A randomized, double-blind, placebo- and active comparator-controlled, crossover trial to examine the effect of multiple doses of CVL-865 on panic symptoms induced by carbon dioxide inhalation in healthy subjects

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Primary: To investigate if CVL-865 decreases subjective anxiety symptoms elicited by a 35% CO2 inhalation challenge.Secondary: To investigate if CVL-865 decreases subjective fear symptoms elicited by a 35% CO2 inhalation challenge. To investigate if...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Anxiety disorders and symptoms
Study type	Interventional

Summary

ID

NL-OMON49640

Source
ToetsingOnline

Brief title
Effect of CVL-865 on Panic Symptoms Induced by CO2 in Healthy Subjects

Condition

- Anxiety disorders and symptoms

Synonym
anxiety disorder, Panic disorder

Research involving

Human

Sponsors and support

Primary sponsor: Cerevel Therapeutics, LLC
Source(s) of monetary or material Support: Pharmaceutical Industry

Intervention

Keyword: benzodiazepine, cross over, GABAa receptor, panic symptoms

Outcome measures

Primary outcome

Change in the PSL-IV score from pre-CO2 to post-CO2 challenge value.

Secondary outcome

Change in VAS Fear score from pre-CO2 to post-CO2 challenge value.

Change from pre-CO2 to post-CO2 challenge values in vital sign measurements

(systolic blood pressure, diastolic blood pressure, heart

rate) related to the physiological response to CO2 inhalation challenge using

Finapres Assessment.

Treatment-emergent AEs, clinically significant changes in ECGs, clinical

laboratory assessments, vital sign measurements, and physical and neurological

examination results. Suicidality assessed using the C-SSRS.

Summary listing of CVL-865 (and alprazolam, if appropriate) concentrations by

dose and time point.

Change from baseline in NeuroCart

assessments:

o Saccadic eye movements (saccadic reaction time, saccadic peak velocity

[deg/sec], and saccadic inaccuracy)

o Body sway (antero-posterior sway [mm/2 minutes])

o Adaptive tracking (%)

o Bond & Lader VAS (alertness, calmness, mood subscales [mm])

o Quantitative EEG

Study description

Background summary

CVL-865 (formerly known as PF-06372865) is a potent ligand of the allosteric benzodiazepine (BZD) site of the *-aminobutyric acid type A (GABAA) receptor, which is being developed for the treatment of neurological and neuropsychiatric disorders. CVL-865 has the potential to retain highly effective anxiolytic activity through *2 and *3 subunit-containing GABAA receptors, which are thought to mediate the anxiolytic effects of BZDs without the BZD-associated adverse effects that are mediated via the GABAA *1 subunits. The aim of this trial is to evaluate the anxiolytic effects of multiple doses of CVL-865 using an experimental medicine model of carbon dioxide (CO_2) inhalation that is associated with symptoms of anxiety/panic in healthy subjects and is known to be sensitive to the effects of marketed anxiolytic BZDs.

Study objective

Primary:
To investigate if CVL-865 decreases subjective anxiety symptoms elicited by a 35% CO_2 inhalation challenge.

Secondary:
To investigate if CVL-865 decreases subjective fear symptoms elicited by a 35% CO_2 inhalation challenge.
To investigate if CVL-865 modulates the physiological responses elicited by a 35% CO_2 inhalation challenge.
To evaluate the safety and tolerability of CVL-865 following multiple oral doses.
To evaluate the plasma exposure of CVL-865 (and alprazolam, if appropriate) following multiple oral doses.
To evaluate the PD of CVL-865 following multiple oral doses in healthy subjects using NeuroCart assessments.

Study design

This is a 3-cohort, randomized, double-blind, sponsor-open, placebo- and active-controlled, crossover trial in which the pharmacodynamic (PD) effect of multiple doses of CVL-865 and alprazolam will be examined in separate cohorts of 18 subjects
each. The trial will be conducted as a 2-period, 2-sequence crossover design in each cohort comparing high-dose CVL-865 (25 mg twice daily [BID]), low-dose CVL-865 (7.5 mg BID), and alprazolam (1 mg BID) against placebo. Within each of these cohorts, the subjects will be randomized equally to 1 of 2 treatment sequences as shown in Table 2 of the protocol.

Intervention

Test:
CVL-865 7.5 mg (BID)
CVL-865 25 mg (BID)
Alprazolam with extended release 1 mg (BID)

Study burden and risks

CVL-865
CVL-865 is not expected to provide any clinical benefit to healthy subjects. The trial is designed primarily to generate preliminary efficacy, safety, tolerability, and pharmacokinetic (PK) data which will inform further clinical development for the treatment of anxiety disorders. There are no important identified risks for CVL-865. Fetal toxicity, bone marrow suppression, and decrease in peripheral hematologic parameters are important potential risks identified nonclinically; however, these risks will be minimized during the trial by monitoring of hematologic parameters and requiring the use of appropriate contraception and regular pregnancy testing. More detailed information about the known and expected benefits and risks and reasonably expected AEs of CVL-865 are found in the Investigator*s Brochure.

Alprazolam
The BZD alprazolam is a non-selective GABAA PAM and is indicated for the short-term treatment of moderate or severe anxiety states and anxiety associated with depression. The most frequently reported side effects of alprazolam include drowsiness, tiredness, sedation, dizziness, cognitive dysfunction (including memory impairment), constipation, depression, difficulty in urinating, speech disorder, headache, menstrual disease, nervousness, skin rash, tremor, weight gain, weight loss, anxiety, blurred vision, diarrhea, insomnia, decreased libido, increased appetite, irritability, and decreased appetite. In addition, BZDs are associated with a risk of tolerance and dependence following chronic
use. As the subjective anxiogenic effects elicited by the 35% CO_2 double breath inhalation challenge were previously shown to be decreased by alprazolam 1 mg BID (Salvadore et al, 2019), it will be used as active comparator to facilitate

the interpretation of the PD effects of CVL-865. GABAA related PD effects, as well as adverse effects will be monitored using NeuroCart, safety measures, and AE reporting as indicated in the
schedule of assessments. Administration of alprazolam over a period of 8 days is not expected to induce dependence in the selected trial population.

Carbon Dioxide Inhalation Challenge Model
The acute inhalation of 35% CO2 has been developed and validated as a reliable challenge model to induce an acute panic reaction that adequately resembles panic attacks phenomenologically. Both CO2 and O2 are harmless physiological substances that are
inhaled according to a standardized challenge protocol that has been developed by Maastricht University. Numerous trials in several hundred healthy volunteers and patients suffering from panic disorder, social anxiety disorder, post-traumatic stress disorder, and major depressive disorder have been conducted according to this protocol over the past 30 years. In the majority of these trials, a mixture of 35% CO2/65% O2 had been administered as either single or double vital capacity inhalation. To our knowledge in all performed trials, neither acute nor chronic AEs have been reported and no SAEs have occurred. Evidence from prospective trials point out that healthy volunteers who underwent 35% CO2 inhalation were not at greater risk to develop panic disorder in the years following the challenge. To ensure subject safety for the current trial, absolute and relative contra-indications are harmonized with previous protocols and are incorporated into the inclusion and exclusion criteria of the protocol. Details about the 35% CO2 double-breath inhalation procedure, continuous blood pressure, heart rate, and respiratory rate measurement, will be provided in a separate manual attached to this protocol.

Upon arrival, all subjects are required to complete a questionnaire related to the presence of COVID-19 symptoms and/or contact with individuals diagnosed with COVID-19. In addition, a temperature check will be performed. Despite these measures, it cannot be ruled out for certain that an asymptomatic infected subject might undergo the CO2 challenge. Therefore, additional measures regarding disinfection of the CO2 challenge set up will be taken and will be added to the current SOP for performing the CO2 challenge. Staff performing the CO2 challenge will be thoroughly trained on these updated hygiene measures. First, all parts of the set-up that can be disinfected, such as the flowmeter, will be disinfected and all parts that cannot will be replaced after each use. This is described in the updated SOP. Second, subjects should not exhale into the respiratory mask during the double-breath execution as instructed before and during the challenge. However, if by a small chance, this happens, the Microgard II filter inside the respiratory mask has a viral filter efficacy of 99.995% tested on bacteriophages of approximately 30 nm. Per current knowledge, the SARS-CoV-2 virus is approximately 80 to 160 nm in size, thus, the filter will filter out the SARS-CoV-2 virus. This means that every component distal to the filter can be regarded as sterile. Third, the demand valve is 1-directional only, making it impossible to contaminate the gas

canister. Fourth, the CO2 sample line proximal to the filter that runs to the capnograph is also 1-directional only, meaning the air is directed away from the subject, which implies no virus loaded air can be inhaled by the subject. Finally, to guarantee a well-ventilated environment, the room in which the CO2 challenge is being performed is equipped with mechanical ventilation, and doors and windows will be kept open for a minimum of 30 minutes after performing each challenge, to ventilate the room. Altogether, conducting the CO2 challenge is considered safe under the condition that the extra safety measures related to hygiene, as described in the updated SOP, are taken. The risk of transmission of the SARS-CoV-2 virus by conducting the CO2 challenge during trial periods is assessed as not being increased: all subjects staying in the clinic overnight will be tested for SARS-CoV-2 infection and only subjects testing negative will be included in the trial. Two different CO2 challenge set ups will be used; one for the screening period and one for the trial periods. This ensures that the set up for the trial periods will only be used by subjects who have tested negative for infection with SARS-CoV2.

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. Healthy male and female subjects, ages 18 to 55 years, inclusive, at the time of signing the ICF.
3. A female subject of childbearing potential who is sexually active with a nonsterilized male partner must agree to use a highly effective method of contraception from signing of informed consent and for 30 days post last dose. A male subject with a pregnant or a nonpregnant partner of childbearing potential must agree to use condom during treatment and until the end of relevant systemic exposure in the male
subject for 94 days following the last dose with IMP.
6. Defined as sensitive to the anxiogenic effects of double-breath CO2 inhalation as defined in the protocol section 4.1.

Exclusion criteria

1. Subjects with a current history of clinically significant cardiovascular (eg, history or suspicion of infarct, cardiomyopathy, cardiac failure, transient ischemic attack, angina pectoris, cardiac arrhythmias, or cerebrovascular accident), pulmonary, gastrointestinal, renal, hepatic, metabolic, hematological, immunological, or neurological disease that, in the opinion of the investigator or medical monitor, could compromise either subject safety or the results of the trial.
2. Subjects with a current or past history of clinically significant respiratory conditions, including asthma, lung fibrosis, and non-invalidating chronic obstructive pulmonary disease.
3. Subject with a personal or family history of sickle cell anemia.
4. Subject with a personal or family history of cerebral aneurysm.
5. Subjects with a clinically significant current or past personal or family history of any
psychiatric disorder as classified by DSM-4 or DSM-5 criteria.
27. Subjects that test positive for a SARS-CoV-2 infection on day -1

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):	06-10-2020
Enrollment:	54
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	CVL-865 (formerly known as PF-06372865)
Generic name:	NA
Product type:	Medicine
Brand name:	Xanax
Generic name:	Alprazolam
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	24-03-2020
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	08-05-2020
Application type:	First submission

Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	01-09-2020
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	EUCTR2019-004199-20-NL
CCMO	NL72639.056.20