A Double-Blind, Placebo-Controlled, Randomized, Single-Center, Cross-Over Study to Investigate the Pharmacodynamic, Pharmacokinetic, Safety, and Tolerability Profiles of Padsevonil in Healthy Study Participants Receiving Either Ethanol or Cannabidiol.

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Primary- Part A: Evaluation of pharmacodynamic (PD) interaction between steady-state treatment with padsevonil (PSL) and ethanol- Part B: Evaluation of pharmacokinetic (PK) interaction between steady-state treatment with padsevonil (PSL) and...

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

Summary

ID

NL-OMON49954

Source
ToetsingOnline

Brief title
Padsevonil interaction study with ethanol or cannabidiol

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: Cannabidiol, Epilepsy, Ethanol, Interaction, Padsevonil

Outcome measures

Primary outcome

1. Percentage of smooth pursuit eye movements during Part A

2. Cmax for padsevonil during part B

3. Cmax for cannabidiol during Part B

4. AUC0-tau for padsevonil during Part B

5. AUC0-tau for cannabidiol during Part Bart B

Secondary outcome

1.Ethanol dose infused over time during Part A

2. Cmax for padsevonil during Part A

3. AUC0-tau for padsevonil during Part A

4. T1/2 for padsevonil during Part B

5. T1/2 for cannabidiol during Part B

6. CLss/F for padsevonil during Part B

7. CLss/F for cannabidiol during Part B

8. Saccadic peak velocity to assess sedation during Part A

9. Saccadic peak velocity to assess sedation during Part B

10. Adaptive tracking to assess visuo-motor control and vigilance during Part A

11. Adaptive tracking to assess visuo-motor control and vigilance during Part B

12 Smooth pursuit (%) to assess eye movement coordination and attention for

Part B only

13. Body sway to assess postural stability during Part A

14. Body sway to assess postural stability during Part B

15. Number of participants with Adverse events during Part A

16. Number of participants with Adverse events during Part B

17. Number of participants with Serious Adverse events during Part A

18. Number of participants with Serious Adverse events during Part B

19. Number of participants with Treatment-related Adverse events during Part A

20. Number of participants with Treatment-related Adverse events during Part B

21. Number of participants with Adverse events leading to discontinuation of

the study during Part A

22. Number of participants with Adverse events leading to discontinuation of

the study during Part B

Study description

Background summary

Padsenovnil (PSL) is a new chemical entity that aims to treat refractory focal epilepsy, a disease with high unmet need. PSL has a unique workingmechanism by acting on the presynaptic vesicle protein 2 isoforms with high affinity, as simultaneously acting on the postsynaptic cBZR sites on the GABA-A receptor.

Epilepsy is often concomitantly treated. Drug interactions should therefore be investigated at an early stage, as well as the interaction with CNS-acting and commonly used drugs such as alcohol. Alcohol is one of the most (mis)used products in the developed world, and is known to have an effect on the CNS. A PD interaction with PSL is therefore considered possible and must be

investigated. Cannabidiol (CBD), in the form of Epidiolex, has recently been registered as treatment for epilepsy in America. Since studies have shown that CBD is a potent suppressor of certain CYP enzymes, that PSL is broken down by this same route, and that both substances may potentially serve as treatment for the same patient population, this study will be conducted to assess the possible effects on PK / PD, safety and observe tolerance when PSL is administered in combination with CBD, or alcohol.

Study objective

Primary
- Part A: Evaluation of pharmacodynamic (PD) interaction between steady-state treatment with padsevonil (PSL) and ethanol
- Part B: Evaluation of pharmacokinetic (PK) interaction between steady-state treatment with padsevonil (PSL) and cannabidiol (CBD)

Secondary
- Part A: Evaluation of pharmacokinetic (PK) interaction between steady-state treatment with padsevonil (PSL) and ethanol
- Part B: Evaluation of pharmacokinetic (PK) interaction between steady-state treatment with padsevonil (PSL) and cannabidiol (CBD)
- Parts A and B: Evaluation of pharmacodynamic (PD) interaction between steady-state treatment with padsevonil (PSL) and ethanol or between steady-state treatment with padsevonil (PSL) and cannabidiol (CBD)
- Parts A and B: Evaluation of safety and tolerability of padsevonil (PSL) in study participants receiving concomitant ethanol or cannabidiol (CBD)

Study design

This is a Phase 1, double-blind, randomized, placebo-controlled, single-center, cross-over study to evaluate the PD, PK, safety, and tolerability of steady state treatment of PSL in healthy study participants receiving either ethanol (Part A) or steady-state treatment of CBD (Part B). Study participants that complete Part A of the study are not eligible to complete Part B; similarly, study participants that complete Part B are not eligible to complete Part A.

Intervention

Padsevonil, placebo of padsevonil ethanol, placebo of ethanol, cannabidiol

Study burden and risks

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 as expected 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.

The healthy study participants included in this study will receive no medical benefit from participation. The risks from taking part in the study will be minimized through the selection of appropriate dose levels, selection of appropriate study participants defined by the inclusion/exclusion criteria, and safety monitoring.

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

- Participant must be 18 to 55 years of age inclusive, at the time of signing the informed consent.
- Participants who are overtly healthy as determined by medical evaluation including medical history, physical examination, laboratory tests, and cardiac monitoring.
- Participant must have previous experience with alcohol consumption and, therefore, must be familiar with the effects and able to tolerate social amounts of alcohol.
- Participant has a body weight of at least 50 kg (males) or 45 kg (females) and body mass index (BMI) within the range 18 to 30 kg/m2 (inclusive)
- Participants are male or female:
A male participant must agree to use contraception as detailed in the protocol during the treatment period and for at least 7 days after the last dose of study treatment and refrain from donating sperm during this period
A female participant is eligible to participate if she is not pregnant, not breastfeeding, and at least 1 of the following conditions applies:
+Not a woman of childbearing potential (WOCBP) as defined n the protocol
OR
+A WOCBP who agrees to follow the contraceptive guidance in the protocol during the Treatment Period and for at least 90 days after the last dose of study treatment.
-Participant must be capable of giving signed informed consent as described in Appendix 1 (Section 10.1), which includes compliance with the requirements and restrictions listed in the informed consent form (ICF).
- Participant must be considered reliable and capable of adhering to the protocol, according to the judgment of the Investigator, and is capable of communicating satisfactorily with the Investigator.

Exclusion criteria

-Participant has any medical or psychiatric condition that, in the opinion of the Investigator, could jeopardize or would compromise the study participant*s ability to participate in this study, such as 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.
- Participant has history or presence of cardiovascular, respiratory, hepatic, renal, gastrointestinal, endocrinological, hematological, or neurological disorders capable of significantly altering the absorption, metabolism, or elimination of drugs; constituting a risk when taking the study intervention; or interfering with the interpretation of data

- Participant has a history of chronic alcohol or drug abuse within the previous 6 months or the presence of drug or alcohol dependency at Screening or Day -1 or tests positive for alcohol and/or drugs at Screening or Day -1
-Participant has a positive prestudy drug screen (to include at minimum: amphetamines, barbiturates, cocaine, opiates, cannabinoids and benzodiazepines).
- Participant has a known hypersensitivity to any components of the study medication or comparative drugs (and/or an investigational device) as stated in this protocol
-Participant has abnormal blood pressure.
-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 Screening.
- Participant has a history of unexplained syncope or a family history of sudden death due to long QT syndrome
- Participant has lymphoma, leukemia, or any malignancy within the past 5 years except for basal cell or squamous epithelial carcinomas of the skin that have been resected with no evidence of metastatic disease for 3 years
- Participant has past or intended use of over-the-counter or prescription medication including herbal medications within 2 weeks or 5 half-lives prior to dosing. Specific mediactions listed in section 6.5.1. may be allowed.
- Participant has used hepatic enzyme-inducing drugs (eg, glucocorticoids, phenobarbital, isoniazid, phenytoin, rifampicin etc.) within 2 months prior to dosing. In case of uncertainty, the Medical Monitor should be consulted.
- Participant has previously received PSL in this or any other study.
- Participant has participated in another study of an IMP (and/or an investigational device) within the previous 30 days of Screening or 5 half-lives whichever is longer or is currently participating in another study of an IMP (and/or an investigational device).
- Participant has alanine transaminase (ALT), aspartate aminotransferase (AST), or alkaline phosphatase (ALP) >1.0x upper limit of normal (ULN)
- Participant has bilirubin >1.0xULN (isolated bilirubin >1.0xULN is acceptable if bilirubin is fractionated and direct bilirubin <35%).
- Participant has current or chronic history of liver disease or known hepatic or biliary abnormalities (with the exception of Gilbert's syndrome or asymptomatic gallstones)
- 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 participants 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.
- Participant has other clinical laboratory test results outside the local reference ranges that are considered as clinically significant by the Investigator. In the case of uncertainty, lab parameters outside the reference ranges can be retested once. If lab parameters outside the reference range are considered as clinically insignificant, the study participant may be allowed in the study, but such inclusions should be agreed with the UCB Study Physician.
- Participant has the presence of hepatitis B surface antigen (HBsAg) at Screening or within 3 months prior to dosing
- Participant has a positive hepatitis C antibody test result at Screening.
- Participant has a positive human immunodeficiency virus (HIV) antibody test at screening.
-Participant has made a blood or plasma donation or has had a comparable blood loss (>450mL) within the last 90 days prior to the Screening Visit. Blood donation during the study is not permitted.
-Participant has a consumption of more than 600mg of caffeine/day (200mL of coffee contains approximately 100mg of caffeine, 200mL of black tea approximately 30mg, and 200mL of cola approximately 20mg).
-Participant smokes more than 5 cigarettes per day (or equivalent) or has done so within 6 months prior to the Screening Visit. Smoking within 48 hours prior to CNS assessments is prohibited.
-Participant ingests grapefruit, passion fruit, or pawpaw (as beverage, fruit, or supplements) within 72 hours before each administration of IMP. If this is the case at the start of the study, study participants may be rescreened.
-Female participants tests positive for pregnancy, plans to get pregnant during the participation in the study, or who is breastfeeding.
-Study participant has a diet that deviates notably from the *normal* amounts of protein, carbohydrate, and fat, as judged by the Investigator.
-Study participant has undergone sudden and/or extreme changes in exercise levels for 2 weeks prior to Screening Visit.

Study design

Design

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

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	17-07-2019
Enrollment:	44
Type:	Actual

Medical products/devices used

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

Ethics review

Approved WMO Date:	19-06-2019
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	21-06-2019
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	01-08-2019
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	05-08-2019
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	10-01-2020

Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	15-01-2020
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	25-02-2020
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	EUCTR2019-000703-32-NL
CCMO	NL69595.056.19