A 2-Part, Randomized, Double-blind, Double-Dummy, Placebo- and Active Comparator-controlled, Repeat Dose Study to Establish Proof-of-Concept of GRX-917 in Experimentally Induced Panic and to Further Characterize its Repeated Dose Pharmacokinetics and Pharmacodynamics in Healthy Subjects

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Part 1:Primary Objective- To investigate whether repeated dose GRX-917 reduces panic symptoms elicited by an experimental 35% CO2 -induced fear challenge administered in healthy CO2-sensitive subjects. Secondary Objectives- To investigate whether...

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

Summary

ID

NL-OMON51369

Source
ToetsingOnline

Brief title
GRX-917 on CO2 Challenge Induced Panic in Healthy Subjects

Condition

- Anxiety disorders and symptoms

Synonym
anxiety disorder, Panic disorder

Research involving
Human

Sponsors and support

Primary sponsor: GABA Therapeutics Australia Pty. Ltd.
Source(s) of monetary or material Support: GABA therapeutics

Intervention

Keyword: CO2 challenge, GRX-917, Healthy volunteers, Panic

Outcome measures

Primary outcome

Part 1:

• Difference in mean change from baseline in the PSL-IV total score from

pre-CO2 to post-CO2 challenge

Part 2:

• Geometric mean accumulation ratios (Day 27 vs. Day 1) for GRX-917 and major

metabolite (M4) for Cmax and AUC0-24 in plasma.

• GRX-917 and major metabolite, M4, concentrations by dose and time point. CSF

PK parameters to be assessed include Tmax, Cmax, Cmin, AUC0-t, AUC0-24,

AUC0-inf, t*, CSF/plasma and metabolite-parent ratios.

Secondary outcome

Part 1 and 2

• Difference in mean change in VAS Fear score from pre-CO2 to post-CO2

challenge

• Difference in mean change from pre-CO2 to post-CO2 challenge in vital sign measurements (systolic blood pressure, diastolic blood pressure, heart rate) related to the cardiovascular response to CO2 inhalation challenge using Finapres Assessments

• GRX 917 and major metabolite, M4 plasma concentrations

• NeuroCart assessments:

o Absolute measurements and change from baseline of saccadic eye movements (saccadic reaction time, saccadic peak velocity [deg/sec], and saccadic inaccuracy)

o Absolute and change from baseline body sway (antero-posterior sway [mm/2 minutes])

o Absolute and change from baseline of adaptive tracking (%)

o Absolute and change from baseline of Bond & Lader VAS (alertness, calmness, mood subscales [mm])

• Absolute and change from baseline of Quantitative electroencephalograms (qEEG) (eyes open-eyes closed)

• Treatment-emergent AEs, clinically significant changes in Electrocardiogram (ECG) parameters, clinical laboratory assessments, vital sign measurements, physical and neurological examination results, and suicidality as assessed by C-SSRS

Study description

Background summary

The pharmacological treatment of anxiety disorders and anxiety-related states is limited by important shortcomings. Currently available first-line treatments such as Selective serotonin reuptake inhibitors (SSRIs) and Serotonin and Norepinephrine Reuptake Inhibitors (SNRIs) are characterized by slow onset of action and/or (partial) ineffectiveness in up to 50% of patients, and although benzodiazepines (BZDs) as second line treatment are effective, their use is limited by side effects such as sedation, memory deficits, risk of falling, and liability for dependence and abuse. Altogether, there is a need for novel anxiolytic compounds with superior efficacy and improved side effect profiles compared to currently available drugs.

Etifoxine hydrochloride (etifoxine; Stresam®) is an anxiolytic drug approved in France in 1979 and has demonstrated efficacy comparable to BZDs such as lorazepam, alprazolam, and clonazepam. It primarily potentiates neurosteroidogenesis via targets distinct from those engaged by BZDs, and demonstrates a side effect profile superior to BZDs. Moreover, etifoxine demonstrates therapeutic uses in anxiety-related states, depression, and epilepsy.

GRX-917 is a novel, deuterated form of etifoxine hydrochloride that potentiates neurosteroidogenesis. The major circulating metabolite of GRX-917 M4 (N-desethyl metabolite) does not contribute to the anxiolytic activity.

In early phase CNS drug trials, challenge paradigms are often applied to demonstrate pharmacodynamic effects in healthy human subjects. Particularly, in anxiolytic drug development, challenges that experimentally induce anxiety and/or fear are especially relevant to novel mechanisms-of-action such as neurosteroidogenesis, since anxiolytic effects are not expected under basal, non-challenged circumstances in healthy volunteers. This approach can increase confidence moving forward towards larger proof-of-concept and/or therapeutic trials in anxiety patient populations. Although various pharmacological and behavioural challenges have been used to this effect in the past, outcomes have been largely inconsistent due to inadequate validation and/or methodological variability across research groups. Acute intrapulmonary administration of carbon dioxide (CO_2) has however consistently demonstrated the provocation of a panic reaction in sensitive healthy volunteers that phenomenologically and physiologically resembles panic attacks in patients with anxiety disorders. In addition, it has been shown to be sensitive to pharmacological manipulation by a range of drugs used to treat anxiety disorders and emerging new treatments with novel mechanisms of action. CO_2 inhalation in humans therefore displays adequate face-validity as a panic challenge in experimental drug research for proof-of-anxiolysis of novel compounds such as GRX-917.

Study objective

Part 1:
Primary Objective
- To investigate whether repeated dose GRX-917 reduces panic symptoms elicited by an experimental 35% CO2 -induced fear challenge administered in healthy CO2-sensitive subjects.

Secondary Objectives
- To investigate whether repeated dose GRX-917 reduces subjective fear elicited by an experimental 35% CO2 -induced fear challenge in healthy CO2-sensitive subjects
- To investigate if repeated doses of GRX-917 modulate the cardiovascular response elicited by an experimental 35% CO2 -induced fear challenge in healthy CO2-sensitive subjects
- To further characterize the plasma pharmacokinetics (PK) of repeated doses of GRX-917 and its major metabolite, M4, in healthy CO2-sensitive subjects
- To evaluate the pharmacodynamic (PD) effects of GRX-917 following single and multiple oral doses using NeuroCart assessment in healthy CO2-sensitive subjects
- To further investigate the safety and tolerability of multiple dose GRX-917 in healthy CO2-sensitive subjects

Part 2:
Primary Objective
- To explore whether repeated doses of GRX-917 up to 27 days is associated with auto-induction of its metabolism in healthy subjects
- To characterize the CSF PK of GRX-917 and its major metabolite M4 following repeated doses up to 27 days

Secondary Objectives
- To further characterize the plasma PK of GRX-917 and its major metabolite M4 following repeated doses up to 27 days
- To further explore the safety and tolerability of GRX-917 repeated doses up to 27 days
- To evaluate the pharmacodynamic (PD) effects of GRX-917 following multiple oral doses using NeuroCart assessment in healthy subjects

Study design

Part 1 (Proof-of-Concept)
Randomized, Double-blind, Double-Dummy, Placebo- and Active Comparator-controlled study investigating the potential panicolytic effects of GRX-917 following repeated dosing using an experimental CO2 inhalation challenge in healthy volunteers.
The 35% CO2 double-breath inhalation challenge test will be used to provoke subjective fear and its related physical symptoms.

Part 2 (Plasma and CSF pharmacokinetics and pharmacodynamics)
Open-label, repeated dose administration of 27 days (10 days total in-house

dosing and 17 days total outpatient dosing).

Intervention

GRX-917
Alprazolam

Study burden and risks

GRX-917
GRX-917 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 amongst others anxiety disorders.
There are no important identified risks for GRX-917, however, preclinical testing with GRX-917 has demonstrated the potential for prolongation of the QT interval. More detailed information about the known and expected benefits and risks and reasonably expected AEs of GRX-917 are found in the Investigator*s Brochure.
The study design has been used previously in many studies and is accepted by scientists and regulatory authorities. All study drug administrations for part 1 will be done in the clinic under medical supervision. Thus, the subjects can be closely monitored for any adverse signs during the different treatments. Therefore, providing the protocol is adhered to, careful observation and medical management will minimize any associated risk in this study. For part 2, the first two dosing will be done under medical supervision. Subsequently, the subject leaves the Clinical Research Unit if the IMP is well tolerated by the subjects. The subjects then continue the outpatient dosing at his own home.

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. As the subjective anxiogenic effects elicited by the 35% CO2 double breath inhalation challenge were previously shown to be decreased by alprazolam 1 mg BID (Salvadore et al, 2019, and Cerevel 2022), it will be used as active comparator to facilitate the interpretation of the PD effects of GRX-917. Administration of alprazolam over a period of 8 days is not expected to induce dependence in the selected trial population.

CO2 inhalation
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 the best of CHDR*s knowledge in all performed trials, neither acute nor chronic related AEs have been reported and no related 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.

CSF sampling
The procedure of continuous CSF sampling by indwelling CSF catheters has been demonstrated to be safe and well tolerated in previous studies performed by CHDR. Side effects were generally mild, with headache, back pain and catheter site pain most frequently reported.

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

- Healthy male and female subjects ages 18 to 55 years (Part 1) and 45 to 65 years (Part 2), inclusive, at the time of signing the ICF.
- (Part 1 only): Defined as sensitive to the anxiogenic effects of double-breath CO2 inhalation as defined in the protocol.
- A female subject of childbearing potential who is sexually active with a non-sterilized male partner must agree to use double highly effective method of contraception from signing of informed consent and for 90 days post last dose. A male subject with a pregnant or a nonpregnant partner of childbearing potential must agree to also use double highly effective method of contraception (i.e., condom or abstinence) during treatment and until the end of relevant systemic exposure in the male subject for 90 days following the last dose.

Exclusion criteria

- Subjects with a current history of clinically significant cardiovascular, pulmonary, gastrointestinal, renal, hepatic, metabolic, haematological, 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.
- (Part 1 only): Subjects with a current or past history of clinically significant respiratory conditions, including asthma, lung fibrosis, and non-invalidating chronic obstructive pulmonary disease.
- 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.
- Subjects with epilepsy.
- (Part 2 only): Females with irregular cycles or females with regular cycles of more than 35 days
- Subject has a history of malignancy within 5 years before screening.
- Use or intend to use any medications/products which are known moderate or strong inhibitors or inducers of the CYP2B6, CYP3A4, CYP2C19 or CYP2D6 enzymes for 28 days prior to Check-in on Day 1 and throughout the trial

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:	Pending
Start date (anticipated):	15-12-2022
Enrollment:	89
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	GRX-917
Generic name:	NA
Product type:	Medicine
Brand name:	Xanax
Generic name:	Alprazolam
Registration:	Yes - NL intended use

Ethics review

Approved WMO

Date:	07-11-2022
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

Approved WMO

Date:	25-11-2022
Application type:	First submission
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	EUCTR2022-003134-39-NL
CCMO	NL82626.056.22