A multicenter, randomized, double-blind, placebo-controlled, parallel-group study to evaluate the efficacy and safety of padsevonil as adjunctive treatment of focal-onset seizures in adult subjects with drug-resistant epilepsy

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Objectives:Primary objective:To evaluate the efficacy of the 3 selected dose regimens of Padsevonil (PSL) administered concomitantly with up to 3 antiepileptic drugs (AEDs) compared with Placebo for treatment of observable focal-onset seizures in...

Ethical review	Approved WMO
Status	Will not start
Health condition type	Neurological disorders NEC
Study type	Interventional

Summary

ID

NL-OMON49060

Source
ToetsingOnline

Brief title
EP0092

Condition

- Neurological disorders NEC

Synonym
Epilepsy, falling disease

Research involving

Human

Sponsors and support

Primary sponsor: UCB Biopharma SRL
Source(s) of monetary or material Support: Farmaceutische industrie

Intervention

Keyword: Drug-resistant epilepsy, Focal-onset seizures, Padsevonil, Phase 3

Outcome measures

Primary outcome

Criteria for Evaluation:

Efficacy variables:

Primary efficacy variable for the US Food and Drug Administration (FDA), Pharmaceuticals and Medical Devices Agency (PMDA), Chinese FDA, and other regulatory authorities except for European Medicines Agency (EMA) or regulatory authorities who reference EMA.

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

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

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

Safety variables:

Primary safety variables

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

Secondary outcome

Criteria for Evaluation:

Efficacy variables:

Secondary efficacy variables for the US FDA, PMDA, Chinese FDA, and other regulatory authorities except for EMA or regulatory authorities who reference EMA

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

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

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

Other efficacy variables (this list applies for all regulatory authorities)

- Change from Baseline in log-transformed observable focal-onset seizure frequency over the first 4 weeks, second 4 weeks, and third 4 weeks of the 12-week Maintenance Period.
- Change from Baseline in log-transformed observable focal-onset seizure frequency over the 16 week Treatment Period.
- The 50% responder rate, where a responder is a subject experiencing a *50% reduction in observable focal-onset seizure frequency from Baseline, over the 16-week Treatment Period.
- The 75% responder rate, where a responder is a subject experiencing a *75% reduction in observable focal-onset seizure frequency from Baseline, over the 16-week Treatment Period.
- The 90% responder rate, where a responder is a subject experiencing a *90% reduction in observable focal-onset seizure frequency from Baseline, over the

12-week Maintenance Period.

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

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

- The 50% responder rate, where a responder is a subject experiencing a *50% reduction in focal-onset (Type I) seizure frequency from Baseline, over the 12-week Maintenance Period.

- The 75% responder rate, where a responder is a subject experiencing a *75% reduction in focal-onset (Type I) seizure frequency from Baseline, over the 12-week Maintenance Period.

- The 90% responder rate, where a responder is a subject experiencing a *90% reduction in focal-onset (Type I) seizure frequency from Baseline, over the 12-week Maintenance Period.

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

- Seizure freedom status (*Yes*/*No*) during the 12-week Maintenance Period and the 16 week Treatment Period.

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

- Cumulative responder rate during the 16-week Treatment Period.

- Change in the Seizure Severity Global Item (SSG) scores from Baseline to Week 4 during the Maintenance Period (Visit 4) and the end of the 16-week Treatment Period (Visit 7).

- Change in Quality of Life Inventory in Epilepsy-31-P (QOLIE 31 P) scores from Baseline to Week 4 during the Maintenance Period (Visit 4) and the end of the 16 week Treatment Period (Visit 7).
- Change in Hospital Anxiety and Depression Scale scores from Baseline to Week 4 during the Maintenance Period (Visit 4) and to the end of the 16-week Treatment Period (Visit 7).
- Time to return to Baseline observable focal-onset seizure frequency during the 12 week Maintenance Period.
- Use of health-related outcomes and HRU, including healthcare provider consultations not foreseen by protocol, caregiver support, concurrent medical procedures, concomitant medications, and hospitalizations.

Safety variables:

Other safety variables
- Incidence of TEAEs reported by the subject and/or caregiver or observed by the Investigator during the following periods: 16-week Treatment Period, 12-week Maintenance Period, 4 week Titration/Stabilization Period, and 3-week Taper Period.
- Number of and reason for subjects requiring premature tapering due to TEAEs.
- Number of and reason for subjects requiring a dose reduction during the Stabilization Period due to TEAEs.
- Incidence of treatment-emergent SAEs during the following periods: 16-week Treatment Period, 12-week Maintenance Period, 4-week Titration/Stabilization

Period.

- Changes in clinical laboratory test parameters (including hematology, blood chemistry, and urinalysis).

- Changes in vital sign parameters (including pulse rate, systolic and diastolic blood pressure, and respiratory rate).

- Changes in 12-lead ECG parameters.

- Physical examination (including body weight) and neurological examination findings.

- Changes in Psychiatric and Mental Status exam.

- Occurrence of valvular abnormalities or pericardial effusion changes or other significant abnormalities as identified by 2-dimensional Doppler echocardiogram at each assessment by central reader.

- Changes in withdrawal symptoms using Clinical Institute Withdrawal Assessment Benzodiazepines (CIWA-B) from the end of the 16 week Treatment Period (Visit 7) to the end of the Taper Period (Visit 8) and the end of the SFU Period (Visit 9 [30 days after the last intake of PSL/Placebo]).

Pharmacokinetic variables:

- Blood concentrations of PSL from samples obtained in the study during the Treatment Period to investigate the population PK profiles of PSL.

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

- Comparison may be made between blood concentration data of PSL and desmethyl

metabolite derived from the volumetric absorptive microsampling MITRA®

technology. Evaluation of PSL and desmethyl metabolite in plasma from trough

samples. The collection of plasma samples for this comparison may cease during

the study based on periodic review of the data.

Study description

Background summary

With over 25 AEDs approved (15 in the last 15 years), the majority of patients with epilepsy and focal-onset or focal to bilateral tonic-clonic previously called *secondary generalized*) seizures have options for effective monotherapy and/or combination therapies early in the treatment
paradigm; however, none of the options differentiate by superior efficacy. Seizure control has only changed marginally even with the latest new AED treatments (Brodie et al, 2012) and for the majority of severely affected and drug-resistant patients, there are few, if any, treatment options remaining.

Padsevonil is an AED with a dual mechanism of action, specifically synthesized and designed for increased anticonvulsant activity and hence for the treatment of seizures in patients with epilepsies resistant to currently available drug therapies. Based on the evidence of superior seizure control compared with other marketed AEDs across several preclinical models of epilepsy and the results of the proof of concept study, EP0069, treatment with PSL has the potential to benefit an underserved epilepsy population with high unmet medical need, namely those who have drug-resistant epilepsy whose uncontrolled focal-onset seizures constitute a UCB 27 Sep 2018 Clinical Study Protocol Padsevonil EP0092 Confidential Page 20 of 97 substantial threat to their health and well-being. The current study, EP0092, will evaluate the efficacy and safety of 3 dose regimens of PSL administered concomitantly with up to 3 AEDs compared with placebo for treatment of observable focal-onset seizures in subjects with
drug-resistant epilepsy.

Study objective

Objectives:

Primary objective:
To evaluate the efficacy of the 3 selected dose regimens of Padsevonil (PSL) administered concomitantly with up to 3 antiepileptic drugs (AEDs) compared

with Placebo for treatment of observable focal-onset seizures in subjects with drug-resistant epilepsy.

Secondary objective:
To assess the safety and tolerability of PSL in relation to Placebo.

Other objectives:
Efficacy:
To assess healthcare resource utilization (HRU) and quality of life.
Pharmacokinetic:
- To evaluate the steady-state pharmacokinetics (PK) of PSL.
- To evaluate the impact of enzyme-inducing concomitant AEDs on PSL exposure.
- To evaluate concomitant AED (and/or relevant metabolites) plasma levels.

Study design

This is a multicenter, randomized, double-blind, placebo-controlled, parallel-group study in adults (*18 years of age) with drug-resistant epilepsy who continue to have uncontrolled focal-onset seizures despite treatment with at least 4 prior AEDs, including current AEDs.

The study consists of up to 4 periods: Baseline, Treatment (Titration, Stabilization, and Maintenance), Taper, and Safety Follow-up (SFU) Periods; for subjects entering the Open-label Extension (OLE) study, the study consists of 3 periods: Baseline, Treatment (Titration, Stabilization and Maintenance) and Conversion. The list of activities to be carried out at each of these periods is detailed in the schedule of assessments table provided below.

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

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

Intervention

Padsevonil will be supplied as 25 mg, 100 mg, and 200 mg film-coated tablets of different sizes and appearance. Placebo will be provided as tablets of matching size and aspect to PSL tablets allowing a double-blind packaging.

All subjects will be instructed to take 5 tablets during the Titration and

Taper Periods or 6 tablets during the Stabilization, Maintenance, and Conversion Periods from the appropriate medication wallets containing either PSL or Placebo twice daily (bid), approximately 12 hours apart. PSL/Placebo should be dosed within 30 minutes after food when practically feasible.

Subjects will be allocated to 1 of the following 4 treatment arms using the interactive response technology system at the Baseline Visit (Visit 2): Padsevonil 100 mg bid, Padsevonil 200 mg bid, Padsevonil 400 mg bid or Placebo.

Study burden and risks

What participation involves:

Your participation in this study could last up to 27 weeks. Overall, you may have to attend up to 9 scheduled appointments with your study doctor and up to 3 telephone appointments. There may be additional unscheduled visits, depending on your needs and health conditions. After approximately 20 weeks in the study, you will have the opportunity to enroll in an open label extension study (EP0093) in which all participants will receive padsevonil, or to discontinue the blinded study drug.

Please refer to Appendix C for a complete overview of the visits.
Please refer to Appendix D for an explanation of the tests and examinations.

Screening
We will first evaluate whether you may participate. The following will be done or asked:
- Demographic data, habits and lifestyle, medical history and, in addition your seizure count during the period 8 weeks prior to screening.
- Questionnaires
- Vital signs
- Physical and neurological examination
- Physical and mental status
- Electrocardiogram (ECG)
- Echocardiogram (live images of your heart)
- Blood and urine for laboratory tests
- Pregnancy test (if applicable)
- Subject trial card and a diary card dispensing
- Your past and current antiepileptic medications, with or without neurostimulation device (implantable that deliver electrical stimulation to specific parts of the brain)
- Health-related outcomes and healthcare resource utilization (HRU) (your use of healthcare services)
- Brain magnetic resonance imaging (MRI), if not performed in recent years and/or no report available

More information on all tests and examinations performed during the screening

can be found in Appendix C and D of the main ICF.

Treatment
During your participation, you will receive study drug for up to 19 weeks. Neither you nor your study doctor, the study team or the Sponsor will know whether the tablets you take in the study contain padsevonil or placebo. The reason for this is to guarantee that the effect of the treatment will be evaluated in an unbiased way by the study participants. The exact treatment you are receiving can be identified in case of emergency.

If you are eligible to continue the study and receive study drug, you will continue to take your other antiepileptic drug(s) and will be randomized to one of the 4 treatment groups. Randomization means that you will be randomly assigned (like rolling a dice) to receive one of the study treatments. You will receive 1 of the following treatments: padsevonil 200 mg/day, padsevonil 400 mg/day, padsevonil 800 mg/day or placebo. If you are in the placebo group, you will receive tablets that look like padsevonil but do not contain any medicinally active substances.

Study drug instructions
You will be instructed to take either 5 or 6 tablets (depending on the period you are participating in) containing either padsevonil or placebo twice per day, approximately 12 hours apart. The study drug should be taken within 30 minutes after food. You should not take padsevonil if you have any allergies to the ingredients in the tablet (or the liquid formulation in studies where applicable) or have had serious side effects to drugs which are closely related to padsevonil, for example levetiracetam or benzodiazepines. Your doctor will inform you on how to take your study drug and increase the dose over the course of 3 weeks to reach the dose corresponding to the treatment group to which you have been allocated. The dose will then stay the same for 12 weeks during the Maintenance Period. Your current antiepileptic treatment will be continued during the entire duration of the study. The study drug will be taken in addition to your current treatment.

Visits and tests
Treatment Period (16 weeks)
The following will take place in addition to the tests and examinations mentioned during screening:
- Your study doctor will confirm that you still fulfill the requirements to participate in the study.
- Your ongoing treatments will be reviewed.
- Your study diary will be reviewed.
- You will be asked about your health condition, current medications, any seizures you may have had and any side-effects you experienced.
- Further study drug will be given to you and remaining study drug will be taken back.

The Treatment Period will consist of 3 different periods with 6 visits and 2 telephone calls as explained below:
1. Titration Period (3 weeks)
This period involves 2 visits and 1 telephone call.
2. Stabilization Period (1 week)
This period only involves 1 telephone call.
3. Maintenance Period (12 weeks)
This period involves 4 visits in which the End of Treatment Visit / Early Discontinuation Visit is one of them.

End of Treatment Visit / Early Discontinuation Visit
If you decide to discontinue the study, you will be asked to complete a questionnaire about drug withdrawal experience and given directions on how to gradually decrease your dosage over the next 3 weeks until you are not taking any more study drug. If you decide to continue in the open-label extension study (EP0093), you will be given directions on how to convert to the appropriate dosage.

Conversion (3 weeks) or Taper Period (4 weeks)
Subjects who choose to enter the open-label extension study (EP0093) will enter the Conversion Period and subjects who choose not to enter the open-label extension study (EP0093) will enter the Taper Period.

Study drug will be taken during this period. This period involves 1 telephone call and 1 visit. The Conversion visit will be 3 weeks after the End of Treatment Visit / Early Discontinuation Visit and the Taper visit will be 4 weeks after the End of Treatment Visit / Early Discontinuation Visit. No further study drug will be given to you for this study during this visit.

Safety Follow-Up Visit
This visit will be performed only if you do not continue in the open-label extension study (EP0093). You will undergo assessments to check that you are not experiencing any delayed or long-term side-effects after discontinuation of the study drug.

Unscheduled Visit/Telephone Call
There may be additional unscheduled visits or telephone calls, if deemed necessary by your study doctor. If an unscheduled visit is done due to safety or efficacy reasons, you will be asked to complete a questionnaire.

More information on all tests and examinations performed during the visits can be found in Appendix C and D of the main ICF.

Possible side effects and discomforts:

Just like any medication, padsevonil may cause side-effects. So far 201 healthy people have received various doses of padsevonil. In addition, 75 patients with

epilepsy have received padsevonil. While some of these side-effects are already known, there may be other risks associated with the use of padsevonil that are currently unforeseeable.

The side-effects of padsevonil reported as of October 2018 included:

- Very Common (occurring in more than 1 in 10 patients):
Sleepiness; dizziness; irritability; tiredness; and headache.

- Common (occurring between 1 and 10 in 100 patients):
Majority of these side effects occurred in only 1 patient.

Tremor; disturbance in attention; trouble with speaking; troubles with your memory; jerking of the eye; memory loss; tingling; seizure or convulsion; lack of coordination; mental disability or difficulty; seizure without loss of contact and consciousness; slow speech; continuous seizures; a warning sensation or unusual feeling experienced before a seizure (fit); burning; clumsiness; abnormal coordination; feeling dizzy upon standing up; impaired learning; unable to make good decisions; muscle weakness; abnormal sense of smell; trouble sleeping; a strong urge to move your legs; disorder or changes in senses (e.g., seeing, smelling, hearing, touch); confusion/confused and impaired responsiveness; feeling of dissatisfaction, anxiety, and restlessness; rapid changes in mood; nervousness; aggressive behavior; depressed mood; anxious or nervous behavior; feeling mad; moods and emotions not appropriate for situation; seeing, hearing, tasting, or feeling something that is not really there; excessive talking; nightmare; oversensitivity to rejection leading to desire to be alone; perception of time is abnormal; difficulty in walking; weakness; feeling cold; chest pain not related to heart condition; upper stomach discomfort and pain; frequent loose bowel movement; constipation; dry mouth; nausea; swollen tongue; fall; double vision; blurred vision; trouble seeing; irritation of the eye; rash; inflammation of nose; weight increased; weight decreased; decreased appetite; number of white bloods cells called neutrophils is abnormally low; decreased number of blood cells that help to clot blood; low blood sodium level; muscle spasms; muscle and/or bone pain; menstrual cramps; sudden reddening; low blood pressure; irregular or extra heart beats; acne; sweating; bloody nose; and ringing in the ears.

Any of these side-effects that are caused by padsevonil usually get better over time, some may be present only initially and get better within a few days. If you experience any of these (or other) symptoms and they are very bothersome, you can decide to stop the study. If you stop taking the study drug (note * the dose will be reduced gradually to minimize any potential withdrawal effects), these side-effects will usually go away quickly.

If you experience any side-effects or any unusual symptoms (see most common side-effects above), it is essential that you tell your study doctor immediately and that you note these in your diary. The same applies if you have

other health problems in addition to epilepsy, and these get worse during the use of padsevonil.

The study doctor will explain all important points about padsevonil to you during the information meeting and will discuss the next steps with you. As with any new drug, new and, so far, unknown side-effects may also occur.

If you think that being in the study is causing you to get worse, you are experiencing side-effects that you feel are too severe, or if it is damaging your health, you can stop your participation in the study at any time.

Please refer to Appendix E of the main ICF for less common side effects and the risk and discomforts of the tests and procedures.

Contacts

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Scientific
UCB Biopharma SRL

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

Inclusion criteria,
General,
1. An Institutional Review Board (IRB)/Independent Ethics Committee (IEC) approved written informed consent form (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 according to country-specific regulations.
2. Subject/legal representative is considered reliable and capable of adhering to the protocol (eg, able to understand and complete diaries), visit schedule, and medication intake according to the judgment of the Investigator.
3. Subject is an adult (18 years of age or more).
4. Subject is of normal weight of at least 40 kg (for males and females)., Epilepsy,
5. Subject fulfills diagnostic criteria for epilepsy and has observable focal-onset (IA1, IB, and IC) seizures for at least 3 years at the time of enrollment (according to the International League Against Epilepsy [ILAE] Classification of Epileptic Seizures, 1981):
- Epileptic seizures have been documented using video-electroencephalogram (EEG) recordings or ictal EEG (±simultaneous video) in the past (description or report is available). The Investigator must consult with the UCB Study Physician or representative for confirmation of eligibility as per instructions in the Study Manual.
If no video-EEG report is available and, in the opinion of the Investigator, epileptic seizures are definite (ie, eye-witnessed seizure report, home video documentation of habitual events, or other proof), the Investigator must consult with the UCB Study Physician or representative for a case review.
- A brain magnetic resonance imaging (MRI) is to be performed before randomization, if no such scan was performed in the last 10 years, and a report is not available. If a scan was performed within the last 10 years but the clinical condition of the subject was progressive since the last scan, a new scan should be obtained. If MRI is contraindicated, a head computed tomography scan within the last 3 years before randomization will suffice.
6. Subject has on average *4 spontaneous and observable focal-onset seizures per 28 days (based on Investigator assessment of subject report) with at least 1 seizure during each 4 week interval of the 8 weeks prior to the Screening Visit. Additionally, subject must experience *4 spontaneous and observable focal-onset seizures per 28 days (based on Investigator assessment of subject report) during the 4-week Baseline Period.
7. Subject has failed to achieve seizure control with *4 tolerated and appropriately chosen prior AEDs, including past and ongoing treatments that were individually optimized for adequate dose and duration. Prior discontinued AED treatment would need to be assessed by the Investigator considering the patient medical records and patient and/or caregiver interview. "Prior AED" is defined as all past and ongoing AED treatments with a start date before the

Screening Visit (Visit 1).,
Concomitant epilepsy treatment,
8. Subject is currently treated with an individually optimized and stable dose of at least 1 and up to 3 AEDs for the 8 weeks prior to the Screening Visit (Visit 1) with or without additional concurrent vagus nerve stimulation (VNS) or other neurostimulation treatments. The latter will not be counted as AEDs for the purpose of eligibility.,
Laboratory parameters,
9. Subject has clinical laboratory test results within the reference ranges of the laboratory or isolated test results that are outside the specified ranges and deemed as not clinically significant by the Investigator, eg mild and moderate renal impairment.,
Birth control,
10. Female subjects of child bearing potential must have a negative serum pregnancy test at the Screening Visit (Visit 1), which is confirmed to be negative by urine testing prior to the first dose of PSL/Placebo at Day 1 (Visit 2) and 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 for a period of 3 months after their last intake of PSL/Placebo. Hormonal contraception may be susceptible to an interaction with the PSL/Placebo, 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 male condom) also be used.
Birth control methods considered as an efficient form 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 Screening [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 Screening [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 male 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 abstinent (as described in the preceding bullet) or be of nonchildbearing potential, defined as being postmenopausal (for at least 2 years before the Screening Visit [Visit 1]), verified by serum follicle stimulating hormone level >40mIU/mL at the Screening Visit (Visit 1), 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 last intake of PSL/Placebo.

Exclusion criteria

Exclusion criteria,
General,
1. Subject has previously been randomized in this study, or a study of the medication under investigation in this study. Re-screening of a subject may be permitted but requires prior Medical Monitor approval and is not permitted in case of screen failure due to seizure count.
2. Subject has participated in another study of an investigational medication (or a medical device) within the previous 30 days or 5 half-lives (whichever is longer) or is currently participating in another study of an investigational medication (or a medical device).
Laboratory parameters
3. Subject has either:
- >2.0x 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). If subject has elevations only in total bilirubin that are >ULN and <1.5xULN, fractionate bilirubin to identify possible undiagnosed Gilbert*s syndrome (ie, direct bilirubin <35%).
For randomized subjects with a Baseline result >ULN for ALT, AST, ALP, or total bilirubin, a Baseline diagnosis and/or the cause of any clinically meaningful elevation must be understood and recorded.
If subject has >ULN ALT, AST, or ALP that does not meet the exclusion limit at screening, repeat the tests, if possible, prior to dosing to ensure there is no further ongoing clinically relevant increase. In case of a clinically relevant increase, inclusion of the subject must be discussed with the Medical Monitor. Tests that result in ALT, AST, or ALP up to 25% above the exclusion limit may

be repeated once for confirmation before Baseline (Visit 2).,
Medical conditions,
4. Subject has a history or current medical condition that, in the opinion of the Investigator, could jeopardize or would compromise the subject*s ability to participate in this study.
5. Subject has a current psychiatric condition that occurred within the last 12 months which, in the opinion of the Investigator, could compromise the subject*s safety or ability to participate in this study, including but not limited to schizophrenia, schizoaffective disorder, bipolar disorder, severe unipolar depression, dementia, or irreversible severe or progressive encephalopathy.
6. Subject has a lifetime history of suicide attempt (including an actual attempt, interrupted attempt, or aborted attempt), or has suicidal ideation in the past 6 months as indicated by a positive response (*Yes*) to either question 4 or question 5 of the *Screening/Baseline* version of the Columbia-Suicide Severity Rating Scale (C-SSRS) at screening.
7. Subject has a history of chronic alcohol or drug abuse within the last 2 years.
8. Subject has a history of cerebrovascular accident, including transient ischemic attack, in the last 6 months.
9. Subject has presence of any sign (clinical or imaging techniques) suggesting rapidly progressing (ie, not expected to stay stable during study participation) brain disorder or brain tumor. Stable lesions such as arteriovenous malformations, meningiomas, or other benign tumors are acceptable if no surgical removal is planned or likely for the duration of the study.
10. Subject has any clinical condition (eg, bone marrow depression, chronic hepatic disease, and/or severe renal impairment) that could impair reliable participation in the study or necessitate the use of medication not allowed by the protocol.
11. Subject has the presence of a terminal illness.
12. Subject has the presence of a serious infection.
13. Subject has a clinically significant abnormality on electrocardiogram (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) interval >450 ms.
- Bundle branch blocks and other conduction abnormalities that are clinically significant according to the Investigator and/or with a PR interval *220 ms, 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.
14. Subject has an abnormality on the echocardiogram at Screening (Visit 1) as

assessed by the central reader that is accompanied by clinical symptoms (eg, shortness of breath, palpitations, and murmur) or a *Grade 2*/moderate severity abnormality or a history of rheumatic heart disease or other known valvular abnormalities (*according to the ASE Guidelines).
Subjects whose echocardiograms are not interpretable at Screening Visit (Visit 1) by transthoracic echocardiogram (TTE), eg, due to technical difficulties or position of the heart will be excluded from the study.,
Epilepsy,
15. Subject has a history of or signs of generalized (formerly referred to as *idiopathic generalized*) or combined generalized and focal (formerly referred to as *symptomatic generalized*) epilepsy.
16. Subject has a history of status epilepticus within the 6-month period prior to Screening (Visit 1).
17. Subject has seizures on a regular basis that are uncountable, eg, due to clustering (ie, an episode lasting less than 30 minutes in which several seizures occur with such frequency that the initiation and completion of each individual seizure cannot be distinguished) during the 8 weeks prior to the Screening Visit and during the 4-week Baseline Period.
18. Subject has isolated auras only (ie, focal-onset seizures which involve subjective sensory or psychic phenomena only, without impairment of consciousness or awareness, [formerly referred to as simple partial seizures without an observable component]).
19. Subject has a current diagnosis of pseudo- or nonepileptic seizures, or other nonepileptic events that could be confused with epileptic seizures.
20. Subject had resective surgery for epilepsy in the last 6 months prior to study entry or plans for such a surgery within the timeframe of the study.,
Epilepsy treatment,
21. Subject had an epilepsy dietary therapy initiated <3 months prior to Screening (Visit 1).
22. Subject has VNS, deep brain stimulation, Responsive Neurostimulator System, or other neurostimulation for epilepsy device:
- Implanted and activated <1 year prior to enrollment, or
- With stimulation parameters that have been stable for <3 months, or
- With battery life of unit not anticipated to extend for duration of study.
23. Subject is currently treated with carbamazepine, phenytoin, primidone, or phenobarbital.
24. Subject previously had serious side-effects with drugs where the side-effects were related to specific SV2A and GABA-ergic mechanisms of action.,
Medical treatment,
25. Subject has a known hypersensitivity to any components of PSL formulation or a history of drug or other allergy that, in the opinion of the Investigator or UCB Study Physician or delegate, contraindicates her/his participation.
26. Subject has taken or is taking any prescription, nonprescription, dietary (eg, grapefruit or passion fruit), or herbal products (eg, St. John's wort) that are strong inducers or strong inhibitors of the CYP3A4 or 2C19 pathway for 2 weeks (or 5 half lives, whichever is longer) prior to the Baseline Visit

(Visit 2). Subjects taking sensitive substrates of CYP2C19 are similarly excluded. Please also note the prohibited concomitant medications.
27. Subject has been taking vigabatrin for less than 2 years at study entry.
28. Subject has been taking vigabatrin for at least 2 years without documented normal visual fields following at least 2 years of intake.
29. Subject with a history of vigabatrin treatment who did not have a visual perimetry test at least 6 months following conclusion of treatment or the results of the visual perimetry test showed either a damage or a visual field defect associated with 1 of the following 2 conditions:
- There was a change from a visual field test done at some point while the subject was taking vigabatrin, or
- There was a change from a visual field test done within weeks after stopping vigabatrin administration.
30. Subject has been taking felbamate for less than 12 months and/or has no appropriate laboratory tests showing no indication of aplastic anemia or hepatic failure.
31. Subject has been taking retigabine for less than 4 years. In addition, subject is currently taking retigabine or has been exposed to retigabine with no documentation (at least every 6 months or 6 months after last exposure) of normal/stable visual acuity, slit lamp examination, dilated fundus photography, and macular Optical Coherence Tomography imaging.
32. Subject is taking GABA A ergic drugs regularly (agonists [ie, barbiturates] or receptor positive allosteric modulators [ie, BZDs or non-BZDs]), excluding as needed (PRN) intake of GABA A ergic AEDs <3 times per week for emergencies., Pregnancy,
33. Female subject who plans to become pregnant or is breastfeeding.

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Will not start
Enrollment:	15
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	Padsenovil
Generic name:	Padsenovil

Ethics review

Approved WMO Date:	22-01-2019
Application type:	First submission
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	07-03-2019
Application type:	First submission
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	16-04-2019
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	08-05-2019
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	22-05-2019
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	23-05-2019

Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	05-06-2019
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	31-07-2019
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	01-10-2019
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	11-02-2020
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	12-02-2020
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	11-05-2020
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	12-05-2020
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2018-002303-33-NL
ClinicalTrials.gov	NCT03739840
CCMO	NL68175.028.19