinuation of subject. For a Grade 3 of severe, subject should be discontinued regardless of accompanying clinical symptoms.
Grade increase by 2 levels	Increasing from: Grade 0 to 2 or Grade 1 to 3	Rapid onset of above signs/symptoms	A jump of 2 grades to Grade 2/moderate accompanied with moderate to severe

Echocardiogram Valvular Abnormality	Severity / Description	Potential Cardiovascular Signs/Symptoms	Action
			signs/symptoms results in subject discontinuation. A jump of 2 grades to Grade 3/severe (with/without symptoms) will result in subject discontinuation.

14 AMENDMENT(S) TO THE SAP

14.1 Amendment 1

Rationale for the amendment

The primary purpose of this amendment is to clarify details in the planned analyses and the early termination of the study.

Modifications and changes

Major specific changes

Change #1

The following has been added:

Table 2-1: Schedule of assessments

Change #2

The following has been deleted:

2.2.2.1 Other efficacy variables

Changes in drug load (ie, number of products, daily dose per given product, ratio of dose and Defined Daily Dose [WHO Collaborating Centre for Drug Statistics Methodology], frequency, drug class) of AEDs from Baseline to Visit 8, and to Visit 12 or EOS

Change #3

The following has been deleted:

2.4 Determination of sample size

The individual starting dose of each subject is 400 mg/day. This entry dose level was selected considering benefit-risk and is based on clinical pharmacology and positron emission tomography data in healthy human subjects. Once subjects enter EP0093, further individual dose adjustments are allowed between 100mg/day up to a maximum of 800mg/day to the extent possible with combination of tablet strengths available (ie, 25mg, 100mg, and 200mg). Integrity of the tablets should not be tampered with (eg, cut) to obtain lower dosages. More details on dosing can be found in the protocol in section 7.2

Change #4

The following has changed:

3.2.2.2 Relative day

Study day for each subject is calculated relative to the date of the first study visit (Entry Visit). 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 the first study visit plus 1. For days after the last dose of study drug (during safety follow-up), 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).

Generally, relative days for an event or measurement occurring during the study will be calculated as follows:

- Relative Day = (Event Date-Date of first visit) + 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 Date. 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)

All study level variables should be defined in subsections below. This includes analysis time points and definitions of study periods to be analyzed.

Has been changed to:

Relative days for an event or measurement occurring before the date of first dose of PSL in EP0093 will have a '-' prefix and will be calculated as follows:

Relative Day=−[(Event date-Date of first dose)]

Relative days for an event or measurement occurring on or after the date of first dose of PSL but not after the date of last dose of PSL in EP0093 will be calculated as follows:

Relative Day = (Event date-Date of first dose) + 1

For events or measurements occurring after the date of last dose of PSL in EP0093, relative day in this case will be prefixed with '+' in the data listings and will be calculated as follows:

Relative Day = + (Event date-Date of last dose)

All study level variables should be defined in subsections below. This includes analysis time points and definitions of study periods to be analyzed

Change #5

3.2.2.3 Study Entry Visit

The study Entry Visit (EV) corresponds to assessments performed at the time of entry into the EP0093. Subjects will not have any interruption in study drug dosing during the transition to EP0093. Selected assessments from the EOS Visit of the parent study will be transferred to the EV of EP0093 study. The following assessments are to be performed for all subjects at the above time points:

C-SSRS since last visit, vital signs, body weight, physical and neurological examination,

psychiatric and mental status, 12-lead ECG, blood/urine sample, pregnancy test, seizure evaluation, concomitant medications and procedures, adverse events, health related outcomes and HRU.

Has been changed to:

The Entry Visit (EV, Visit 1) will be done on the same day as the last visit of the parent study.

Change #6

The following has been changed:

3.2.2.4 End date of the Treatment Period

The Treatment Period is called Evaluation Period in EP0093. The end date of the Evaluation Period will be either EOS at Month 24 or EDV for subjects who discontinue early. If a subject does not have an EOS or EDV Visit, then either the date of the last scheduled or unscheduled visit during the Evaluation Period or the date of last known dose of study drug during the Evaluation Period, whichever is later, will define the end date of the Evaluation Period. Subjects benefitting from the drug and willing to continue on it will either take commercial drug, if available, or will be transferred to a Managed Access Program or another PSL study, depending on local regulations.

Has been changed to:

3.2.2.4 End date of the Evaluation Period

The end date of the Evaluation Period will be either EOS at Month 24 or EDV for subjects who discontinue early. If a subject does not have an EOS or EDV Visit, then the date of last available visit before end of taper visit will define the end date of the Evaluation Period. At the time of a clinical cutoff prior to the study completion, if a subject is ongoing and doesn't have the EDV, the end of the Evaluation Period is set to the clinical cutoff date.

Change #7

3.2.3 Study Periods

The start and end dates of each study period are used for the classification of seizure data into study periods and for the classification of TEAEs by study period for applicable summaries. The End Date of the Evaluation Period is also used for the calculation of the duration of exposure to study drug for the Evaluation Period. The exact start and end of each of these periods is described for calculation purposes in Table 3–1. Measurements from diaries returned on the start date of a subsequent period would be included in calculations for the previous period.

Table 3 Start and end of EP0093 study periods

Period	Start of Period	End of Period	Details
Entry Visit (Visit 1)	Day 1 of Study	N/A	The Entry Visit will be done on the same day as the last visit of the parent study.
Evaluation Period	The date of Visit 2 (week 2, Day 2 -Day 21)	EOS at Month 24 (Day 730, Day 686 – Day 744) or the date of EDV.	Subjects will return to clinic every 2 weeks during Month 1, every month during Month 2-3, every 3 months after Month 3 up to Month 24.
Taper Period/ Safety Follow-Up Period	1 day after EOS or EDV.	The date of the Safety Follow-Up Visit (30 days after last PSL dose)	Applies only to patients who discontinue the study or complete it without continuation of PSL treatment.

Has been changed to:

3.2.3 Analysis Periods

The start and end dates of each study period are used for the classification of seizure data and TEAEs for applicable summaries. The exact start and end of each of these periods is described for calculation purposes in Table 3–3.21.

Table 3–14.11: Start and end of EP0093 analysis periods

Description	Start	End	Details
Evaluation Period	Entry Visit (EV, Visit 1)	EOS or EDV or the last contact date if neither EOS or EDV Visit is available. At the time of a clinical cutoff prior to the study completion, if a subject is ongoing and doesn't have the EDV, the end of the period is set to the clinical cutoff date.	The Entry Visit (EV, Visit 1) will be done on the same day as the last visit of the parent study. Subjects will return to clinic every 2 weeks during Month 1, every month during Month 2-3, every 3 months after Month 3 up to Month 24.
Taper Period/ Safety Follow-Up Period	1 day after end of evaluation period.	The date of final contact. At the time of a clinical cutoff prior to the study completion, if a subject is ongoing, the end of the period is set to the clinical cutoff date.	Applies only to patients who discontinue the study or complete it without continuation of PSL treatment.
Exposure Period	Date of first dose of PSL	Date of last dose of PSL	Extends from the date of first dose until the last dose of PSL in EP0093. It may include the Evaluation and Taper Period. (Section 3.2.2.1).

At the time of a clinical cutoff prior to the study completion, subjects without the Study Termination Case Report Form (CRF) will be classified as "ongoing." Only the data on or prior to the clinical cutoff date will be included in the analyses.

Change #8

The following sentence was changed:

3.2.3.1 Mapping of data from early discontinuation visits

In-clinic safety assessments at an EDV that occurs on a day between two scheduled visits will be assigned to the next clinic visit.

Was changed to:

In-clinic safety assessments at an EDV that occurs on a day between two scheduled visits will be assigned to the next scheduled clinic visit.

Change #9

The following was deleted:

3.2.3.2 Mapping of data to visits

Change #10

The following were deleted:

3.2.4 Study duration and study medication exposure

3.2.5 Last visit during the treatment period

Change #11

The following were added:

3.2.4 Last visit during Exposure Period

The Last Visit for an assessment is the last non-missing assessment prior to or on the date of last dose of PSL (Section 3.2.2.1). All scheduled and unscheduled will be considered. Last Visit will be determined separately for each study assessment. Last Visit during the Exposure Period will be included in the by-visit summary unless noted otherwise. Similarly, the minimum and maximum values are defined as the minimum and maximum values prior to or on the date of last dose of PSL.

3.2.5 Interval duration

A month is defined as 30 days and time intervals based on monthly durations are defined as a multiple of 30 days (eg, 12 months is defined as 360 days).

Interval Duration Definition:

- Months 0-3 Days 1-90
- Months >3-6 Days 91-180
- Months >6-9 Days 181-270
- Months >9-12 Days 271-360

Subsequent intervals are defined in a similar manner. For the analysis of seizure data during the Evaluation Period, 3-month intervals will be derived for the Evaluation Period. For the analysis of AEs and safety variables, 3-month intervals will be derived for the Exposure Period.

3.2.6 Number of completers by time interval

Each subject will be classified into one or more of the following intervals based on the duration of the Evaluation Period:

≥3 months = ≥90 days
≥6 months = ≥180 days
≥12 months = ≥360 days
≥18 months = ≥540 days
≥24 months = ≥720 days

The duration of the Evaluation Period is calculated as the date of the end of the Evaluation Period – EV +1. Selected efficacy variables will be analyzed for completers by time intervals. The number of completers by time interval is also defined as completer cohort.

Change #12

The following was deleted:

3.3 Definition of Baseline values

Entry visit refers to Visit 1 of EP0093.

Change #13

The following was removed:

3.3.1 Baseline for variables based on seizure count

Baseline values for observable focal-onset seizures need to be obtained from the parent studies for each patient who enters the study.

Change #14

The following was changed:

3.3.2 Baseline for other variables

For calculating change in other efficacy variables (SSG, QOLIE-31-P, HADS and in AED drug load) also the Baseline period of the parent study is used. For calculating change in safety variables the Entry Visit is used.

Has been changed to:

3.3.2 Baseline for other variables

Unless otherwise specified, Baseline values from the parent study will be used in the analysis which is defined as the last valid measurement before the first study medication administration, including the pre-dose assessments on the day of Visit 2. If a Baseline visit measurement is missing, and a Screening visit measurement is available, the most recent Screening value will be utilized. Both scheduled and unscheduled Screening visits will be considered.

If a scheduled Baseline assessment is taken on the same day as first administration of study medication and no time is collected, it will be assumed to have been taken prior to study medication. The time point used 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.

Change #15

The following sentence was changed:

3.6 Treatment assignment and treatment groups

For all subjects the same PSL transition dose of 400mg/day will be administered at the start of the study.

Has been changed to:

The individual starting dose of each subject will be the one recommended at the end of the parent study.

Change #16

The following was 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 the SAP.

Section in this SAP	Description	Change from the protocol
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.
3.10	COVID-19 eCRF	Added, see section 3.10 for details
4.4	Examination of subgroups	Removed China as a region
10.2.1.8	Derivation of other efficacy variables	Removed: Drug Loads of AEDs Changes in drug load are captured by number of products and daily dose per given product recorded in the AED Medication CRF. Drug load will be assessed using ratio of actual daily

		dose and World Health Organization defined daily dose (DDD). "https://www.whocc.no/atc_ddd_index/?code=N03A&showdescription=no". The daily dose of the administered AED will be calculated at Entry Visit, Visit 8, and EOS. All AEDs which has the stop date at the visit (EV, Visit 8, EOS) or ongoing and the start date prior to the visit will considered administered at that specific visit. The drug load of all AEDs will be calculated as the sum of ratios of dose and DDD for each of the AEDs at the respective visit. The drug load of each AED class will be calculated as the sum of ratios of dose and DDD for each of the AEDs within the AED class. AED classes included in this analysis are: • SV2A: levetiracetam and brivaracetam • BZD: ATC code N05BA • sodium channel-blocking AED (SCB (+): carbamazepine, oxcarbazepine, eslicarbazepine, phenytoin and lamotrigine Ratio of dose and DDD, absolute change from EV in the ratio, and percent change from EV in the ratio will be summarized by all AEDs, AED drug class and by each of the AEDs. For two visits, the absolute change of a given AED drug load can be calculated if the product is administered at one of the visits; and the percent change can only be calculated if the AED is administered at EV. The change in number of all AEDs at Visit 8 and EOS relative to EV will also be summarized.
11	COVID-19 Impact	The impact of COVID-19 global pandemic on this study is detailed in section 3.10. COVID-19 impact will be listed by impacted visit, date, impact category, and relationship to COVID-19 (confirmed, suspected, general circumstances around COVID-19 without infection or other) for each subject in the ES.
15	Addendum	Added: All tables described in the SAP will be repeated for Japan and non-Japan subgroups.

Change #17

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.

Listing and table (see Section 11 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 #18

The following has been changed:

4.1.1 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.
Handling of missing data for efficacy variables based on diary-collected seizure frequency: Seizure frequency will be computed over non-missing diary days. Missing seizure diary days will not be considered in the calculation of seizure frequency. For subjects who prematurely discontinue, or otherwise have missing diary days, the calculation of the seizure frequency over a specified period will be based on available seizure diary up to the last diary entry of the period. This effectively imputes the unobserved seizures after discontinuation with the seizure frequency observed prior to discontinuation.

Changed to:

4.1.1 Handling of missing data in seizure frequency

Seizure frequency will be calculated over non missing diary days during an analysis period or time interval. Days with missing seizure diary (ie, “Not Done” is ticked on the Seizure Count CRF) will not be considered in the calculation of seizure frequency or seizure free days. No imputation will be applied to missing seizure diary data. Seizure frequency during a time interval will be calculated if seizure data are available for at least 1 day during the interval.

Change #19

The following has been added:

4.1.3 Incomplete dates for first epileptic seizure

To calculate the time since the first seizure relative to the date of EV of EP0093 at onset of first seizure, a complete date will be imputed for partially missing first seizure date as following:

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

Change #20

The following has been removed:

4.4 Examination of subgroups

- Parent study
- China

Change #21

The following has been removed:

5.2 Protocol deviations

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

Change #22

The following has been changed:

6.1 Demographics

Demographic variables are collected on the Demographics CRF.

All demographic collected in EP0093 (age in years, sex, weight and country), obtained at the Entry Visit will be summarized descriptively for ES, FAS and SS.

- The following age categories will be summarized in the same table: (i) ≤18 years, 19 - <65 years and ≥65 years; (ii) 18- <65 years, 65 - <85 years and ≥ 85 years.
- 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 from the parent studies will be included as baseline characteristics. Seizure counts are collected by diary.

- The number of previous AEDs used by the subject will be summarized descriptively. The count for an individual subject is the number of unique Preferred Names, using the current version of WHODD.

Listings including all demographic variables as well as socio-economic status and child-bearing potential will be provided.

Has been changed to:

6.1 Demographics

Demographic variables are collected on the Demographics CRF. The following demographic variables will be summarized for the SS by region:

Based on data collected at EV of EP0093:

- Age (in years)
- The following age categories will be summarized in the same table: (i) ≤18 years, 19 - <65 years and ≥65 years; (ii) 18- <65 years, 65 - <85 years and ≥ 85 years

Based on data collected at study entry of the parent study:

- Sex (male, female)
- Race (all categories on the CRF)
- Ethnicity (Hispanic or Latino, not Hispanic or Latino)
- Ethnic sub-group (Japanese, not Japanese)
- Height (in cm)
- Weight (in kg)
- Body mass index (BMI) (kg/m2) and BMI category (<18.5, 18.5 to <25, 25 to <30, 30 to <40, ≥40)

Change #23

The following has been added:

6.2 Other Baseline characteristics

The following data collected at the time of entry into the parent study will be summarized for the SS. The parameters derived in the parent will be directly used.

- Number of lifetime AEDs taken prior to the parent study: <4, 4 or 5, 6 or 7, 8 to 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 eCRF

- Number of AEDs taken at the entry of the parent study: 1, 2, 3, and > 3 AEDs
- Current use of AEDs with binding to SV2A proteins (LEV and/or BRV): Yes or No

Change #24

The following has been changed:

6.2 Medical history and concomitant diseases

A medical history update is done at the Entry Visit. All medical conditions that were not reported in the prior study including start and stop dates are captured in the Medical History CRF. Medical history update will be summarized and listed 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.

Has been changed to:

6.3 Medical history and concomitant diseases

6.3.1 Medical History

Medical history reported at the entry of the parent study and any medical history update will be summarized and listed 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.

A medical history update is done at the Entry Visit. Of note, medical history update CRF should only be used after the database of the parent study is already locked. All efforts will be taken to make sure medical history are completed in the database of the parent study.

6.3.2 Medical history of epilepsy

Selected medical history of epilepsy collected at the entry of the parent study will be summarized for the SS.

6.3.2.1 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.

6.3.2.2 History of epileptic seizures and diagnosis of epilepsy

History of epileptic seizures, including 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 first seizure relative to the Entry Visit of EP0093 (ie, Entry Visit of EP0093 minus the date of the first epileptic seizure plus 1 divided by 365.25) and the age at onset of first seizure will be summarized for the SS.

Change #25

The following has been changed:

6.3 Concomitant medications/procedures

Concomitant AED and non-AED medication are collected on separate CRFs. These include the AED Medication CRF and the Concomitant medication CRF. All concomitant medication started in the parent studies and are ongoing at the time of Entry Visit in EP0093 are collected on separate CRFs (Prior and Concomitant Medications_Parent Study CRF, AED Medication_Parent Study CRF).

A medication will be included in a concomitant summary if:

- (Date of Entry Visit) ≤ (Start date of medication) ≤ (Date of last IMP intake); or
- Start date of medication is unknown but medication is ongoing at study entry.

The number and percentage of subjects (SS) taking 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. Summaries will be provided for concomitant non-AED medication started in parent study, AED medication started in parent study, concomitant AED medication, and concomitant non-AED medication. Subjects with more than one medication within a level of categorization are counted only once within that level. For each CRF a listing is provided including dose per intake, frequency, indication and start and stop dates.

Previous AEDs are AEDs taken previously and which has stopped prior to the Entry Visit. The data will be taken from the parent studies.

Vagus nerve stimulation status is collected in the Vagus Nerve Stimulation Status CRF and all visits with Vagus nerve stimulation will be prepared as listing.

Concomitant medical procedures will be listed only, including date of procedure, reported term and relation.

Has been changed to:

6.4 Concomitant medications

Concomitant AED and non-AED medication are collected on separate CRFs. These include the AED Medication CRF and the Concomitant medication CRF. All concomitant medication started in the parent studies and are ongoing at the time of Entry Visit in EP0093 are collected on separate CRFs (Prior and Concomitant Medications_Parent Study CRF, AED Medication_Parent Study CRF).

A medication will be included in a concomitant summary if:

- (Date of first dose of PSL in EP0093) ≤ (Start date of medication) ≤ (Date of last dose of PSL in EP0093); or

- Start date of medication is prior to the first dose of PSL in EP0093 or unknown but medication is ongoing at study entry.

6.4.1 AED medication

The number and percentage of subjects taking concomitant AED medications will be summarized by chemical/therapeutic/pharmacological subgroup (ATC classification level 4), and preferred drug name.

6.4.2 Use of vagus nerve stimulation

The number and percentage of subjects with Vagus Nerve Stimulation (VNS) in Previous Study (collected at EV) will be summarized. Subjects with VNS setting changed during the Evaluation Period will also be summarized. All other VNS data will be provided in subject data listings and will not be summarized for the SS.

6.4.3 Non-AED medication

The number and percentage of subjects (SS) 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.

Change #26

7. Treatment Compliance

The following was added:

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.

Change #27

The following has been changed:

9.1 Extent of exposure

Extent of exposure will be presented in the following way:

- Cumulative months of exposure: Study medication exposure defined in section 3.2.4 will becategorized into the following cumulative months categories of exposure: >0 weeks, >=3 months, >=6 months, >=9 months, >=12 months, >=15 months and >=21 months.

- Study medication exposure as defined in section 3.2.4.

- Total time at risk (subject-years) as defined in section 3.2.4.

Exposure will be summarized overall and for Evaluation Period.

A summary of the PSL doses per visit will be provided. The exact PSL doses at each visit will be classified according to the following 8 categories:

<100mg/day

≥100mg/day - <200mg/day

≥200mg/day - <300mg/day

≥300mg/day - <400mg/day

≥400mg/day - <500mg/day

≥500mg/day - <600mg/day

≥600mg/day - <700mg/day

≥700mg/day - ≤800mg/day.

Listings will include the study medication exposure per subject and the administration of study medication per dispense interval.

Of special interest will be the tolerability of the study drug; a worse tolerability will lead to dose reductions. A listing of subjects with dose reductions in the prescribed dose since the prior visit will be provided. The Prescribed Padsevonil Dose CRF will contain all information on this.

Has been changed to:

9.1 Extent of exposure

The overall duration of exposure of the study will be calculated as the date of last dose of PSL minus the date of first dose of PSL (Section 3.2.2.1) in EP0093 plus 1 day.

Modal daily dose of a subject will be calculated as the daily dose the subject received for the longest duration during EP0093. In the event of a tie, the modal dose will be set to the lower of the tied doses. Modal daily dose will be categorized as ≤200mg/day, >200mg/day to ≤400mg/day, >400mg/day to ≤600mg/day, and >600mg/day.

The duration of exposure will be summarized overall and by modal dose for the SS and by region:

- Cumulative months of exposure: duration of exposure in days will be summarized. Duration of exposure will also be categorized into the following cumulative months categories of exposure: >=3 months, >=6 months, >=9 months, >=12 months, >=18 months, and >=24 months.

Total time at risk (subject-years of exposure) will be calculated by summing the exposure duration in days for all subjects and dividing the resulting value by 365.25.

Listings will include the study medication exposure per subject and the administration of study medication per dispense interval. Data collected on the Prescribed Padsevonil Dose CRF will be listed.

Change #28

The following has been changed:

9.2 Adverse events

Adverse events are recorded on the Adverse Event 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). Also, adverse events during the respective parent study will be recorded in the Adverse Event_Parent Study CRF.

Overview summaries and listings will be also done for adverse events during the respective parent study.

SAEs will be included in the Safety Database up to the completion of the 6-month echocardiogram.

A treatment-emergent adverse event (TEAE) is defined as any event not present prior to the initiation of the first dose of study treatment in this study or any unresolved event already present before initiation of the first dose that worsens in intensity following exposure to the treatment. The number and percentage of subjects who experience TEAEs at any time during the study will be summarized (using the SS) by SOC and PT. All AEs will be coded using the latest available MedDRA version (MedDRA 21.1).

The following tables will be provided for the entire study and stratified by the respective parent study using the SS:

- Overview of Incidence of AEs reported over the entire study
- Overview of Incidence of AEs reported over the parent study
- Incidence of TEAEs reported by the subject and/or caregiver or observed by the Investigator during the entire study Incidence of TEAEs reported by the subject and/or caregiver or observed by the Investigator during parent study
- Incidence of serious TEAEs
- Incidence of TEAEs (subjects and events) leading to Dose Reduction
- Incidence of TEAEs (subjects and events) leading permanent Discontinuation of Study Drug

- Incidence of TEAEs by Maximum Relationship
- Incidence of TEAEs by Relationship
- Incidence of TEAEs by Maximum Intensity

In addition a summary of the occurrence of any TEAE and any drug-related TEAE during the entire study per PSL dose at the time of the TEAE onset will pre presented.

The following per-subject listings will be prepared using the SS showing all AEs per patient including the mapped visit and date:

- All AEs
- SAEs
- AEs leading to discontinuation of study
- AEs leading to dose reduction
- AEs leading to death (just to be prepared if an AE leading to death occurred)

These summaries will be presented based on standard Sponsor AE table formats or other 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 to suggest that the AE started prior to the first dose of study treatment or the investigator determines the AE is unrelated to 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.

Adverse event summaries will be ordered in terms of decreasing frequency for SOC, and PT within SOC.

Has been changed to:

9.2 Adverse events

Adverse events are recorded on the Adverse Event 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). Also, adverse events ongoing at the Entry Visit in EP0093 will be recorded in the Adverse Event_Parent Study CRF.

A treatment-emergent adverse event (TEAE) is defined as any event not present prior to the initiation of the first dose of study treatment in this study or any unresolved event already present before initiation of the first dose that worsens in intensity following exposure to the treatment. TEAEs are AEs with start dates on or after the date of first dose of PSL in EP0093. The number and percentage of subjects who experience TEAEs at any time during the study will be summarized (using the SS) by SOC and PT.

Unless noted otherwise, TEAEs during the study will be summarized. At the time of a clinical cutoff, TEAEs with onset date prior to or on the clinical cutoff date will be included. TEAEs are assigned into an analysis period or time interval based on the start date. Adverse event summaries will be ordered in terms of decreasing frequency for SOC, and PT within SOC. The following tabular summaries will be presented for the SS:

- Ongoing AEs at EP0093 study entry
- Incidence of TEAEs during the Study – Overview by Region
- Incidence of TEAEs by Region
- Incidence of TEAEs by 3-month time interval during the Exposure Period
- Incidence of Serious TEAEs
- Incidence of TEAEs by Relationship
- Incidence of SAEs by Relationship. Of note, this table is needed for data transparency reporting.
- Incidence of Fatal TEAEs by Relationship. Of note, this table is needed for data transparency reporting.
- Incidence of TEAEs by Maximum Intensity
- Incidence of TEAEs leading to discontinuation (ie, drop out)
- Incidence of TEAEs leading to dose reduction
- Incidence of TEAEs occurring in at least 5% of Subjects
- Incidence of TEAEs by Dose at Onset (≤ 200mg/day, >200mg/day to ≤400mg/day, >400mg/day to ≤600mg/day, and >600mg/day) during the Exposure Period.
- Incidence of Non-Serious TEAEs above the Threshold of 5% of Subjects. This table is needed for data transparency reporting.

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 SOC and PT will be counted only once in the subject counts, but all events will be included.

In summaries of relationship to study treatment per the investigator, the following relationships will be summarized: 'Not related', 'Related'. Events with missing relationship will be considered as 'Related' for summary purposes but recorded as missing in the listings.

In summaries of maximum intensity, the following intensity categories will be summarized: 'Mild', 'Moderate', 'Severe'. Subjects who experience the same event multiple times 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.

Listings will be provided for AEs, SAEs, AEs leading to discontinuation (ie, drop out), and AEs leading to death by subject for the SS.

Change #29

The following has been modified:

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

Hy's Law is defined as:

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

Has been changed to:

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

Potential Hy's Law is defined as:

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

Change #30

9.4.1 Vital signs

Vital measurements (including SBP, DBP, PR and RR) are taken at every scheduled visit. These measurements 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 (SS) will be prepared for vitals variables including absolute change from Entry Visit and PCST abnormality.

The observed value and absolute change from Entry Visit will be summarized (SS) descriptively by scheduled study visit for all vital signs. These summaries will be organized by vital signs. Data collected at unscheduled visits will not be summarized.

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 12.1. For vital sign parameters with PCS criteria, the number and percentage of subjects with a treatment emergent potentially clinically significant low or high value by visit will be summarized. In the same table, the number and percentage of subjects with a treatment emergent PCS will be summarized for all scheduled visits.

Has been changed to:

9.5.1 Vital signs

Vital measurements (including SBP, DBP, PR and RR) are taken at every scheduled visit. These measurements 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 including absolute change from Baseline and abnormality criteria flag.

The observed value and absolute change from Baseline will be summarized (SS) descriptively by scheduled study visit, as well as Last Visit, maximum value, and minimal value Data collected at unscheduled visits will not be included in the by-visit summary.

The number and percentage of subjects with abnormal vital signs (Appendix 12.2) will be summarized for the overall and by 3-month interval during the Exposure Period. Subject numbers for those meeting the abnormal criteria will also be presented.

Change #31

The following has been removed:

9.5.2 Electrocardiograms

The QTcB [QT corrected for heart rate using Bazett's formula], and QTcF [QT corrected for heart rate using Fridericia's formula] will be derived for each subject as shown below:

$$QTcB = \frac{QT}{\sqrt{60/HR}} \; and \; QTcF = \frac{QT}{\sqrt[3]{60/HR}}$$

where QT is the QT interval as reported in the ECG transfer and HR is the heart rate as reported in the ECG transfer.

Change #32

The following has been removed:

9.5.4.1 Changes in CIWA-B

A descriptive summary table will be prepared of observed and absolute change in CIWA-B scores from Entry Visit by scheduled visit.

Change #33

The following has been removed:

9.5.4.5 Changes in Psychiatric and Mental Status

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.

Change #34

The following has been changed:

10. Efficacy analyses

For the efficacy variables described below, seizure frequency refers to a 28-day adjusted frequency; observable focal-onset seizures refer to Type IA1, IB, and IC (ILAE Classification of Epileptic Seizures, 1981); focal-onset seizures include all Type I seizures; and seizure-free status and seizure-free days include all seizure types (Types I, II, and III).

10.1.1 Derivations of primary efficacy variable

The primary efficacy variable is the change from Baseline in the observable focal-onset seizure frequency over the Evaluation Period.

- Calculation of seizure frequency:

The total number of observable focal-onset seizures (Types IA1, IB, and IC) will be calculated for each subject across all diary records during the study period being evaluated. For the primary variable, this is the Evaluation Period. The diary days for this period, which are collected onto the Seizure Count eCRF, are obtained from the diaries returned at Evaluation Period Visit 2 up to EOS in cases where the patient completed the Evaluation Period. Otherwise diary days for this period will be obtained from the diaries returned between Visit 2 and Early Discontinuation Visit.

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

- Calculation of absolute Change from Baseline of the parent study in seizure frequency:

The (absolute) change from Baseline is calculated for each subject by subtracting the 28-day adjusted seizure frequency during the 4-week Baseline period of the parent study from the 28-day adjusted seizure frequency during the Evaluation Period as follows:

focal-onset seizure frequency during Evaluation – focal-onset seizure frequency during Baseline of the parent study, where seizure frequency refers to the 28-day adjusted frequency for the period.

Has been changed to:

10. Efficacy analyses

Unless noted otherwise, analyses of efficacy endpoints will be performed on the FAS.

10.1.1 Derivations of primary efficacy variable

10.1.1.1 Seizure frequency

Seizure frequency (SF) refers to the 28-day adjusted seizure frequency, which is defined as:

SF = (Number of Seizures) x (28 / D)

- where Number of Seizures = total number of seizures during an analysis period or time interval. For cluster seizures, the number of cluster episodes will be included.
- D = number of days for which the diary was available during the analysis period or time interval.

Change from Baseline in seizure frequency will be calculated as seizure frequency during an analysis period or time interval minus the Baseline seizure frequency.

The primary efficacy variable is the change from Baseline in the observable focal-onset seizure frequency over the Evaluation Period.

Change #35

The following was deleted:

10.2.1.1 Other efficacy variables based on seizure frequencies

Seizure frequency calculations

The total number of observable focal-onset seizures (Types IA1, IB, and IC) will be calculated for each subject across all diary records during the study period being evaluated. The diary days for the 3-month intervals which are collected onto the Seizure Count eCRF, are obtained from the diaries returned at Visit 2 – Visit 12 or EDV Visit. In case of an Early Discontinuation Visit, the last available 3-month period is used.

The subject's 28-day adjusted seizure frequency of observable focal-onset seizures (types IA1, IB, IC) will be calculated as in section 8.1.1 for the following 3-months intervals:

Visit 1-Visit 5 (seizure count refers to time between week 0 and month 3)
Visit 6 (refers to time between month 4 and 6)
Visit 7 (refers to time between month 7 and 9)
Visit 8 (refers to time between month 10 and 12)
Visit 9 (refers to time between month 13 and 15)
Visit 10 (refers to time between month 16 and 18)
Visit 11 (refers to time between month 19 and 21)
Visit 12 (refers to time between month 22 and 24).

Seizure-free status

Seizure-free status (yes/no) for all seizure types is calculated over the same time intervals as the seizure frequency. The corresponding visits are the 3-month time periods between Visit 5 and Visit 12. Additionally, seizure free status will be determined for the overall Evaluation Period up to EOS or EDV Visit, respectively.

A subject is defined as seizure free during a specific evaluation period if all of the following criteria are met:

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.

Seizure-free rate

The seizure-free rate (%) for a specific time period considers all seizure types and will be calculated as:

$$\frac{\text{Count of seizure free subjects during the period}}{\text{Seizure-free count of subjects + Non-seizure free count of subjects during the period}} \times 100$$

Seizure-free days

The percentage of seizure-free days for a specific time period considers all seizure types and will be calculated as:

$$\frac{\text{Count of seizure free days during the period}}{\text{Seizure-free day count + Non-seizure free day count during the period}} \times 100$$

Change #36

The following were added:

10.2.1.1 Percent reduction in seizure frequency from Baseline of parent study

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 or time interval and SFB corresponds to the Baseline seizure frequency. A negative PRD indicates an increase in seizure frequency from Baseline of parent study.

10.2.1.2 50%, 75% and 90% Responder

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

10.2.1.3 Seizure-free status (Yes or No)

Subjects will be considered seizure-free for a given period or time interval if the subject, completes the period, reports zero seizures during the period, and has no more than 10% of days in the period for which seizure data is not available (ie, "Not Done" is reported on the Seizure Count CRF).

10.2.1.4 Number and percentage of Seizure-free days

The number of seizure-free days will be the total number of days within an analysis period or time 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.

Change #37

The following were renumbered:

10.2.1.2 Seizure Severity Global Item (SSG) variables

10.2.1.3 QOLIE-31-P

10.2.1.4 Hospital Anxiety and Depression Scale (HADS) score variables

10.2.1.7 Treatment satisfaction

Renumbered to:

10.2.1.5 Seizure Severity Global Item (SSG) variables

10.2.1.6 QOLIE-31_P

10.2.1.7 Hospital Anxiety and Depression Scale (HADS) score variables

10.2.1.9 Treatment satisfaction

Change #38

The following has been removed:

10.2.1.5 Drug Load of AEDs

Changes in drug load are captured by number of products and daily dose per given product recorded in the AED Medication CRF. The ratio of daily dose and Defined Daily Dose (DDD) gives details on the daily dose compared to the average maintenance dose used for its main indication for adults [WHO Collaborating Centre for Drug Statistics Methodology. ATC/DDD Index 2017]. DDDs for AEDs can be found in Appendix 12.4.

The daily dose of every administered AED will be collected at each study visit. The change from Visit 8 to Entry Visit and to EOS Visit will be calculated for daily dose and number of products. All AEDs which has the same start or stop date as at the visit (Entry Visit, Visit 8, EOS) or which is ongoing and the start date is prior to the visit will be used for calculation. The change in the number of products is defined as the absolute difference in the number of simultaneously given products. The absolute change in the daily dose is calculated per product. For two visits a change can only be calculated if the same product is administered at both visits. Otherwise no change will be calculated.

Change #39

The following has been changed:

10.2.1.6 Time to Discontinuation

Time to discontinuation is defined as the time to discontinuation of treatment. Time to discontinuation of treatment is calculated by the date of the last PSL dose minus the date of Entry Visit +1. All subjects who will not have a last PSL dose as they are transferred in a Managed Access Program or another PSL study are considered as censored. Time to discontinuation is analyzed by Kaplan-Meier method.

Has been changed to:

10.2.1.8 Time to Discontinuation to Treatment

Time to discontinuation of treatment is calculated by the date of the last PSL dose minus the date of first dose +1.

Change #40

The following has been changed:

10.2.2.1 Seizure frequency by 3-month interval

The observed and the absolute change in 28-day adjusted seizure frequency of observable focal onset seizures by the 3-month intervals over the Evaluation Period will be summarized in

descriptive tables for all seizures and for type I seizures only.

The seizure free rate is summarized by 3-month interval over the Evaluation Period and overall as number of subjects who are seizure-free, percentages and 95%-confidence intervals using the Binomial exact method. The number of seizure free days is summarized over the Evaluation Period and by 3-month intervals over the Evaluation Period. A per-subject listing will include the number of seizure-free days during the Evaluation Period.

10.2.2.2 50%, 70%, and 90% responder rate for all types of observable focal onset seizures

Summaries and listings for the 50%, 75% and 90% responder rate will be provided for the specified 3-month intervals over the Evaluation Period and for the complete Evaluation Period.

10.2.2.3 50%, 70%, and 90% responder rate for Type I observable focal onset seizures

Summaries for the 50%, 75% and 90% responder rate will be provided for the specified 3-month intervals over the Evaluation Period and for complete Evaluation Period.

10.2.2.4 Seizure-freedom status for all seizure types by 3-month intervals over the Evaluation Period

By Visit summaries about the seizure freedom status including the seizure-free rate and the corresponding 95% confidence intervals will be provided by 3 months intervals over the Evaluation Period as well as a descriptive summary table of seizure free days, including n, mean, 95%CI for the mean, SD, Min, Max, Median, Q1 and Q3. In addition, the seizure freedom status as well as seizure free days will be captured in a listing.

Has been changed to:

10.2.2.1 Seizure frequency by 3-month interval

The observed and the absolute change in 28-day adjusted seizure frequency of observable focal-onset seizures by the 3-month intervals over the Evaluation Period will be summarized by region in descriptive tables. The same summary will be repeated for the number of completers by time interval.

The observed and change from baseline in seizure frequency of Type IA1, IB, and IC seizures will be summarized separately by seizure type. Summary will be provided for the overall and by 3-month interval during the Evaluation Period. Summary will also be provided by 3-month interval for each completer cohort. The same summary will also be provided for the all Type I seizures.

10.2.2.2 50%, 70%, and 90% responder rates by 3-month interval for observable focal onset seizures over the Evaluation Period

Summaries and listings for the 50%, 75% and 90% responder rates for observable focal-onset seizures will be provided for the overall Evaluation Period and by 3-month interval. Summaries will also be provided by 3-month interval for number of completers by time interval.

10.2.2.3 50%, 70%, and 90% responder rates for focal-onset seizures (all Type I) over the Evaluation Period

Summaries for the 50%, 75% and 90% responder rates for all Type I seizures will be provided for the overall Evaluation Period and by 3-month interval. Summaries will also be provided by 3-month interval number of completers by time interval.

10.2.2.4 Seizure-freedom status for all seizure types by 3-month interval over the Evaluation Period

The number and percentage of subjects achieving a seizure-free status will be summarized by 3-month interval for each completer cohort. After the study completion, the same summary will be performed for the overall and by 3-month interval for the Evaluation Period.

Change #41

The following have been added:

10.2.2.5 Percentage of seizure-free days (for all seizure types) by 3-month interval over the Evaluation Period

The percentage of seizure-free days and change from baseline in percentage of seizure-free days will be summarized for the overall Evaluation Period and by 3-month interval. Summaries will also be provided by 3-month interval for number of completers by time interval.

10.2.2.6 Percentage of reduction in seizure frequency by 3-month interval over the Evaluation Period

The percentage of reduction in seizure frequency from baseline for observable focal-onset seizures and all Type I seizures will be summarized for the overall Evaluation Period and by 3-month interval. Summaries will also be provided by 3-month interval for each completer cohort.

Change #42

The following have been renumbered:

10.2.2.5 Change in the SSG Score

10.2.2.6 Change in the QOLIE-31-P score

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

10.2.2.9 Health-related Outcomes and HRU

10.2.2.10 Time to discontinuation

10.2.2.11 Treatment satisfaction

Have been renumbered to:

10.2.2.7 Change in the SSG Score

10.2.2.8 Change in the QOLIE-31-P score

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

10.2.2.10 Health-related Outcomes and HRU

10.2.2.11 Time to Discontinuation to Treatment

10.2.2.12 Treatment satisfaction

Change #43

The following has been changed:

10.2.2.7 Change in the SSG score

The numbers and percentages of subjects in each severity category will be summarized descriptively for Entry Visit and at each scheduled assessment visit along with the numbers and percentages of subjects in each of the 7 categories of change (much better through much worse).

Summary will be provided for each scheduled visit and the Last Visit during the Evaluation Period. All data will be listed by subject

Changed to:

Data will be listed for each scheduled visit and the Last Visit during the Evaluation Period by subject.

Change #44

The following has been changed:

10.2.2.8 Changes in the QOLIE-31-P score

For each time point, summary statistics will be presented for the change from baseline of the parent study in addition to summaries of the observed values. Only subjects with a non-missing change from baseline will be summarized at each time point.
In addition, all data will be listed by subject for total and subscales.

Changed to:

For each time point, the change from baseline of the parent study will be listed by subject for total and subscales.

Change #45

The following has been changed:

10.2.2.9 Changes in the Hospital Anxiety and Depression Scale (HADS) score

The observed scores and changes in the scores will be summarized using descriptive statistics and in addition presented in a subject listing.

Changed to:
The observed scores and changes in the scores for depression and anxiety will be presented in a subject listing.

Change #46

The following has been changed:

10.2.2.9 Health-related Outcomes and HRU

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

- Socio-professional status

Socio-professional status data are collected at Entry Visit and EOS/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 Entry Visit, EOS or the Last Visit during the Evaluation Period.

- Healthcare provider consultations not foreseen by the protocol

The number of health care provider consultations per subject with onset during the Evaluation 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 Evaluation Period.

- Hospital and ER visits

The number of hospitalization per subject will be summarized as a continuous variable and categorical variable for the Evaluation 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”. 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 Evaluation Period will be summarized using the categories 0, 1, 2, and 3 or more.

Has been changed to:

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

- Socio-professional status

Socio-professional status data are collected at Entry Visit and EOS/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

Healthcare consultations by type of provider
(general practitioner, specialist physician, nurse, and other) will be listed for each subject during the study.

- 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".

- Number of school or working days lost

Number of school/working days lost data are collected on the CRFs "School and Workdays Lost". The number and percentages of subjects who lose school or work days as a result of epilepsy will be listed by visit. The percentage of days lost will be calculated as:

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

Change #47

The following has been changed:

10.2.2.10 Time to discontinuation

Time to discontinuation is summarized descriptively for FAS overall and by region and parent study.
A Kaplan-Meier figure will be provided for all subjects and by region and parent study.

Has been changed to:

10.2.2.11 Time to discontinuation

Kaplan-Meier estimates of the percentage of subjects completing 3, 6, 12, 18, and 24 months of treatment will be provided for the SS. For subjects who discontinued from the study, the event date is set to the date of last dose of PSL and the time to event will be calculated as the date of last dose minus the date of first dose of PSL in EP0093 plus 1. Subjects who completed the study will be censored as of the date of last dose of PSL in EP0093. At a clinical cutoff, subjects who are ongoing will be censored as of the date of last dose of PSL defined for the interim analyses (Section 3.2.2.1).

Change #48

The following has been removed:

10.2.2.12 Treatment satisfaction

Subscale items will be summarized descriptively for FAS overall and by region.

Change #49

The following has been added:

11. COVID-19 impact

The impact of COVID-19 global pandemic on this study is detailed in section 3.10. COVID-19 impact will be listed by impacted visit, date, impact category, and relationship to COVID-19 (confirmed, suspected, general circumstances around COVID-19 without infection or other) in the ES. Impact of COVID-19 for any reason by country will be tabulated in the ES

Change #50

The following has been added:

15. Addendum

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

15 ADDENDUM

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

16 STATISTICAL ANALYSIS PLAN SIGNATURE PAGE

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

Approval Signatures

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