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A study to evaluate the safety, tolerability, pharmacokinetics, and pharmacodynamics of single and multiple ascending doses of PRAX-628 in healthy participants

Submission date 25/11/2022	**Recruitment status** No longer recruiting	[X] Prospectively registered [_] Protocol [_] Statistical analysis plan [_] Results [_] Individual participant data [_] Record updated in last year
Registration date 30/11/2022	**Overall study status** Completed	
Last Edited 14/02/2023	**Condition category** Other	

Plain English summary of protocol

Background and study aims
Epilepsy is a brain disease with typical seizures in which the nerve cells in the brain experience some kind of electrical short. As a result, patients with this disease have seizures. There is medication to prevent these attacks, but not all medicines work well enough for everyone. Many patients also experience side effects from current medications. PRAX-628 is a new drug that potentially allows the nerve cells to fire less uncontrollably. The idea is that the new drug will also have fewer side effects than the existing drugs already available. PRAX-628 has not been used in humans before. However, it has been tested in the laboratory and also on animals.

Who can participate?
Healthy male or female between the ages of 18 and 55 years inclusive

What does the study involve?
In this study, it will be investigated how safe the new drug PRAX-628 is and how the body processes the drug. PRAX-628 will be tested in different strengths in healthy subjects and will be compared with the effect of a placebo.

What are the possible benefits and risks of participating?
PRAX-628 has not previously been studied in humans and there are no known benefits. There might be side effects or adverse events from the study treatment.

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?
October 2022 to July 2023

Who is funding the study?
Praxis Precision Medicines (USA)

Who is the main contact?
W. ten Voorde (Project Leader), wtvoorde@chdr.nl

Contact information

Type(s)
Principal investigator

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Clinical Trials Information System (CTIS)
2022-003054-31

Protocol serial number
PRAX-628-101, CHDR2224

Study information

Scientific Title
A phase 1, randomized, double-blind, placebo-controlled trial to evaluate the safety, tolerability, pharmacokinetics, and pharmacodynamics of single and multiple ascending doses of PRAX-628 in healthy participants

Acronym
PRAX-628-101

Study objectives
PRAX-628 is a novel sodium channel (Nav) blocker that is mechanistically differentiated from currently available Nav blockers and being developed for the treatment of adult focal onset epilepsy. Standard-of-care Nav blockers used to treat epilepsy are limited by a narrow therapeutic index and a requirement to titrate to efficacious concentrations in an effort to manage tolerability concerns. The expectation is that by preferential targeting of Nav activity states, PRAX-628 will have greater efficacy and lower side effects.

Ethics approval required

Old ethics approval format

Ethics approval(s)
Approved 25/11/2022, Stichting BEBO (Doctor Nassaulaan 10, 9401 HK Assen, The Netherlands; +31 592-405871; info@stbebo.nl), ref: NL82665.056.22

Primary study design
Interventional

Study design
Interventional randomized controlled trial

Study type(s)
Other

Health condition(s) or problem(s) studied
PRAX-628 is a new investigational drug that is being developed as part of the treatment of epilepsy.

Interventions
Part A is randomized, double-blinded, and placebo-controlled. Part A is designed to investigate the safety, PK, and PD of single ascending doses of PRAX-628.

Part B is randomized, double-blinded, and placebo-controlled. Part B is designed to investigate the safety, PK, and PD of multiple ascending doses of PRAX-628.

Part C (optional) is a randomized, open-label, crossover design food effect evaluation to investigate the PK of a single dose of PRAX-628 in the fasted and fed state.

Intervention Type
Drug

Phase
Phase I

Drug/device/biological/vaccine name(s)
PRAX-628

Primary outcome(s)
Part A:
To assess the safety and tolerability of single oral doses of PRAX-628, measured by:
1. Incidence and severity of adverse events (AEs) monitored continuously throughout the study
2. Changes in vital sign measurements monitored continuously throughout the study
3. Changes in clinical laboratory results monitored continuously throughout the study
4. Changes in electrocardiogram (ECG) parameters monitored continuously throughout the study

Part B:
To assess the safety and tolerability of 10-day repeat oral doses of Prax-628, measured by:
1. Incidence and severity of adverse events (AEs)
2. Changes in vital sign measurements monitored continuously throughout the study
3. Changes in clinical laboratory results monitored continuously throughout the study

4. Changes in electrocardiogram (ECG) parameters monitored continuously throughout the study
5. Incidence of Columbia-Suicide Severity Rating Scale (C-SSRS) measured suicidal ideation or behavior.

Part C:
To assess the safety and tolerability of a single oral dose of PRAX-628 either fasted or fed, measured by:
1. Incidence and severity of adverse events (AEs)
2. Changes in vital sign measurements monitored continuously throughout the study
3. Changes in clinical laboratory results monitored continuously throughout the study
4. Changes in electrocardiogram (ECG) parameters monitored continuously throughout the study

Key secondary outcome(s)
Part A:
To evaluate the pharmacokinetics (PK) of single oral doses of PRAX-628, measured by:
1. Plasma concentrations of PRAX-628 collected throughout the study
2. Maximum observed concentration (cmax)
3. Time to maximum observed concentration (tmax)
4. Area under the drug concentration-time curve from time zero to infinity (AUCinf)
5. Area under the concentration time curve from time zero to the last measurable concentration (AUClast)
6. Apparent terminal elimination half-life (t1/2)
7. Clearance
8. Volume of distribution (Vd/F)
9. Dose normalized Cmax
10. Dose normalized AUCinf

Part B:
To evaluate the PK of 10-day repeat oral doses of PRAX-628
1. Plasma concentrations of PRAX-628 collected throughout the study
2. Cmax
3. tmax
4. AUClast
5. AUCtau
6. t1/2
7. Accumulation ratio based on AUC (Rac(AUC))
8. Accumulation ratio based on Cmax (Rac(Cmax))

Part C:
To evaluate the effect of food on the PK of PRAX-628
1. Plasma concentrations of PRAX-628 collected throughout the study
2. Cmax
3. tmax
4. AUCinf
5. AUClast

Completion date
31/07/2023

Eligibility

Key inclusion criteria
1. Willing and able to provide informed consent indicating that they understand the purpose of the clinical trial and the procedures that are required for the clinical trial, and that they are willing to comply with scheduled visits, and all study related procedures.
2. Male or female between the ages of 18 and 55 years, inclusive.
3. Body mass index (BMI) of 18.0 to 32.0 kg/m², inclusive, and a total body weight of at least 50 kg.
4. Females of childbearing potential are not pregnant or breast-feeding, have a negative serum pregnancy test at Screening and a negative urine pregnancy test at Baseline and are not planning to get pregnant for the duration of the trial.
5.1. Female of nonchildbearing potential by reason of surgery or at least 1 year postmenopausal (ie, 12 months since last menses) with confirmation by follicle stimulating hormone (FSH) at Screening only, or
5.2. Female of childbearing potential who is willing to use a highly effective method or methods of contraception as defined in this protocol and for the duration prescribed in this protocol, or
5.3. Male who is willing and able to use a highly effective method or methods of contraception as defined in this protocol and for the duration prescribed in this protocol.

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. Any clinically significant abnormalities, medical, or psychiatric conditions identified by a detailed medical history,or physical examination, that in the opinion of the investigator would pose an additional safety risk to theparticipant or compromise the objectives of the study.
2. A history or cardiac disease(s)/cardiac conduction disorders/or cardiac structural abnormality (ies) (e.g., atrial orventricular septal defects, valvular heart disease, coarctation of the aorta, or hypertrophic obstructivecardiomyopathy).
3. Has a history of any lifetime suicide attempt or active suicidal ideation as confirmed by C-SSRS BaselineVersion.
4. Any surgical or medical condition which might significantly alter the absorption, distribution, metabolism, orexcretion of drugs or which may jeopardize the participant in case of participation in the study.
5. Abnormal vital signs after at least 5 minutes resting in the supine position.
6. Abnormal standard 12-lead ECG after at least 5 minutes resting in the supine position.
7. Any finding that, in the judgement of the investigator, is a clinically significant abnormality,

including serumchemistry, hematology, coagulation, and urinalysis test values (abnormal test results may be repeated forconfirmation).
8. An elevation of ≥1.5× ULN for AST or ALT/ serum glutamic pyruvic transaminase (SGPT) or ≥2×ULN for totalbilirubin.
9. Positive test for HIV, hepatitis B (HBsAg), or hepatitis C.
10. History of drug or alcohol abuse.
11. Positive drug or alcohol test at Screening or Baseline. (Abnormal test results may be repeated forconfirmation).
12. Smoker (use of tobacco or nicotine-containing products in the previous 3 months) or evidence of such use asindicated by cotinine testing at Screening and Baseline.
13. Use of an investigational drug or device within 90 days or 5 half-lives preceding the first dose of study drug,whichever is longer.
14. Use of prescription or nonprescription drugs or dietary or herbal supplements of clinical concern within 7 daysor within 5 times the elimination half-life (whichever is longer) prior to the first dose of study drug. Refer to therelevant section(s) of the protocol for potential exceptions which must be approved by the sponsor/designee.
15. Inability to abstain from eating or drinking grapefruit or grapefruit-related citrus fruits (eg, Seville oranges,pomelos) from 7 days prior to the first dose of study drug until collection of the final PK blood sample.
16. Any vaccination within 14 days of the first dose of study drug.
17. Blood donation (excluding plasma donations) or significant blood loss of approximately 500 mL or more within 90 days (male) or 120 days (female) prior to first dose of study drug.
18. Presence or history of any allergy or hypersensitivity to any component of the study drug product , or history of severe allergy or anaphylaxis to a drug, food, or other exposure.
19. Unwilling or unable to comply with the lifestyle considerations described in this protocol.
20. An employee or family member of an employee of the sponsor, or an employee or family member of the study site staff.

Date of first enrolment
02/12/2022

Date of final enrolment
24/07/2023

Locations

Countries of recruitment
Netherlands

Study participating centre
Centre for Human Drug Research
Zernikedreef 8
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Sponsor information

Organisation
Praxis Precision Medicines

Funder(s)

Funder type
Industry

Funder Name
Praxis Precision Medicines

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