PROTOCOL EP0093 AMENDMENT 2.0

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

EudraCT Number: 2017-003241-26

IND Number: 135622

Sponsor:
UCB Biopharma SRL
Allée de la Recherche 60
1070 Brussels
BELGIUM

Protocol/Amendment number	Date	Type of amendment
Final Protocol	25 Oct 2017	Not applicable
Protocol Amendment 0.1 (Bulgaria)	15 Aug 2018	Nonsubstantial
Protocol Amendment 1[a]	26 Oct 2018	Substantial
Protocol Amendment 1.1 (Switzerland)	15 Jul 2019	Nonsubstantial
Protocol Amendment 2[b]	04 Feb 2020	Substantial

[a] Protocol Amendment 1 incorporated changes in Protocol Amendment 0.1 (Bulgaria).

[b] Protocol Amendment 2 incorporates changes in Protocol Amendment 1.1 (Switzerland).

Confidential Material

STUDY CONTACT INFORMATION

Sponsor

UCB Biopharma SRL
Allée de la Recherche 60
1070 Brussels
BELGIUM

Sponsor Study Physician

Name:	[redacted], MD PhD
Address:	UCB Biosciences GmbH Alfred Nobel Strasse, 10 40789 Monheim am Rhein, Germany
Phone:	[redacted]

Clinical Project Manager

Name:	[redacted]
Address:	UCB Biosciences GmbH Alfred Nobel Strasse, 10 40789 Monheim am Rhein, Germany
Phone:	[redacted]

Clinical Trial Biostatistician

Name:	[redacted]
Address:	UCB BIOSCIENCES, Inc 810 Arco Corporate Drive Raleigh, NC 27617 United States
Phone:	[redacted]

Clinical Monitoring Contract Research Organization

Name:	PAREXEL International (IRL) Limited
Address:	70 Sir John Rogerson's Quay Dublin 2 Ireland
Phone:	+353 1 473 9500
Fax:	+353 1 477 3390

SERIOUS ADVERSE EVENT REPORTING

Serious adverse event reporting (24h)	
Fax	**Europe and Rest of the World:** +32 2 386 24 21 **USA:** +1 800 880 6949 or +1 866 890 3175
Email	**Global:** DS_ICT@ucb.com or DSICT.-@ucb.com

TABLE OF CONTENTS

LIST OF ABBREVIATIONS 10
1 SUMMARY 12
2 INTRODUCTION 13
2.1 Drug-resistant epilepsy 13
2.2 Padsevonil mechanism of action 13
2.3 Nonclinical studies 13
2.4 Clinical studies 13
2.5 Benefit Risk Assessment 14
2.6 Rationale for this study 16
3 STUDY OBJECTIVES 16
3.1 Primary objective 16
3.2 Secondary objective 16
3.3 Exploratory objective 16
4 STUDY VARIABLES 17
4.1 Safety variables 17
4.1.1 Primary safety variables 17
4.1.2 Other safety variables 17
4.2 Efficacy variables 17
4.2.1 Primary efficacy variable 17
4.2.2 Other efficacy variables 17
4.3 Pharmacokinetic and pharmacodynamic variables 18
5 STUDY DESIGN 18
5.1 Study description 18
5.1.1 Study duration per subject 19
5.1.2 Planned number of subjects and sites 19
5.1.3 Anticipated regions and countries 19
5.2 Schedule of study assessments 20
5.3 Rationale for study design and selection of dose 25
6 SELECTION AND WITHDRAWAL OF SUBJECTS 25
6.1 Inclusion criteria 25
6.2 Exclusion criteria 27
6.3 Withdrawal criteria 28
6.3.1 Potential drug-induced liver injury PSL discontinuation criteria 30
6.3.2 Echocardiogram valvular abnormalities assessments 31
7 STUDY TREATMENTS 32
7.1 Description of investigational medicinal product 32
7.2 Treatments to be administered 32

7.3 Packaging 33
7.4 Labeling 33
7.5 Handling and storage requirements 33
7.6 Drug accountability 33
7.7 Procedures for monitoring subject compliance 34
7.8 Concomitant medications/treatments 34
7.8.1 Permitted concomitant treatments (medications and therapies) 34
7.8.2 Prohibited concomitant treatments (medications and therapies) 35
7.8.3 Rescue medication 35
7.9 Blinding 35
7.10 Randomization and numbering of subjects 35
8 STUDY PROCEDURES BY VISIT 35
8.1 Evaluation Period 36
8.1.1 Visit 1 (Entry Visit; Day 1) 36
8.1.2 Visit 2 (Week 2 ±1 week) 37
8.1.3 Visit 3 (Week 4 ±1 week) 37
8.1.4 Visit 4 (Month 2 ±1 week) 38
8.1.5 Visit 5 (Month 3 ±1 week) 38
8.1.6 Visit 6 (Month 6), Visit 7 (Month 9), Visit 8 (Month 12), Visit 9 (Month 15), Visit 10 (Month 18), and Visit 11 (Month 21) ±1 month 39
8.1.7 Early Discontinuation Visit 40
8.1.8 End of Study Visit 40
8.2 Taper Period 41
8.2.1 End of Taper Visit; up to 4 weeks (± 1 week) including 1 week of drug free 41
8.3 Safety Follow-up 42
8.3.1 Safety Follow-up Visit (30 days after the last PSL intake) ± 1 week 42
8.4 Unscheduled Visit/Telephone Call 42
9 ASSESSMENT OF SAFETY 43
9.1 Adverse events 43
9.1.1 Definitions 43
9.1.1.1 Adverse event 43
9.1.1.2 Serious adverse event 43
9.1.1.3 Adverse events of special interest 45
9.1.2 Procedures for reporting and recording adverse events 45
9.1.3 Description of adverse events 45
9.1.4 Rule for repetition of an adverse event 45
9.1.5 Additional procedures for reporting serious adverse events 45
9.1.6 Follow up of adverse events 46

9.1.7 Pregnancy 46
9.1.8 Suspected transmission of an infectious agent 47
9.1.9 Overdose of investigational medicinal product 47
9.1.10 Safety signal detection 48
9.2 Laboratory measurements 48
9.2.1 Evaluation of PDILI 49
9.2.1.1 Consultation with Medical Monitor and local hepatologist 53
9.2.1.2 Immediate action: determination of PSL discontinuation 53
9.2.1.3 Testing: identification/exclusion of alternative etiology 54
9.2.1.4 Follow-up evaluation 55
9.3 Other safety measurements 55
9.3.1 Vital signs measurement 56
9.3.2 Electrocardiograms 56
9.3.3 Echocardiograms 56
9.3.4 Physical examination 57
9.3.5 Neurological examination 57
9.3.6 Assessment of suicidality 58
9.3.7 Psychiatric and Mental Status 58
9.3.8 Withdrawal monitoring 58
10 ASSESSMENT OF EFFICACY 59
10.1 Seizure frequency 59
10.2 Quality of Life Inventory in Epilepsy-31-P 59
10.3 Seizure Severity Global Item 59
10.4 Hospital Anxiety and Depression Scale 60
10.5 Health-related outcomes and healthcare resource utilization 60
10.6 Treatment Satisfaction 60
10.7 Personal outcomes assessment 61
10.8 Caregiver survey 61
11 STUDY MANAGEMENT AND ADMINISTRATION 61
11.1 Adherence to protocol 61
11.2 Monitoring 61
11.2.1 Definition of source data 62
11.2.2 Source data verification 63
11.3 Data handling 63
11.3.1 Case Report form completion 63
11.3.2 Database entry and reconciliation 63
11.3.3 Subject Enrollment log/Subject Identification Code list 64
11.4 Termination of the study 64

11.5 Archiving and data retention 64
11.6 Audit and inspection 64
11.7 Good Clinical Practice 65
12 STATISTICS 65
12.1 Definition of analysis sets 65
12.1.1 Enrolled Set 65
12.1.2 Safety Set 65
12.1.3 Full Analysis Set 65
12.2 General statistical considerations 65
12.3 Planned safety analyses 65
12.4 Planned efficacy analyses 66
12.4.1 Analysis of the primary efficacy variable 66
12.4.2 Analysis of the other efficacy variables 66
12.4.3 Analysis of the subject/caregiver personal outcomes 67
12.5 Handling of protocol deviations 67
12.6 Handling of dropouts or missing data 67
12.7 Planned interim analysis and data monitoring 67
12.8 Determination of sample size 67
13 ETHICS AND REGULATORY REQUIREMENTS 68
13.1 Informed consent 68
13.2 Subject identification cards 68
13.3 Institutional Review Boards and Independent Ethics Committees 68
13.4 Subject privacy 69
13.5 Protocol amendments 69
14 FINANCE, INSURANCE, AND PUBLICATION 69
15 REFERENCES 70
16 APPENDICES 73
16.1 Protocol Amendment 1.0 73
16.2 Protocol Amendment 2.0 104
17 DECLARATION AND SIGNATURE OF INVESTIGATOR 113
18 SPONSOR DECLARATION 114

LIST OF TABLES

Table 5-1: Schedule of assessments 21
Table 6-1: Valvular abnormality grading criteria 31
Table 9–1: Anticipated SAEs for the epilepsy population 44
Table 9–2: Laboratory measurements 49

Table 9-3: Required investigations and follow up for PDILI 51
Table 9–4: PDILI laboratory measurements 54
Table 9–5: PDILI information to be collected 55
Table 9–6: Laboratory measurements 95
Table 9–7: Laboratory measurements 96

LIST OF ABBREVIATIONS

AE	adverse event
AED	antiepileptic drug
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
bid	twice daily
BP	blood pressure
cBZR	central benzodiazepine receptor
CDMS	clinical data management system
CIWA-B	Clinical Institute Withdrawal Assessment-Benzodiazepines
CRO	contract research organization
C-SSRS	Columbia-Suicide Severity Rating Scale
CYP	cytochrome P450
DMC	Data Monitoring Committee
ECG	electrocardiogram
eCRF	electronic Case Report form
EDV	early discontinuation visit
EOS	End of Study
ES	Enrolled Set
GABA-A	gamma-aminobutyric acid-A
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
HADS	Hospital Anxiety and Depression Scale
HRU	healthcare resources utilization
IB	Investigator's Brochure
ICF	Informed Consent form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
ILAE	International League Against Epilepsy
IMP	investigational medicinal product
IRB	Institutional Review Board

IRT	interactive response technology
MedDRA	Medical Dictionary for Regulatory Activities
OLE	open-label extension
PDILI	potential drug-induced liver injury
PK	pharmacokinetics
PS	Patient Safety
PSL	padsevonil
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
RR	responder rate
SAE	serious adverse event
SAP	Statistical Analysis Plan
SDV	source data verification
SFU	Safety Follow-up
SOC	System Organ Class
SOP	Standard Operating Procedure
SS	Safety Set
SSG	Seizure Severity Global Item
SV2	synaptic vesicle 2
TEAE	treatment-emergent adverse event
TSQM	Treatment Satisfaction Questionnaire for Medication
ULN	upper limit of normal

1 SUMMARY

Padsevonil (PSL) is a novel chemical entity that has selective affinity for both presynaptic synaptic vesicle 2 (SV2) proteins and postsynaptic central benzodiazepine receptor (cBZR) sites on the gamma-aminobutyric acid-A (GABA-A) receptor. Specifically synthesized and designed for an increased anticonvulsant activity, PSL has the potential to benefit an underserved population with high unmet medical need, namely those with drug-resistant epilepsy and uncontrolled focal-onset seizures, which constitute a substantial threat to their health and well-being.

EP0093 will assess the long-term safety, tolerability, and efficacy of PSL as an adjunctive treatment for focal-onset seizures in adult subjects with drug-resistant epilepsy. This open-label, long-term study will provide subjects, who participated in previous PSL studies, the opportunity to have continued access to PSL.

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

This study will enroll subjects who have completed a PSL parent study. Subjects will continue to report their seizures in a diary. After the Entry Visit (Visit 1), subjects will return to the clinic for the following visit schedule during the Evaluation Period:

- 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 antiepileptic drugs (AEDs), and/or neurostimulation devices is allowed at any time during the study, if seizure control is insufficient, or in case of safety or tolerability issues. Subjects who complete the study and do not continue PSL treatment or who discontinue early from the study will return for an End of Study (EOS) Visit or Early Discontinuation Visit (EDV) and will be progressively tapered off PSL over 4 weeks and return to the site after the last PSL intake for a Safety Follow-Up (SFU) Visit 30 days after the last PSL intake (including echocardiogram) and a 6-month follow-up echocardiogram to complete echocardiographic monitoring.

Safety will be evaluated based on the incidence of treatment-emergent adverse events (TEAEs) reported by the subject and/or caregiver; subject withdrawals due to adverse events (AEs); changes in periodic clinical laboratory tests; electrocardiogram (ECG) parameters; echocardiography results; withdrawal symptoms, vital signs; Psychiatric and Mental Status; and findings from physical and neurological examinations.

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. Secondary and other efficacy variables will allow further exploration of the effect of PSL on seizure frequency during the entire Evaluation Period, seizure severity, quality of life, anxiety and depression, and unforeseen medical resource utilization.

The total duration of the study per subject will be up to approximately 2 years. Subjects benefitting from the drug and willing to continue will either take commercial drug, if available, or will be transferred to a Managed Access Program or another PSL study, depending on local regulations.

It is estimated that up to 1000 subjects will be included at approximately 350 sites worldwide.

2 INTRODUCTION

2.1 Drug-resistant epilepsy

The International League Against Epilepsy (ILAE) defines drug resistance as failure of adequate trials of 2 tolerated and appropriately chosen AEDs either as monotherapy or in combination to achieve sustained seizure freedom (ILAE Classification of Epileptic Seizures, 1981). In the US, there are 3 million adults with active epilepsy (Zack and Kobau, 2017). Assuming epilepsy with focal-onset seizures in 60% of patients and resistance to AEDs in 20% to 40% of patients, approximately 360,000 to 720,000 patients suffer from drug-resistant epilepsy (Semah, et al 1998; Kwan and Sander, 2004; Giussani, et al 2016). It is this drug-resistant epilepsy population that represents the greatest burden of disease for individuals, physicians, and the healthcare system. A treatment that provides a significant reduction in seizure frequency will reduce mortality and significantly improve quality of life.

2.2 Padsevonil mechanism of action

Padsevonil is a novel chemical entity that has selective affinity for SV2 proteins and postsynaptic cBZR sites on the GABA-A receptor. It has shown compelling efficacy in several preclinical models of epilepsy, including the amygdala kindling model. This model is considered the most translatable approach to assess compounds with potential efficacy against drug-resistant focal epilepsy. Based on this compelling preclinical profile, UCB designed and conducted a proof-of-concept study (EP0069) in patients with highly drug-resistant focal epilepsy.

2.3 Nonclinical studies

A comprehensive nonclinical development program has been conducted with PSL, including oral toxicology studies up to 26 weeks in rats and 39 weeks in dogs, a standard battery of genotoxicity studies, safety pharmacology and secondary pharmacology studies, and fertility and embryofetal development studies in rats and rabbits. Details of these nonclinical studies can be found in the Investigator's Brochure (IB). Padsevonil was well tolerated up to 150mg/kg twice daily (bid) (ie, 300mg/kg/day) over 26 weeks in rats and up to 50mg/kg bid (ie, 100mg/kg/day) over 39 weeks in dogs. The minimal cardiac findings reported in a limited number of animals in the 39-week toxicity study in dogs were judged to be of very low risk (long-term exposure) to nonexistent risk (short-term exposure) to humans by a panel of internal and external experts. Furthermore, echocardiographic screening of human study participants at Baseline (to exclude study participants with valvulopathies) and ongoing echocardiographic monitoring during treatment and post treatment has been implemented in the Phase 2 studies. There have been no major findings to date.

2.4 Clinical studies

Clinical development (Phase 1 and Phase 2) of PSL is underway, the objective of which is to address an unmet medical need by developing a treatment that will provide incremental efficacy

when added to existing AED treatment for patients with drug-resistant epilepsy. The proposed indication of PSL is as an adjunctive therapy in the treatment of focal-onset seizures in adult patients with epilepsy.

Phase 1

Studies of single oral doses of PSL up to 490mg and repeated oral dose of up to 400mg bid for up to 12 days have been completed. In addition, studies to determine SV2A receptor occupancy and pharmacokinetics (PK) in Japanese study participants are ongoing. Tolerability up to 400mg bid was considered acceptable to progress to Phase 2. At the time of initiation of Phase 2, the important identified risks based on the human pharmacology studies included drug-drug interactions with potent cytochrome P450(CYP)3A4 enzyme inducers and the risk of developing psychiatric symptoms. Further details of the Phase 1 studies are available in the IB.

Phase 2

A Phase 2 study, EP0069, conducted in the in the EU to evaluate the potential efficacy, safety/tolerability, and PK profile of PSL administered to subjects with highly drug-resistant focal epilepsy was recently completed. The analysis is ongoing, but the study showed that PSL 400mg bid as an adjunctive treatment to each study participant's current, stable AED regimen was associated with clinically meaningful improvements in seizure control. There were no new or unexpected safety signals. Interim data (cutoff date of 07 Mar 2017) from the ongoing open-label extension (OLE) study (EP0073) to EP0069 indicate that the safety and tolerability profile continues to remain acceptable and support the maintenance of PSL efficacy. Refer to the IB for full details regarding the safety and efficacy.

UCB proposes the initiation of a Phase 2 dose-finding study of PSL (EP0091) and the current OLE study (EP0093), in adult patients having focal-onset seizures associated with drug-resistant epilepsy.

2.5 Benefit Risk Assessment

The following is the benefit risk assessment based on a cut-off date of 06 Dec 2019 and presented in the current version of the Investigator's Brochure.

In patients with drug-resistant epilepsy, seizures have a negative impact on mortality, psychosocial functioning, and quality of life across multiple domains. Patients with resistant, focal epilepsy, and focal unaware or focal to bilateral tonic-clonic seizures have a 5 to 10 times higher mortality rate (Fazel et al, 2013; Hesdorffer and Tomson, 2013; Holst et al, 2013; Sperling, 2004), including a risk of SUDEP (Devinsky, 2011) when compared with the general population. An estimated 1% of patients diagnosed with drug-resistant epilepsy die every year of SUDEP, and 12% die within 2 years of the diagnosis from all causes (Jehi, 2016). Moreover, resistant, focal epilepsy is regarded by many experts as a progressive disease in which ongoing seizures result in an increased risk of further seizures. These patients are prone to falls and injuries; cannot drive; can rarely live independently; feel isolated and stigmatized; have difficulty finding and keeping a job; and often depend on disability benefits (Azuma and Akechi, 2014; Taylor et al, 2001; Baker et al, 1997).

Padsevonil is an AED with a dual mechanism of action (acting at presynaptic SV2 proteins and postsynaptic $GABA_A$ receptors), specifically synthesized and designed for an increased anticonvulsant activity and hence for the treatment of seizures in patients with epilepsies

resistant to current available drug therapies. The efficacy of PSL has been demonstrated in 10 nonclinical models of epilepsy and a more recently completed Phase 2 study in patients with highly drug resistant epilepsy revealed clinically meaningful reductions in seizure frequency. Study participants in the PSL/PSL treatment group were 4.14 times more likely to achieve a ≥75% reduction from the Baseline Period in focal seizure frequency during the 2-week Inpatient Period compared with study participants in the Placebo/PSL treatment group (p=0.0679). The 75% responder rate (RR) approached statistical significance and was clinically meaningful. The median percentage of seizure-free days during the 2-week Inpatient Period in the PSL/PSL treatment group (57.14%) was greater than in the Placebo/PSL treatment group (21.43%). Therefore, based on the evidence demonstrating superior seizure control compared with other marketed AEDs across several preclinical models of epilepsy (Leclercq et al, 2017), and the results of the proof of concept study, EP0069 (Muglia et al, 2017), treatment with PSL has the potential to benefit an underserved epilepsy population with high unmet medical need.

Overall, the clinical pharmacology and clinical studies in drug-resistant epilepsy demonstrated the AE profile of PSL is generally consistent with the pharmacological activity of the product, and in the context of early dose-escalation studies in healthy study participants and patients with epilepsy. The safety findings to date suggest that the AEs experienced by study participants receiving single and repeated doses of PSL are limited principally to CNS effects. The AEs tend to be dose-related in frequency and intensity, self-limiting, and tend to decrease in intensity over the first few days of dosing.

Potential risks identified and relevant to clinical studies (cardiovascular events, psychiatric events, suicidal ideation and behavior [class risk], interactions with other medicinal products, pregnancy and lactation, worsening of seizures, substance abuse and dependence, and overdose) are all described in detail in Section 6.3 of the Investigator's Brochure and suggested lay language is provided to sites for study participants in the Informed Consent form (ICF). Reported acute psychiatric SAEs are consistent with adverse effects of other AEDs, including SV2A ligands. Although events were transient and acute, the occurrence of acute psychiatric effects in 3 study participants administered PSL in completed clinical studies required admission to psychiatric care and medical treatment. Therefore, the possibility of significant psychiatric adverse effects highlights the need to maintain vigilance for such effects. In view of the nonclinical histopathological cardiac findings of some minor asymptomatic, focal cardiac valvular, and epicardial inflammatory lesions in dogs, screening of study participants at Baseline and ongoing echocardiogram monitoring during treatment and post-treatment have been implemented as a precaution in the studies that have a >3-week treatment duration. To date, no clinically significant echocardiogram findings (only minor/trace or Grade 1 findings) have been observed. Based on vital signs, ECGs, echocardiograms, and cardiovascular TEAEs evaluated in clinical studies to date, there is no evidence that PSL causes cardiovascular harm in study participants. Data from in vitro studies and clinical pharmacology studies in healthy study participants and epilepsy patients have shown that PSL at high doses moderately increased exposure of sensitive substrates of cytochrome P450 (CYP)2C19. Although less clear, strong inhibitors and inducers of CYP2C19 may also impact the PK and metabolism of PSL and metabolites. Strong inducers of CYP3A4 have also been shown to have a significant interaction with PSL. Therefore, concomitant administration of strong inducers and inhibitors of CYP3A4 with PSL is prohibited. Additionally, when moderate CYP3A4 inhibitors are introduced or withdrawn from a study participant's treatment regimen, the study participant should be closely

monitored for changes in clinical response and tolerability. Risks associated with suicidal ideation and behavior, pregnancy and lactation, worsening of seizures, and potential overdose are common to all AEDs.

Risk minimization activities for all relevant risks include study protocol inclusion, exclusion, and withdrawal criteria, and safety monitoring measures as deemed appropriate. The routine core pharmacovigilance activities include: signal detection for any new and existing safety concerns, specific follow-up, and aggregate reporting as well as questionnaires for suicidality, withdrawal symptoms, psychiatric and mental status, and anxiety and depression.

Additional routine risk minimization activities include: ICFs that describe the applicable potential risks and discomforts and risks associated with procedures; inclusion, exclusion, and withdrawal criteria and safety monitoring measures as deemed appropriate in clinical study protocols; ECG monitoring for arrhythmias; and clinical laboratory panels for hepatotoxicity. Study participants will also have routine echocardiograms performed, which provide a grading for valvular findings and/or the presence of any accompanying clinical signs/symptoms.

Important risks associated with PSL treatment are managed through standard safety surveillance and routine pharmacovigilance activities. In addition, all ongoing studies are overseen by an independent DMC. Systematic review of aggregate safety data and AE reporting will be performed by the DMC (for all clinical studies) in order to identify safety trends and signals.

2.6 Rationale for this study

This open-label, long-term study will provide subjects, who participated in previous PSL studies, the opportunity to have continued access to PSL.

EP0093 will assess the long-term safety, tolerability, and efficacy of PSL as an adjunctive treatment for focal-onset seizures in adult subjects with drug-resistant epilepsy.

3 STUDY OBJECTIVES

3.1 Primary objective

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

3.2 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.

3.3 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).

4 STUDY VARIABLES

4.1 Safety variables

4.1.1 Primary safety variables

The primary safety variables are the following:

- Incidence of TEAEs reported by the subject and/or caregiver or observed by the Investigator
- Incidence of TEAEs leading to study withdrawal

4.1.2 Other safety variables

Other safety variables are the following:

- Changes in laboratory tests (including hematology, blood chemistry, urinalysis)
- Changes in 12-lead ECG parameters
- Changes in withdrawal symptoms using Clinical Institute Withdrawal Assessment-Benzodiazepines (CIWA-B) from the EOS Visit, to the end of Taper Period and to the end of the 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

4.2 Efficacy variables

Seizure frequency refers to 28-day adjusted frequency.

Observable focal-onset seizures refers to Type IA1, IB, and IC (according to the 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.

4.2.1 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.

4.2.2 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
- 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
- Use of health-related outcomes and HRU, including healthcare provider consultations not foreseen by protocol, caregiver support, concurrent medical procedures, concomitant medications, and hospitalizations

4.3 Pharmacokinetic and pharmacodynamic variables

No PK nor pharmacodynamic variables will be assessed in this study.

5 STUDY DESIGN

5.1 Study description

This is an 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).

At the Entry Visit (same day as the end of Conversion Period Visit in the parent study), subjects will sign a written Informed Consent form (ICF) prior to the conduct of any study-related procedure or pre-treatment assessments, and the subject's eligibility will be determined on the basis of the inclusion/exclusion criteria by the Investigator. Eligible subjects must be educated to record all types of seizures that occur in their seizure diary and to complete their diary entries after each seizure or at least once a day. A caregiver is allowed to help the subject with the completion of the subject diary.

Evaluation Period

After the Entry Visit (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. Concomitant AED(s) may be tapered and discontinued to achieve PSL monotherapy, if clinically appropriate in which case the UCB Physician or delegate must be contacted to discuss with the Investigator. New concomitant AEDs, as allowed per protocol (see Section 7.8.1), may be introduced to optimize seizure control. 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 Visit or 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. If a subject transfers into either a Managed Access Program or another PSL study, or takes commercially available PSL, the Taper Period may be skipped and the subject may continue treatment without tapering.

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 echocardiograms will be required at approximately 1 month and 6 months after the last PSL intake.

5.1.1 Study duration per subject

The total study duration per subject will be up to approximately 2 years. Subjects benefitting from the drug and willing to continue will either take commercial drug, if available, or will be transferred to a Managed Access Program or another PSL study, depending on local regulations.

The end of the study is defined as the date of the last SFU Visit (30 days after the last PSL intake) of the last subject in the study. Serious adverse events (SAEs) will continue to be reported until the 6-month follow-up echocardiogram is obtained.

5.1.2 Planned number of subjects and sites

It is estimated that approximately 1000 subjects will be included in approximately 350 sites worldwide. Additional sites may be added if the study is extended to other regions or countries.

5.1.3 Anticipated regions and countries

The study will be conducted in North America, Europe, Japan, and China with possible extension to other regions or countries.

5.2 Schedule of study assessments

The schedule of assessments in presented in Table 5-1.

Table 5-1: 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
	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	X											
Dispensation of Subject Trial card	X											
Demographic data	X											
Verification of inclusion/exclusion criteria	X											
Verification of withdrawal criteria		X	X	X	X	X	X		X			
Medical history update	X											
C-SSRS since last visit [d]	X*	X	X	X	X	X	X	X	X	X	X	
HADS [d]	X			X		X	X	X	X			
SSG	X				X	X	X	X	X			
QOLIE-31-P [d]						X		X	X			
CIWA-B [d]								X[e]	X	X	X	
TSQM-9 [d]								X	X			

Table 5-1: 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
	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**		
Vital signs [f]	X*	X	X	X	X	X	X	X	X	X	X	
Body weight	X*		X		X	X	X	X	X		X	
Physical examination [g] (XF = Full – XB = Brief)	XF*		XB		XB	XB	XB	XB	XB	XB	XB	
Neurological examination [h] (XF = Full – XB = Brief)	XF*		XB		XB	XB	XB	XB	XB	XB	XB	
Psychiatric and Mental Status	X*		X		X	X	X	X	X	X	X	
Personal Outcomes assessment[i]						X	X					
12-lead ECG [j]	X*		X		X		X	X	X		X	
Echocardiogram [k]		X			X	X	X	X [k]			X	
Blood/urine sample for clinical laboratory analysis	X*		X	X	X	X	X	X	X			
Pregnancy test (female subjects only) [l]	X*	X	X	X	X	X	X	X	X	X		

Table 5-1: 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
	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**		
Seizure evaluation (count and type) [m]	X*	X	X	X	X	X	X	X	X	X	X	
Concomitant medications and procedures [n]	X*	X	X	X	X	X	X	X	X	X	X	
Recording of adverse events	X*	X	X	X	X	X	X	X	X	X	X	
Health-related outcomes and HRU	X*	X	X	X	X	X	X	X	X	X	X	
IRT call	X										X	
PSL dispensing (IRT)	X	X	X	X	X	X	X	X [p]	X			
PSL accountability and return [o]		X	X	X	X	X	X	X	X	X		
Study termination								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

[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) (see Section 6.3).

[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.

5.3 Rationale for study design and selection of dose

EP0093 will assess the long-term safety, tolerability, and efficacy of PSL as an adjunctive treatment for focal-onset seizures in adult subjects with drug-resistant epilepsy.

This OLE study will provide subjects, who participated in previous PSL studies, the opportunity to have continued access to PSL.

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

This entry dose level was selected considering benefit-risk and is based on clinical pharmacology and positron emission tomography data in healthy human subjects suggesting that it will provide full occupancy at the SV2A binding site while maintaining some minimal binding to the GABA-A binding site. For subjects previously on placebo in the parent study, a full SV2A occupancy is desirable to obtain a meaningful anticonvulsive effect while the minimal benzodiazepine binding more likely will make a better tolerance to GABA-related central nervous system toxicity. On the other hand, participants exposed to a high maintenance dose of PSL in the parent study (800mg/day), a target transition dose of 400mg/day will likely maintain the full SV2A-related effect while not entirely eliminating GABA-binding related effects. 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).

6 SELECTION AND WITHDRAWAL OF SUBJECTS

6.1 Inclusion criteria

To be eligible to participate in this study, all of the following criteria must be met:

General

1. An Institutional Review Board (IRB)/Independent Ethics Committee (IEC) approved written ICF is signed and dated by the subject or by the parent(s) or legal representative (where legally permitted). The ICF or a specific Assent form, where required, will be signed and dated by minors, according to country-specific regulations.
2. Subject/legal representative/caregiver (where legally permitted) is considered reliable and capable of adhering to the protocol (eg, able to understand and complete diaries), visit schedule, or medication intake according to the judgment of the Investigator.
3. Subject is an adult (18 years of age or more).

Epilepsy

4. Subject with epilepsy who has completed 1 of the previous PSL studies which allow access to the present study.

Birth control

5. Female subjects of child bearing potential must have a serum negative pregnancy test at the Entry Visit, which is confirmed to be negative by urine testing prior to further dispensing at each study visit thereafter. Subjects will be withdrawn from the study as soon as pregnancy is known.

Female subjects will use an efficient form of contraception for the duration of the study and for a period of 3 months after their final dose of PSL. Hormonal contraception may be susceptible to an interaction with PSL, which may reduce the efficacy of the contraception method. The potential for reduced efficacy of any hormonal contraception method requires that a barrier method (preferably a condom) also be used.

Birth control methods considered as efficient forms of contraception:

- Combined (estrogen- and progesterone-containing) hormonal contraception (oral, implant, injectable) associated with inhibition of ovulation (which must be stable for at least 1 full month prior to the Entry Visit [Visit 1], and should remain stable during the study) in combination with a barrier method (preferably a condom).
- Progesterone-only hormonal contraceptives (oral, implant, injectable) associated with inhibition of ovulation (which must be stable for at least 1 full month prior to Entry Visit [Visit 1], and should remain stable during the study) in combination with a barrier method (preferably a condom).
- Progesterone-releasing intrauterine systems or the TCu 380A intrauterine device in combination with a barrier method (preferably a condom).
- Progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mode of action, in combination with a barrier method (preferably a condom).
- Male or female condom with spermicide (ie, double-barrier).
- Cap, diaphragm or sponge with spermicide (ie, double-barrier).
- Bilateral tubal ligation.
- Vasectomized partner (provided sole partner, and partner has medical proof of surgical success).
- True heterosexual sexual abstinence is an acceptable form of contraception when this is in line with the preferred and usual lifestyle of the person. Periodic abstinence (eg, calendar, ovulation, symptothermal, post-ovulation methods), declaration of abstinence for the duration of the study, and withdrawal are not acceptable methods of contraception.
- Women not agreeing to use birth control must be of non-childbearing potential, defined as being postmenopausal (for at least 2 years before the Entry Visit), verified by serum follicle stimulating hormone level >40mIU/mL at the Entry Visit, or permanently sterilized (eg, bilateral tubal occlusion, hysterectomy, bilateral salpingectomy), or congenitally sterile.
- Both male and female subjects must use the above-mentioned contraception during the study.
- To ensure a proper birth control, females who use hormonal contraception should use an efficient barrier contraceptive in the 3 months after their final intake of PSL.

6.2 Exclusion criteria

Subjects are not permitted to enroll in the study if any of the following criteria is met:

General

1. Subject has any severe medical, neurological, or psychiatric condition, or laboratory value which may have an impact on the safety of the subject.
2. [redacted] as indicated by a positive response ("Yes") to either Question 4 or Question 5 of the "Since Last Visit" version of the Columbia-Suicide Severity Rating Scale (C-SSRS). The subject should be referred immediately to a mental healthcare professional and must be withdrawn from the study.

Laboratory parameters

3. Subject has >2x upper limit of normal (ULN) of any of the following: alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), or >ULN total bilirubin (≥1.5xULN total bilirubin if known Gilbert's syndrome) at the Entry Visit. If the subject has elevations only in total bilirubin that are >ULN and <1.5xULN, fractionated bilirubin must be used to identify possible undiagnosed Gilbert's syndrome (ie, direct bilirubin <35%).

   For enrolled subjects with a Baseline result >ULN for ALT, AST, ALP, or total bilirubin, a Baseline diagnosis and/or the cause of any clinically-significant elevation must be understood and recorded.

   If subject has >ULN for ALT, AST, or ALP that does not meet the exclusion limit at the Entry Visit (ie, the value is >ULN but ≤2xULN at the Entry Visit of EP0093), the tests must be repeated, if possible, prior to dosing to ensure there is no further ongoing clinically-significant increase. In case of a clinically-significant increase, inclusion of the subject must be discussed with the Medical Monitor.

Medical conditions

4. Subject has a clinically-significant abnormality on ECG that, in the opinion of the Investigator, increases the risks associated with participating in the study. In addition, any subject with any of the following findings will be excluded:
   - QT interval corrected for heart rate using Bazett's formula (QTcB) or QT interval corrected for heart rate using Fridericia's formula (QTcF) >450ms.
   - Bundle branch blocks and other conduction abnormalities that are clinically significant according to the Investigator and/or with a PR interval ≥220ms, irregular rhythms other than sinus arrhythmia or occasional, rare supraventricular or rare ventricular ectopic beats in the judgment of the Investigator, or T-wave configurations are not of sufficient quality for assessing QT interval duration.
   - Subject has a history of unexplained syncope or a family history of sudden death due to long QT syndrome.

5. Subject has an abnormality on echocardiogram at last echocardiogram assessment, or foreseen in parent study as assessed by central reader that is accompanied by clinical symptoms (eg, shortness of breath, palpitations, and murmur) or a Grade 2* (or higher)/moderate severity abnormality, or a history of rheumatic heart disease, or other known valvular abnormalities (*according to the ASE Guidelines, 2017; Zoghbi et al 2017).

Pregnancy

6. Female subject who plans to be pregnant or is breastfeeding.

6.3 Withdrawal criteria

Subjects are free to withdraw from the study at any time, without prejudice to their continued care.

Subjects should be withdrawn from the study if any of the following events occur:

1. Subject withdraws his/her consent.
2. The Sponsor or a regulatory agency requests withdrawal of the subject.
3. Subject is noncompliant with the study procedures or medications in the opinion of the Investigator.
4. Subject and/or Investigator do(es) not think that PSL is effective (ie, lack or loss of efficacy).
5. Subject cannot tolerate the minimum PSL dose of 50mg bid (100mg/day).
6. Subject takes prohibited concomitant medications, prescribed or over-the-counter as defined in this protocol.
7. A prolongation or worsening of overall seizure duration, frequency, type, or pattern considered by the Investigator as serious enough to warrant discontinuation from the study.
8. Subjects with an echocardiogram showing a Grade 2 finding (moderate regurgitation/stenosis) if accompanied with moderate to severe signs/symptoms or a Grade 3 finding (severe regurgitation/stenosis) will be discontinued from the study regardless of accompanying clinical symptoms, and should begin discontinuation of PSL. Additionally, a jump of 2 grades from Grade 0 to Grade 2 (moderate regurgitation/stenosis) accompanied with moderate to severe symptoms or from Grade 1 to Grade 3 (severe regurgitation/stenosis) will result in subject discontinuation (see Section 6.3.2).
9. Changes in the ECG that are regarded as clinically significant and/or that worsens over time.
   - An ECG shows an absolute value for QTcB or QTcF ≥500ms or ≥60ms above Baseline.
   - Subject develops second- or third-degree atrioventricular block or another clinically-relevant change in ECG as determined by the Investigator.
10. [redacted] as indicated by a positive response ("Yes") to Question 4 of the "Since Last Visit" version of the C-SSRS. The subject should be referred immediately to a mental healthcare professional and may be withdrawn from the study based upon the Investigator's judgment of the benefit/risk ratio of continuing the subject in the study on PSL.

- [redacted] as indicated by a positive response ("Yes") to Question 5 of the "Since Last Visit" version of the C-SSRS. The subject should be referred immediately to a mental healthcare professional and must be withdrawn from the study.

11. Subject develops an illness that would interfere with his/her continued participation.
12. For subject developing psychiatric/mood/behavioral signs or disturbances (see examples in list below) that are clinically concerning or that worsen over time, the PSL dose should be gradually reduced and, if symptoms persist, withdrawal from the study should be considered. The subject should be referred to a mental health professional, and continuation of PSL should only be allowed with the approval and under close oversight of the mental health specialist, and upon confirmation of the positive benefit/risk by the Investigator.
    - Auditory or visual hallucinations
    - Delusions/paranoia/grandeur
    - Disorganized thought process
    - Agitation/aggression/apathy
    - Dysphoria/depression/mood lability/euphoria
    - Disinhibition
    - Cognitive changes/memory impairment/delirium
    - Aberrant motor behavior
13. Subject is suspected of having a serious multiorgan hypersensitivity reaction. Serious suspected multiorgan hypersensitivity cases may be identified and reported to the Sponsor by the Investigator using the following algorithm:
    - An AE or laboratory value (as defined below) suggestive of internal organ involvement including but not limited to hepatitis, nephritis, pneumonitis, carditis, colitis, encephalitis, pancreatitis, myositis, arthritis, or hematologic system involvement combined with at least one of the following: fever, rash, lymphadenopathy, or eosinophilia.
    - Treatment-emergent abnormal laboratory value criteria suggestive of internal organ involvement or eosinophilia:
    - Eosinophils percentage ≥10%
    - Eosinophils absolute ≥0.5G/L
    - Neutrophils absolute <1.5G/L
    - Platelets absolute ≤100G/L
14. There is confirmation of a pregnancy during the study, as evidenced by a positive pregnancy test.

Investigators should attempt to obtain information on subjects in the case of withdrawal or discontinuation. For subjects considered as lost to follow up, the Investigator should make an effort (at least 1 phone call and 1 written message to the subject), and document his/her effort

(date and summary of the phone call and copy of the written message in the source documents), to complete the final evaluation. All results of these evaluations and observations, together with a narrative description of the reason(s) for removing the subject, must be recorded in the source documents. The eCRF must document the primary reason for withdrawal or discontinuation.

Investigators should contact the Medical Monitor, whenever possible, to discuss the withdrawal of a subject in advance.

6.3.1 Potential drug-induced liver injury PSL discontinuation criteria

Subjects with potential drug-induced liver injury (PDILI) must be assessed to determine if PSL must be discontinued. In addition, all concomitant medications and herbal supplements that are not medically necessary should also be discontinued.

The PDILI criteria below require immediate and permanent discontinuation of PSL:

- Subjects with either of the following:
  - ALT or AST ≥5xULN
  - ALT or AST ≥3xULN and coexisting total bilirubin ≥2xULN

The PDILI criterion below requires immediate discontinuation of PSL:

- Subjects with ALT or AST ≥3xULN who exhibit temporally associated symptoms of hepatitis or hypersensitivity. Hepatitis symptoms include fatigue, nausea, vomiting, right upper quadrant pain or tenderness. Hypersensitivity symptoms include fever (without clear alternative cause), rash, or eosinophilia (ie, ≥5%).

The PDILI criterion below allows for subjects to continue on PSL at the discretion of the Investigator.

- Subjects with ALT or AST ≥3xULN (and ≥2x Baseline) and <5xULN, total bilirubin <2xULN, and no eosinophilia (ie, ≤5%), with no fever, rash, or symptoms of hepatitis (eg, fatigue, nausea, vomiting, right upper quadrant pain or tenderness).

Evaluation of PDILI must be initiated immediately. It consists of the diagnostic testing and continued monitoring (specific tests dependent on laboratory results and corresponding symptoms) and consultation with a local hepatologist. The local hepatologist is the expert usually consulted by the treating physician for assessment and management of potential hepatic disease. This would usually be a hepatologist, but may be a gastroenterologist. Additional investigation and monitoring may be required and adapted based on the diagnosis after the cause of the liver injury/abnormality is confirmed.

Evaluation of PDILI must be initiated as described in Section 9.2.1. If subjects are unable to comply with the applicable monitoring schedule, PSL must be discontinued immediately. Investigators should attempt to obtain information on subjects in the case of PSL discontinuation to complete the final evaluation. Subjects with PDILI should not be withdrawn from the study until investigation and monitoring are complete. All results of these evaluations and observations, as well as the reason(s) for PSL discontinuation and subject withdrawal (if applicable), must be recorded in the source documents. The eCRF must document the primary reason for PSL discontinuation.

6.3.2 Echocardiogram valvular abnormalities assessments

Table 6-1 shows the grading of valvular abnormalities defined by a 0 to 3 Grade scale (according to the ASE Guidelines, 2017; Zoghbi et al 2017) as well as the respective severity descriptions of absent, mild, moderate and severe. Potential cardiovascular signs/symptoms that may accompany valvular abnormalities are included in the table as potential indicators of new or increasing severity of valvular changes and will be identified through routine physical examinations and AE/symptom reporting. However, symptom reporting often occurs only at an advanced stage of the disease (Iung and Vahanian, 2011), suggesting that valvular disease may or may not have accompanying clinical symptoms.

Table 6-1: Valvular abnormality grading criteria

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

[a] New York Heart Association Classification of symptoms; for other echocardiogram measurements, see the Echocardiogram Manual.

Echocardiograms will be obtained every 3 months and will be repeated sooner if new or worsening abnormalities are present (detailed below). Echocardiograms will be examined at the site by the local physician and then provided to the central reader where all study echocardiograms will be centrally read and interpreted by a cardiologist. When local reads warrant, central reads will be expedited. An expedited review of an echocardiogram should be performed if the following conditions are met: (1) a Grade 2 finding of moderate severity, accompanied by moderate or severe signs/symptoms; (2) a Grade 3 finding of severe severity (with or without accompanying symptoms; or (3) an increase (or jump) in 2 grades (0 to 2 or 1 to 3) between echocardiograms. When any of these findings are observed, the Investigator/site should initiate an expedited review from the central reader.

Subjects with Grade 0 or 1 (absent or mild symptoms) will not undergo any additional procedures, other than continued monitoring for any symptomatic clinical events (as listed in Table 6-1).

Subjects with an echocardiogram showing a Grade 2 finding (moderate regurgitation/stenosis) will undergo a repeat echocardiogram within 1 month (unscheduled visit) to confirm the finding. For a Grade 2 echocardiogram of moderate severity, a decision to discontinue is based on the severity of clinical signs/symptoms; if accompanied with moderate to severe signs/symptoms this would result in subject discontinuation. Investigators may contact the Medical Monitor if they wish to discuss the subject's clinical signs/symptoms.

Subjects with an echocardiogram showing a Grade 3 finding (severe regurgitation/stenosis) will undergo a repeat echocardiogram within 2 weeks (unscheduled visit) to confirm the finding. For a Grade 3 echocardiogram with a severe severity, the subject should be discontinued from the study regardless of accompanying clinical signs/symptoms and should begin discontinuation of PSL.

Any subject that shows an increase in 2 grades levels (Grade 0 to 2 or Grade 1 to 3) will undergo a repeat echocardiogram within 2 weeks (unscheduled visit) to confirm the finding. A jump of 2 grades to Grade 2 (moderate) accompanied with moderate to severe symptoms will result in subject discontinuation. If the clinical symptoms are mild, the subject is not required to discontinue. Investigators may contact the Medical Monitor if they wish to discuss the subject's clinical signs/symptoms. However, a jump of 2 grades to Grade 3 (severe) will result in subject discontinuation with/without and signs/symptoms.

Regulatory authorities will be notified of any subject who is discontinued due to an abnormal echocardiogram.

7 STUDY TREATMENTS

7.1 Description of investigational medicinal product

Padsevonil will be supplied by UCB as 25mg, 100mg, and 200mg film-coated tablets of different sizes and appearance (ie, shape and color).

7.2 Treatments to be administered

Padsevonil will be administered in an open-label manner. All subjects will be instructed to take 2 doses approximately 12 hours apart each day 30 minutes after food when practically feasible. The individual starting dose of each subject will be the one at the end of the parent study. The

first dose of the study will be the dose on the day of Visit 1. Once subjects enter EP0093 further individual dose adjustments are allowed after 1 week, between 100mg/day up to a maximum of 800mg/day to the extent possible with the 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. Twice daily dosing with equivalent morning and evening doses approximately 12 hours apart is deemed necessary to ensure more regular exposure over the 24-hour interval; however, the dosing schedule may be adjusted as needed to improve tolerability and efficacy. The decision to advise subjects to divide their morning and evening daily dose unequally should be documented in the eCRF and the UCB Study Physician or delegate should be notified. Increases or decreases to the dose of PSL should not exceed a maximum 200mg/day per week. A faster/slower decrease/increase of the dose than 200mg/day per week is allowed in case of emergency in the Investigator's medical judgment.

7.3 Packaging

Padsevonil tablets are manufactured, packaged, and labeled according to Good Manufacturing Practice (GMP) guidelines and applicable laws or regulations. Padsevonil will be supplied in bottles for each dosage strength. Appropriate bottle size will be dispensed through the interactive response technology (IRT) system as per visit schedule and visit interval.

7.4 Labeling

Clinical drug supplies will be labeled in accordance with the current International Conference on Harmonisation (ICH) guidelines on Good Clinical Practice (GCP) and GMP and will include any locally required statements. If necessary, labels will be translated into the local language.

7.5 Handling and storage requirements

The Investigator (or designee) is responsible for the safe and proper storage of PSL at the site. Investigational medicinal product stored by the Investigator is to be kept in a secured area with limited access according to the storage conditions mentioned on the label.

Appropriate storage conditions must be ensured either by controlling the temperature (eg, room, refrigeration unit) or by completion of a temperature log in accordance with local requirements on a weekly basis, including the capture of minimum and maximum temperatures reached over a time interval.

In case an out-of-range temperature is noted, it must be immediately reported as per instructions in the investigational medicinal product (IMP) Handling Manual.

The Investigator (or designee) will instruct the subject to store the PSL following the instructions on the label.

7.6 Drug accountability

A Drug Accountability form will be used to record PSL dispensing and return information on a by-subject basis and will serve as source documentation during the course of the study. Details of any PSL lost, damaged (due to breakage or wastage), not used, partially used, disposed of at the study site, or returned to the Sponsor or designee must also be recorded on the appropriate forms. All supplies and pharmacy documentation must be made available throughout the study for UCB (or designee) to review.

The Investigator (or designee) is responsible for retaining all used, unused, and partially used containers of PSL until returned or destroyed.

The Investigator may assign some of the Investigator's duties for drug accountability at the study site to an appropriate pharmacist/designee.

The Investigator must ensure that the PSL is used only in accordance with the protocol.

Periodically, and/or after completion of the clinical phase of the study, all used (including empty containers) or partially used, unused, damaged, and expired PSL must be reconciled and either destroyed at site according to local laws, regulations, and UCB Standard Operating Procedures (SOPs) returned to UCB (or designee). Padsevonil intended for the study cannot be used for any other purpose than that described in this protocol.

7.7 Procedures for monitoring subject compliance

At each visit after PSL is dispensed and at the end of the Taper Period, subjects must return all unused PSL and empty PSL containers. Drug accountability must be done in the subject's presence in order to obtain explanations regarding discrepancies in compliance with the dosing regimen. Drug accountability must be recorded on the Drug Accountability form.

If a subject is found to be persistently noncompliant (defined as <75% or >125% compliant with the dosage schedule), the Sponsor, in conjunction with the Investigator, will make a decision as to whether the subject should be withdrawn from the study.

Timely completion of the subject diary is essential for evaluation of safety and efficacy. A caregiver is allowed to help the subject with the completion of the subject diary. Subject diary completion will be reviewed at each visit.

7.8 Concomitant medications/treatments

7.8.1 Permitted concomitant treatments (medications and therapies)

Concomitant AEDs and AED dose(s), or settings for vagus nerve stimulation or other neurostimulation device for epilepsy may be adjusted throughout the study as per the Investigator's clinical judgment based on tolerability and seizure control for each individual subject.

Tapering of all concomitant AED(s) to achieve PSL monotherapy, if clinically appropriate, should only be made in agreement with Study Physician and Sponsor.

New concomitant AEDs may be introduced to optimize tolerability and seizure reduction with the following restrictions:

- Vigabatrin, retigabine, and felbamate are allowed and count as add-on AEDs
  - if taken for more than 2, 1, and 4 years respectively prior to Visit 1 in parent PSL study and, if requirements mentioned in the relevant Exclusion Criteria pertaining to vigabatrin, retigabine, and felbamate in parent PSL study were met.

    Although omeprazole is classified as a sensitive substrate, high doses of omeprazole have been well tolerated, and adjustment of the omeprazole dose is not generally required except with severe hepatic impairment and if long-term treatment is indicated. Therefore, omeprazole is permitted (see omeprazole prescribing information).

7.8.2 Prohibited concomitant treatments (medications and therapies)

The following concomitant medications are prohibited during the study:

- GABA-A-ergic drugs: including agonists (ie, barbiturates) or receptor positive allosteric modulators (ie, benzodiazepines or nonbenzodiazepines like zolpidem) taken >3 times within 7 days. Regular intake of benzodiazepines with an indication for epileptic seizures is not allowed. However, PRN intake of GABA-A-ergic drugs up to 3 times within 7 days is allowed, ie, for emergencies.
- Strong CYP3A4 inhibitors/inducers (for more details refer to Table 3-2 and Table 3-3 in FDA Drug Development Resources, Drug development and drug interactions: Table of substrates, inhibitor and inducers).
  - AEDs including carbamazepine, phenytoin, phenobarbital, and primidone
  - Non-AED strong CYP3A4 enzyme inducers/inhibitors (ie, prescription drugs, nonprescription drugs, medical cannabis, cannabidiol, dietary [eg, grapefruit or passion fruit].
- Strong CYP2C19 strong sensitive substrates/inhibitors/inducers including S-mephenytoin, , fluconazole, fluoxetine, fluvoxamine, ticlopidine, rifampin, ritonavir] (for more details refer to Table 3-1, Table 3-2, and Table 3-3 in FDA Drug Development Resources, Drug development and drug interactions: Table of substrates, inhibitor and inducers).

7.8.3 Rescue medication

Benzodiazepines (as a rescue medication) are allowed for up to 3 doses within 7 days.

7.9 Blinding

This is an open-label study. Therefore, no blinding is required.

7.10 Randomization and numbering of subjects

Randomization is not applicable in the current study. Subjects will be identified with the subject number they received in the parent study.

An IRT will generate individual assignments for subject kits of PSL, as appropriate, according to the visit schedule and the dose the subject should receive.

The subject number will be required in all communication between the Investigator or designee and the IRT regarding a particular subject.

8 STUDY PROCEDURES BY VISIT

Details of the study assessments to be performed at specific time points prior to and after PSL administration are provided in Table 5-1, and an outline of all assessments performed is provided in the sections below.

8.1 Evaluation Period

8.1.1 Visit 1 (Entry Visit; Day 1)

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

The following procedures will be performed:

- Obtain written informed consent (for subjects/caregivers willing to perform the personal outcomes interview/survey, sign and date consent).
- Dispense Subject Trial card
- Completion of HADS and SSG
- Obtain medical history update
- Collect demographic data
- Verify Inclusion and Exclusion criteria (consider results from last scheduled assessment from parent study where relevant (eg, laboratory tests, ECG where applicable)
- Call IRT
- Dispense PSL using IRT

The following assessments noted with * will be obtained in the parent study and do not need to be recorded on the eCRF for this study:

- * Obtain C-SSRS data since last visit
- * Obtain full physical examination data (refer to Section 9.3.4 for details)
- * Obtain full neurological examination data (refer to Section 9.3.5 for details)
- * Obtain vital signs data (pulse rate, systolic BP, diastolic BP, and respiratory rate), in supine position after 5 minutes of rest
- * Obtain body weight measurement data
- * Seizure evaluation (count and type) from subject's daily record card
- * Record concomitant medication and procedures
- * Record AEs
- * Record health-related outcomes and HRU (refer to Section 10.5 for details)
- * Perform Psychiatric and Mental Status assessment
- * Collect blood and urine samples for clinical laboratory analyses
- * Collect 12-lead ECG data
- * Collect results of serum pregnancy test from parent study (End-of-Treatment Visit) and perform urine pregnancy test (end of conversion visit) (female subjects only)

8.1.2 Visit 2 (Week 2 ±1 week)

The following procedures will be performed:

- Verify withdrawal criteria
- Obtain C-SSRS data since the last visit
- Measure vital signs (pulse rate, systolic BP, diastolic BP, and respiratory rate), in supine position after 5 minutes of rest
- Perform urine pregnancy test (female subjects only)
- Seizure evaluation (count and type) from subject's daily record card
- Record concomitant medication and procedures
- Obtain echocardiogram
- Record AEs
- Record health-related outcomes and HRU (refer to Section 10.5 for details), with the exception of socio-professional status
- Call IRT
- Dispense PSL
- Check PSL accountability

8.1.3 Visit 3 (Week 4 ±1 week)

The following procedures will be performed:

- Verify withdrawal criteria
- Obtain C-SSRS data since the last visit
- Measure vital signs (pulse rate, systolic BP, diastolic BP, and respiratory rate), in supine position after 5 minutes of rest
- Measure body weight
- Perform brief physical examination (refer to Section 9.3.4 for details)
- Perform brief neurological examination (refer to Section 9.3.5 for details)
- Perform Psychiatric and Mental Status assessment
- Obtain 12-lead ECG
- Collect blood and urine samples for clinical laboratory analyses
- Perform urine pregnancy test (female subjects of childbearing potential only)
- Seizure evaluation (count and type) from subject's daily record card
- Record concomitant medication and procedures
- Record AEs

- Record health-related outcomes and HRU (refer to Section 10.5 for details), with the exception of socio-professional status
- Dispense PSL
- Check PSL accountability

8.1.4 Visit 4 (Month 2 ±1 week)

The following procedures will be performed:

- Verify withdrawal criteria
- Obtain C-SSRS data since the last visit
- Obtain HADS data
- Measure vital signs (pulse rate, systolic BP, diastolic BP, and respiratory rate), in supine position after 5 minutes of rest
- Collect blood and urine samples for clinical laboratory analyses
- Perform urine pregnancy test (female subjects only)
- Seizure evaluation (count and type) from subject's daily record card
- Record concomitant medication and procedures
- Record AEs
- Record health-related outcomes and HRU (refer to Section 10.5 for details), with the exception of socio-professional status
- Dispense PSL
- Check PSL accountability

8.1.5 Visit 5 (Month 3 ±1 week)

The following procedures will be performed:

- Verify withdrawal criteria
- Obtain C-SSRS data since the last visit
- Obtain SSG data
- Measure vital signs (pulse rate, systolic BP, diastolic BP, and respiratory rate), in supine position after 5 minutes of rest
- Measure body weight
- Perform brief physical examination (refer to Section 9.3.4 for details)
- Perform brief neurological examination (refer to Section 9.3.5 for details)
- Perform Psychiatric and Mental Status assessment
- Obtain 12-lead ECG
- Obtain echocardiogram

- Collect blood and urine samples for clinical laboratory analyses
- Perform urine pregnancy test (female subjects only)
- Seizure evaluation (count and type) from subject's daily record card
- Record concomitant medication and procedures
- Record AEs
- Record health-related outcomes and HRU (refer to Section 10.5 for details), with the exception of socio-professional status
- Dispense PSL
- Check PSL accountability

8.1.6 Visit 6 (Month 6), Visit 7 (Month 9), Visit 8 (Month 12), Visit 9 (Month 15), Visit 10 (Month 18), and Visit 11 (Month 21) ±1 month

The following procedures will be performed:

- Verify withdrawal criteria
- Obtain C-SSRS data since the last visit
- Obtain HADS data
- Obtain SSG data
- Obtain QOLIE-31-P data (Visit 6, Visit 8, and Visit 10 only)
- Perform Personal Outcomes assessment (Visit 6 and Visit 11 only)
- Measure vital signs (pulse rate, systolic BP, diastolic BP, and respiratory rate), in supine position after 5 minutes of rest
- Measure body weight
- Perform brief physical examination (refer to Section 9.3.4 for details)
- Perform brief neurological examination (refer to Section 9.3.5 for details)
- Perform Psychiatric and Mental Status assessment
- Obtain 12-lead ECG (Visit 7, Visit 9, and Visit 11 only)
- Obtain echocardiogram
- Collect blood and urine samples for clinical laboratory analyses
- Perform urine pregnancy test (female subjects of childbearing potential only)
- Seizure evaluation (count and type) from subject's daily record card
- Record concomitant medication and procedures
- Record AEs
- Record health-related outcomes and HRU (refer to Section 10.5 for details), with the exception of socio-professional status

- Dispense PSL
- Check PSL accountability

8.1.7 Early Discontinuation Visit

The following procedures will be performed by all subjects discontinuing the study early:

- Verify withdrawal criteria
- Obtain TSQM-9
- Obtain C-SSRS data since the last visit
- Obtain HADS data
- Obtain QOLIE-31-P data
- Obtain SSG
- Obtain CIWA-B data
- Measure vital signs (pulse rate, systolic BP, diastolic BP, and respiratory rate), in supine position after 5 minutes of rest
- Measure body weight
- Perform brief physical examination (refer to Section 9.3.4 for details)
- Perform brief neurological examination (refer to Section 9.3.5 for details)
- Perform Psychiatric and Mental Status assessment
- Obtain 12-lead ECG
- Collect blood and urine samples for clinical laboratory analyses
- Perform urine pregnancy test (female subjects of childbearing potential only)
- Seizure evaluation (count and type) from subject's daily record card
- Record concomitant medication and procedures
- Record AEs
- Record health-related outcomes and HRU (refer to Section 10.5 for details)
- Dispense PSL for the Taper Period
- Check PSL accountability

8.1.8 End of Study Visit

The following procedures will be performed by all subjects completing the study:

- Obtain TSQM-9
- Obtain C-SSRS data since the last visit
- Obtain HADS data
- Obtain QOLIE-31-P data

- Obtain SSG
- Obtain CIWA-B data (in case of discontinuation of PSL treatment)
- Measure vital signs (pulse rate, systolic BP, diastolic BP, and respiratory rate), in supine position after 5 minutes of rest
- Measure body weight
- Perform brief physical examination (refer to Section 9.3.4 for details)
- Perform brief neurological examination (refer to Section 9.3.5 for details)
- Perform Psychiatric and Mental Status assessment
- Obtain 12-lead ECG
- Obtain echocardiogram if required. 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.
- Collect blood and urine samples for clinical laboratory analyses
- Perform urine pregnancy test (female subjects of childbearing potential only)
- Seizure evaluation (count and type) from subject's daily record card
- Record concomitant medication and procedures
- Record AEs
- Record health-related outcomes and HRU (refer to Section 10.5 for details)
- Dispense PSL to those subjects requiring a Taper Period
- Check PSL accountability
- Study termination (for subjects completing the study and continuing PSL treatment)

8.2 Taper Period

8.2.1 End of Taper Visit; up to 4 weeks (± 1 week) including 1 week of drug free

The following procedures will be performed for subjects discontinuing the study or completing it without continuation of PSL treatment:

- Obtain C-SSRS data since the last visit
- Obtain CIWA-B data
- Measure vital signs (pulse rate, systolic BP, diastolic BP, and respiratory rate), in supine position after 5 minutes of rest
- Perform brief physical examination (refer to Section 9.3.4 for details)
- Perform brief neurological examination
- Perform Psychiatric and Mental Status assessment

- Perform urine pregnancy test (female subjects of childbearing potential only)
- Seizure evaluation (count and type) from subject's daily record card
- Record concomitant medication and procedures
- Record AEs
- Record health-related outcomes and HRU (refer to Section 10.5 for details) with the exception of socio-professional status
- Check PSL accountability

8.3 Safety Follow-up

8.3.1 Safety Follow-up Visit (30 days after the last PSL intake) ± 1 week

The following procedures will be performed for subjects discontinuing the study or completing it without continuation of PSL treatment:

- Obtain C-SSRS data since the last visit
- Obtain CIWA-B data
- Measure vital signs (pulse rate, systolic BP, diastolic BP, and respiratory rate), in supine position after 5 minutes of rest
- Measure body weight
- Perform brief physical examination (refer to Section 9.3.4 for details)
- Perform brief neurological examination (refer to Section 9.3.5 for details)
- Perform Psychiatric and Mental Status assessment
- Obtain 12-lead ECG
- Obtain echocardiogram
- Seizure evaluation (count and type) from subject's daily record card
- Record concomitant medication and procedures
- Record AEs
- Record health-related outcomes and HRU (refer to Section 10.5 for details) with the exception of socio-professional status
- Call IRT
- End of diary recording
- Study termination

An echocardiogram will be performed 6 months after last PSL intake for all subjects.

8.4 Unscheduled Visit/Telephone Call

At any time, the subject may have an unscheduled study visit/telephone call if the Investigator and/or the subject deem it necessary. An unscheduled visit may be conducted due to safety or

efficacy reasons and appropriate assessments will be conducted in relation to the reason for the visit. All information, including reason for visit/telephone call, any information on AEs, etc., should be collected in the source documents and recorded in the appropriate section of the eCRF.

9 ASSESSMENT OF SAFETY

9.1 Adverse events

9.1.1 Definitions

9.1.1.1 Adverse event

An AE is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding or echocardiogram), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

In order to ensure complete safety data collection, all AEs occurring during the study (ie, after the signing of the ICF until the SFU Visit), including any pretreatment and posttreatment periods required by the protocol, must be reported in the eCRF even if no PSL was taken but specific study procedures were conducted. This includes all AEs not present prior to the initial visit and all AEs that recurred or worsened after the initial visit.

Signs or symptoms of the condition/disease for which the PSL is being studied (ie, seizures) should be recorded as AEs only if their nature changes considerably or their frequency or intensity increases in a clinically significant manner as compared with the clinical profile known to the Investigator from the subject's history, including their participation in parent studies.

9.1.1.2 Serious adverse event

Once it is determined that a subject experienced an AE, the seriousness of the AE must be determined. An SAE must meet 1 or more of the following criteria:

- Death
- Life-threatening

  (Life-threatening does not include a reaction that might have caused death had it occurred in a more severe form.)
- Significant or persistent disability/incapacity
- Congenital anomaly/birth defect (including that occurring in a fetus)
- Important medical event that, based upon appropriate medical judgment, may jeopardize the subject and may require medical or surgical intervention to prevent 1 of the other outcomes listed in the definition of serious

  (Important medical events may include, but are not limited to, potential Hy's Law [see Section 9.1.1.3]), allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse)

- Initial inpatient hospitalization or prolongation of hospitalization

  (A patient admitted to a hospital, even if he/she is released on the same day, meets the criteria for the initial inpatient hospitalization. An emergency room visit that results in admission to the hospital would also qualify for the initial inpatient hospitalization criteria. However, emergency room visits that do not result in admission to the hospital would not qualify for this criterion and, instead, should be evaluated for 1 of the other criteria in the definition of serious [eg, life-threatening adverse experience, important medical event].

  Hospitalizations for reasons not associated with the occurrence of an AE [eg, preplanned surgery or elective surgery for a pre-existing condition that has not worsened or manifested in an unusual or uncharacteristic manner] do not qualify for reporting. For example, if a subject has a condition recorded on his/her medical history and later has a preplanned surgery for this condition, it is not appropriate to record the surgery or hospitalization as an SAE, since there is no AE upon which to assess the serious criteria. Please note that, if the pre-existing condition has worsened or manifested in an unusual or uncharacteristic manner, this would then qualify as an AE and, if necessary, the seriousness of the event would need to be determined.)

9.1.1.2.1 Anticipated serious adverse events

The following anticipated SAEs are anticipated to occur in the epilepsy population at some frequency that is independent of drug exposure.

This list does not change the Investigator's obligation to report all SAEs (including Anticipated SAEs) as detailed in Section 9.1.2.

Table 9–1: Anticipated SAEs for the epilepsy population

MedDRA System Organ Class	MedDRA Preferred Term
Congenital and hereditary disorders	Teratogenicity
General disorders and administration site conditions	Sudden unexplained death in epilepsy
Injury, poisoning, and procedural complication	Fall[a], fracture[a], injury[a]
Nervous system disorders	Cluster seizures, convulsion, incontinence[a], memory impairment, status epilepticus
Pregnancy, puerperium, and perinatal disorders	Abortion spontaneous
Psychiatric disorders	Abnormal behavior, acute psychosis, anxiety, cognitive disorder, confusional state, psychotic behavior, sleep disorder and disturbances
Reproductive system and breast disorders	Impotence, menstrual disorder

MedDRA=Medical Dictionary for Regulatory Activities, Version 19.1; SAE=serious adverse event; SOC=System Organ Class

[a] Event are anticipated when occurring in the context of seizure, but not classified in MedDRA primary SOC.

9.1.1.3 Adverse events of special interest

An AE of special interest is any AE that a regulatory authority has mandated to be reported on an expedited basis, regardless of the seriousness, expectedness, or relatedness of the AE to the administration of a UCB product/compound.

Potential Hy's Law, defined as ≥3xULN ALT or AST with coexisting ≥2xULN total bilirubin in the absence of ≥2xULN ALP, with no alternative explanation for the biochemical abnormality, must ALWAYS be reported to UCB as an AE of special interest (ie, without waiting for any additional etiologic investigations to have been concluded). Follow up information should then be reported if an alternative etiology is identified during investigation and monitoring of the subject.

9.1.2 Procedures for reporting and recording adverse events

The subject will be given the opportunity to report AEs spontaneously. A general prompt will also be given at each study visit to detect AEs. For example:

"Did you notice anything unusual about your health (since your last visit)?"

In addition, the Investigator should review any self-assessment procedures (eg, diary cards) employed in the study.

9.1.3 Description of adverse events

When recording an AE, the Investigator should use the overall diagnosis or syndrome using standard medical terminology, rather than recording individual symptoms or signs. The eCRF and source documents should be consistent. Any discrepancies between the subject's own words on his/her own records (eg, diary card) and the corresponding medical terminology should be clarified in the source documentation.

Details for completion of the Adverse Event eCRF (including judgment of relationship to PSL) are described in the eCRF Completion Guidelines.

9.1.4 Rule for repetition of an adverse event

An increase in the intensity of an AE should lead to the repetition of the AE being reported with:

- The outcome date of the first AE that is not related to the natural course of the disease being the same as the start date of the repeated AE, and the outcome of "worsening"
- The AE verbatim term being the same for the first and repeated AE, so that the repeated AE can be easily identified as the worsening of the first one

9.1.5 Additional procedures for reporting serious adverse events

If an SAE is reported, UCB must be informed within 24 hours of receipt of this information by the site (see contact information for SAE reporting listed in the SAE Reporting section at the front of the protocol). The Investigator must forward to UCB (or its representative) a duly completed "Investigator SAE Report Form for Development Drug" (SAE report form) provided by UCB, even if the data are incomplete, or if it is obvious that more data will be needed in order to draw any conclusions. Information recorded on this form will be entered into the global safety database.

An Investigator SAE report form will be provided to the Investigator. The Investigator SAE Report form must be completed in English.

It is important for the Investigator, when completing the SAE report form, to include the assessment as to a causal relationship between the SAE and the PSL administration. This insight from the Investigator is very important for UCB to consider in assessing the safety of the PSL and in determining whether the SAE requires reporting to the regulatory authorities in an expedited manner. Expedited reporting to regulatory authorities will be in line with local laws.

Additional information (eg, autopsy or laboratory reports) received by the Investigator must be provided within 24 hours. All documents in the local language must be accompanied by a translation in English, or the relevant information included in the same document must be summarized in the Investigator SAE report form.

The Investigator is specifically requested to collect and report to UCB (or its representative) any SAEs (even if the Investigator is certain that they are in no way associated with the PSL), up to 6 months from last PSL intake for each subject (ie, until the 6-month follow-up echocardiogram), and to also inform participating subjects of the need to inform the Investigator of any SAE within this period. Serious AEs that the Investigator thinks may be associated with the PSL must be reported to UCB regardless of the time between the event and the end of the study.

Upon receipt of the SAE report form, UCB will perform an assessment of expectedness of the reported SAE. The assessment of the expectedness of the SAE is based on the IB.

9.1.6 Follow up of adverse events

An AE should be followed until it has resolved, has a stable sequela, the Investigator determines that it is no longer clinically significant, or the subject is lost to follow up.

If an AE is ongoing at the end of the study for a subject, follow up should be provided until resolution/stable level of sequelae is achieved, or until the Investigator no longer deems that it is clinically significant, or until the subject is lost to follow up. If no follow up is provided, the Investigator must provide a justification. The follow up will usually be continued for 30 days after the subject has discontinued his/her PSL.

Information on SAEs obtained after final clinical database lock will be captured through the Patient Safety (PS) database without limitation of time.

9.1.7 Pregnancy

If an Investigator is notified that a subject has become pregnant after the first intake of any PSL, the Investigator must immediately notify UCB's PS department by providing the completed Pregnancy Report and Outcome form (for contact details see SAE reporting information at the beginning of this protocol). The subject should be withdrawn from the study as soon as pregnancy is known (by positive urine pregnancy test), and the following should be completed:

- The subject should return for an EDV.
- The subject should immediately stop the intake of the PSL or be tapered as instructed at the EDV.
- Safety Follow-up Visit should be scheduled 1 week after the subject has discontinued PSL.

The Investigator must inform the subject of information currently known about potential risks and about available treatment alternatives.

The pregnancy will be documented on the Pregnancy Report and Outcome form provided to the Investigator. The progression of the pregnancy and the eventual birth (if applicable) must be followed up using the Pregnancy Report and Outcome form in which the Investigator has to report on the health of the mother and of the child. Every reasonable attempt should be made to follow the health of the child for 30 days after birth for any significant medical issues. In certain circumstances, UCB may request that follow up is continued for a period longer than 30 days. If the subject is lost to follow up and/or refuses to give information, written documentation of attempts to contact the subject needs to be provided by the Investigator and filed at the site. UCB's PS department is the primary contact for any questions related to the data collection for the pregnancy, eventual birth, and follow up.

In cases where the partner of a male subject enrolled in a clinical study becomes pregnant, the Investigator or designee is asked to contact the subject to request consent of the partner via the Partner Pregnancy Consent form that has been approved by the responsible IRB/IEC and should be available in the Investigator site file. In case of questions about the consent process, the Investigator may contact the UCB/contract research organization (CRO) contract monitor for the study. The Investigator will complete the Pregnancy Report and Outcome form and send it to UCB's PS department (for contact details see SAE reporting information at the beginning of this protocol) only after the partner has agreed that additional information can be captured and has provided the signed Partner Pregnancy Consent form. UCB's PS department is also the primary contact for any questions related to the data collection for the partner pregnancy, eventual birth, and follow up.

A pregnancy becomes a SAE in the following circumstances: miscarriage, abortion (elective or spontaneous), unintended pregnancy after hormonal contraceptive failure (if the hormonal contraceptive was correctly used), ectopic pregnancy, fetal demise, or any congenital anomaly/birth defect of the baby. Those SAEs must be additionally reported using the Investigator SAE Report form.

9.1.8 Suspected transmission of an infectious agent

For the purposes of reporting, any suspected transmission of an infectious agent via a medicinal product should be considered as an SAE; such cases must be reported immediately, recorded in the AE module of the eCRF, and followed as any other SAE. Any organism, virus, or infectious particle (eg, prion protein transmitting transmissible spongiform encephalopathy), pathogenic or nonpathogenic, is considered an infectious agent.

9.1.9 Overdose of investigational medicinal product

Excessive dosing (beyond that prescribed in the protocol and including overdose) should be recorded in the eCRF. Any SAE or nonserious AE associated with excessive dosing must be followed as any other SAE or nonserious AE. These events are only considered AEs or SAEs if there are associated clinical signs and symptoms or if the act of taking the excess medicine itself is an AE or SAE (eg, suicide attempt).

9.1.10 Safety signal detection

Selected data from this study will be reviewed periodically to detect as early as possible any safety concern(s) related to the PSL so that Investigators, clinical study subjects, regulatory authorities, and IECs will be informed appropriately and as early as possible.

The Study Physician or medically qualified designee/equivalent will conduct an ongoing review of SAEs and perform ongoing SAE reconciliations in collaboration with the PS representative.

As appropriate for the stage of development and accumulated experience with the IMP, medically qualified personnel at UCB may identify additional safety measures (eg, AEs, vital signs, laboratory, ECG and echocardiogram results) for which data will be periodically reviewed during the course of the study.

In addition, an unblinded Data Monitoring Committee (DMC) will oversee safety data approximately every 6 months (subject to DMC recommendation) during the course of the study during which the safety of PSL will be assessed. The safety variables and the decision rules to be used will be specified in the DMC charter. This analysis will inform any decisions regarding changes in study conduct, and/or study termination. The precise membership, scope, and responsibilities of the DMC are described in the DMC Charter.

9.2 Laboratory measurements

Laboratory assessments will be conducted using standard methods at a central laboratory. The central laboratory will provide the Investigator with dedicated, standardized sampling equipment (labels, needles, tubes), and a study-specific Laboratory Manual, which will explain how to use the equipment and how to ship the samples to the central laboratory. The laboratory parameters measured are presented in Table 9–2.

The total blood volume drawn for clinical laboratory assessments per subject will be a maximum of 7mL by sampling, which includes 2mL for hematology and 5mL for blood chemistry.

Table 9–2: 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 to postmenopausal women

In addition, for females of childbearing potential, a urine pregnancy test (beta-human chorionic gonadotropin) will be performed at the scheduled time points presented in Table 5-1. If pregnancy is suspected at any time during the study, an interim test should be performed.

9.2.1 Evaluation of PDILI

The PDILI PSL discontinuation criteria for this study are provided in Section 6.3.1, with the accompanying required follow-up investigation and monitoring detailed below. All PDILI events must be reported as an AE and reported to the study site and Sponsor within 24 hours of learning of their occurrence. Any PDILI event that meets the criterion for potential Hy's Law must be reported as an AE of special interest (see Section 9.1.1.3), and, if applicable, also reported as an SAE (see Section 9.1.1.2).

Evaluation of PDILI consists of the diagnostic testing and continued monitoring included in Table 9-3 (specific tests dependent on laboratory results and corresponding symptoms) and consultation with a local hepatologist (if applicable; discussed in Section 9.2.1.1). The local hepatologist is the expert usually consulted by the treating physician for assessment and management of potential hepatic disease. This would usually be a hepatologist, but may be a gastroenterologist. Additional investigation and monitoring may be required and adapted based on the diagnosis after the cause of the liver injury/abnormality is confirmed (details in Section 9.2.1.4).

The results of all monitoring, including laboratory testing and other testing, should be made available to the study site and Sponsor.

All initial tests resulting in abnormal hepatic laboratory values need to be repeated, but appropriate medical action must not be delayed waiting for the repeat result.

If tests are done locally for more rapid results, a concurrent sample should also be sent to the central laboratory whenever possible. Medical care decisions are to be made initially using the most rapidly available results and a conservative approach must be taken if the results from the 2 laboratory tests are significantly different. Data from the local and central laboratory are to be recorded on the applicable eCRF pages.

When PSL is discontinued, all concomitant medications and herbal supplements that are not medically necessary should also be discontinued. In these cases, the Investigator should also consider dose reduction for medically necessary concomitant medication and consider changing any medically required concomitant medication known to be hepatotoxic to a suitable alternative.

When PSL is stopped due to PDILI (as described in Section 6.3.1), PSL must be permanently discontinued unless a subsequent alternative diagnosis fully explains the hepatic findings. If a subsequent alternative diagnosis fully explains the hepatic findings, and the requirements provided in Section 9.2.1.2.1 are met, rechallenge with PSL may be appropriate after discussion with the Sponsor.

Rechallenge with a substance potentially causing drug-induced liver injury is dangerous, may be fatal, and must not occur.

The approach to investigate PDILI is summarized in Table 9-3.

Table 9-3: Required investigations and follow up for PDILI

Laboratory value			Immediate		Follow up	
ALT or AST	**Total bilirubin**	**Symptoms [a] of hepatitis or hypersensitivity**	**Consultation requirements**	**Actions**	**Testing**	**Evaluation**
≥3xULN	≥2xULN [b]	NA	Hepatology consult.[c] Medical Monitor must be notified within 24 hours (eg, by laboratory alert) and subject discussed with Medical Monitor ASAP.	Immediate, permanent PSL discontinuation.	Essential: Must have repeat liver chemistry values and additional testing completed ASAP (see Section 9.2.1.3); recommended to occur at the site with HCP.	Monitoring of liver chemistry values at least twice per week until values normalize, stabilize, or return to within Baseline values. [d]
≥8xULN	NA	NA				
≥3xULN	NA	Yes		Immediate, temporary or permanent, PSL discontinuation.		
≥3xULN (and ≥2x Baseline) and <5xULN	<2xULN	No	Discussion with Medical Monitor required if the criterion that allows for PSL continuation is met.	Further investigation – immediate PSL discontinuation not required (see Section 9.2.1.2).	Not required unless otherwise medically indicated (at discretion of Investigator).	
≥5xULN (and ≥2x Baseline)	<2xULN	No	Discussion with Medical Monitor required.	Immediate, permanent PSL discontinuation.	Essential: Every attempt must be made to have repeat liver chemistry values and additional testing completed within 48 hours at the site with HCP (see Section 9.2.1.3).	Monitoring of liver chemistry values at least twice per week until values normalize, stabilize, or return to within Baseline value. [d]

ALP=alkaline phosphatase; ALT=alanine aminotransferase; ASAP=as soon as possible; AST=aspartate aminotransferase; HCP=healthcare practitioner; NA=not applicable; PDILI=potential drug-induced liver injury; ULN=upper limit of normal

[a] Hepatitis symptoms include fatigue, nausea, vomiting, and right upper quadrant pain or tenderness; hypersensitivity symptoms include eosinophilia (>5%), rash, and fever (without clear alternative cause).

[b] If the subject also has ≥2xULN ALP, the possibility of an indication of biliary obstruction should be discussed with the Medical Monitor.

[c] Details provided in Section 9.2.1.1. The local hepatologist is the expert usually consulted by the treating physician for assessment and management of potential hepatic disease. This would usually be a hepatologist, but may be a gastroenterologist.

[d] Unless an alternative monitoring schedule is agreed by the Investigator and UCB Study Physician. Determination of stabilization is at the discretion of the Investigator in consultation with the hepatologist (as applicable) and UCB Study Physician, as needed.

9.2.1.1 Consultation with Medical Monitor and local hepatologist

Potential drug-induced liver injury events require notification of the Medical Monitor within 24 hours (eg, by laboratory alert), and the subject must be discussed with the Medical Monitor as soon as possible. If required, the subject must also be discussed with the local hepatologist. The local hepatologist is the expert usually consulted by the treating physician for assessment and management of potential hepatic disease. This would usually be a hepatologist, but may be a gastroenterologist. If determined necessary, this discussion should be followed by a full hepatology assessment (see Section 9.2.1.3) and SAE report (if applicable).

9.2.1.2 Immediate action: determination of PSL discontinuation

All PDILI events require immediate action, testing, and monitoring.

The immediate action is dependent on the laboratory values and symptoms of hepatitis or hypersensitivity and ranges from continuation of PSL (followed by immediate investigation) to immediate and permanent discontinuation (see Section 6.3.1 and Table 9-3 for details).

When PSL is discontinued, all concomitant medications and herbal supplements that are not medically necessary should also be discontinued. The Investigator should also consider dose reduction for medically necessary concomitant medication and consider changing any medically required concomitant medication known to be hepatotoxic to a suitable alternative.

9.2.1.2.1 Padsevonil restart/rechallenge (if applicable)

Rechallenge with a substance potentially causing drug-induced liver injury is dangerous, may be fatal, and must not occur.

Subjects who are immediately discontinued from PSL due to having met certain criteria for PDILI (as described in Section 6.3.1 and Table 9-3), but for whom an alternative diagnosis is confirmed, can rarely restart PSL. Rechallenge with PSL can occur only if ALL of the following requirements are met:

- The results of additional testing and monitoring described in Section 9.2.1.3 and Section 9.2.1.4 confirm a nondrug-related cause for the abnormal hepatic laboratory parameters and any associated symptoms (ie, a subsequent alternative diagnosis fully explains the hepatic findings).
- No alternative treatment options are available to the subject.
- The subject has shown clear therapeutic benefit from the PSL.
- Subject's ALT or AST elevations do not exceed ≥3xULN.
- Subject's total bilirubin is <1.5xULN.
- Subject has no signs or symptoms of hypersensitivity.
- The rechallenge is approved by the UCB Study Physician, DMC, and a hepatologist. The hepatologist must be external to UCB but may be a member of the DMC. It is recommended that the hepatologist be a local hepatology expert or the hepatologist treating the subject.
- Subject agrees to the Investigator-recommended monitoring plan.

9.2.1.3 Testing: identification/exclusion of alternative etiology

The measurements and additional information required for the assessment of PDILI events when there is a reasonable possibility that they may have been caused by the PSL are detailed in Table 9–4 (laboratory measurements) and Table 9–5 (additional information). Results of the laboratory measurements and information collected are to be submitted to the Sponsor on the corresponding eCRF. If the medical history of the subject indicates a requirement for other assessments not included below, these additional assessments should be completed and submitted, as applicable.

All blood samples should be stored, if possible. If tests are done locally for more rapid results, a concurrent sample must also be sent to the central laboratory.

The following measurements are to be assessed:

Table 9–4: PDILI laboratory measurements

Virology-related	Hepatitis A IgM antibody
	HBsAg
	Hepatitis E IgM antibody
	HBcAb-IgM
	Hepatitis C RNA
	Cytomegalovirus IgM antibody
	Epstein-Barr viral capsid antigen IgM antibody (if unavailable, obtain heterophile antibody or monospot testing)
Immunology	Anti-nuclear antibody (qualitative and quantitative)
	Anti-smooth muscle antibody (qualitative and quantitative)
	Type 1 anti-liver kidney microsomal antibodies (qualitative and quantitative)
Hematology	Eosinophil count
Urinalysis	Toxicology screen
Chemistry	Amylase
	If total bilirubin ≥1.5xULN, obtain fractionated bilirubin to obtain % direct bilirubin
	Serum CPK and LDH to evaluate possible muscle injury causing transaminase elevation
Additional	Prothrombin time/INR [a]
	Serum pregnancy test
	PK sample

ALT=alanine aminotransferase; CPK=creatine phosphokinase; HBcAb=hepatitis B core antibody; HBsAg=hepatitis B surface antigen; IgM=immunoglobulin M; INR=international normalized ratio; LDH=lactate dehydrogenase; PDILI=potential drug-induced liver injury; PK=pharmacokinetic; RNA=ribonucleic acid; ULN=upper limit of normal

[a] Measured only for subjects with ALT >8xULN, elevations in total bilirubin, and symptoms of hepatitis or hypersensitivity. Hepatitis symptoms include fatigue, nausea, vomiting, and right upper quadrant pain or tenderness; hypersensitivity symptoms include eosinophilia (>5%), rash, and fever (without clear alternative cause).

The following additional information is to be collected:

Table 9–5: PDILI information to be collected

New or updated information
Concomitant prescription and over-the-counter medications (eg, acetaminophen, herbal remedies, vitamins); dosages and dates should be included.
Pertinent medical history, including the following: • History of liver disease (eg, autoimmune hepatitis, nonalcoholic steatohepatitis or other "fatty liver disease") • Adverse reactions to drugs • Allergies • Relevant family history or inheritable disorders (eg, Gilbert's syndrome, alpha-1 antitrypsin deficiency) • Recent travel • Progression of malignancy involving the liver (Note: Metastatic disease to the liver, by itself, should not be used as an explanation for significant AST and/or ALT elevations.)
The appearance or worsening of clinical symptoms of hepatitis or hypersensitivity (eg, fatigue, nausea, vomiting, right upper quadrant pain or tenderness, decreased appetite, abdominal pain, jaundice, fever, or rash)
Recent clinically significant hypotension or hypoxemia with compromised cardiopulmonary function
Alcohol and illicit drug use
Results of liver imaging or liver biopsy, if done
Results of any specialist or hepatology consult, if done
Any postmortem/pathology reports

ALT=alanine aminotransferase; AST=aspartate aminotransferase; PDILI=potential drug-induced liver injury

9.2.1.4 Follow-up evaluation

Potential drug-induced liver injury events require follow-up monitoring as described in Table 9-3. Monitoring should continue until liver chemistry values normalize, stabilize, or return to Baseline. Determination of stabilization is at the discretion of the Investigator in consultation with the hepatologist (as applicable) and UCB Study Physician, as needed.

9.3 Other safety measurements

Other safety measurements will include vital signs measurement, 12-lead ECGs, echocardiograms, physical examination, neurological examination, assessment of suicidality, assessment of withdrawal symptoms, and Psychiatric and Mental Status assessments. These will be conducted at the time points shown in Table 5-1.

9.3.1 Vital signs measurement

Vital signs will be measured at the scheduled time points presented in Table 5-1.

Vital signs including pulse rate, systolic BP, diastolic BP, and respiratory rate will be measured in supine position, after 5 minutes of rest. Any clinically significant abnormality in the view of the Investigator will be recorded as an AE.

9.3.2 Electrocardiograms

The 12-lead ECG recordings will be measured by a qualified technician at the scheduled time points presented in Table 5-1.

All ECG recordings will be performed with the subject resting in the supine position for at least 5 minutes. The ECGs will be recorded at a speed of 25mm/s and with a calibration of 1cm/mV.

The Investigator should review all ECG recordings and determine if there are any abnormalities that are considered clinically significant for a particular subject. The ECGs will also be sent to a specified central reader for review as detailed in the ECG Manual. The following ECG parameters will be recorded: heart rate, PR-interval, QRS-duration, QT-interval, QTcB or QTcF, and Investigator's conclusion on ECG profile.

9.3.3 Echocardiograms

Echocardiograms will be performed at the scheduled time points presented in Table 5-1. The echocardiogram will be repeated at 6 months (±1 month) after the last PSL intake to assess any abnormalities that may have newly occurred or worsened after the last dose.

Two-dimensional Doppler echocardiography will include the following measurements/observations:

- Epicardial Abnormalities
  - Functional measurements
  - Diastology (ie, Mitral Valve E/A waves, etc.)
  - Systolic (ie, Left Ventricular Ejection Fraction, LVEF, etc.)
- Epicardial Effusion
  - Amount of effusion
  - Pericardial thickness
- Valvular Abnormalities
  - Measurement of valve regurgitation/stenosis
  - Measurement of left atrial volume

For subjects whose echocardiograms are not interpretable by transthoracic echocardiography during the study, alternative assessments should be done using either transesophageal echocardiography or cardiac magnetic resonance imaging in these particular instances.

Echocardiograms should be acquired by a qualified technician. The echocardiograms will be examined by the local physician. Echocardiograms will also be sent to a central cardiologist for review as detailed in the Echocardiography Manual.

A repeat echocardiogram will be performed for subjects with a new finding or Grade 2 severity (moderate) or Grade 3 severity (severe).

Subjects with an echocardiogram showing an abnormality meeting the withdrawal criteria (see Section 6.3) are to be discontinued from the study. An expedited review of an echocardiogram (at the central reader) should be requested if the following conditions are met: (1) a Grade 2 finding of moderate severity, accompanied by moderate or severe signs/symptoms; (2) a Grade 3 finding of severe severity (with or without accompanying symptoms); or (3) an increase (jump) in 2 Grades (0 to 2 or 1 to 3) between echocardiograms. When any of these conditions are met, the Investigator/site should initiate an expedited review from the central reader (see Echocardiography Manual). Regulatory authorities will be notified of any discontinuations.

In case of discontinuation, the subject should return for an EDV and SFU Visit including an echocardiogram within approximately 1 month after last PSL intake and should also return for a 6-month echocardiogram. The corresponding TEAEs occurring before the SFU echocardiogram visit should be followed up until they have resolved, have stable sequelae, or the subject is lost to follow up. During the 6-month echocardiogram period, Investigators will report any SAEs through the UCB SAE reporting process until the final echocardiogram is obtained.

9.3.4 Physical examination

Physical examinations will be performed at the scheduled time points presented in Table 5-1. Findings that are considered clinically-significant changes since the physical examination at the Entry Visit will be recorded as AEs.

A 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.

A brief physical examination will include, review of the following body systems: general appearance including mental status; skin; respiratory; cardiovascular; gastrointestinal; and hepatic.

Body weight will be measured at the scheduled time points presented in Table 5-1. Body weight will be measured with the subject in underwear or light clothing and without wearing shoes; the outcome will be rounded to the nearest 0.1kg.

9.3.5 Neurological examination

Neurological examinations will be performed at the scheduled time points presented in Table 5-1. Findings that are considered clinically-significant changes since the neurological examination at the Entry Visit will be recorded as AEs.

A full neurological examination will include, general assessment; evaluation of reflexes, muscle strength and coordination and cerebellar function; evaluation of cranial nerves, motor system (general – muscle strength and tone); and sensations in upper/lower extremities.

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

9.3.6 Assessment of suicidality

The C-SSRS will be completed at the scheduled time points presented in Table 5-1.

Suicidality will be assessed by trained study personnel using the C-SSRS (Posner et al, 2011). This scale will be used for screening for the parent study as well as to assess suicidal ideation and behavior that may occur during the study. The Investigator's decision about subject continuation in the study or subject withdrawal from the study if the subject has a positive response to the C-SSRS Question 4, should be based on the benefit/risk balance for continuation or discontinuation of study treatment in view of the individual subject circumstances, condition, attained efficacy, causality, alternative risk management options, etc.

If an additional visit (or 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 additional visit (or 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.

Details of the case must be documented by the Investigator (PI or Investigator physician, not site staff conducting the C-SSRS) and provided to UCB via the SAE reporting process.

9.3.7 Psychiatric and Mental Status

The psychiatric and mental status of participating subjects will be closely monitored. Assessment of specific domains of psychiatric and cognitive symptoms will be performed by a staff member trained in the identification of psychiatric symptoms. The Psychiatric and Mental Status assessment will be performed at Entry Visit and all scheduled visits (Table 5-1). The parameters that will be evaluated are orientation, attention, memory, mood, calculus, behavior, and thinking or feeling. These parameters will be assessed as normal or abnormal and then determined whether clinically significant. If present and abnormal, psychiatric symptoms, mental impairment, and behavioral problems will be assessed as to whether they are clinically significant.

9.3.8 Withdrawal monitoring

Any symptoms of withdrawal reactions will be monitored using the CIWA-B questionnaire at the scheduled time points presented in Table 5-1. The CIWA-B questionnaire contains questions and observations which are selected to distinguish withdrawal symptoms from other symptoms (Busto et al, 1989).

Subjects should be monitored during the Taper Period for withdrawal symptoms, including withdrawal-related AEs or seizures as well as the severity of the CIWA-B withdrawal scores. Withdrawal symptoms may require medical treatment for management of severe withdrawal symptoms.

Further details about this questionnaire will be covered in the Study Manual.

10 ASSESSMENT OF EFFICACY

The efficacy variables are described in detail in Section 4.2.

10.1 Seizure frequency

During the study, subjects will keep diaries to record daily seizure activity from the Entry Visit until the end of study participation. Subjects should be reminded to bring their diaries with them to each clinic visit.

The written information will be discussed with the subjects at each visit in order to ensure completeness and accuracy. As a result of the discussion, the Investigator will assess the seizures according to the ILAE codes and record the seizure types and frequency in the eCRF; he/she will also confirm the presence of AEs if applicable.

Subjects should be educated to complete their diary entries after each seizure or at least once a day (eg, when taking evening tablets). A caregiver can assist in completing the diary if necessary. Substantial noncompliance with diary completion (seizure recording) may result in subject discontinuation from the study at any time by the Investigator or the Sponsor; see Section 6.3.

The following seizure information will be recorded in the diary:

- Seizure type
- Seizure frequency

10.2 Quality of Life Inventory in Epilepsy-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 according to the tabular schedule of study procedures in Section 5.1. At the very beginning of the visit, the QOLIE-31-P will be provided to all subjects. It is preferred that the subject complete the questionnaire on his/her own; however, assistance may be provided by the study staff or caregiver if needed. Once completed, the subject will return the completed questionnaire to the Investigator or designee, who will verify that all questions have been answered. Further details about the QOLIE-31-P will be covered in the Study Manual.

10.3 Seizure Severity Global Item

The SSG consist of 1 or 2 items from the Seizure Severity Questionnaire asking the subjects to evaluate the severity of their seizures for the last 4-weeks and/or since the Baseline (in parent

study). Subjects should describe their most common type of seizure when answering the questions.

The SSG will be completed according to the tabular schedule of study procedures in Table 5-1. At the very beginning of the visit, the SSG will be provided to all subjects. It is preferred that the subject complete the questionnaire on his/her own; however, assistance may be provided by either the study staff or caregiver if needed. Once completed, the subject will return the completed questionnaire to the Investigator or designee, who will verify that all questions have been answered. Further details about the SSG will be covered in the Study Manual.

10.4 Hospital Anxiety and Depression Scale

The HADS was chosen for its well-established psychometric properties both in general population and more recently in patients with epilepsy (Lin et al, 2017; Wiglush et al, 2016; de Oliviera 2014). The HADS scores for anxiety and for depression range from 0 to 21 with higher scores indicating worse state. A score below 8 is considered to be normal (Zigmond and Snaith, 1983). It is preferred that the subject complete the questionnaire on his/her own; however, assistance may be provided by either the study staff or caregiver if needed.

10.5 Health-related outcomes and healthcare resource utilization

Health-related outcomes and HRU will be collected in the eCRF and/or diary during the study according to the tabular schedule of study procedures in Table 5-1.

These assessments will include:

- Socio-professional status
- Healthcare provider consultations not foreseen by protocol including the type of provider (general practitioner, specialist physician, nurse), the site of care (office-private, office-hospital, home, emergency room) and the reason leading to the consultation
- Concurrent medical procedures
- Concomitant medications
- Hospitalizations including the reason leading to the hospitalization, the admission ward transfers, and length of stay
- Caregiver support needs
- Number of school or working days lost due to the medical condition of the subjects

10.6 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-12, which has an additional subscale that measures side effects (3 items) (Atkinson et al, 2004). The estimated completion time for this questionnaire is less than 5 minutes. Scores range from 0 (worst) to 100 (best).

The TSQM-9 will be completed according to the tabular schedule of assessments (Table 5-1). At the very beginning of the visit, the TSQM-9 will be provided to all subjects. It is preferred that the subject complete the questionnaire on his/her own; however, assistance may be provided by either the study staff or caregiver if needed. Once completed, the subject will return the completed questionnaire to the Investigator or designee, who will verify that all questions have been answered.

10.7 Personal outcomes assessment

Subjects who have accepted to participate in the entry and exit personal outcome interview during the parent study will be invited to further provide qualitative follow-up interviews/surveys after 6 months and 21 months in the OLE study. Participation in this additional portion of the study is optional and does not preclude participation in the main study. For subjects who choose to participate, the interviews will be conducted by a study nurse/study personnel using a semistructured interview guide and will be audio-recorded (refer to Section 12.4.3 for details on analyses of the corresponding data).

The aim of the interview is to evaluate if and which aspects (domains) of the subject's life is impacted by the treatment and the extent to which the treatment achieves what is considered a meaningful change by the subject. If a subject leaves the study prematurely, he/she will also be invited to participate in an exit interview at his/her Early Discontinuation Visit.

10.8 Caregiver survey

Caregivers who participated in the entry and exit caregiver survey for the parent study will be invited at the 6 Month and 21 Month Visits to complete an additional survey. Participation in the caregiver survey is optional and does not preclude a subject's participation in the main study.

The optional caregiver survey aims to gather the caregiver's perspective on the impact of epilepsy on the subject's life and expectations of meaningful change. The caregiver's survey will also assess the impact of caring for a subject with epilepsy on his/her own life across various domains (social, relationship, independence, work, etc). This survey will allow UCB to gather differences in perspective and expectations from the subject and his/her caregiver's point of view. Refer to Section 12.4.3 for details on analyses of the corresponding data.

11 STUDY MANAGEMENT AND ADMINISTRATION

11.1 Adherence to protocol

The Investigator should not deviate from the protocol. However, the Investigator should take any measure necessary in deviation from or not defined by the protocol in order to protect clinical study subjects from any immediate hazard to their health and safety. In this case, this action should be taken immediately, without prior notification of the regulatory authority, IRB/IEC, or Sponsor.

After implementation of such measure, the Investigator must notify the Clinical Project Manager of the Sponsor within 24 hours and follow any local regulatory requirements.

11.2 Monitoring

UCB (or designee) will monitor the study to meet the Sponsor's monitoring SOPs, ICH-GCP guidelines, and applicable regulatory requirements, and to ensure that study initiation, conduct,

and closure are adequate. Monitoring of the study may be delegated by UCB to a CRO or a contract monitor.

The Investigator and his/her staff are expected to cooperate with UCB (or designee) and to be available during the monitoring visits to answer questions sufficiently and to provide any missing information. The Investigator(s)/Institution(s) will permit direct access to source data/documents for study-related monitoring, audits, IRB/IEC review, and regulatory inspection(s).

The Investigator will allow UCB (or designee) to periodically review all eCRFs and corresponding source documents (eg, hospital and laboratory records for each study participant). Monitoring visits will provide UCB (or designee) with the opportunity to evaluate the progress of the study, verify the accuracy and completeness of eCRFs, ensure that all protocol requirements, applicable authorities regulations, and Investigator's obligations are being fulfilled, and resolve any inconsistencies in the study records.

11.2.1 Definition of source data

All source documents must be accurate, clear, unambiguous, permanent, and capable of being audited. They should be made using some permanent form of recording (ink, typing, printing, optical disc). They should not be obscured by correction fluid or have temporary attachments (such as removable self-stick notes).

Source documents are original records in which raw data are first recorded. These may include hospital/clinic/general practitioner records, charts, diaries, x-rays, laboratory results, printouts, pharmacy records, care records, ECG or other printouts, completed scales, or quality of life questionnaires, for example. Source documents should be kept in a secure, limited access area.

If they are not included in the clinical dossier/hospital file of the subjects, the following data may be written directly in the eCRF and will therefore be considered as source data:

- Demographic data
- Childbearing potential and birth control
- Vital signs
- Body weight and height
- Physical and neurological examinations
- Psychiatric and Mental Status
- Health care provider consultation not foreseen by the protocol
- Caregiver use
- Socio-professional data
- Number of school/working days lost

Diaries will be transcribed into the eCRF and will be considered as source documentation.

Source documents that are computer generated and stored electronically must be printed for review by the monitor (eg, ECG reports). Once printed, these copies should be signed and dated

by the Investigator and become a permanent part of the subject's source documents. The Investigator will facilitate the process for enabling the monitor to compare the content of the printout and the data stored in the computer to ensure all data are consistent.

Electronic data records, such as echocardiogram records, must be saved and stored as instructed by UCB (or designee).

The minimum requirements for source documents used in clinical studies are that they should contain the identity of the subject and study-related identifiers (such as patient identifier, or similar), they should mention the subject's participation in the study and identification of that study (study title or number), they should record the obtaining of consent (date of consent), the exposure to IMP, the subject's medical history, the concomitant medication treatments and dates (including contraceptive treatment), AEs and SAEs, and the dates of the visits. The source documents should provide evidence that Inclusion/Exclusion criteria have been met.

11.2.2 Source data verification

Source data verification (SDV) ensures accuracy and credibility of the data obtained. During monitoring visits, reported data are reviewed with regard to being accurate, complete, and verifiable from source documents (eg, subject files and reports, recordings from automated instruments, tracings [ECG], x-ray films, laboratory notes). All data reported on the eCRF should be supported by source documents, unless otherwise specified in Section 11.2.1. A risk-based approach will be used to monitor the data from the site including tools such as SDV and remote data review. These processes will be described in the study manuals.

11.3 Data handling

11.3.1 Case Report form completion

This study is performed using remote data capture. The Investigator is responsible for prompt reporting of accurate, complete, and legible data in the eCRFs and in all required reports.

Any change or correction to the eCRF after saving must be accompanied by a reason for the change.

Corrections made after the Investigator's review and approval (by means of a password/electronic signature) will be reapproved by the Investigator.

The Investigator should maintain a list of personnel authorized to enter data into the eCRF.

Detailed instructions will be provided in the eCRF Completion Guidelines.

11.3.2 Database entry and reconciliation

Case Report forms/external electronic data will be entered/loaded into a validated electronic database using a clinical data management system (CDMS). Computerized data cleaning checks will be used in addition to manual review to check for discrepancies and to ensure consistency of the data. The data are entered into the eCRFs once and are subsequently verified.

An electronic audit trail system will be maintained within the CDMS to track all data changes in the database once the data have been saved initially into the system or electronically loaded. Regular backups of the electronic data will be performed.

11.3.3 Subject Enrollment log/Subject Identification Code list

The subject's enrollment will be recorded in the Subject Screening and Enrollment Log.

The Investigator will keep a Subject Identification Code list. This list remains with the Investigator and is used for unambiguous identification of each subject.

The subject's consent, assent forms (where applicable), caregiver consent (where applicable), and enrollment in the study must be recorded in the subject's medical record. These data should identify the study and document the dates of the subject's participation.

11.4 Termination of the study

UCB reserves the right to temporarily suspend or prematurely discontinue this study either at a single site, multiple sites, or at all sites at any time for reasons including, but not limited to, safety or ethical issues, inaccurate or incomplete data recording, noncompliance, or unsatisfactory enrollment with respect to quality or quantity.

If the study is prematurely terminated or suspended, UCB (or its representative) will inform the Investigators/Institutions and the regulatory authority(ies) of the termination or suspension and the reason(s) for the termination or suspension, in accordance with applicable regulatory requirement(s). The IRB/IEC should also be informed and provided with reason(s) for the termination or suspension by the Sponsor or by the Investigator/Institution, as specified by the applicable regulatory requirement(s). In addition, arrangements will be made for the return of all unused PSL and other material in accordance with UCB procedures for the study.

11.5 Archiving and data retention

The Investigator will maintain adequate records for the study, including eCRFs, medical records, laboratory results, Informed Consent documents, drug dispensing and disposition records, safety reports, information regarding participants who discontinued, and other pertinent data.

All essential documents are to be retained by the Investigator until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region, or at least 2 years have elapsed since the formal discontinuation of clinical development of the PSL. These documents should be retained for a longer period, however, if required by the applicable regulatory requirement(s) or by an agreement with UCB (CPMP/ICH/135/95, 2002 [Section 4.9.5]). The Investigator will contact UCB for authorization prior to the destruction of any study records or in the event of accidental loss or destruction of any study records. The Investigator will also notify UCB should he/she relocate or move the study-related files to a location other than that specified in the Sponsor's study master file.

11.6 Audit and inspection

The Investigator will permit study-related audits mandated by UCB, after reasonable notice, and inspections by domestic or foreign regulatory authorities.

The main purposes of an audit or inspection are to confirm that the rights and well-being of the subjects enrolled have been protected, that enrolled subjects (ie, signing consent and undergoing study procedures) are appropriate for the study, and that all data relevant for the evaluation of the PSL have been processed and reported in compliance with the planned arrangements, the

protocol, investigational site, and IRB/IEC SOPs, ICH GCP, and applicable regulatory requirements.

The Investigator will provide direct access to all study documents, source records, and source data. If an inspection by a regulatory authority is announced, the Investigator will immediately inform UCB (or designee).

11.7 Good Clinical Practice

Noncompliance with the protocol, ICH-GCP, or local regulatory requirements by the Investigator, Institution, Institution staff, or designees of the Sponsor will lead to prompt action by UCB to secure compliance. Continued noncompliance may result in the termination of the site's involvement in the study.

12 STATISTICS

A description of statistical methods follows and will be described in more detail in the Statistical Analysis Plan (SAP).

12.1 Definition of analysis sets

12.1.1 Enrolled Set

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

12.1.2 Safety Set

The Safety Set (SS) will consist of all enrolled subjects who were administered at least 1 dose of PSL.

12.1.3 Full Analysis Set

The Full Analysis Set 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.

12.2 General statistical considerations

Descriptive statistics, such as the mean, standard deviation, standard error, median, minimum value, and maximum value for quantitative variables, and counts and percentages for categorical variables, will be provided. Key supporting data will be provided in data listings. Summary statistics will be presented by the overall PSL group, unless otherwise indicated.

12.3 Planned safety analyses

All safety variables will be analyzed by descriptive methods and listed on the SS.

Treatment-emergent AEs will be summarized by study period (Evaluation, Taper, and SFU) and reported for cumulative 3-month time intervals and categories of total duration of exposure, using the Medical Dictionary for Regulatory Activities (MedDRA®) primary System Organ Class (SOC) and Preferred Term in incidence tables. Separate tables will be provided for AEs leading to withdrawal from the study and SAEs overall and by the subcategories listed above.

Laboratory values, ECG data (heart rate, PR interval, QTcB, QTcF, and QRS interval), vital signs, and weight will be summarized by period and visit (actual values and change from Entry Visit). Possible clinically significant treatment-emergent abnormalities for laboratory values,

vital signs, and weight will be listed and summarized by period and visit. Electrocardiogram abnormalities will also be listed by period and visit.

Summary tables (and graphical outputs if needed) will be performed on the Doppler echocardiography data.

Physical and neurological examinations, psychiatric assessments and the withdrawal symptoms using the CIWA-B assessment will be provided as listing by period and visit (actual values and change from Entry Visit). The C-SSRS results will be displayed in a listing.

Any additional listings or tabulations will be described in the SAP.

12.4 Planned efficacy analyses

12.4.1 Analysis of the 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.

Seizure frequency will be standardized to a 28-day duration. Potential sensitivity analyses of the primary efficacy variable will be described in the SAP.

12.4.2 Analysis of the other efficacy variables

The following efficacy variables will be summarized with descriptive statistics:

- Observable focal-onset seizure frequency per 28 days by 3-month intervals over the Evaluation Period; the median will be considered as the key statistic
- Observable focal-onset seizure frequency per 28 days by seizure type and by 3-month intervals over the Evaluation Period; the median will be considered as the key statistic
- The 50%, 75%, and 90% RR by 3-month intervals or 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 observable focal-onset seizure frequency relative to the Baseline Period in the parent study.
- The 50%, 75%, and 90% RR by 3-month intervals for focal-onset (Type I) seizures 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
- Change from Baseline from parent study in the Seizure Severity Global Item (SSG) scores at each assessment
- Changes from Baseline from parent study in QOLIE-31-P scores at each assessment
- Changes from Baseline from parent study in HADS scores at each assessment
- 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 Visit12 or EOS

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

12.4.3 Analysis of the subject/caregiver personal outcomes

The data from the qualitative personal outcomes interviews/surveys are considered exploratory and will be maintained separate from the clinical database. The subject/caregiver's interviews/surveys will be analyzed by a third party not involved in the clinical conduct of the study and will be reported outside the clinical study report.

12.5 Handling of protocol deviations

After all data have been verified/entered into a database and prior to database lock, a data evaluation meeting will take place. The purpose of the data evaluation will be to examine all protocol deviations and to verify the quality of the data. The data evaluation will also help in guiding decisions on how to manage data issues on a case-by-case basis (eg, withdrawals, dropouts, and protocol deviations).

Accepted deviations from theoretical time points will be described in the appropriate documents and included in the Study Master File. After the data review, resolution of all issues, and documentation of all decisions, the database will be locked.

12.6 Handling of dropouts or missing data

The methods for handling dropouts will be described in the SAP. Safety and efficacy variables will be analyzed as they are available. Days with missing information will be ignored in the calculation of the seizure frequency. Since subjects will drop out at different times from the study, results will be presented by categories of duration of exposure.

12.7 Planned interim analysis 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 DMC will systematically monitor and report on the progress, safety, and/or critical efficacy endpoints of this study by convening to review the ongoing program safety and efficacy data. This includes evaluating the safety signals and benefit-risk ratio for the study subjects in relationship to new data relevant for PSL efficacy and safety.

A DMC Charter will define the composition, roles, and responsibilities of the DMC, specify the data to be reviewed and the periodicity of data review, and determine the procedures to be followed.

12.8 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 the previous study. Approximately 1000 subjects may be included.

13 ETHICS AND REGULATORY REQUIREMENTS

13.1 Informed consent

Subject's informed consent must be obtained and documented in accordance with local regulations, ICH-GCP requirements, and the ethical principles that have their origin in the principles of the Declaration of Helsinki.

Prior to obtaining informed consent, information should be given in a language and at a level of complexity understandable to the subject in both oral and written form by the Investigator (or designee). Each subject will have the opportunity to discuss the study and its alternatives with the Investigator.

Prior to participation in the study, the ICF should be signed and personally dated by the subject, or his/her legal representative, and by the person who conducted the informed consent discussion (Investigator or designee). The subject or his/her legal representative must receive a copy of the signed and dated ICF. As part of the consent process, each subject must consent to direct access to his/her medical records for study-related monitoring, auditing, IRB/IEC review, and regulatory inspection.

If the ICF is amended during the study, the Investigator (or the Sponsor, if applicable) must follow all applicable regulatory requirements pertaining to the approval of the amended ICF by the IRB/IEC and use of the amended form.

All studies conducted at centers in the United States must include the use of a Health Insurance Portability and Accountability Act Authorization form.

The subject may withdraw his/her consent to participate in the study at any time. A subject is considered as enrolled in the study when he/she has signed the ICF. An eCRF must not be started, nor may any study specific procedure be performed for a given subject, without having obtained his/her written consent to participate in the study.

13.2 Subject identification cards

Upon signing the Informed Consent and Assent form (as applicable), the subject or legal representative will be provided with a subject identification card in the language of the subject. The Investigator will fill in the subject identifying information and medical emergency contact information. The Investigator will instruct the subject to keep the card with him/her at all times.

13.3 Institutional Review Boards and Independent Ethics Committees

The study will be conducted under the auspices of an IRB/IEC, as defined in local regulations, ICH-GCP, and in accordance with the ethical principles that have their origin in the Declaration of Helsinki.

The Investigator/UCB will ensure that an appropriately constituted IRB/IEC that complies with the requirements of the current ICH-GCP version or applicable country-specific regulations will be responsible for the initial and continuing review and approval of the clinical study. Prior to initiation of the study, the Investigator/UCB will forward copies of the protocol, ICF, IB, Investigator's curriculum vitae (if applicable), advertisement (if applicable), and all other subject-related documents to be used for the study to the IRB/IEC for its review and approval.

Before initiating a study, the Investigator will have written and dated full approval from the responsible IRB/IEC for the protocol.

The Investigator will also promptly report to the IRB/IEC all changes in the study, all unanticipated problems involving risks to human subjects or others, and any protocol deviations, to eliminate immediate hazards to subjects.

The Investigator will not make any changes in the study or study conduct without IRB/IEC approval, except where necessary to eliminate apparent immediate hazards to the subjects. For minor changes to a previously approved protocol during the period covered by the original approval, it may be possible for the Investigator to obtain an expedited review by the IRB/IEC, as allowed.

As part of the IRB/IEC requirements for continuing review of approved studies, the Investigator will be responsible for submitting periodic progress reports to the IRB/IEC (based on IRB/IEC requirements), at intervals appropriate to the degree of subject risk involved, but no less than once per year. The Investigator should provide a final report to the IRB/IEC following study completion.

UCB (or its representative) will communicate safety information to the appropriate regulatory authorities and all active Investigators in accordance with applicable regulatory requirements. The appropriate IRB/IEC will also be informed by the Investigator or the Sponsor, as specified by the applicable regulatory requirements in each concerned country. Where applicable, Investigators are to provide the Sponsor (or its representative) with evidence of such IRB/IEC notification.

13.4 Subject privacy

UCB staff (or designee) will affirm and uphold the subject's confidentiality. Throughout this study, all data forwarded to UCB (or designee) will be identified only by the subject number assigned at the Entry Visit.

The Investigator agrees that representatives of UCB, its designee, representatives of the relevant IRB/IEC, or representatives of regulatory authorities will be allowed to review that portion of the subject's primary medical records that directly concerns this study (including, but not limited to, laboratory test result reports, ECG reports, admission/discharge summaries for hospital admissions occurring during a subject's study participation, and autopsy reports for deaths occurring during the study).

13.5 Protocol amendments

Protocol changes may affect the legal and ethical status of the study and may also affect the statistical evaluations of sample size and the likelihood of the study fulfilling its primary objective.

Significant changes to the protocol will only be made as an amendment to the protocol and must be approved by UCB, the IRB/IEC, and the regulatory authorities (if required), prior to being implemented.

14 FINANCE, INSURANCE, AND PUBLICATION

Insurance coverage will be handled according to local requirements.

Finance, insurance, and publication rights are addressed in the Investigator and/or CRO agreements, as applicable.

15 REFERENCES

Atkinson MJ, Sinha A, Hass SL, Colman SS, Kumar RN, Brod M, et al. Validation of a general measure of treatment satisfaction, the Treatment Satisfaction Questionnaire for Medication (TSQM), using a national panel study of chronic disease. Health Qual Life Outcomes. 2004;2:12.

Azuma H, Akechi T. Effects of psychosocial functioning, depression, seizure frequency, and employment on quality of life in patients with epilepsy. Epilepsy Behav. 2014;41:18-20.

Baker GA, Jacoby A, Buck D, Stalgis C, Monnet D. Quality of life of people with epilepsy: a European study. Epilepsia. 1997;38(3):353-62.

Bharmal M, Payne K, Atkinson MJ, Desrosiers MP, Morisky DE, Gemmen E. Validation of an abbreviated Treatment Satisfaction Questionnaire for Medication (TSQM-9) among patients on antihypertensive medications. Health Qual Life Outcomes. 2009;7:36.

Busto UE, Sykora K, Sellers EM. A clinical scale to assess benzodiazepine withdrawal. J Clin Psychopharmacol. 1989;9(6):412-6.

Commission on Classification and Terminology of the International League Against Epilepsy. Proposal for revised clinical and electroencephalographic classification of epileptic seizures. Epilepsia. 1981;22:489-501.

CPMP/ICH/135/95 Note for guidance on Good Clinical Practice (EMEA) Jul 2002.

Cramer JA, Van Hammée G, N132 Study Group. Maintenance of improvement in health-related quality of life during long-term treatment with levetiracetam. Epilepsy Behav. 2003;4(2):118-23.

Cramer JA, Perrine K, Devinsky O, Bryant-Comstock L, Meador K, Hermann B. Development and cross-cultural translations of a 31-item quality of life in epilepsy inventory. Epilepsia. 1998;39(1):81-8.

de Oliveira GN, Lessa JM, Goncalves AP, Portela EJ, Sander JW, Teixeira Al. Screening for depression in people with epilepsy: comparative study among neurological disorders depression inventory for epilepsy (NDDI-E), hospital anxiety and depression scale depression subscale (HADS-D), and Beck depression inventory (BDI). Epilepsy Behav. 2014;34:50-4.

Devinsky O. Sudden, unexpected death in epilepsy. N Engl J Med. 2011;365:1801-11.

Fazel S, Wolf A, Långström N, Newton CR, Lichtenstein P. Premature mortality in epilepsy and the role of psychiatric comorbidity: a total population study. Lancet. 2013;382:1646-54.

Food and Drug Administration. Development Resources. Drug development and drug interactions: Table of substrates, inhibitor and inducers. Accessed Sep 2017. https://www.fda.gov/drugs/developmentapprovalprocess/developmentresources/druginteractionslabeling/ucm093664.htm

Food and Drug Administration. Guidance for Industry. Guidelines for the clinical evaluation of antiepileptic drugs (adults and children). US Department of Health and Human Services. Center for Drug Evaluation and Research, 81-3110, 01/1981.

Giussani G, Canelli V, Bianchi E, Erba G, Franchi C, Nobili A, et al. Long-term prognosis of epilepsy, prognostic patterns and drug resistance: a population-based study. Eur J Neurol. 2016;23(7):1218-27.

Hesdorffer DC, Tomson T. Sudden unexpected death in epilepsy: Potential role of antiepileptic drugs. CNS Drugs. 2013;27(2):113-9.

Holst AG, Winkel BG, Risgaard B, Nielsen JB, Rasmussen PV, Haunsø S, et al. Epilepsy and risk of death and sudden unexpected death in the young: a nationwide study. Epilepsia. 2013;54(9):1613-20.

Iung B, Vahanian A. Epidemiology of valvular heart disease in the adult. Nat Rev Cardiol. 2011;8(3):162-72

Jehi L. Neurology's Silent Killer: Drug-Resistant Epilepsy. Epilepsy Curr. 2016;16:232-3.

Kwan P, Sander JW. The natural history of epilepsy: an epidemiological view. J Neurol Neurosurg Psychiatry. 2004;75(10):1376-81.

Leclercq K, Matagne A, Provins L, Klitgaard H, Kaminski R. Protective effects of padsevonil in acute seizure models. (Abstract 1.272), 2017. www.aesnet.org.

Lin CY, Pakpour AH. Using Hospital Anxiety and Depression Scale (HADS) on patients with epilepsy: Confirmatory factor analysis and Rasch models. Seizure. 2017;45:42-6.

Muglia P, Toledo T, Steinhoff, BJ, et al. Efficacy and tolerability of adjunctive padsevonil in adults with drug-resistant focal onset seizures: a randomized, double-blind, placebo-controlled, proof-of-concept trial. (Abstract 1.283), 2017. American Epilepsy Society Annual Meeting, www.aesnet.org.

Posner K, Brown GK, Stanley B, Brent DA, Yershova KV, Oquendo MA, et al. The Columbia-Suicide Severity Rating Scale: initial validity and internal consistency findings from three multisite studies with adolescents and adults. Am J Psychiatry. 2011;168:1266-77.

Semah F, Picot MC, Adam C, Broglin D, Arzimanoglou A, Bazin B, et al. Is the underlying cause of epilepsy a major prognostic factor for recurrence? Neurology. 1998;51(5):1256-62.

Sperling MR. The consequences of uncontrolled epilepsy. CNS Spectr. 2004;9(2):98-101, 106-9.

Taylor DC, McMackin D, Staunton H, Delanty N, Phillips J. Patients' aims for epilepsy surgery: desires beyond seizure freedom. Epilepsia. 2001;42(5):629-33.

WHO Collaborating Centre for Drug Statistics Methodology. ATC/DDD Index 2017. Accessed Sep 2017. http://www.whocc.no/atc_ddd_index/

Wiglusz MS, Landowski J, Michalak L, Cubala WJ. Validation of the Hospital Anxiety and Depression Scale in patients with epilepsy. Epilepsy Behav. 2016;58:97-101.

Zack MM, Kobau R. National and state estimates of the numbers of adults and children with active epilepsy-United States, 2015. MMWR Morb Mortal Wkly Rep 2017;66:821-825.

Zigmond RP, Snaith AS. The Hospital Anxiety and Depression Scale. Act Psychiatr, Scand, 1994;67:361-70.

Zhoghbi WA, Adams D, Bonow RO, Enriquwz-Sarano M, Foster E, Grayburn PA, et al. Recommendations for noninvasive evaluation of native valvular regurgitation: A report from the

American Society of Echocardiography developed in collaboration with the society for cardiovascular magnetic resonance. JASE. 2017;30:303-71.

16 APPENDICES

16.1 Protocol Amendment 1.0

Rationale for the amendment

The protocol did allow subjects without access to a Managed Access Plan to continue participation in EP0093 after the second year and until a Marketing Authorization is granted by any health authority for the adjunctive treatment of focal-onset seizures in adults with drug-resistant epilepsy**.** This amendment limits duration of participation of all subjects to 2 years. Subjects without access to a Managed Access Plan will be offered the option to transfer to another study if approved by the relevant country agencies. This has been noted in several locations in the protocol.

Other changes include the following:

- Updates to study contact information.
- Increase in number of sites from 150 to approximately 350.
- Modification of the proposed indication statement (removal of drug-resistant).
- Clarification of study objectives to specify that subjects have focal-onset seizures as well as drug-resistant epilepsy.
- Removal of log-transformation of observable focal-onset seizures for the analysis.
- Addition of other efficacy variable, time to discontinuation.
- Minor revisions to wording of some variables.
- Specification that follow-up echocardiograms at 1 and 6 months after the last PSL intake are required.
- Addition of China to anticipated regions and countries in which the study will be conducted.
- Revisions to the Schedule of Study Assessments consistent with the main change in the amendment. This includes a split of the EDV and EOT (now called End of Study) visits into separate visits. This is also reflected in the Study Procedures by Visit Section. In addition, some footnotes were added/clarified.
- Substitution of "where legally permitted" for "where applicable" in Inclusion Criteria 1 and 2.
- Revision of valvular abnormality grading criteria and withdrawal criterion pertaining to echocardiographic findings to add stenosis wherever regurgitation is noted. This makes the criterion consistent with those in the feeder studies.
- Clarification of the description of the interpretation of echocardiograms
  - The original description stated that the echocardiograms would be interpreted at the sites by local cardiologists and then provided to a central reader where they would be interpreted. Given that all echocardiograms are to be centrally read and a report provided within 7 business days of receipt, in the absence of queries, there is no need for local cardiologist. Therefore, the protocol was modified to say that it is only necessary that the

local physician examines the echocardiograms for suitability for central reading and for determination if an expedited review by the central reader is required. It has also been made explicit that the central reader is a cardiologist.

- Revision of prohibited concomitant treatments to make them consistent with the feeder studies.
- Addition of FSH to the laboratory measurements with specification that it is only applicable to postmenopausal women. In addition, a footnote was added to urine microscopy to indicate this is only performed in case of other abnormalities. This makes the table consistent with the feeder studies.
- The description of the measurements and observations included in the echocardiograms was revised for consistency with the feeder studies.
- The Treatment Satisfaction Questionnaire for Medication (TSQM)-9 has been added to study assessments. References pertaining to this questionnaire have been added.
- Clarifications regarding administration of the QOLIE-31-P, SSG, and HADS.

Modifications and changes

Specific changes

Change #1

Study contact information (bolded information revised)

Sponsor Study Physician

Name:	[redacted]
Address:	UCB Biosciences GmbH Alfred Nobel Strasse, 10 40789 Monheim am Rhein, Germany
Phone:	[redacted]

Clinical Project Manager

Name:	[redacted]
Address:	**UCB Biopharma SPRL** **Allée de la Recherche 60** **1070 Brussels** **Belgium**
Phone:	[redacted]

Clinical Trial Biostatistician

Name:	[redacted]
Address:	**UCB Biosciences GmbH** **Alfred Nobel Strasse, 10** **40789 Monheim am Rhein,** **Germany**
Phone:	[redacted]

Has been changed to (bolded information added or revised):

Sponsor Study Physician

Name:	[redacted] **MD PhD**
Address:	UCB Biosciences GmbH Alfred Nobel Strasse, 10 40789 Monheim am Rhein, Germany
Phone:	[redacted]

Clinical Project Manager

Name:	[redacted]
Address:	**UCB Biosciences GmbH** **Alfred Nobel Strasse, 10** **40789 Monheim am Rhein,** **Germany**
Phone:	[redacted]

Clinical Trial Biostatistician

Name:	[redacted]
Address:	**UCB Pharma Ltd** **280 Bath Road** **Berkshire SL1 3WE Slough,** **UK**
Phone:	[redacted]

Change #2

List of Abbreviations

Has been added:

EOS=End of Study (replaces EOT)

TSQM=Treatment Satisfaction Questionnaire for Medication

Change #3

Section 1, Summary (bolded text has been deleted)

Padsevonil (PSL) is a novel chemical entity that has selective affinity for both presynaptic synaptic vesicle 2 (SV2) proteins and postsynaptic central benzodiazepine receptor (cBZR) sites on the gamma-aminobutyric acid-A (GABA-A) receptor. Specifically synthesized and designed for an increased anticonvulsant activity, PSL has the potential to benefit an underserved population with high unmet medical need, namely those with drug-resistant epilepsy and uncontrolled focal-onset seizures, which constitute a substantial threat to their health and well-being.

EP0093 will assess the long-term safety, tolerability, and efficacy of PSL as an adjunctive treatment for focal-onset seizures in adult subjects with drug-resistant epilepsy. This open-label, long-term study will provide subjects, who participated in previous PSL studies, the opportunity to have continued access to PSL.

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

This study will enroll subjects who have completed a PSL parent study. Subjects will continue to report their seizures in a diary. After the Entry Visit (Visit 1), subjects will return to the clinic for the following visit schedule during the Evaluation Period:

- 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
- **Every 6 months from the beginning of Year 3**

Dose adjustment of PSL, and/or concomitant antiepileptic drugs (AEDs), and/or neurostimulation devices is allowed at any time during the study, if seizure control is insufficient, or in case of safety or tolerability issues. Subjects who complete the study **(**and do not continue PSL treatment**)** or who discontinue early from the study will return for an End of **Treatment (EOT)** Visit or Early Discontinuation Visit (EDV) and will be progressively tapered off PSL over 4 weeks and return to the site after the last PSL intake for a Safety Follow-Up (SFU) Visit 30 days after the last PSL intake (including echocardiogram) and a 6-month follow-up echocardiogram to complete echocardiographic monitoring. **In case PSL becomes**

available either via a Managed Access Program or after Marketing Authorization, the Taper Period may be skipped and the subjects may continue treatment without tapering.

Safety will be evaluated based on the incidence of treatment-emergent adverse events (TEAEs) reported by the subject and/or caregiver; subject withdrawals due to adverse events (AEs); changes in periodic clinical laboratory tests; electrocardiogram (ECG) parameters; echocardiography results; withdrawal symptoms, vital signs; Psychiatric and Mental Status; and findings from physical and neurological examinations.

The primary efficacy variable will be the change from Baseline from the respective parent study in **log-transformed** observable focal-onset seizure frequency over the Evaluation Period. Secondary and other efficacy variables will allow further exploration of the effect of PSL on seizure frequency during the entire Evaluation Period, seizure severity, quality of life, anxiety and depression, and unforeseen medical resource utilization.

The total duration of the study per subject will be up to 2 years**, in countries where subjects can be transferred to a Managed Access Program. Subjects may continue in EP0093 in countries where a Managed Access Program is inexistent until a Marketing Authorization is granted by any health authority for the adjunctive treatment of focal-onset seizures in adults with drug-resistant epilepsy.** It is estimated that up to 1000 subjects will be included at approximately **150** sites worldwide.

Has been changed to (new text bolded):

Padsevonil (PSL) is a novel chemical entity that has selective affinity for both presynaptic synaptic vesicle 2 (SV2) proteins and postsynaptic central benzodiazepine receptor (cBZR) sites on the gamma-aminobutyric acid-A (GABA-A) receptor. Specifically synthesized and designed for an increased anticonvulsant activity, PSL has the potential to benefit an underserved population with high unmet medical need, namely those with drug-resistant epilepsy and uncontrolled focal-onset seizures, which constitute a substantial threat to their health and well-being.

EP0093 will assess the long-term safety, tolerability, and efficacy of PSL as an adjunctive treatment for focal-onset seizures in adult subjects with drug-resistant epilepsy. This open-label, long-term study will provide subjects, who participated in previous PSL studies, the opportunity to have continued access to PSL.

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

This study will enroll subjects who have completed a PSL parent study. Subjects will continue to report their seizures in a diary. After the Entry Visit (Visit 1), subjects will return to the clinic for the following visit schedule during the Evaluation Period:

- 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 antiepileptic drugs (AEDs), and/or neurostimulation devices is allowed at any time during the study, if seizure control is insufficient, or in case of safety or tolerability issues. Subjects who complete the study and do not continue PSL treatment or who discontinue early from the study will return for an End of Study (EOS) Visit or Early Discontinuation Visit (EDV) and will be progressively tapered off PSL over 4 weeks and return to the site after the last PSL intake for a Safety Follow-Up (SFU) Visit 30 days after the last PSL intake (including echocardiogram) and a 6-month follow-up echocardiogram to complete echocardiographic monitoring.

Safety will be evaluated based on the incidence of treatment-emergent adverse events (TEAEs) reported by the subject and/or caregiver; subject withdrawals due to adverse events (AEs); changes in periodic clinical laboratory tests; electrocardiogram (ECG) parameters; echocardiography results; withdrawal symptoms, vital signs; Psychiatric and Mental Status; and findings from physical and neurological examinations.

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. Secondary and other efficacy variables will allow further exploration of the effect of PSL on seizure frequency during the entire Evaluation Period, seizure severity, quality of life, anxiety and depression, and unforeseen medical resource utilization.

The total duration of the study per subject will be up to 2 years. **Subjects benefitting from the drug and willing to continue will either take commercial drug, if available, or will be transferred to a Managed Access Program or another PSL study, depending on local regulations.**

It is estimated that up to 1000 subjects will be included at approximately **350** sites worldwide.

Change #4

Section 2.4, Clinical studies, Paragraph 1 (bolded text has been deleted)

Clinical development (Phase 1 and Phase 2) of PSL is underway, the objective of which is to address an unmet medical need by developing a treatment that will provide incremental efficacy when added to existing AED treatment for patients with drug-resistant epilepsy. The proposed indication of PSL is an adjunctive therapy in the treatment of focal-onset seizures in adult patients with **drug-resistant** epilepsy.

Has been changed to (new text bolded):

Clinical development (Phase 1 and Phase 2) of PSL is underway, the objective of which is to address an unmet medical need by developing a treatment that will provide incremental efficacy when added to existing AED treatment for patients with drug-resistant epilepsy. The proposed

indication of PSL is **as** an adjunctive therapy in the treatment of focal-onset seizures in adult patients with epilepsy.

Change #5

Section 3.1, Primary objective

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

Has been changed to (new text bolded):

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

Change #6

Section 3.3, Exploratory objective

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

Has been changed to (new text bolded):

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).

Change #7

Section 4.1.2, Other safety variables, bullets 3 and 5 (bolded text has been deleted)

- Changes in withdrawal symptoms using Clinical Institute Withdrawal Assessment-Benzodiazepines (CIWA-B) from the EO**T** Visit, to the end of Taper Period and to the end of the SFU Period (30 days after last PSL intake)
- Occurrence of a clinically-significant valvular or pericardial effusion **change** or other clinically-significant abnormalities as identified by 2-dimensional Doppler echocardiogram at each assessment by central reader

Has been changed to (new text bolded):

- Changes in withdrawal symptoms using Clinical Institute Withdrawal Assessment-Benzodiazepines (CIWA-B) from the EO**S** Visit, to the end of Taper Period and to the end of the SFU Period (30 days after last PSL intake)
- 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

Change #8

Section 4.2.1, Primary efficacy variable (bolded text has been deleted)

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

Has been changed to:

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.

Change #9

Section 4.2.2, Other efficacy variables (bolded text has been deleted)

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

Has been changed to (new text bolded):

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

Change #10

Section 5.1, Study description (bolded text has been deleted)

This is an 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).

At the Entry Visit (same day as the end of Conversion Period Visit in the parent study), subjects will sign a written Informed Consent form (ICF) prior to the conduct of any study-related procedure or pre-treatment assessments, and the subject's eligibility will be determined on the

basis of the inclusion/exclusion criteria by the Investigator. Eligible subjects must be educated to record all types of seizures that occur in their seizure diary and to complete their diary entries after each seizure or at least once a day. A caregiver is allowed to help the subject with the completion of the subject diary.

Evaluation Period

After the Entry Visit (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
- **Every 6 months from the beginning of Year 3 (see Section 5.1.1)**

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. Concomitant AED(s) may be tapered and discontinued to achieve PSL monotherapy, if clinically appropriate in which case the UCB Physician or delegate must be contacted to discuss with the Investigator. New concomitant AEDs, as allowed per protocol (see Section 7.8.1), may be introduced to optimize seizure control. 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 **after the 2-year Evaluation Period** or who discontinue early will return for an End-of-Study Visit or 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. **In case PSL becomes available** either **via** a Managed Access Program or **after a Marketing Authorization**, the Taper Period may be skipped and the subject**s** may continue treatment without tapering.

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 **performed** at approximately 1 month and 6 months after the last PSL intake.

Has been changed to (new text bolded):

This is an 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).

At the Entry Visit (same day as the end of Conversion Period Visit in the parent study), subjects will sign a written Informed Consent form (ICF) prior to the conduct of any study-related procedure or pre-treatment assessments, and the subject's eligibility will be determined on the basis of the inclusion/exclusion criteria by the Investigator. Eligible subjects must be educated to

record all types of seizures that occur in their seizure diary and to complete their diary entries after each seizure or at least once a day. A caregiver is allowed to help the subject with the completion of the subject diary.

Evaluation Period

After the Entry Visit (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. Concomitant AED(s) may be tapered and discontinued to achieve PSL monotherapy, if clinically appropriate in which case the UCB Physician or delegate must be contacted to discuss with the Investigator. New concomitant AEDs, as allowed per protocol (see Section 7.8.1), may be introduced to optimize seizure control. 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 Visit or 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. **If a subject transfers into** either a Managed Access Program or **another PSL study**, **or takes commercially available PSL,** the Taper Period may be skipped and the subject may continue treatment without tapering.

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**s** will be **required** at approximately 1 month and 6 months after the last PSL intake.

Change #11

Section 5.1.1, Study duration per subject, Paragraph 1 (bolded text has been deleted)

The total study duration per subject will be up to approximately 2 years **in countries where subjects can be transferred to a Managed Access Program. In countries where a Managed Access Program is inexistent, subjects may continue in EP0093 until a Marketing Authorization is granted by the health authority for the adjunctive treatment of focal-onset seizures in adults with drug-resistant epilepsy.**

Has been changed to (new text bolded):

The total study duration per subject will be up to approximately 2 years. **Subjects benefitting from the drug and willing to continue will either take commercial drug, if available, or will be transferred to a Managed Access Program or another PSL study, depending on local regulations.**

Change #12

Section 5.1.2, Planned number of subjects and sites (bolded text has been deleted)

It is estimated that approximately 1000 subjects will be included in approximately **1**50 sites worldwide.

Has been changed to (new text bolded):

It is estimated that approximately 1000 subjects will be included in approximately **3**50 sites worldwide. **Additional sites may be added if the study is extended to other regions or countries.**

Change #13

Section 5.1.3, Anticipated regions and countries (bolded text has been deleted)

The study will be conducted in North America, Europe, **and** Japan, with possible extension to other regions or countries.

Has been changed to (new text bolded):

The study will be conducted in North America, Europe, Japan**, and China** with possible extension to other regions or countries.

Change #14

Section 5.2, Table 5-1: Schedule of study assessments

Has been changed to:

The following changes have been made:

- Column with heading, "Visits every 6 M" in the Evaluation Period has been removed.
- The column for the EOT/EDV Visit was split into 2 columns, one for the EOT visit, which is now called the End of Study (EOS) Visit, and a second for the EDV Visit.
- The TSQM-9 was added to the table, and the abbreviation was defined under the table.
- An echocardiogram was added to the EOS Visit.
- The following footnotes have been removed:
  - Footnote b: The total duration per subject will be up to 2 years. In countries where allowed, subjects will be transferred to a Managed Access Program. In countries where a Managed Access Program is inexistent, subjects may continue in EP0093 until a Marketing Authorization is granted by any health authority for the adjunctive treatment of focal-seizure epilepsy in adults with drug-resistant epilepsy. If subjects participate in the study beyond the end of Year 2, subjects will return for clinic visits every 6 months.
  - Footnote q: For subject completing the study and continuing PSL treatment in case PSL becomes available either via a Managed Access Program or after Marketing Authorization.
- Footnote e (now footnote d) was revised as follows:

  From:

Questionnaires to be completed by all subjects prior to any other study procedures at the visit.

To (new text bolded):

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

- Footnote j (now footnote i) was revised as follows:

  From:

  Personal outcome assessments will be completed at Visit 6 (Month 6) and Visit 11 (Month 21).

  To:

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

- Footnote k (now footnote j) was revised as follows:

  From (bolded text has been deleted):

  An ECG at the SFU will be performed only if abnormal at **end of treatment** or **premature discontinuation v**isit. All ECG recordings will be performed with the subject resting in supine position for at least 5 minutes

  To (new text bolded):

  An ECG at the SFU will be performed only if abnormal at **the EOS** or **EDV V**isit. All ECG recordings will be performed with the subject resting in supine position for at least 5 minutes

- Footnote l (now footnote k) was revised as follows:

  From (bolded text has been deleted):

  An echocardiogram will also be performed 6 months after the subject's last PSL intake. A repeat echocardiogram will be performed for subjects with a new finding, Grade 2 severity (moderate), or Grade 3 severity (severe) (see Section 6.3).

  To (new text bolded):

  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) (see Section 6.3).

- Footnote p was added to PSL dispensing (IRT) at the EOS Visit:

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

- A new footnote q was added to Study termination at the EOS Visit:

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

- Footnote r was added to Study termination at the SFU Visit:

  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.

Change #15

Section 6.1, Inclusion Criteria, Inclusion Criterion 1 (bolded text has been deleted)

1. An Institutional Review Board (IRB)/Independent Ethics Committee (IEC) approved written ICF is signed and dated by the subject or by the parent(s) or legal representative where **applicable**. The ICF or a specific Assent form, where required, will be signed and dated by minors, according to country-specific regulations.

Has been changed to (new text bolded):

1. An Institutional Review Board (IRB)/Independent Ethics Committee (IEC) approved written ICF is signed and dated by the subject or by the parent(s) or legal representative **(**where **legally permitted)**. The ICF or a specific Assent form, where required, will be signed and dated by minors, according to country-specific regulations.

Change #16

Section 6.1, Inclusion Criteria, Inclusion Criterion 2

2. Subject/legal representative/caregiver is considered reliable and capable of adhering to the protocol (eg, able to understand and complete diaries), visit schedule, or medication intake according to the judgment of the Investigator.

Has been changed to (new text bolded):

2. Subject/legal representative/caregiver **(where legally permitted)** is considered reliable and capable of adhering to the protocol (eg, able to understand and complete diaries), visit schedule, or medication intake according to the judgment of the Investigator.

Change #17

Section 6.3, Withdrawal criteria, Withdrawal criterion 8

8. Subjects with an echocardiogram showing a Grade 2 finding (moderate regurgitation) if accompanied with moderate to severe signs/symptoms or a Grade 3 finding (severe regurgitation) will be discontinued from the study regardless of accompanying clinical symptoms, and should begin discontinuation of PSL. Additionally, a jump of 2 grades from Grade 0 to Grade 2 (moderate regurgitation) accompanied with moderate to severe symptoms or from Grade 1 to Grade 3 (severe regurgitation) will result in subject discontinuation (see Section 6.3.2).

Has been changed to (new text bolded):

8. Subjects with an echocardiogram showing a Grade 2 finding (moderate regurgitation/**stenosis**) if accompanied with moderate to severe signs/symptoms or a Grade 3 finding (severe regurgitation/**stenosis**) will be discontinued from the study regardless of accompanying clinical symptoms, and should begin discontinuation of PSL. Additionally, a jump of 2 grades

from Grade 0 to Grade 2 (moderate regurgitation/**stenosis**) accompanied with moderate to severe symptoms or from Grade 1 to Grade 3 (severe regurgitation/**stenosis**) will result in subject discontinuation (see Section 6.3.2).

Change #18

Section 6.3.2, Table 6-1: Valvular abnormality grading criteria

Table 6-1: Valvular abnormality grading criteria

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

[a] New York Heart Association Classification of symptoms; for other echocardiogram measurements, see the Echocardiogram Manual.

Has been changed to (new text bolded):

Table 6-1: Valvular abnormality grading criteria

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

[a] New York Heart Association Classification of symptoms; for other echocardiogram measurements, see the Echocardiogram Manual.

Change #19

Section 6.3.2, Echocardiogram valvular abnormalities assessments, text below Table 6-1 (bolded text has been deleted)

Echocardiograms will be obtained every 3 months and will be repeated sooner if new or worsening abnormalities are present (detailed below). Echocardiograms will be **interpreted** at the site by the local **cardiologist** and then provided to the central reader where all study echocardiograms will be centrally read and interpreted. When local reads warrant, central reads will be expedited. An expedited review of an echocardiogram should be performed if the following conditions are met: (1) a Grade 2 of moderate severity, accompanied by moderate or

severe signs/symptoms; (2) a Grade 3 finding of severe severity (with or without accompanying symptoms; or (3) an increase (or jump) in 2 grades (0 to 2 or 1 to 3) between echocardiograms. When any of these findings are observed, the Investigator/site should initiate an expedited review from the central reader.

Subjects with Grade 0 or 1 (absent or mild symptoms) will not undergo any additional procedures, other than continued monitoring for any symptomatic clinical events (as listed in Table 6-1).

Subjects with an echocardiogram showing a Grade 2 finding (moderate regurgitation) will undergo a repeat echocardiogram within 1 month (unscheduled visit) to confirm the finding. For a Grade 2 echocardiogram of moderate severity, a decision to discontinue is based on the severity of clinical signs/symptoms; if accompanied with moderate to severe signs/symptoms this would result in subject discontinuation. Investigators may contact the Medical Monitor if they wish to discuss the subject's clinical signs/symptoms.

Subjects with an echocardiogram showing a Grade 3 finding (severe regurgitation) will undergo a repeat echocardiogram within 2 weeks (unscheduled visit) to confirm the finding. For a Grade 3 echocardiogram with a severe severity, the subject should be discontinued from the study regardless of accompanying clinical signs/symptoms and should begin discontinuation of PSL.

Any subject that shows an increase in 2 grades levels (Grade 0 to 2 or Grade 1 to 3) will undergo a repeat echocardiogram within 2 weeks (unscheduled visit) to confirm the finding. A jump of 2 grades to Grade 2 (moderate) accompanied with moderate to severe symptoms will result in subject discontinuation. If the clinical symptoms are mild, the subject is not required to discontinue. Investigators may contact the Medical Monitor if they wish to discuss the subject's clinical signs/symptoms. However, a jump of 2 grades to Grade 3 (severe) will result in subject discontinuation with/without and signs/symptoms.

Regulatory authorities will be notified of any **discontinuations**.

Has been changed to (new text bolded):

Echocardiograms will be obtained every 3 months and will be repeated sooner if new or worsening abnormalities are present (detailed below). Echocardiograms will be **examined** at the site by the local **physician** and then provided to the central reader where all study echocardiograms will be centrally read and interpreted **by a cardiologist**. When local reads warrant, central reads will be expedited. An expedited review of an echocardiogram should be performed if the following conditions are met: (1) a Grade 2 **finding** of moderate severity, accompanied by moderate or severe signs/symptoms; (2) a Grade 3 finding of severe severity (with or without accompanying symptoms; or (3) an increase (or jump) in 2 grades (0 to 2 or 1 to 3) between echocardiograms. When any of these findings are observed, the Investigator/site should initiate an expedited review from the central reader.

Subjects with Grade 0 or 1 (absent or mild symptoms) will not undergo any additional procedures, other than continued monitoring for any symptomatic clinical events (as listed in Table 6-1.

Subjects with an echocardiogram showing a Grade 2 finding (moderate regurgitation/**stenosis**) will undergo a repeat echocardiogram within 1 month (unscheduled visit) to confirm the finding. For a Grade 2 echocardiogram of moderate severity, a decision to discontinue is based on the severity of clinical signs/symptoms; if accompanied with moderate to severe signs/symptoms this would result in subject discontinuation. Investigators may contact the Medical Monitor if they wish to discuss the subject's clinical signs/symptoms.

Subjects with an echocardiogram showing a Grade 3 finding (severe regurgitation/**stenosis**) will undergo a repeat echocardiogram within 2 weeks (unscheduled visit) to confirm the finding. For a Grade 3 echocardiogram with a severe severity, the subject should be discontinued from the study regardless of accompanying clinical signs/symptoms and should begin discontinuation of PSL.

Any subject that shows an increase in 2 grades levels (Grade 0 to 2 or Grade 1 to 3) will undergo a repeat echocardiogram within 2 weeks (unscheduled visit) to confirm the finding. A jump of 2 grades to Grade 2 (moderate) accompanied with moderate to severe symptoms will result in subject discontinuation. If the clinical symptoms are mild, the subject is not required to discontinue. Investigators may contact the Medical Monitor if they wish to discuss the subject's clinical signs/symptoms. However, a jump of 2 grades to Grade 3 (severe) will result in subject discontinuation with/without and signs/symptoms.

Regulatory authorities will be notified of any **subject who is discontinued due to an abnormal echocardiogram**.

Change #20

Section 7.8.2, Prohibited concomitant treatments (medications and therapies) (bolded text has been deleted)

The following concomitant medications are prohibited during the study:

- **Benzodiazepines (**GABA-A-ergic drugs **be it** agonists **[**ie, barbiturates**]** or receptor positive allosteric modulators **[**ie, benzodiazepines or nonbenzodiazepines like zolpidem**]**) taken >3 times per week. **B**enzodiazepines with an indication for epileptic seizures **like clonazepam or clobazam are** not allowed **as concomitant drugs**.
- Strong CYP3A4 inhibitors/inducers: AEDs including carbamazepine, phenytoin, phenobarbital, primidone (for more details refer to Table 3-2 and Table 3-3 in FDA Drug Development Resources, Drug development and drug interactions: Table of substrates, inhibitor and inducers).

  Non-AED strong CYP3A4 enzyme inducers/inhibitors (ie, prescription drugs, nonprescription drugs, medical cannabis, cannabidiol, dietary [eg, grapefruit or passion fruit].
- Strong CYP2C19 strong sensitive substrates/inhibitors/inducers including S-mephenytoin, omeprazole, fluconazole, fluoxetine, fluvoxamine, ticlopidine, rifampin, ritonavir] (for more details refer to Table 3-1, Table 3-2, and Table 3-3 in FDA Drug Development Resources, Drug development and drug interactions: Table of substrates, inhibitor and inducers).

Has been changed to (new text bolded):

The following concomitant medications are prohibited during the study:

- GABA-A-ergic drugs: **including** agonists (ie, barbiturates) or receptor positive allosteric modulators (ie, benzodiazepines or nonbenzodiazepines like zolpidem) taken >3 times per week. **Regular intake of** benzodiazepines with an indication for epileptic seizures is not allowed. **However, PRN intake of GABA-A-ergic drugs <3 times per week is allowed, ie, for emergencies.**
- Strong CYP3A4 inhibitors/inducers (for more details refer to Table 3-2 and Table 3-3 in FDA Drug Development Resources, Drug development and drug interactions: Table of substrates, inhibitor and inducers).
  - AEDs including carbamazepine, phenytoin, phenobarbital, and primidone
  - Non-AED strong CYP3A4 enzyme inducers/inhibitors (ie, prescription drugs, nonprescription drugs, medical cannabis, cannabidiol, dietary [eg, grapefruit or passion fruit].
- Strong CYP2C19 strong sensitive substrates/inhibitors/inducers including S-mephenytoin, omeprazole, fluconazole, fluoxetine, fluvoxamine, ticlopidine, rifampin, ritonavir] (for more details refer to Table 3-1, Table 3-2, and Table 3-3 in FDA Drug Development Resources, Drug development and drug interactions: Table of substrates, inhibitor and inducers).

Change #21

Section 8.1.7, Visit 12 and every 6 months thereafter (± 1 week)

Has been changed to:

This visit was deleted.

Change #22

Section 8.1.8, Early Discontinuation Visit or End of Treatment (bolded text has been deleted)

Section **8.1.8** Early Discontinuation Visit **or End of Treatment**

The following procedures will be performed by all subjects discontinuing the study **or completing it**:

- Verify withdrawal criteria
- Obtain C-SSRS data since the last visit
- Obtain HADS data
- Obtain QOLIE-31-P data
- Obtain SSG
- Obtain CIWA-B data **(in case of discontinuation of PSL treatment)**
- Measure vital signs (pulse rate, systolic BP, diastolic BP, and respiratory rate), in supine position after 5 minutes of rest

- Measure body weight
- Perform brief physical examination (refer to Section 9.3.4 for details)
- Perform brief neurological examination (refer to Section 9.3.5 for details)
- Perform Psychiatric and Mental Status assessment
- Obtain 12-lead ECG
- Collect blood and urine samples for clinical laboratory analyses
- Perform urine pregnancy test (female subjects of childbearing potential only)
- Seizure evaluation (count and type) from subject's daily record card
- Record concomitant medication and procedures
- Record AEs
- Record health-related outcomes and HRU (refer to Section 10.5 for details)
- **Dispense PSL unless PSL becomes available either via a Managed Access Program or after Marketing Authorization)**
- Check PSL accountability
- **Study termination (for subjects completing the study and continuing PSL treatment)**

Has been changed to (new text bolded):

Section **8.1.7** Early Discontinuation Visit

The following procedures will be performed by all subjects discontinuing the study **early**:

- Verify withdrawal criteria
- **Obtain TSQM-9**
- Obtain C-SSRS data since the last visit
- Obtain HADS data
- Obtain QOLIE-31-P data
- Obtain SSG
- Obtain CIWA-B data
- Measure vital signs (pulse rate, systolic BP, diastolic BP, and respiratory rate), in supine position after 5 minutes of rest
- Measure body weight
- Perform brief physical examination (refer to Section 9.3.4 for details)
- Perform brief neurological examination (refer to Section 9.3.5 for details)
- Perform Psychiatric and Mental Status assessment
- Obtain 12-lead ECG

- Collect blood and urine samples for clinical laboratory analyses
- Perform urine pregnancy test (female subjects of childbearing potential only)
- Seizure evaluation (count and type) from subject's daily record card
- Record concomitant medication and procedures
- Record AEs
- Record health-related outcomes and HRU (refer to Section 10.5 for details)
- **Dispense PSL to those subjects requiring a Taper Period**
- Check PSL accountability

Change #23

Section 8.1.8, End of Study Visit

This is a new section.

Has been changed to (new text bolded):

Section 8.1.8 End of Study Visit

The following procedures will be performed by all subjects completing the study:

- **Obtain TSQM-9**
- **Obtain C-SSRS data since the last visit**
- **Obtain HADS data**
- **Obtain QOLIE-31-P data**
- **Obtain SSG**
- **Obtain CIWA-B data (in case of discontinuation of PSL treatment)**
- **Measure vital signs (pulse rate, systolic BP, diastolic BP, and respiratory rate), in supine position after 5 minutes of rest**
- **Measure body weight**
- **Perform brief physical examination (refer to Section 9.3.4 for details)**
- **Perform brief neurological examination (refer to Section 9.3.5 for details)**
- **Perform Psychiatric and Mental Status assessment**
- **Obtain 12-lead ECG**
- **Obtain echocardiogram if required. 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.**
- **Collect blood and urine samples for clinical laboratory analyses**
- **Perform urine pregnancy test (female subjects of childbearing potential only)**

- **Seizure evaluation (count and type) from subject's daily record card**
- **Record concomitant medication and procedures**
- **Record AEs**
- **Record health-related outcomes and HRU (refer to Section 10.5 for details)**
- **Dispense PSL to those subjects requiring a Taper Period**
- **Check PSL accountability**
- **Study termination (for subjects completing the study and continuing PSL treatment)**

Change #24

Section 9.2, Laboratory measurements

Laboratory assessments will be conducted using standard methods at a central laboratory. The central laboratory will provide the Investigator with dedicated, standardized sampling equipment (labels, needles, tubes), and a study-specific Laboratory Manual, which will explain how to use the equipment and how to ship the samples to the central laboratory. The laboratory parameters measured are presented in Table 9-2.

The total blood volume drawn for clinical laboratory assessments per subject will be a maximum of 7mL by sampling, which includes 2mL for hematology and 5mL for blood chemistry.

Table 9–6: 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)
MCHC	Chloride	
MCV	Creatinine	
Monocytes	Glucose	
Neutrophils	HDL	
Platelet count	LDH	
RBC count	LDL	
WBC count	Magnesium	
	Potassium	
	Sodium	
	Total bilirubin	
	Total cholesterol	

ALP=alkaline phosphatase; ALT=alanine aminotransferase; AST=aspartate aminotransferase; BUN=blood urea nitrogen; HDL=high-density lipoprotein; 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

In addition, for females of childbearing potential, a urine pregnancy test (beta-human chorionic gonadotropin) will be performed at the scheduled time points presented in Table 5-1.

Has been changed to (new text bolded):

Laboratory assessments will be conducted using standard methods at a central laboratory. The central laboratory will provide the Investigator with dedicated, standardized sampling equipment (labels, needles, tubes), and a study-specific Laboratory Manual, which will explain how to use the equipment and how to ship the samples to the central laboratory. The laboratory parameters measured are presented in Table 9-2.

The total blood volume drawn for clinical laboratory assessments per subject will be a maximum of 7mL by sampling, which includes 2mL for hematology and 5mL for blood chemistry.

Table 9–7: 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; **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 to postmenopausal women**

In addition, for females of childbearing potential, a urine pregnancy test (beta-human chorionic gonadotropin) will be performed at the scheduled time points presented in Table 5-1. **If pregnancy is suspected at any time during the study, an interim test should be performed.**

Change #25

Section 9.3.2, Electrocardiograms, Paragraph 3 (bolded text has been deleted)

The Investigator should review all ECG recordings and determine if there are any abnormalities that are considered clinically significant for a particular subject. The ECGs will also be sent to a specified central reader for review as detailed in the ECG Manual. **The ECGs will also be sent to a central reader for review as detailed in the ECG manual.** The following ECG parameters will be recorded: heart rate, PR-interval, QRS-duration, QT-interval, QTcB or QTcF, and Investigator's conclusion on ECG profile.

Has been changed to:

The Investigator should review all ECG recordings and determine if there are any abnormalities that are considered clinically significant for a particular subject. The ECGs will also be sent to a specified central reader for review as detailed in the ECG Manual. The following ECG parameters will be recorded: heart rate, PR-interval, QRS-duration, QT-interval, QTcB or QTcF, and Investigator's conclusion on ECG profile.

Change #26

Section 9.3.3, Echocardiograms (bolded text has been deleted)

Echocardiograms will be performed at the scheduled time points presented in Table 5-1. The echocardiogram will be repeated at 6 months (±1 month) after the last PSL intake to assess any abnormalities that may have newly occurred or worsened after the last dose.

Two-dimensional Doppler echocardiography will **be performed with**:

1. **Diastolic measurements (mitral forward flow E and A waves and deceleration time)**
2. **Tissue Doppler on medial and lateral mitral valve annulus (S, E, and A waves)**
3. **Standardized views for left atrial volume measurements**

In the event echocardiograms are not interpretable by transthoracic echocardiography during the study, alternative assessments should be done using either transesophageal echocardiography or cardiac magnetic resonance imaging in these particular instances.

Echocardiograms should be acquired by a qualified technician. The echocardiograms will be **interpreted locally** by **a qualified cardiologist who should also determine the clinical significance of any abnormality**. Echocardiograms will also be sent to a central **reader** for review as detailed in the Echocardiography Manual.

A repeat echocardiogram will be performed for subjects with a new finding or Grade 2 severity (moderate) or Grade 3 severity (severe).

Subjects with an echocardiogram showing an abnormality meeting the withdrawal criteria (see Section 6.3) are to be discontinued from the study. An expedited review of an echocardiogram (at the central reader) should be requested if the following conditions are met: (1) a Grade 2 of moderate severity, accompanied by moderate or severe signs/symptoms; (2) a Grade 3 finding of severe severity (with or without accompanying symptoms); or (3) **a deterioration** in 2 Grades (0 to 2 or 1 to 3) between echocardiograms. When any of these conditions are met, the Investigator/site should initiate an expedited review from the central reader (see Echocardiography Manual). Regulatory authorities will be notified of any discontinuations.

In case of discontinuation, the subject should return for an EDV and SFU Visit including an echocardiogram within approximately 1 month after last PSL intake. The corresponding TEAEs should be followed up until they have resolved, have a stable sequelae, or the subject is lost to follow up.

Has been changed to (new text bolded):

Echocardiograms will be performed at the scheduled time points presented in Table 5-1. The echocardiogram will be repeated at 6 months (±1 month) after the last PSL intake to assess any abnormalities that may have newly occurred or worsened after the last dose.

Two-dimensional Doppler echocardiography will **include the following measurements/observations:**

- **Epicardial Abnormalities**
  - **Functional measurements**
  - **Diastology (ie, Mitral Valve E/A waves, etc.)**
  - **Systolic (ie, Left Ventricular Ejection Fraction, LVEF, etc.)**
- **Epicardial Effusion**
  - **Amount of effusion**
  - **Pericardial thickness**
- **Valvular Abnormalities**
  - **Measurement of valve regurgitation/stenosis**
  - **Measurement of left atrial volume**

For subjects whose echocardiograms are not interpretable by transthoracic echocardiography during the study, alternative assessments should be done using either transesophageal echocardiography or cardiac magnetic resonance imaging in these particular instances.

Echocardiograms should be acquired by a qualified technician. The echocardiograms will be **examined** by **the local physician**. Echocardiograms will also be sent to a central **cardiologist** for review as detailed in the Echocardiography Manual.

A repeat echocardiogram will be performed for subjects with a new finding or Grade 2 severity (moderate) or Grade 3 severity (severe).

Subjects with an echocardiogram showing an abnormality meeting the withdrawal criteria (see Section 6.3) are to be discontinued from the study. An expedited review of an echocardiogram (at the central reader) should be requested if the following conditions are met: (1) a Grade 2 **finding** of moderate severity, accompanied by moderate or severe signs/symptoms; (2) a Grade 3 finding of severe severity (with or without accompanying symptoms); or (3) **an increase (jump)** in 2 Grades (0 to 2 or 1 to 3) between echocardiograms. When any of these conditions are met, the Investigator/site should initiate an expedited review from the central reader (see Echocardiography Manual). Regulatory authorities will be notified of any discontinuations.

In case of discontinuation, the subject should return for an EDV and SFU Visit including an echocardiogram within approximately 1 month after last PSL intake **and should also return for a 6-month echocardiogram.** The corresponding TEAEs **occurring before the SFU echocardiogram visit** should be followed up until they have resolved, have stable sequelae, or the subject is lost to follow up. **During the 6-month echocardiogram period, Investigators**

will report any SAEs through the UCB SAE reporting process until the final echocardiogram is obtained.

Change #27

Section 10.2, Quality of Life Inventory in Epilepsy-31-P, Paragraph 4 (bolded text has been deleted)

The QOLIE-31-P will be completed according to the tabular schedule of study procedures in Section 5.1. At the very beginning of the visit, the QOLIE-31-P will be provided to all subjects. **The** subject **will be asked to** complete the questionnaire on his/her own. Once completed, the subject will return the completed questionnaire to the Investigator or designee, who will verify that all questions have been answered. Further details about the QOLIE-31-P will be covered in the Study Manual.

Has been changed to (new text bolded):

The QOLIE-31-P will be completed according to the tabular schedule of study procedures in Section 5.1. At the very beginning of the visit, the QOLIE-31-P will be provided to all subjects. **It is preferred that the** subject complete the questionnaire on his/her own; **however, assistance may be provided by the study staff or caregiver if needed**. Once completed, the subject will return the completed questionnaire to the Investigator or designee, who will verify that all questions have been answered. Further details about the QOLIE-31-P will be covered in the Study Manual.

Change #28

Section 10.3, Seizure Severity Global Item, Paragraph 2 (bolded text has been deleted)

The SSG will be completed according to the tabular schedule of study procedures in Table 5.1. At the very beginning of the visit, the SSG will be provided to all subjects. **The** subject **will be asked** to complete the questionnaire on his/her own. Once completed, the subject will return the completed questionnaire to the Investigator or designee, who will verify that all questions have been answered. Further details about the SSG will be covered in the Study Manual.

Has been changed to (new text bolded):

The SSG will be completed according to the tabular schedule of study procedures in Table 5-1. At the very beginning of the visit, the SSG will be provided to all subjects. **It is preferred that the** subject complete the questionnaire on his/her own**; however, assistance may be provided by either the study staff or caregiver if needed**. Once completed, the subject will return the completed questionnaire to the Investigator or designee, who will verify that all questions have been answered. Further details about the SSG will be covered in the Study Manual.

Change #29

Section 10.4, Hospital Anxiety and Depression Scale

The HADS was chosen for its well-established psychometric properties both in general population and more recently in patients with epilepsy (Lin et al, 2017; Wiglush et al, 2016; de Oliviera 2014). The HADS scores for anxiety and for depression range from 0 to 21 with higher scores indicating worse state. A score below 8 is considered to be normal (Zigmond and Snaith, 1983).

Has been changed to (new text bolded):

The HADS was chosen for its well-established psychometric properties both in general population and more recently in patients with epilepsy (Lin et al, 2017; Wiglush et al, 2016; de Oliviera 2014). The HADS scores for anxiety and for depression range from 0 to 21 with higher scores indicating worse state. A score below 8 is considered to be normal (Zigmond and Snaith, 1983**). It is preferred that the subject complete the questionnaire on his/her own; however, assistance may be provided by either the study staff or caregiver if needed.**

Change #30

Section 10.6, Treatment Satisfaction

Has been changed to (new section added):

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). The estimated completion time for this questionnaire is less than 5 minutes. Scores range from 0 (worst) to 100 (best).

The TSQM-9 will be completed according to the tabular schedule of assessments (Table 5-1). At the very beginning of the visit, the TSQM-9 will be provided to all subjects. It is preferred that the subject complete the questionnaire on his/her own; however, assistance may be provided by either the study staff or caregiver if needed. Once completed, the subject will return the completed questionnaire to the Investigator or designee, who will verify that all questions have been answered.

Change #31

Section 12.4.1, Analysis of the primary efficacy variable, Paragraph 1 (bolded text has been deleted)

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

Has been changed to:

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.

Change #32

Section 12.4.2, Analysis of the other efficacy variables (bolded text has been deleted)

The following efficacy variables will be summarized with descriptive statistics:

- Observable focal-onset seizure frequency per 28 days by 3-month intervals over the Evaluation Period; the median will be considered as the key statistic

- Observable focal-onset seizure frequency per 28 days by seizure type and by 3-month intervals over the Evaluation Period; the median will be considered as the key statistic
- The 50%, 75%, and 90% RR **status** by 3-month intervals or 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 observable focal-onset seizure frequency relative to the Baseline Period in the parent study.
- The 50%, 75%, and 90% RR **status** by 3-month intervals for focal-onset (Type I) seizures 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
- Change from Baseline from parent study in the Seizure Severity Global Item (SSG) scores at each assessment
- Changes from Baseline from parent study in QOLIE-31-P scores at each assessment
- Changes from Baseline from parent study in HADS scores at each assessment
- 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 EO**T**)
- Use of Health-related outcomes and HRU, including healthcare provider consultations not foreseen by protocol, caregiver support, concurrent medical procedures, concomitant medications and hospitalizations

Has been changed to (new text bolded):

The following efficacy variables will be summarized with descriptive statistics:

- Observable focal-onset seizure frequency per 28 days by 3-month intervals over the Evaluation Period; the median will be considered as the key statistic
- Observable focal-onset seizure frequency per 28 days by seizure type and by 3-month intervals over the Evaluation Period; the median will be considered as the key statistic
- The 50%, 75%, and 90% RR by 3-month intervals or 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 observable focal-onset seizure frequency relative to the Baseline Period in the parent study.
- The 50%, 75%, and 90% RR by 3-month intervals for focal-onset (Type I) seizures 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

- Change from Baseline from parent study in the Seizure Severity Global Item (SSG) scores at each assessment
- Changes from Baseline from parent study in QOLIE-31-P scores at each assessment
- Changes from Baseline from parent study in HADS scores at each assessment
- 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 EO**S**)
- Use of Health-related outcomes and HRU, including healthcare provider consultations not foreseen by protocol, caregiver support, concurrent medical procedures, concomitant medications and hospitalizations

Change #33

Section 12.7, Planned interim analysis and data monitoring

A DMC will systematically monitor and report on the progress, safety, and/or critical efficacy endpoints of this study by convening to review the ongoing program safety and efficacy data. This includes evaluating the safety signals and benefit-risk ratio for the study subjects in relationship to new data relevant for PSL efficacy and safety.

A DMC Charter will define the composition, roles, and responsibilities of the DMC, specify the data to be reviewed and the periodicity of data review, and determine the procedures to be followed.

Has been changed to (new text bolded):

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 DMC will systematically monitor and report on the progress, safety, and/or critical efficacy endpoints of this study by convening to review the ongoing program safety and efficacy data. This includes evaluating the safety signals and benefit-risk ratio for the study subjects in relationship to new data relevant for PSL efficacy and safety.

A DMC Charter will define the composition, roles, and responsibilities of the DMC, specify the data to be reviewed and the periodicity of data review, and determine the procedures to be followed.

Change #34

Section 15, References

Has been changed to (new text bolded):

The following 2 references have been added:

Atkinson MJ, Sinha A, Hass SL, Colman SS, Kumar RN, Brod M, et al. Validation of a general measure of treatment satisfaction, the Treatment Satisfaction Questionnaire for Medication (TSQM), using a national panel study of chronic disease. Health Qual Life Outcomes. 2004;2:12.

Bharmal M, Payne K, Atkinson MJ, Desrosiers MP, Morisky DE, Gemmen E. Validation of an abbreviated Treatment Satisfaction Questionnaire for Medication (TSQM-9) among patients on antihypertensive medications. Health Qual Life Outcomes. 2009;7:36.

16.2 Protocol Amendment 2.0

Rationale for the amendment

The primary rationale for this global amendment is to update the name of the legal form of the Sponsor, UCB Biopharma. Belgium has recently adopted a new Code of Companies and Associations, resulting in a mandatory change of the name of the legal form of the entity "*société privée à responsabilité limitée*", abbreviated "*SPRL*", to "*société à responsabilité limitée*", abbreviated "*SRL*". This change does not involve any change to the legal form itself, and the company name, company number and VAT number of UCB Biopharma remain the same.

A benefit risk assessment in order to comply with Section 6 of the ICH-GCP. This summary has been revised as part of the most recent Investigator's Brochure update and is now included in this global protocol amendment.

The detailed dosage of 400mg/day as staring dose was deleted to allow more flexibility when adding further parent studies. The starting dose is defined as the dose at the end of the parent study.

Modifications and changes

Specific changes

Change #1

Sponsor name on the title page and in the study contact information (bolded text revised)

Sponsor

UCB Biopharma **SPRL**
Allée de la Recherche 60
1070 Brussels
BELGIUM

Has been changed to (new text bolded):

Sponsor

UCB Biopharma **SRL**
Allée de la Recherche 60
1070 Brussels
BELGIUM

Change #2

Sponsor Contact Information (bolded text has been revised)

Sponsor Study Physician

Name:	[redacted] **MD PhD**
Address:	UCB Biosciences GmbH Alfred Nobel Strasse, 10 40789 Monheim am Rhein, Germany
Phone:	[redacted]

Clinical Project Manager

Name:	[redacted]
Address:	UCB Biosciences GmbH Alfred Nobel Strasse, 10 40789 Monheim am Rhein, Germany
Phone:	[redacted]

Clinical Trial Biostatistician

Name:	[redacted]
Address:	**UCB Pharma Ltd** **280 Bath Road** **Berkshire SL1 3WE Slough,** **UK**
Phone:	[redacted]

Has been changed to:

Sponsor Study Physician

Name:	[redacted] **MD PhD**
Address:	UCB Biosciences GmbH Alfred Nobel Strasse, 10 40789 Monheim am Rhein, Germany
Phone:	[redacted]

Clinical Project Manager

Name:	[redacted]
Address:	UCB Biosciences GmbH Alfred Nobel Strasse, 10 40789 Monheim am Rhein, Germany
Phone:	[redacted]

Clinical Trial Biostatistician

Name:	[redacted]
Address:	**UCB BIOSCIENCES, Inc** **810 Arco Corporate Drive** **Raleigh, NC 27617** **United States**
Phone:	[redacted]

Change #3

Summary, second to last paragraph

The total duration of the study per subject will be up to 2 years. Subjects benefitting from the drug and willing to continue 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 (bolded text has been added):

The total duration of the study per subject will be up to **approximately** 2 years. Subjects benefitting from the drug and willing to continue will either take commercial drug, if available, or will be transferred to a Managed Access Program or another PSL study, depending on local regulations.

Change #4

Section 2.5, Benefit Risk Assessment

This section has been added. The section number of the following section, Rationale for this study, has been increased from 2.5 to 2.6.

Change #5

Section 5.3, Rationale for study design and selection of dose, bolded text deleted or revised

EP0093 will assess the long-term safety, tolerability, and efficacy of PSL as an adjunctive treatment for focal-onset seizures in adult subjects with drug-resistant epilepsy.

This OLE study will provide subjects, who participated in previous PSL studies, the opportunity to have continued access to PSL.

The individual starting dose of each subject will be the one recommended at the end of the parent study **(400mg/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 suggesting that it will provide full occupancy at the SV2A binding site while maintaining some minimal binding to the GABA-A binding site. For subjects previously on placebo in the parent study, a full SV2A occupancy is desirable to obtain a meaningful anticonvulsive effect while the minimal benzodiazepine binding more likely will make a better tolerance to GABA-related central nervous system toxicity. On the other hand, participants exposed to a high maintenance dose of PSL in the parent study (800mg/day), **the** target transition dose of 400mg/day will likely maintain the full SV2A-related effect while not entirely eliminating GABA-binding related effects. 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).

Has been changed to (bolded text has been added):

EP0093 will assess the long-term safety, tolerability, and efficacy of PSL as an adjunctive treatment for focal-onset seizures in adult subjects with drug-resistant epilepsy.

This OLE study will provide subjects, who participated in previous PSL studies, the opportunity to have continued access to PSL.

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

This entry dose level was selected considering benefit-risk and is based on clinical pharmacology and positron emission tomography data in healthy human subjects suggesting that it will provide full occupancy at the SV2A binding site while maintaining some minimal binding to the GABA-A binding site. For subjects previously on placebo in the parent study, a full SV2A occupancy is desirable to obtain a meaningful anticonvulsive effect while the minimal benzodiazepine binding more likely will make a better tolerance to GABA-related central nervous system toxicity. On the other hand, participants exposed to a high maintenance dose of PSL in the parent study (800mg/day), **a** target transition dose of 400mg/day will likely maintain the full SV2A-related effect while not entirely eliminating GABA-binding related effects. 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).

Change #6

Section 7.2, Treatments to be administered (bolded text has been deleted)

Padsevonil will be administered in an open-label manner. All subjects will be instructed to take 2 doses approximately 12 hours apart each day 30 minutes after food when practically feasible. The individual starting dose of each subject will be the one at the end of the parent study **(400mg/day)**. The first dose of the study will be the dose on the day of Visit 1. Once subjects enter EP0093 further individual dose adjustments are allowed after 1 week, between 100mg/day up to a maximum of 800mg/day to the extent possible with the 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. Twice daily dosing with equivalent morning and evening doses approximately 12 hours apart is deemed necessary to ensure more regular exposure over the 24-hour interval; however, the dosing schedule may be adjusted as needed to improve tolerability and efficacy. The decision to advise subjects to divide their morning and evening daily dose unequally should be documented in the eCRF and the UCB Study Physician or delegate should be notified. Increases or decreases to the dose of PSL should not exceed a maximum 200mg/day per week. A faster/slower decrease/increase of the dose than 200mg/day per week is allowed in case of emergency in the Investigator's medical judgment.

Has been changed to:

Padsevonil will be administered in an open-label manner. All subjects will be instructed to take 2 doses approximately 12 hours apart each day 30 minutes after food when practically feasible. The individual starting dose of each subject will be the one at the end of the parent study. The first dose of the study will be the dose on the day of Visit 1. Once subjects enter EP0093 further individual dose adjustments are allowed after 1 week, between 100mg/day up to a maximum of 800mg/day to the extent possible with the 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. Twice daily dosing with equivalent morning and evening doses approximately 12 hours apart is deemed necessary to ensure more regular exposure over the 24-hour interval; however, the dosing schedule may be adjusted as needed to improve tolerability and efficacy. The decision to advise subjects to divide their morning and evening daily dose unequally should be documented in the eCRF and the UCB Study Physician or delegate should be notified. Increases or decreases to the dose of PSL should not exceed a maximum 200mg/day per week. A faster/slower decrease/increase of the dose than 200mg/day per week is allowed in case of emergency in the Investigator's medical judgment.

Change #7

Section 7.5, Handling and storage requirements, Paragraph 3 (bolded text has been deleted)

In case an out-of-range temperature is noted, it must be immediately reported as per instructions in the **investigational medicinal product (**IMP**)** Handling Manual.

Has been changed to:

In case an out-of-range temperature is noted, it must be immediately reported as per instructions in the IMP Handling Manual.

Change #8

Section 7.8.1, Permitted concomitant treatments (medications and therapies),

Concomitant AEDs and AED dose(s), or settings for vagus nerve stimulation or other neurostimulation device for epilepsy may be adjusted throughout the study as per the Investigator’s clinical judgment based on tolerability and seizure control for each individual subject.

Tapering of all concomitant AED(s) to achieve PSL monotherapy, if clinically appropriate, should only be made in agreement with Study Physician and Sponsor.

New concomitant AEDs may be introduced to optimize tolerability and seizure reduction with the following restrictions:

- Vigabatrin, retigabine, and felbamate are allowed and count as add-on AEDs
  - if taken for more than 2, 1, and 4 years respectively prior to Visit 1 in parent PSL study and, if requirements mentioned in the relevant Exclusion Criteria pertaining to vigabatrin, retigabine, and felbamate in parent PSL study were met.

Has been changed to (bolded text has been added):

- Vigabatrin, retigabine, and felbamate are allowed and count as add-on AEDs
  - if taken for more than 2, 1, and 4 years respectively prior to Visit 1 in parent PSL study and, if requirements mentioned in the relevant Exclusion Criteria pertaining to vigabatrin, retigabine, and felbamate in parent PSL study were met.

    Although omeprazole is classified as a sensitive substrate, high doses of omeprazole have been well tolerated, and adjustment of the omeprazole dose is not generally required except with severe hepatic impairment and if long-term treatment is indicated. Therefore, omeprazole is permitted (see omeprazole prescribing information).

Change #9

Section 7.8.2, Prohibited concomitant treatments (medications and therapies) (bolded text has been deleted)

The following concomitant medications are prohibited during the study:

- GABA-A-ergic drugs: including agonists (ie, barbiturates) or receptor positive allosteric modulators (ie, benzodiazepines or nonbenzodiazepines like zolpidem) taken >3 times **per week**. Regular intake of benzodiazepines with an indication for epileptic seizures is not allowed. However, PRN intake of GABA-A-ergic drugs <3 times per week is allowed, ie, for emergencies.
- Strong CYP3A4 inhibitors/inducers (for more details refer to Table 3-2 and Table 3-3 in FDA Drug Development Resources, Drug development and drug interactions: Table of substrates, inhibitor and inducers).
  - AEDs including carbamazepine, phenytoin, phenobarbital, and primidone
  - Non-AED strong CYP3A4 enzyme inducers/inhibitors (ie, prescription drugs, nonprescription drugs, medical cannabis, cannabidiol, dietary [eg, grapefruit or passion fruit].
- Strong CYP2C19 strong sensitive substrates/inhibitors/inducers including S-mephenytoin, **omeprazole**, fluconazole, fluoxetine, fluvoxamine, ticlopidine, rifampin, ritonavir] (for more details refer to Table 3-1, Table 3-2, and Table 3-3 in FDA Drug Development Resources, Drug development and drug interactions: Table of substrates, inhibitor and inducers).

Has been changed to (bolded text has been added):

The following concomitant medications are prohibited during the study:

- GABA-A-ergic drugs: including agonists (ie, barbiturates) or receptor positive allosteric modulators (ie, benzodiazepines or nonbenzodiazepines like zolpidem) taken >3 times **within 7 days**. Regular intake of benzodiazepines with an indication for epileptic seizures is not allowed. However, PRN intake of GABA-A-ergic drugs **up to** 3 times within 7 days is allowed, ie, for emergencies.
- Strong CYP3A4 inhibitors/inducers (for more details refer to Table 3-2 and Table 3-3 in FDA Drug Development Resources, Drug development and drug interactions: Table of substrates, inhibitor and inducers).
  - AEDs including carbamazepine, phenytoin, phenobarbital, and primidone
  - Non-AED strong CYP3A4 enzyme inducers/inhibitors (ie, prescription drugs, nonprescription drugs, medical cannabis, cannabidiol, dietary [eg, grapefruit or passion fruit].
- Strong CYP2C19 strong sensitive substrates/inhibitors/inducers including S-mephenytoin, , fluconazole, fluoxetine, fluvoxamine, ticlopidine, rifampin, ritonavir] (for more details refer to Table 3-1, Table 3-2, and Table 3-3 in FDA Drug Development Resources, Drug development and drug interactions: Table of substrates, inhibitor and inducers).

Change #10

Section 8.1.6, Visit 6 (Month 6), Visit 7 (Month 9), Visit 8 (Month 12), Visit 9 (Month 15), Visit 10 (Month 18), and Visit 11 (Month 21) ±1 week

Section title has been changed to (visit window for Visit 11 has been revised from 1 week to 1 month):

Visit 6 (Month 6), Visit 7 (Month 9), Visit 8 (Month 12), Visit 9 (Month 15), Visit 10 (Month 18), and Visit 11 (Month 21) ±1 month

Change #11

Section 9.1.5, Additional procedures for reporting serious adverse events, Paragraph 3

It is important for the Investigator, when completing the SAE report form, to include the assessment as to a causal relationship between the SAE and the PSL administration. This insight from the Investigator is very important for UCB to consider in assessing the safety of the PSL and in determining whether the SAE requires reporting to the regulatory authorities in an expedited manner.

Has been changed to (bolded text from Amendment 1.1 for Switzerland has been added):

It is important for the Investigator, when completing the SAE report form, to include the assessment as to a causal relationship between the SAE and the PSL administration. This insight from the Investigator is very important for UCB to consider in assessing the safety of the PSL and in determining whether the SAE requires reporting to the regulatory authorities in an

expedited manner. **Expedited reporting to regulatory authorities will be in line with local laws.**

Change #12

Section 9.3.8, Withdrawal monitoring, Paragraph 1 (bolded text has been deleted)

Any symptoms of withdrawal reactions will be monitored using the CIWA-B questionnaire at the scheduled time points presented in Table 5-1. The CIWA-B questionnaire contains **22** questions which are selected to distinguish withdrawal symptoms from other symptoms (Busto et al, 1989).

Has been changed to (bold text has been added):

Any symptoms of withdrawal reactions will be monitored using the CIWA-B questionnaire at the scheduled time points presented in Table 5-1. The CIWA-B questionnaire contains questions **and observations** which are selected to distinguish withdrawal symptoms from other symptoms (Busto et al, 1989).

Change #13

Section 10.6, Treatment Satisfaction, Paragraph 1 (bolded text has been revised)

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). The estimated completion time for this questionnaire is less than 5 minutes. Scores range from 0 (worst) to 100 (best).

Has been changed to (bolded text is the revised text):

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-12**, which has an additional subscale that measures side effects (3 items) (Atkinson et al, 2004). The estimated completion time for this questionnaire is less than 5 minutes. Scores range from 0 (worst) to 100 (best).

Change #14

Section 15, References

The following references have been added:

Azuma H, Akechi T. Effects of psychosocial functioning, depression, seizure frequency, and employment on quality of life in patients with epilepsy. Epilepsy Behav. 2014;41:18-20.

Baker GA, Jacoby A, Buck D, Stalgis C, Monnet D. Quality of life of people with epilepsy: a European study. Epilepsia. 1997;38(3):353-62.

Devinsky O. Sudden, unexpected death in epilepsy. N Engl J Med. 2011;365:1801-11.

Fazel S, Wolf A, Långström N, Newton CR, Lichtenstein P. Premature mortality in epilepsy and the role of psychiatric comorbidity: a total population study. Lancet. 2013;382:1646-54.

Hesdorffer DC, Tomson T. Sudden unexpected death in epilepsy: Potential role of antiepileptic drugs. CNS Drugs. 2013;27(2):113-9.

Holst AG, Winkel BG, Risgaard B, Nielsen JB, Rasmussen PV, Haunsø S, et al. Epilepsy and risk of death and sudden unexpected death in the young: a nationwide study. Epilepsia. 2013;54(9):1613-20.

Jehi L. Neurology's Silent Killer: Drug-Resistant Epilepsy. Epilepsy Curr. 2016;16:232-3.

Leclercq K, Matagne A, Provins L, Klitgaard H, Kaminski R. Protective effects of padsevonil in acute seizure models. (Abstract 1.272), 2017. www.aesnet.org.

Muglia P, Toledo T, Steinhoff, BJ, et al. Efficacy and tolerability of adjunctive padsevonil in adults with drug-resistant focal onset seizures: a randomized, double-blind, placebo-controlled, proof-of-concept trial. (Abstract 1.283), 2017. American Epilepsy Society Annual Meeting, www.aesnet.org.

Sperling MR. The consequences of uncontrolled epilepsy. CNS Spectr. 2004;9(2):98-101, 106-9.

Taylor DC, McMackin D, Staunton H, Delanty N, Phillips J. Patients' aims for epilepsy surgery: desires beyond seizure freedom. Epilepsia. 2001;42(5):629-33.

17 DECLARATION AND SIGNATURE OF INVESTIGATOR

I confirm that I have carefully read and understood this protocol and agree to conduct this clinical study as outlined in this protocol, according to current Good Clinical Practice and local laws and requirements.

I will ensure that all subInvestigators and other staff members read and understand all aspects of this protocol.

I have received and read all study-related information provided to me.

The objectives and content of this protocol as well as the results deriving from it will be treated confidentially, and will not be made available to third parties without prior authorization by UCB.

All rights of publication of the results reside with UCB, unless other agreements were made in a separate contract.

Investigator:

Printed name	Date/Signature

18 SPONSOR DECLARATION

I confirm that I have carefully read and understand this protocol and agree to conduct this clinical study as outlined in this protocol and according to current Good Clinical Practice.

Approval Signatures

Name: EP0093-protocol-amend-2

Version: 1.0

Document Number: CLIN-000148104

Title: EP0093 Protocol Amendment 2

Approved Date: 06 Feb 2020

Document Approvals	
Approval Verdict: Approved	Name: [redacted] Capacity: Clinical Date of Signature: 05-Feb-2020 22:25:30 GMT+0000
Approval Verdict: Approved	Name: [redacted] Capacity: Clinical Date of Signature: 06-Feb-2020 08:55:44 GMT+0000
Approval Verdict: Approved	Name: [redacted] Capacity: Clinical Date of Signature: 06-Feb-2020 15:15:42 GMT+0000