ISRCTN18262237 https://doi.org/10.1186/ISRCTN18262237

Study to investigate the safety of ENX-101 and how well it works in healthy volunteers.

Submission date
06/07/2023

Recruitment status
No longer recruiting

Registration date
19/07/2023

Overall study status
Completed

Last Edited
19/07/2023

Condition category
Other

[ ] Prospectively registered
[ ] Protocol
[ ] Statistical analysis plan
[ ] Results
[ ] Individual participant data
[ ] Record updated in last year

Plain English summary of protocol

Background and study aims
ENX-101 is a new investigational drug that is being developed as part of the treatment of epilepsy and anxiety disorders, among others. It will be investigated how safe the new drug ENX-101 is, how well it works and what its effects are. The effect of ENX-101 will be compared with the effect of a placebo (dummy drug).

Who can participate?
Healthy male and female volunteers aged 18 to 55 years

What does the study involve?
Part 1:
Participants will be screened within 28 days of Day 1. Eligible participants will be admitted to the inpatient unit on Day –2 (2 days before the start of dosing on Day 1). Participants are expected to remain confined for 15 days, and discharge will be contingent upon the clinical assessment and judgment of the Investigator. The 15-day period includes a 2-day Baseline Period (Day –2 to Day –1), a 10-day Treatment Period (Day 1 through Day 10), and a 3-day Follow-up Period (Day 11 through Day 13). Discharge is planned for Day 13. A follow-up telephone call will be made at 1 week after discharge.

Part 2:
Participants will be screened within 28 days of Day 1. Eligible participants will be admitted to the inpatient unit on Day –2 and will be expected to remain confined for 15 days; discharge will be contingent upon the clinical assessment and judgment of the Investigator. The 15-day period will include a 2-day Baseline Period (Day -2 to Day -1), a 10-day Treatment Period (Day 1 through Day 10), and a 3-day Follow-up Period (Day 11 and Day 13). Discharge is planned for Day 13. A follow-up telephone call will be made 1 week after discharge.

What are the possible benefits and risks of participating?
No medical benefit can be expected from this study for the participants. ENX-101 has been used in a clinical trial before and was well tolerated, with the most common side effects being fatigue and dizziness.

Where is the study run from?
Centre for Human Drug Research (Netherlands)

When is the study starting and how long is it expected to run for?
January 2021 to September 2022

Who is funding the study?
Engrail Therapeutics, Inc. (USA)

Who is the main contact?
Stephanie Parks, Stephanie.Parks@engrail.com

Contact information

Type(s)
Public

Contact name
Miss Pauline Nettesheim

ORCID ID
https://orcid.org/0000-0002-0330-3467

Contact details
Zernikedreef 8
Leiden
Netherlands
2333 CL
+31 (0)71 5246 400
clintrials@chdr.nl

Additional identifiers

Clinical Trials Information System (CTIS)
2020-006074-73

ClinicalTrials.gov (NCT)
Nil known

Protocol serial number
CHDR2033

Study information

Scientific Title
A multiple ascending dose study to evaluate the safety, tolerability, pharmacokinetics, and pharmacodynamics of ENX-101 at plasma steady state in healthy volunteers

Acronym

ENX-101

Study objectives
ENX101 shows pharmacokinetic and pharmacodynamic preferable profile for future in clinic use

Ethics approval required
Ethics approval required

Ethics approval(s)
approved 22/03/2021, Stichting BEBO (Dr. Nassaulaan 10, Assen, 9401 HK, Netherlands; +31 (0) 592 405 871; info@stbebo.nl), ref: NL76363.056.21

Study design
Randomized double-blind placebo-controlled MAD study

Primary study design
Interventional

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Epilepsy, spasticity and anxiety disorders

Interventions
Administration of up to 50 mg of ENX-101 or a matching placebo.

Intervention Type
Drug

Phase
Phase I

Drug/device/biological/vaccine name(s)
ENX-101

Primary outcome(s)
The safety and tolerability of ENX-101 will be assessed using the following:
1. Adverse events (AEs) recorded throughout the study
2. Physical examination at Screening, Day -2, Day 10, Prior to discharge on Day 13
3. Vital signs* (blood pressure, HR, respiratory rate and tympanic body temperature) at Screening, Day –2, Day –1, Day 1 through Day 10: Pre-dose, 2 and 6 hours after dosing, Day 11 through Day 13
*Vital signs will include two-position blood pressure and heart rate (HR), respiratory rate, and tympanic temperature. Blood pressure and HR will be measured in both the supine and standing positions; measurements will be performed after at least 10 minutes lying down and then at 2 minutes after rising from the supine position to standing
4. Continuous 12-lead ECG holter monitoring on Day –1: timepoints scheduled to approximately match the Day 1 timepoints; Day 1: 60, 45, and 30 minutes pre-dose and 0.5, 1, 2, 3, 4, 5, 6, 7, 8, 10, 12, and 24 hours after dosing; Day 10: 60, 45, and 30 minutes pre-dose and 0.5, 1, 2, 3, 4, 5, 6, 7, 8, 10, 12, and 24 hours

5. Clinical laboratory tests (hematology, serum chemistry, serum coagulation, urinalysis) at Screening, Day -2, Day 5, Day 10, and Day 13
6. Suicidality (suicidal behavior and suicidal ideation) assessed using the Columbia Suicide Severity Rating Scale (C-SSRS) at Screening, Day 1, Day 2, Day 5, Day 11, Day 13
7. Degree of sedation assessed using the Modified Observer's Alertness/Sedation Scale (MOAA /S) at Day 1: Pre-dose and 2, 4, 6, 8, 10, and 24 hours (Day 2) after dosing; Day 10: Pre-dose and 2, 4, 6, 8, 10, and 24 hours (Day 11) after dosing; Day 12: 48 hours after Day 10 dosing; Day 13: 72 hours after Day 10 dosing

Key secondary outcome(s))

1. 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; measured using 12-lead ECG at Screening, Day -2, Day 1: Pre-dose and 2 and 6 hours after dosing, Day 10: Pre-dose and 2 and 6 hours after dosing, Day 13
2. The 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 at 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, 48, and 72 hours respectively, after Day 10 dosing
3. The effects of ENX-101 on a battery of pharmacodynamic (PD) measures (NeuroCart®):
3.1. Saccadic reaction time (seconds), saccadic peak velocity (degrees/second)
3.2. Smooth pursuit eye movements (percentage of time the eyes of the participant are in smooth pursuit of the target) (%)
3.3. Adaptive tracking (average performance) (%)
3.4. Body sway (anteroposterior sway) (mm)
3.5. Pupil size
3.6. VAS according to Bond and Lader, to assess mood, alertness and calmness (mm)
3.7. VAS according to Bowdle, to assess external and internal perception
Measured at Screening, Day -2 (twice during the day for baseline measurement), Day 2 and Day 9: At 2, 4, 6, 8, 10, and 24 hours (i.e. Day 3 and Day 10) after dosing.
4. The effects of ENX-101 on the memory test: Visual Verbal Learning Test (VVLT): immediate recall, delayed recall, delayed recognition; measured on Day –2: Learning and Immediate Recall on first training and Delayed Recall and Delayed
Recognition on second training; Day 2: Learning and Immediate Recall 4 hours after dosing; Delayed Recall and Delayed
Recognition at 6 and 24 hours (pre-dose on Day 3) after dosing; Day 9: Learning and Immediate Recall 4 hours after dosing; Delayed Recall and Delayed Recognition at 6 and 24 (pre-dose on Day 10) hours after dosing
5. The effects of ENX-101 on qEEG parameters: α-band (8.5 <12.5), β-band (12.5 <30.0), δ-band (1.5 <6), γ-band (30.0 <40.0), θ-band (6.0 <8.5); measured at Day –2; Days 2: Pre-dose and 2, 4, 6, 8, 10, and 24 hours (Day 3) after dosing; Day 9: Pre-dose and 2, 4, 6, 8, 10, and 24 hours (Day 10) after dosing
6. The effects of ENX-101 on sedation measured with the MOAA/S on Day 1: Pre-dose and 2, 4, 6, 8, 10, and 24 hours (Day 2) after dosing; Day 10: Pre-dose and 2, 4, 6, 8, 10, and 24 hours (Day 11) after dosing; Day 12: 48 hours after Day 10 dosing; Day 13: 72 hours after Day 10 dosing

Completion date

05/09/2022

Eligibility

Key inclusion criteria
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
4.1. 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
4.2. Of childbearing potential and willing to use two 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:
7.1. Reside in the inpatient unit from Day –2 until discharge on Day 13
7.2. Refrain from strenuous exercise from Day –4 until Day 13
7.3. 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 -29. Subjects must have been sleeping at least 6 to 8 hours per night over the 4 weeks prior to Screening through to Day -2

Participant type(s)
Healthy volunteer

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 years

Upper age limit

55 years

Sex
All

Key exclusion criteria
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 CNS 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 –1:
5.1. History or evidence of any of the following:
5.1.1. Myocardial infarction
5.1.2. Cardiac valvulopathy
5.1.3. Cardiac surgery revascularization (coronary artery bypass grafting or percutaneous transluminal coronary angioplasty)
5.1.4. Unstable angina
5.1.5. Cerebrovascular accident or stroke or transient ischemic attack
5.1.6. Pacemaker
5.1.7. Atrial fibrillation, flutter, or nonsustained or sustained ventricular tachycardia
5.1.8. Pulmonary arterial hypertension
5.1.9. Sick sinus syndrome, second- or third-degree atrioventricular block
5.1.10. Uncontrolled hypertension
5.1.11. Congestive heart failure
5.1.12. Family history of sudden death or personal history of long QT syndrome
5.1.13. Hypokalemia
5.1.14. Unexplained syncope or syncope within the last 3years regardless of etiology
5.2. Electrographically and clinically significant abnormalities, as judged by the Investigator, that might interfere with ECG (electrocardiogram) analysis, including evidence of a previous myocardial infarction, significant left ventricular hypertrophy, flat T waves (particularly in the inferior leads), or more than minor nonspecific STT–wave changes.
5.2.1. Rhythm other than sinus rhythm
5.2.2. Mean HR <50 beats per minute (bpm) or >100 bpm
5.2.3. Mean systolic blood pressure >140 mmHg; mean diastolic blood pressure >90 mmHg
5.2.4. QTc interval using Fridericia's formula (QTcF) >450 msec in males or >470 msec in females
5.2.5. QRS interval ≥120 msec
5.2.6. PR interval >200 msec
6. Reports having experienced suicidal ideation (Type 4 or 5 on the C-SSRS (Colombia-Suicide Severity Rating Scale)) within 30 days prior to Screening, any suicidal behavior within 2 years prior to Screening (any "Yes" answers on the 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 in the last 6 months or as judged significant by the Investigator or daytime symptoms attributable to unsatisfactory sleep or shift worker whose routine work hours overlap with the typical sleep period.

8. History or evidence of moderate or severe substance use disorder as 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 90days 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–1
11. Ingested any concomitant medication (excluding hormonal birth control and hormone replacement therapy for menopause) within 5 halflives or 30 days (whichever is longer) prior to Day 1; ibuprofen and paracetamol may be used during the screening period and yet not within 72 hours of 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 –1.
14. Elevated >2 × upper limit of normal liver enzymes (alanine aminotransferase and/or aspartate aminotransferase) and/or bilirubin at Screening or Day –1.
15. Clinically significant abnormal findings in vital sign assessments at Screening or Day –1.
16. History or evidence of hepatitis B or hepatitis C or demonstration of hepatitis B surface antigen or hepatitis C antibody at Screening.
17. History of HIV infection or demonstration of HIV antibodies at Screening.
18. Clinically significant history of previous allergy/sensitivity to the study drug, any drugs in the same or similar class, or any of the excipients contained within the study drug.
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 5half-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.

Date of first enrolment
03/11/2021

Date of final enrolment
06/12/2021

Locations

Countries of recruitment
Netherlands

Study participating centre
Centre for Human Drug Research
Zernikedreef 8
Leiden
Netherlands
2333 CL

Sponsor information

Organisation
Engrail Therapeutics, Inc.

Funder(s)

Funder type
Industry

Funder Name
Engrail Therapeutics, Inc.

Results and Publications

Individual participant data (IPD) sharing plan
The current data sharing plans for this study are unknown and will be available at a later date.

IPD sharing plan summary
Data sharing statement to be made available at a later date

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Participant information sheet	Participant information sheet	11/11/2025	11/11/2025	No	Yes