A Multiple Ascending Dose Study to Evaluate Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of ENX-101 at Plasma Steady State in Healthy Volunteers

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Primary Objective:- To evaluate the safety and tolerability of ENX-101 following repeated doses in healthy volunteersSecondary Objective:- To evaluate the effects of ENX-101 on the following electrocardiogram (ECG) parameters in healthy volunteers:...

Ethical review	Approved WMO
Status	Completed
Health condition type	Neurological disorders NEC
Study type	Interventional

Summary

ID

NL-OMON51175

Source
ToetsingOnline

Brief title
MAD of ENX-101 in healthy volunteers

Condition

- Neurological disorders NEC

Synonym
and anxiety disorders, Epilepsy, spasticity

Research involving
Human

Sponsors and support

Primary sponsor: Engrail Therapeutics, Inc.
Source(s) of monetary or material Support: Engrail Therapeutics

Intervention

Keyword: ENX-101, Healthy Volunteers, Pharmacodynamics, Pharmacokinetics

Outcome measures

Primary outcome

The safety and tolerability of ENX-101 will be assessed by the following:

- AEs

- Vital signs (2-positional blood pressure and HR, respiratory rate, and

tympanic body temperature)

- 12-lead ECG

- 24-hour continuous 12-lead ECG Holter monitoring (Part 1 only)

- Clinical laboratory tests (hematology, serum chemistry, urinalysis)

- Physical examination

- Pregnancy test (where applicable)

- C-SSRS

- MOAA/S

- LSEQ (Part 2 only)

- CSD-Core (Part 2 only)

Secondary outcome

Pharmacokinetic Measures:

Blood will be collected before and after ENX-101 administration for

bioanalytical measurement of plasma levels of ENX-101 and metabolites

(ENX-101-M3, triazole aldehyde, triazole alcohol, and triazole acid). The time points for collecting blood and the evaluation parameters are as follows:

Part 1

- Day 1: Pre-dose and at 0.5, 1, 2, 3, 4, 5, 6, 7, 8, 10, and 12 hours after dosing
- Day 2: Pre-dose (24 hours after Day 1 dose) and 1, 2, 4, 6, 8, 10, and 12 hours after dosing
- Days 3, 4, 5, 6, 7, and 8: Pre-dose (24 hours after the previous day*s dose)
- Day 9: Pre-dose (24 hours after Day 8) and 1, 2, 4, 6, 8, 10, and 12 hours after dosing
- Day 10: Pre-dose (24 hours after Day 9) and at 0.5, 1, 2, 3, 4, 5, 6, 7, 8, 10, and 12 hours after dosing
- Days 11, 12, 13: At 24, 36, and 72 hours, respectively, after Day 10 dosing

The plasma concentration-time data for ENX-101 and, if possible, its metabolites will be analyzed using non-compartmental methods. The following PK parameters will be evaluated: maximum plasma concentration (Cmax), time to reach maximum plasma concentration (Tmax), area under the plasma concentration-time curve from administration to the end of dosing (AUC0-t), AUC from administration to 24 hours after dosing (AUC0 24), AUC extrapolated to infinite time (AUC0-*), plasma concentration half-life (t1/2),terminal rate constant (*z), apparent total clearance of the drug from plasma after oral administration (CL/F), apparent volume of distribution during terminal phase after non-intravenous administration (Vz/F), and metabolite/parent (M/P) ratio. Other parameters may be evaluated. Actual elapsed time from dosing will be used

to estimate all subject plasma PK parameters.

Part 2

* Day 1: Pre-dose

* Day 2: 12, 16, and 20 hours post-dose

* Day 3 through Day 10: 12 hours post-dose

* Day 11: 12, 16, and 20 hours post-dose

Day 12 and Day 13

Pharmacodynamic Measures:

PD assessments will be conducted at Baseline on Day *2 and on Day 2 and Day 9

as follows:

- NeuroCart assessments

o Saccadic eye movements, saccadic reaction time (seconds), saccadic peak

velocity (degrees/second), and saccadic inaccuracy (%)

o Smooth pursuit eye movements (percentage of time the eyes of the subject are

in smooth pursuit of the target) (%)

o Adaptive tracking (average performance) (%)

o Body sway (antero-posterior sway) (mm)

o Pupil size

o VAS according to Bond and Lader to assess mood, alertness, and calmness (mm)

o VAS according to Bowdle to assess internal perception, external perception,

and feeling high (mm)

- Cognitive assessment

o VVLT (learning+immediate recall/delayed recall/delayed recognition)

- qEEG

Part 2

PD assessments will be conducted at Baseline either on the evening of Day -1 (PSG) or on the morning of Day 1 (NeuroCart, VVLT), followed by pre-dose assessments on the evening of Day 1 prior to either PSG electrode placement (NeuroCart) or approximately 45 minutes prior to night-time dosing (VVLT), and post-dose assessments in the evening of Day 1 and Day 10 (PSG), and in the morning Day 2 and Day 11 (NeuroCart, VVLT), as follows:

* NeuroCart assessments

o Saccadic eye movements, saccadic reaction time (seconds), saccadic peak velocity (degrees/second), and saccadic inaccuracy (%)

o Smooth pursuit eye movements (percentage of time the eyes of the subject are in smooth pursuit of the target) (%)

o Adaptive tracking (average performance) (%)

o Body sway (antero posterior sway) (mm)

o Pupil size

o VAS according to Bond and Lader to assess mood, alertness, and calmness (mm)

o VAS according to Bowdle to assess internal perception, external perception, and feeling high (mm)

* Cognitive assessment

o VVLT (learning + immediate recall/delayed recall/delayed recognition)

* Polysomnography

o EEG spectra

o total sleep time

o latency to persistent sleep

o wake after sleep onset

o rapid-eye movement (REM) sleep variables

Part 1 only

Optional Genetic Testing:

One additional blood sample will be collected for potential genotyping of

cytochrome P450 (CYP) polymorphisms if the PK data are sufficiently variable to

warrant exploration of potential impact of CYP polymorphisms on ENX-101

exposure.

Study description

Background summary

Gamma-aminobutyric acid A (GABAA) receptors are a family of ligand-gated chloride channels that function as inhibitory neurotransmitter receptors in the central nervous system (CNS). The GABAA receptor is a pentameric protein with subtypes composed of *, *, and * subunits. Typical benzodiazepines activate the receptor in a non-selective manner, binding to an allosteric site at the interface of a * subunit and either an *1, *2, *3, or *5 subunit (Schwartz, 1988; Rudolph and Knoflach, 2011). Agonism at the *2 and *3 subtypes is believed to be associated with anxiolytic and spasmolytic activities, whereas *5 subtype activity is believed to have cognitive effects (McKernan and Whiting, 1996). Engrail has advanced ENX-101, a non-benzodiazepine, as a promising subtype-selective GABAA positive allosteric modulator (PAM) for epilepsy, spasticity, and anxiety disorders.

Seizures frequently result from an imbalance of excitation and inhibition due

to a failure of inhibitory neurotransmission (Marafiga et al., 2020). Most agents that enhance GABAA receptor function have antiseizure properties due to their ability to increase inhibitory neurotransmitter tone. The evidence linking epilepsy with dysfunction of GABAergic inhibition is substantial and has been extensively reviewed (Mody and Pearce, 2004; Olsen and Sieghart, 2008; D*Hulst et al., 2009; Rudolph and Knoflach, 2011).

L-838417, which was initially evaluated by Merck as part of a research effort to identify subtype-selective GABAA anxiolytics with reduced sedation and ataxia, was reported to possess a particularly attractive subtype-selective GABAA pharmacologic profile, with partial agonism at *2,3,5 and antagonism at *1, and it was advanced through non-clinical development into Phase 1 clinical evaluation. However, despite its desirable GABAA subtype selectivity, publications from Merck indicate that L-838417 possessed a poor nonclinical PK profile, and it was not further developed (Scott-Stevens et al., 2005).

ENX-101 is a deuterated analog of L-838417 designed to retain the pharmacological activity of L-838417 yet with a preferred PK profile. ENX-101 exhibits potent affinity for GABAA *1, *2, *3, and *5 subtypes (pKi = 0.79, 0.67, 0.67, and 2.3 nm, respectively). Whereas ENX-101 lacks functional activity at *1 (i.e., is an antagonist at *1), it functions as a PAM with approximately 35% to 40% maximal response at *2, *3, and *5. Furthermore, ENX-101 demonstrates an improved PK profile as compared to L-838417. Thus, ENX-101 is an *2,3,5 subtype-selective modulator of the GABAA receptor that represents a potential new therapeutic modality for the treatment of spasticity, epilepsy, and other CNS disorders..

To date, ENX-101 has been tested in 101 volunteers in both single ascending dose (SAD) and multiple ascending dose (MAD) studies. Single doses up to and including 60 mg ENX-101 and multiple daily doses up to and including 12 mg ENX-101 administered for 10 days were safe and generally well tolerated (see Section 6.2.2). ENX-101 also demonstrated dose-related target engagement using positron emission tomography (PET). This study is designed to extend previous clinical investigation of ENX-101 to higher doses administered daily for 10 days.

Study objective

Primary Objective:
- To evaluate the safety and tolerability of ENX-101 following repeated doses in healthy volunteers
Secondary Objective:
- To evaluate the effects of ENX-101 on the following electrocardiogram (ECG) parameters in healthy volunteers: cardiac repolarization (corrected QT interval [QTc]), heart rate (HR), PR and QRS intervals, T-wave morphology, and U-wave presence
- To evaluate the pharmacokinetics (PK) of ENX-101 and, if possible, ENX-101

metabolites (ENX-101-M3, triazole aldehyde, triazole alcohol, and triazole acid), in plasma of healthy volunteers after the first dose and at plasma steady state
- To determine the effects of ENX-101 on a battery of pharmacodynamic (PD) measures (NeuroCart®) including saccadic eye movements, smooth pursuit eye movements, adaptive tracking, body sway, pupil size, Bond and Lader visual analogue scale (VAS), and Bowdle VAS
- To determine the effects of ENX-101 on the Visual Verbal Learning Task (VVLT)
- To determine the effects of ENX-101 on quantitative electroencephalographic (qEEG) parameters
- To determine the effects of ENX-101 on sedation with the Modified Observer's Assessment Alertness/Sedation (MOAA/S)
* To determine the effects of ENX-101 on polysomnography (PSG) parameters
* To evaluate the influence of evening dosing on tolerability of ENX 101

Study design

This is a randomized, double-blind, placebo-controlled, multiple ascending dose study in healthy volunteers.
The study will be conducted in 2 parts.
Part 1 (daily doses administered in the morning)
Part 2 (daily doses administered in the evening)

Intervention

ENX-101 formulated as Size 2 capsules each containing 5 mg ENX-101, which will be supplied to the pharmacy in bulk.
Subjects will be administered ENX-101 orally, once daily, in the morning with water at the following doses:
* Cohort 1: 5 mg (administered as one 5 mg ENX-101 capsule) in the morning with water
* Cohort 2: 10 mg (administered as two 5 mg ENX-101 capsules) in the morning with water
* Cohort 3: 15 mg (administered as three 5 mg ENX-101 capsules) in the morning with water
* Cohort 4: 25 mg (administered as five 5 mg ENX-101 capsules) in the morning with water
* Cohort 5: 50 mg (administered as ten 5 mg ENX-101 capsules) in the morning with water
* Cohort 6: maximum of 25 mg administered in the evening with water; exact dose dependent on DEC review of Part 1 data

Placebo formulated as Size 2 capsules, which will be supplied to the pharmacy in bulk.
Subjects will be administered placebo orally, once daily, as follows:
* Cohort 1: administered as 1 placebo capsule in the morning with water

* Cohort 2: administered as 2 placebo capsules in the morning with water
* Cohort 3: administered as 3 placebo capsules in the morning with water
* Cohort 4: administered as 5 placebo capsules in the morning with water
* Cohort 5: administered as 10 placebo capsules in the morning with water
* Cohort 6: placebo capsules administered in the evening with water; number of capsules dependent on DEC review of Part 1 data (up to cohort 4)

Study burden and risks

No therapeutic benefit is anticipated for participants of this study, as is common for most Phase 1 studies involving healthy participants. The evaluation of potential risks of ENX-101 in humans is based on available data from non-clinical toxicology and safety pharmacology studies as well as prior clinical trial exposure of 101 healthy volunteers.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)

Inclusion criteria

Subjects must meet all the following criteria to be eligible for the study:
1. Healthy male and female volunteers aged 18 to 55 years, inclusive, at Screening
2. Capable of giving written informed consent
3. Willing to give written consent to have data entered into *Verified Clinical Trials*
4. Female subjects
a. Of non-childbearing potential, defined as either permanently sterilized (at least 4 months after surgical sterilization including bilateral salpingectomy, tubal ligation, or oophorectomy with or without hysterectomy) or post-menopausal (defined as amenorrhea for 12 consecutive months and documented plasma follicle-stimulating hormone level >40 IU/mL; in the event a subject's menopausal status has been clearly established and yet serum follicle-stimulating hormone levels are not consistent with a post-menopausal status, determination of the subject*s eligibility to be included in the study will be at the Investigator*s discretion following consultation with the Sponsor), and with a negative pregnancy test at Screening and Day *2; OR
b. Of childbearing potential and willing to use 2 effective methods of contraception (i.e., established method of contraception + condom) or remain abstinent (where abstaining from sexual intercourse is in line with the preferred and usual lifestyle of the subject) from Day *2 through 3 months after the last dose of study drug, and with a negative pregnancy test at Screening and Day *2
5. Male subjects who, if fertile (defined as post-pubertal and not permanently sterile by orchidectomy or vasectomy) must be willing to use a condom or remain abstinent (where abstaining from sexual intercourse is in line with the preferred and usual lifestyle of the subject) from Day *2 through 3 months after the last dose of study drug
6. Body mass index of 18 to 35 kg/m2 at Screening
7. Willing and able to comply with all study requirements including the following:
a. Reside in the inpatient unit from Day *2 until discharge on Day 13
b. Refrain from strenuous exercise from Day *4 until Day 13
c. Abstain from grapefruit-, alcohol-, caffeine-, or xanthine-containing products from Day *4 through Day 13
Part 2 Subjects Only
8. Subjects must have sleep pattern of going to bed between 10:00 pm and 12:00 am over the 4 weeks prior to Screening through to Day -2
9. Subjects must have been sleeping at least 6 to 8 hours per night over the 4 weeks prior to Screening through to Day -2

Exclusion criteria

Subjects meeting any of the following exclusion criteria will not be enrolled in the study:
1. Clinically significant abnormality within 2 years of Screening that in the Investigator*s opinion may place the subject at risk or interfere with study outcome variables; this includes, but is not limited to, history of or current cardiac, renal, neurologic, gastrointestinal, pulmonary, endocrinologic, hematologic, or immunologic disease or history of malignancy
2. History of convulsions (other than benign febrile convulsions of childhood) including epilepsy, or personal history of significant cerebral trauma or central nervous system infections (e.g., meningitis)
3. History or evidence of significant ophthalmologic or neurologic condition that would adversely affect the eye movement assessments
4. History or evidence of any medical condition potentially altering the absorption, metabolism, or elimination of drugs; this includes a surgical history of the gastrointestinal tract affecting gastric motility or altering the gastrointestinal tract
5. Any of the following cardiovascular conditions at Screening or Day *2:
a. History or evidence of any of the following:
i. Myocardial infarction
ii. Cardiac valvulopathy
iii. Cardiac surgery revascularization (coronary artery bypass grafting or percutaneous transluminal coronary angioplasty)
iv. Unstable angina
v. Cerebrovascular accident or stroke or transient ischemic attack
vi. Pacemaker
vii. Atrial fibrillation, flutter, or non-sustained or sustained ventricular tachycardia
viii. Pulmonary arterial hypertension
ix. Sick sinus syndrome, second- or third-degree atrioventricular block
x. Uncontrolled hypertension
xi. Congestive heart failure
xii. Family history of sudden death or personal history of long QT syndrome
xiii. Hypokalemia
xiv. Unexplained syncope or syncope within the last 3 years regardless of etiology
b. Electrographically and clinically significant abnormalities, as judged by the Investigator, that might interfere with ECG analysis, including evidence of a previous myocardial infarction, significant left ventricular hypertrophy, flat T waves (particularly in the inferior leads), or more than minor non-specific ST-T*wave changes
c. Rhythm other than sinus rhythm
d. Mean HR <50 beats per minute (bpm) or >100 bpm
e. Mean systolic blood pressure >140 mm Hg; mean diastolic blood pressure >90 mm Hg

f. QTc interval using Fridericia*s formula (QTcF) >450 msec in males or >470 msec in females
g. QRS interval *120 msec
h. PR interval >200 msec
6. Reports having experienced suicidal ideation (Type 4 or 5 on the C-SSRS) within 30 days prior to Screening, any suicidal behavior within 2 years prior to Screening (any *Yes* answers on Suicidal Behavior section of C-SSRS), and/or the Investigator assesses the subject to be a safety risk to him/herself or others
7. Diagnosis of any sleep disorder (including narcolepsy, central sleep apnea, sleep related hypoventilation, circadian rhythm sleep-wake disorders, substance/medication induced sleep disorder or parasomnias - NREM sleep arousal disorders, nightmare disorder, REM sleep behavior disorder for Part 2) in the last 6 months or current complaints of sleep disturbance or daytime symptoms attributable to unsatisfactory sleep or shift worker whose routine work hours overlap with the typical sleep period (including habitual daytime naps, travel across 3 different time zones in the last 2 weeks for Part 2).
8. History or evidence of moderate or severe Substance Use Disorder as defined by the Diagnostic and Statistical Manual of Mental Disorders (5th Edition)
9. Is a smoker or has used nicotine or nicotine-containing products within 90 days of Screening and/or will not agree to abstain from nicotine use during the study; this includes cigarettes, e-cigarettes, and nicotine replacement or nicotine-containing products
10. Has a positive qualitative drug or alcohol test at Screening or Day *2
11. Ingested any concomitant medication (excluding hormonal birth control) within 5 half-lives or 30 days (whichever is longer) prior to Day 1
12. Any subject who has received any known hepatic- or renal-clearance-altering agents (e.g., erythromycin, cimetidine, barbiturates, phenothiazines, etc.) for a period of 90 days prior to Day 1
13. Clinically significant abnormal findings in serum chemistry, coagulation, hematology, or urinalysis results at Screening or Day *2
14. Elevated >2 × upper limit of normal liver enzymes (alanine aminotransferase and/or aspartate aminotransferase) and/or bilirubin at Screening or Day *2
15. Clinically significant abnormal findings in vital sign assessments at Screening or Day *2
16. History of hepatitis B or hepatitis C or demonstration of hepatitis B surface antigen or hepatitis C antibody at Screening
17. History of human immunodeficiency virus (HIV) infection or demonstration of HIV antibodies at Screening
18. History of any confirmed significant allergic reactions (urticaria or anaphylaxis) against any drug or any multiple drug allergies (non-active hay fever is acceptable)
19. Donated >500 mL blood or plasma within 30 days prior to Day 1 or has lost >1200 mL of blood within 4 months prior to Day 1
20. Receipt of an investigational drug within 90 days or 5 half-lives, whichever is longer, prior to Day 1 or currently in the follow-up period of another clinical trial at the time of Screening

21. Any other condition that, in the Investigator's opinion, might indicate that the subject is unsuitable for the study (e.g., information provided by the general practitioner, if available)
22. Subject is unable to comply with the requirements of the study or, in the opinion of the Investigator, should not participate in the study

Study design

Design

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

Recruitment

NL

Recruitment status:	Completed
Start date (anticipated):	13-04-2021
Enrollment:	53
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	ENX-101
Generic name:	NA

Ethics review

Approved WMO

Date:	04-02-2021
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek

	(Assen)
Approved WMO Date:	22-03-2021
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	08-09-2021
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	21-09-2021
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	EUCTR2020-006074-73-NL
CCMO	NL76363.056.21

Study results

Date completed:	03-12-2021
Results posted:	12-09-2022

First publication
03-08-2022