A multicenter, open-label, parallel-group study in study participants with epilepsy to evaluate the effect of oxcarbazepine on the pharmacokinetics, safety, and tolerability of padsevonil.

Published: 09-08-2018
Last updated: 10-01-2025

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Ethical review	Approved WMO
Status	Completed
Health condition type	Seizures (incl subtypes)
Study type	Interventional

Summary

ID

NL-OMON46271

Source
ToetsingOnline

Brief title
Drug-drug interaction study with padsevonil and oxcarbazepine

Condition

- Seizures (incl subtypes)

Synonym
Epilepsy, seizures

Research involving
Human

Sponsors and support

Primary sponsor: UCB Pharma
Source(s) of monetary or material Support: Pharmaceutical industry

Intervention

Keyword: Epilepsy, Oxcarbazepine, Padsevonil, Pharmacokinetics

Outcome measures

Primary outcome

The primary pharmacokinetic variables will comprise Cmax, tmax, AUC*, and

CL/Fss obtained from the plasma concentration-time profiles for PSL:

- Cmax: maximum observed plasma concentration

- tmax: time of maximum concentration

- AUC*: area under the curve over a dosing interval (12 hours)

- CL/Fss: apparent total clearance at steady-state

Secondary outcome

Pharmacokinetic parameters

The secondary PK variable will be the trough plasma concentration of MHD (OXC

metabolite) before, during, and after dosing to steady state with PSL.

Additionally, the secondary PK variables for PSL metabolites (UCB1431322-000

and UCB1447499-000) will comprise Cmax, tmax, AUC*, and the ratio of metabolite

to PSL based on AUC*.

The following other PK variables will be assessed during the study:

- Trough plasma concentrations of LEV, LTG, or BRV before, during, and after

dosing to steady state with PSL

- Comparison of plasma concentrations from MITRA microsampling (dried blood)

with venous sampling for PSL

Safety parameters

- Incidence of AEs and SAEs

- Changes in vital signs (pulse rate [PR], respiratory rate [RR], SBP, and DBP)

- Changes in clinical laboratory test results (hematology, serum chemistry, and

urinalysis)

- Changes in 12-lead ECG parameters

- Physical examination findings

Study description

Background summary

Padsevonil (PSL; previously known as UCB0942) is a novel chemical entity with selective dual synaptic vesicle protein 2 (SV2) and central benzodiazepine receptor (cBZR) site affinity. It is currently being investigated for the treatment of focal-onset seizures in adult patients with drug-resistant epilepsy.
Many antiepileptic drugs (AEDs) are associated with drug-drug interactions. Preclinical data indicate that PSL metabolism is mediated mainly by cytochrome P450 (CYP)3A4 with minor involvement of CYP2C19. Consequently, PSL exposure may be altered by CYP3A4 inhibitors
and inducers. It has already been demonstrated that concomitant administration of a strong CYP3A4 inducer (carbamazepine) significantly reduces exposure to PSL (UP0002).
This is a Phase 1, multicenter, open-label study in study participants with epilepsy, designed to evaluate the pharmacokinetic (PK) interaction between PSL and oxcarbazepine (OXC), a common AED that is known to have CYP3A4 induction potential (Spina et al, 1996), and could therefore have a negative impact on the efficacy of PSL if exposure is reduced significantly as a result.

Study objective

The primary objective of this study is to evaluate the effect of stable coadministered OXC (as monotherapy or adjunctive therapy) on the PK of PSL in study participants with epilepsy compared with study participants co-medicated with stable doses of levetiracetam (LEV), lamotrigine (LTG), or brivaracetam (BRV) therapy.

The secondary objectives of this study are to:
- Evaluate the plasma concentrations of MHD (circulating metabolite of OXC) before, during, and after administration of repeated doses of PSL
- Evaluate the effect of stable coadministered OXC (as monotherapy or adjunctive therapy), on the plasma PK of PSL metabolites, UCB1431322-000 and UCB1447499-000, in study participants with epilepsy compared with study participants co-medicated with stable doses
of LEV, LTG, or BRV therapy.
- Evaluate the safety and tolerability of PSL coadministration with stable OXC, LEV, LTG, or BRV therapy

The exploratory objectives of this study are to:
- Evaluate the plasma concentrations of LTG, LEV, and BRV before, during, and after administration of repeated doses of PSL. (Blood samples for plasma concentrations of LEV, LTG, and BRV samples will be collected and stored during the study; they will only be
measured on an as-needed basis.)
- Evaluate and compare the venous blood and MITRA microsampling (dried blood) PK of PSL following administration of PSL in study participants with epilepsy on stable coadministered OXC compared with study participants co-medicated with stable doses of LEV, LTG, or BRV therapy.

Study design

This is a Phase 1, multicenter, open-label study in study participants with epilepsy, to evaluate the effect of oxcarbazepine (OXC) on the PK and safety and tolerability of Padsevonil (PSL).
A total of 28 study participants will be evaluated in the following 2 groups (14 study participants per group):
- Group 1 (Inducers): study participants on stable therapy with OXC (at least 1200mg/day either as monotherapy or adjunctive to LEV, LTG, or BRV). Oxcarbazepine may be used as monotherapy (at least 7 study participants) or in combination with 1 or more of LEV, LTG,
or BRV). (For adjunctive therapy, the dosing of each AED in the combination [OXC+LEV, OXC+BRV, or OXC+LTG] must be within the range used per label.)
- Group 2 (Neutral [control]): study participants on stable therapy with LTG (at least 150mg/day monotherapy or adjunctive to LEV or BRV), LEV (at least 1g/day monotherapy or adjunctive to LTG), or BRV (up to 200mg/day adjunctive to LTG). Lamotrigine or LEV may be used as monotherapy (at least 7 study participants) or in combination with each other. Brivaracetam may only be used in combination with LTG. (For adjunctive therapy, the

dosing of each AED in the combination [LTG+LEV or LTG+BRV] must be within the range used per label.)

Padsevonil will be dosed to steady state (4.5 days) in both groups and the effect of background therapy on PSL PK will be assessed at steady state.

Intervention

The study consists of 12 days of PSL treatment, increasing in dose from PSL 100mg twice daily (bid) to 400mg bid and then tapering back to 100mg bid.

Study burden and risks

Participation in the study is associated with the risk of possible side effects of the study medication and study procedures. Subjects will be monitored closely at the clinical unit during the treatment period. Vital signs and ECG's will be evaluated daily, as well as a regular CSSRS questionnaire.

Safety pharmacology studies have shown no major adverse effects on the respiratory system and CNS when administered orally in single-dose safety pharmacology studies (rats) and in repeat dose toxicity studies (rats, dogs). A slight prolongation of QTc (*10%) was found in a 4-week study in dogs and a single dose telemetry study at free plasma concentrations at least 6 times above the mean free peak plasma concentration reached in epilepsy patients. This was not seen in other (pre)clinical studies. Valvular inflammatory cell infiltration was observed in a 39 week dog study. These findings were not observed in other (pre) clinical studies. Small, transient increases in heart rate and changes in arterial pressure (hypertension in rats and hypotension in dogs) occurring mainly from single doses are likely related to exaggerated GABAA pharmacologic activity. This was also seen in clinical studies.

PSL has been administered in 8 completed clinical studies, in male and female participants. Single doses were administered up to 490 mg (26 healthy volunteers). Repeated doses were administered up to 400 mg BID, up to 12 days. In total, 129 healthy volunteers and 20 epilepsy patients were exposed to a single dose of Padsevonil. Additionally, 103 healthy volunteers and 20 epilepsy patients were exposed to multiple doses of Padsevonil.
There were no deaths. Adverse events experienced by study participants were generally limited principally to CNS effects and these were consistent with its known pharmacology, dose-related in frequency and intensity, self-limiting, and tended to decrease in intensity over the first few days of dosing.
Three psychiatric SAE's were reported, requiring admission.
- Delirious syndrome (1 healthy volunteer, who received 200 mg BID, soon after start of medication)
- Mania-like symptoms (1 healthy volunteer, who received 400 mg BID, soon after start of medication)

- Acute psychosis (1 epilepsy patient, who received 400 mg BID, a few weeks after the medication, most likely due to forced normalization)
Importantly, these SAE's were seen when the study drug was administered without a titration and tapering period. The mitigation plan of acute psychiatric symptoms after these reports, is to add a gradual titration and taper period to the dosing schedule. Also, there are strict inclusion criteria and there will be intensive monitoring (incl. daily CSSRS questionnaires day -1 to 7).

The AE's that were most frequently reported in clinical studies, were fatigue, somnolence, dizziness, headache and nausea. Also, subjects experienced reduced attention, memory, alertness and coordination in higher dose levels. Minimal reductions in blood pressure were observed.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

1. An Independent Ethics Committee (IEC) approved written ICF is signed and dated by the study participant.
2. Study participant 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. Study participant is male or female between 18 to 64 years of age, inclusive, with a diagnosis of epilepsy according to the International League Against Epilepsy (ILAE) classification (Fisher et al, 2014).
4. Study participant is currently treated for epilepsy with stable doses of the following for at least 3 months:
a) Inducers Group: OXC (at least 1200mg/day as monotherapy or in combination with BRV [up to 200mg/day], LEV [at least 1g/day] or LTG [at least 150mg/day]); or
b) Neutral (control) Group: LTG (at least 150mg/day monotherapy or adjunctive to LEV or BRV), LEV (at least 1g/day monotherapy or adjunctive to LTG), or BRV (up to 200mg/day adjunctive to LTG).
5. Study participant in the Inducers Group is taking OXC and has a trough OXC metabolite (MHD) plasma level in the target range (*12.0 to *35.0 mcg/mL). At the Screening Visit, the blood sample must be collected no later than on Day -7 (with MHD reassessment, if required, no later than Day -4).
6. Study participant is in generally good physical and mental health, in the opinion of the Investigator, determined on the basis of medical history and a general clinical examination at the Screening Visit (ie, study participant has no current or past medical history of clinical significance, other than epilepsy, that would mitigate against their participation in the study).
7. Study participant has clinical laboratory test results within the local reference ranges or values are considered as not clinically relevant by the Investigator and approved by the UCB Study Physician. Laboratory parameters outside the reference ranges can be retested and if the retest result is within the reference range or considered as clinically not relevant the study participant is allowed in the study. Alanine aminotransferase (ALT), aspartate aminotransferase (AST), or alkaline phosphatase (ALP) should be within the normal limits. Liver enzymes up to 25% above the upper limit may be repeated once and should be within normal limits before inclusion.
8. Study participant has a body mass index (BMI) of 18 to 35kg/m^2, inclusive, with a body weight of at least 50kg (male) or 45kg (female).
9. Study participant has BP and PR within normal range in the supine position after 5 minutes rest (SBP: 90mmHg to 145mmHg, DBP: 40mmHg to 95mmHg, PR: 40bpm to 100bpm). Any values outside the normal range, but considered not clinically significant by the Investigator, are allowed.
10. Female study participant has a negative serum pregnancy test at the Screening Visit and agrees to use an efficient form of contraception for the duration of the study (unless menopausal [defined as no menses for 12 months without an alternative medical cause]; a high follicle-stimulating hormone level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy). Hormonal contraception may be susceptible to an interaction with the IMP, which may reduce the efficacy of the contraception method. The potential for reduced

efficacy of any hormonal contraception methods requires that a barrier method (preferably male condom) also be used. Birth control methods considered as an efficient form of contraception:
- Combined (oestrogen and progestogen containing) hormonal contraception (oral, implant, or injectable) associated with inhibition of ovulation in combination with a barrier method (preferably male condom)
- Progestogen-only hormonal contraception associated with inhibition of ovulation in combination with a barrier method (preferably male condom)
- Intrauterine device (IUD)
- Intrauterine hormone-releasing system (IUS) in combination with a barrier method (preferably male condom)
- Bilateral tubal occlusion
- Vasectomized partner
- Sexual abstinence
True 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, postovulation methods), declaration of abstinence for the duration of the study, and withdrawal are not acceptable methods of contraception.
- Progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mode of action in combination with a barrier method (preferably male condom)
- Male or female condom with spermicide (ie, double barrier)
- Cap, diaphragm, or sponge with spermicide
To ensure proper birth control, females who use hormonal contraception should use an efficient barrier contraceptive in the 3 months following the end of the study (ie, for 3 months after the last intake of study medication).
11. Male study participant agrees that, during the study period, when having sexual intercourse with a woman of childbearing potential, he will use an efficient barrier contraceptive (condom plus spermicide) AND that the respective partner will use an additional efficient contraceptive method (eg, oral pills, IUDs, IUSs, or diaphragm, and spermicide).

Exclusion criteria

Study participants are not permitted to enroll in the study if any of the following criteria is met:
1. Study participant has previously received the IMP administered in this study.
2. Study participant has participated in another study of an investigational medication (or a medical device) within the last 3 months before screening (or 5 half-lives, whichever is longer) or is currently participating in another study of an investigational medication (or a medical device).
3. Study participant has a known hypersensitivity to any components of the IMP as stated in this protocol
4. Study participant has a current or past psychiatric condition that, in the opinion of the Investigator, could compromise his/her safety or ability to participate in this study or a history of schizophrenia, or other psychotic disorder, bipolar disorder, or severe unipolar

depression. The presence of potential psychiatric exclusion criteria will be determined based on the psychiatric history collected at the Screening Visit.
5. Study participant has a lifetime history of suicide attempt (including an actual attempt, interrupted attempt, or aborted attempt), or has had 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 C-SSRS at the Baseline Visit.
6. Study participant has any medical condition that, in the opinion of the Investigator, could jeopardize or would compromise the study participant*s ability to participate in this study.
7. Study participant has a history of status epilepticus during the last year.
8. Study participant has a history or presence of drug or alcohol dependency or tests positive for alcohol and/or drugs at the Screening Visit or Day -1.
9. Study participant has a consumption of more than 3 units of alcohol/day in case of females, more than 4 units of alcohol/day in case of males.
10. Study participant smokes more than 5 cigarettes per day (or equivalent) or has done so within 6 months prior to the Screening Visit.
11. Study participant has a consumption of more than 600mg of caffeine/day within 7 days prior to the Baseline Visit and does not agree to limit consumption below this limit for the duration of the study (200mL of coffee contains approximately 100mg of caffeine, 200mL of black tea approximately 30mg, and 200mL of cola approximately 20mg).
12. Study participant ingests grapefruit, starfruit, or pawpaw (as beverage, fruit, or supplements) within 72 hours before first administration of IMP. These fruits are not allowed during the Treatment Period and throughout the study.
13. Study participant has either:
- >2.0x upper limit of normal (ULN) of any of the following:
* ALT
* AST
* ALP
-OR-
- ULN total bilirubin (*1.5xULN total bilirubin if known Gilbert*s syndrome).
If study participant 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 study participant 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 study participant 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 study participant must be discussed with the UCB Study Physician.
Tests that result in ALT, AST, or ALP up to 25% above the exclusion limit may be repeated once for confirmation. If out of range again, the study participant cannot be included.
14. Study participant has made a blood or plasma donation or has had a comparable blood loss (>400mL) within the last 3 months prior to the Screening Visit.
15. Study participant has a history or present condition of respiratory or cardiovascular disorders, eg, cardiac insufficiency, coronary heart disease, hypertension, arrhythmia, tachyarrhythmia, or myocardial infarction.
16. Study participant has any clinically relevant ECG finding at the Screening Visit or at

Baseline. Study participant has an abnormality in the 12-lead ECG that, in the opinion of the Investigator, increases the risks associated with participating in the study. In addition, any study participant with any of the following findings will be excluded: (a) QT interval corrected for heart rate using Bazett*s formula (QTcB) or Fridericia*s formula (QTcF) >450ms in 2 of 3 ECG recordings; (b) other conduction abnormalities (defined as PR interval *220ms); (c) irregular rhythms other than sinus arrhythmia or occasional, rare supraventricular or rare ventricular ectopic beats. In case of an out of range result, 1 repeat will be allowed. If out of range again, the study participant cannot be included.
17. Study participant has a history of unexplained syncope or a family history of sudden death due to long QT syndrome.
18. Study participant tests positive for human immunodeficiency virus-1/2 antibody (HIV-1/2Ab), hepatitis B surface antigen (HBsAg), or hepatitis C antibody (HCV-Ab).
19. Female study participant tests positive for pregnancy, plans to get pregnant during the participation in the study, or is breastfeeding.
20. Study participant has received any prescription or nonprescription medicines, including enzyme inhibitors or inducers, over the counter (OTC) remedies, herbal and dietary supplements (including St. John*s Wort), or vitamins up to 2 weeks or 5 half-lives of the respective drug (whichever is longer) before the first administration of IMP and during the clinical part of the study, unless required to treat an AE. This does not include allowed AEDs per the protocol, oral contraceptives not exceeding 30*g ethinyl estradiol or postmenopausal hormone replacement therapy or implants, patches, or IUDs/IUSs delivering progesterone (for female study participants).

Study design

Design

Study type: Interventional

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Completed
Start date (anticipated):	18-09-2018
Enrollment:	8
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Padsevonil
Generic name:	Padsevonil

Ethics review

Approved WMO Date:	09-08-2018
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	10-08-2018
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	23-08-2018
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	31-08-2018
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	08-01-2019
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

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	EUCTR2018-001941-16-NL
CCMO	NL66527.056.18

Study results

Date completed: 12-04-2019

Results posted: 18-12-2019

First publication
05-11-2019