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A study of the effects of different doses of oliceridine on several brain functions and a pain test, in healthy volunteers, compared to morphine

Submission date
03/02/2022

Recruitment status
No longer recruiting

Registration date
04/02/2022

Overall study status
Completed

Last Edited
15/09/2023

Condition category
Other

[X] Prospectively registered
[_] Protocol
[_] Statistical analysis plan
[X] Results
[_] Individual participant data

Plain English summary of protocol

Background and study aims
A common side effect of strong pain killers such as morphine is a loss of mental ability (cognitive functioning) due to the side effects of this drug on the brain.
Oliceridine is a novel, small molecule mu opioid receptor (MOR) agonist. In-vitro, oliceridine stimulates G protein signaling with higher potency than morphine. In contrast, oliceridine is markedly less effective than morphine, fentanyl, and hydromorphone in stimulating recruitment of β-arrestin2 to the MOR.
Clinicians have reported observing apparent better neurocognitive functioning in patients who were administered oliceridine than in patients being treated with classic opioids such as morphine. This study is designed to evaluate neurocognitive functioning using the NeuroCart test battery at the Centre for Human Drug Research in healthy subjects when administered an IV bolus dose of oliceridine compared to IV doses of morphine or placebo.

Who can participate?
Adult healthy volunteers aged 18 to 55 years

What does the study involve?
For participants, the study involves a screening (duration: 2h). Eligible subjects will present to the research facility on day -1. On the morning of day 1, baseline measurements will be performed and subject will receive the study treatments (olicerdine 1 or 3mg, morphine 5 or 10mg or placebo) intravenously, followed by multiple rounds of measurements. Measurements include blood pressure, temperature, EKG, attention and reaction tests, questionnaires. 12 hours after dosing, subject will be discharged. Participants will have 3 visits separated by 7 days, and a follow-up visit 7-9 days after last drug administration.

What are the possible benefits and risks of participating?
There are no benefits. Oliceridine and Morphine may have side effects, but both are generally considered safe in doses that will be administered in the study, under medical supervision.

Possible side effects may include: constipation, nausea, vomiting, drowsiness, headache, and itching. Respiratory depression (a decrease in the ability to inhale and exhale) may occur at higher doses and can be serious. When used for a prolonged periods of time, these drugs may cause abuse, addiction and opioid withdrawal. Also, blood draws may be unpleasant or painful for some subjects.

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 2021 to June 2022

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

Who is the main contact?
L. Moss, LMoss@chdr.nl

Contact information

Type(s)
Public

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Additional identifiers

Clinical Trials Information System (CTIS)
2021-006334-39

Protocol serial number
CP130-1016 / CHDR2144

Study information

Scientific Title

A randomised, double-blind, placebo-controlled, dose-ranging partial-block crossover study to investigate the effect of intravenous oliceridine on CNS functioning and nociceptive thresholds in healthy subjects, compared to morphine

Study objectives
Morphine will have a different effect on saccadic peak velocity than oliceridine, when compared to placebo.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 21/01/2022, Stichting BEBO (Doctor Nassaulaan 10, 9401 HK Assen, The Netherlands; +31 592-405871; info@stbebo.nl), ref: NL79823.056.21

Study design
Single-centre randomized double-blind placebo-controlled 5-treatment 3-period partial-block crossover study

Primary study design
Interventional

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Effects of oliceridine and morphine on neurocognition and pain in healthy participants

Interventions
20 subjects will receive an intravenous bolus administration of oliceridine 1 or 3mg, morphine 5 or 10mg or placebo. Participants are randomised to receive 3 of 5 treatments in 3 separate visits with 7 days' wash-out between visits. Neurocognitive functioning and pain will be assessed after each treatment, as well as safety parameters and PK. The duration of treatment for each subject will be up to 7 weeks, divided as follows: Screening: Up to 28 days before dosing, Treatment and study assessments: Days -1 to 15 (in clinic period: Days -1 to 1, 7 to 8 and 14 to 15) and Follow-up visit: Approximately 7 days after last dose.

The randomization code will be generated using SAS version 9.4 (or a more recent version if available) by a study-independent, CHDR statistician. The randomization code will be unblinded /broken and made available for data analysis only after study closure, i.e., when the study has been completed, the protocol deviations determined, and the clinical database declared complete, accurate and locked. The randomization code will be kept strictly confidential. Sealed individual randomization codes, per subject and per treatment, will be placed in a sealed envelope with the label 'emergency decoding envelopes' in a safe cabinet at CHDR. These envelopes will only be utilised if it is deemed medically necessary to the treatment of the subject as described in the study protocol.

Intervention Type
Drug

Phase
Phase I

Drug/device/biological/vaccine name(s)
Oliceridine 1 or 3mg, morphine 5 or 10mg or placebo (D5W)

Primary outcome(s)
Neurocognitive function is measured using the saccadic eye movement's peak velocity (°/s) at pre-dose, 30min, 1, 2 , 3, 4, 5, and 6 h.

Key secondary outcome(s))
Measured at pre-dose to 6 hours post-dose:
1. Saccadic eye movement: reaction time (s), inaccuracy (%)
2. Smooth pursuit eye movement: percentage of time the eyes of the subjects are in smooth pursuit of the target (%)
3. Pupillometry (pupil/iris ratio): pupil constriction compared to baseline (mm)
4. Adaptive tracking: average performance (%)
5. Body sway: antero-posterior sway (mm)
6. Symbol-digit substitution test (SDST): total number of correct and incorrect responses, average reaction time for 1st SDST trial until 36th SDST trial (s)
7. Visual analogue scale (VAS) Bond & Lader (Alertness, mood, calmness) (mm)
8. VAS Bowdle (internal perception, external perception, 'feeling high') (mm)
9. For the cold pressor test the following parameters will be measured:
10. Pain Detection Threshold (PDT) (s)
11. Pain Tolerance Threshold (PTT) (s)
12. Area above the curve (AAC) (s*mm)
13. Post-test VAS: cold pressor
14. The following PK parameters will be measured for oliceridine, morphine, and morphine's metabolite morphine-6-glucuronide (M6G):
14.1. The maximum plasma concentration observed (Cmax)
14.2. Time to reach Cmax (tmax)
14.3. The area under the concentration–time curve from time zero to time of last quantifiable concentration (AUClast)
14.4. The area under the concentration–time curve from time zero to 12 hours (AUC0-12)
14.5. The area under the concentration–time curve from time zero and extrapolated from the time of last quantifiable concentration to infinity (AUCinf)
14.6. The half-life (t1/2)
The following safety and tolerability parameters will be measured:
15. Treatment-emergent Adverse events (TEAEs)
16. Clinical laboratory evaluations: haematology, biochemistry including glucose, coagulation and urinalysis
17. Vital signs: systolic and diastolic blood pressure, pulse rate, respiratory rate, and body temperature
18. Safety 12-lead ECG: Heart rate (bpm), PR, RR, QRS, QT, QTcF
19. Specific assessments for opioid effects:
19.1 Pasero Opioid-Induced Sedation Scale (POSS)
19.2 Pulse oximetry

Completion date
10/06/2022

Eligibility

Key inclusion criteria
1. Signed informed consent prior to any study-mandated procedure.
2. Ability to communicate well with the investigator in the Dutch language and willing and able to follow the procedures and comply with study restrictions as outlined in the protocol.
3. Healthy male and female volunteers aged ≥18 years and ≤55 years old at the time of informed consent.
4. Body mass index (BMI) ≥18 and <32 kg/m² at Screening.
5. Females of childbearing potential must agree to the use of the double-barrier contraceptive method, meaning the use of a highly effective method of contraception (e.g., intrauterine device (IUD), diaphragm with spermicide, oral contraceptive, injectable progesterone, subdermal implant or a tubal ligation) in combination with the use of a condom by a male partner of the female subject, from screening through 5 half-lives or 90 days, whichever is longer, after administration of the last dose of investigational product (IP).
6. Males who are sexually active and whose partners are females of childbearing potential must agree to use condoms from screening through 5 half-lives or 90 days, whichever is longer, after administration of the last dose of IP, and their partners must be willing to use a highly effective method of contraception (e.g., IUD, diaphragm with spermicide, oral contraceptive, injectable progesterone, subdermal implant or a tubal ligation) from screening through 5 half-lives or 90 days after administration of the last dose of IP.

Participant type(s)
Healthy volunteer

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 years

Sex
All

Total final enrolment
23

Key exclusion criteria
1. Poor metabolisers of CYP 2D6 substrates, as defined after genotyping assessment at screening.
2. Use of prescription or over-the-counter (OTC) medications that are clinically relevant CYP P450 3A4 or CYP P450 2D6 inducers or inhibitors from 14 days prior to study drug administration until follow up.
3. Any current, clinically significant, known medical condition that would affect sensitivity to cold (such as atherosclerosis, Raynaud’s disease, urticaria, hypothyroidism) or pain (including pain disorders, such as chronic low back pain and osteoarthritis, or diseases or conditions that cause pain, hypaesthesia, hyperalgesia, allodynia, paraesthesia, neuropathy, etc.), in the opinion of the

investigator.
4. Subjects indicating pain test intolerability at Screening or achieving pain tolerance at >80% of maximum input intensity for the cold pressor pain test.
5. Clinically significant illness or disease (e.g., psychiatric disorders, disorders of the gastrointestinal tract, liver [excluding Gilbert's syndrome], kidney [including nephrectomy], respiratory system, endocrine system, haematological system, neurological system, or cardiovascular system, dermatologic condition, clinically significant infection within 2 weeks of dosing, or subjects who have a congenital abnormality in metabolism), or any clinically significant abnormal symptom or
organ impairment, as judged by the investigator, found by medical history, physical examinations, vital signs, electrocardiogram (ECG) finding, or either abnormal laboratory values or laboratory test results at Screening or Baseline.
6. Any finding that may compromise the safety of the subject or affect their ability to adhere to the protocol requirements (e.g., difficulty with venous access or fear of needles).
7. Presence of any condition in which an opioid is contraindicated (e.g., opioid intolerance, significant respiratory depression, acute or severe bronchial asthma, gastrointestinal ileus, etc.).
8. A prolonged corrected QT interval (Fridericia-corrected QT interval [QTcF] >450 ms in males and >470 in females) demonstrated on ECG at Screening or Baseline.
9. A history of risk factors for torsade de pointes (e.g., heart failure, hypokalaemia, family history of long QT syndrome). A history of myocardial infarction, ischaemic heart disease, or cardiac failure at Screening. History of clinically significant arrhythmia or uncontrolled arrhythmia as determined by the investigator at Screening.
10. Left bundle branch block at Screening or Baseline.
11. Systolic blood pressure (BP) >140 or <90 mmHg or diastolic BP >90 or <50 mmHg at Screening or Baseline, or history of clinically significant orthostatic hypotension.
12. Heart rate (HR) <45 beats per minute (bpm) or >100 bpm at Screening or Baseline.
13. Demonstrated allergic reactions (e.g., food, drug, atopic reactions, or asthmatic episodes) which, in the opinion of the investigator, interfere with the subject's ability to participate in the trial.
14. Positive hepatitis B surface antigen (HBsAg), hepatitis B core antibodies (Anti-HBc), hepatitis C antibodies (HCV Ab), or human immunodeficiency virus antibody (HIV Ab) at Screening.
15. Use of nicotine-containing products within 4 weeks before the Screening visit and not able to withhold from smoking during the study.
16. History of opioid use disorder per Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) classification, or other drug/substance or alcohol dependency or abuse before Screening, or those who have a positive drug test or alcohol test at Screening or Baseline.
17. Use of prescription, non-prescription medications or herbal preparations containing St. John' s Wort, and nutritional supplements within 7 days or 5 half-lives prior to dosing, whichever is longer. An exception is made for incidental use of paracetamol or ibuprofen, which is allowed up to 48 hours before start of each visit. Other exceptions are allowed only when clearly documented by the investigator.
18. Any clinically significant lifetime history of suicidal behaviour or ideation and/or poses a current (within the past year) suicide risk, as assessed by scores on the Columbia Suicide Severity Rating Scale (C-SSRS) at Screening per investigator judgment
19. Receipt of blood products within 4 weeks, blood donation or blood loss >250 mL within 8 weeks, or donation of plasma within 1 week of any Study Drug dose administration.
20. Is employed by Trevena, the Centre for Human Drug Research (CHDR), or the investigator or study site (permanent, temporary contract worker, or designee responsible for the conduct of the study), or is immediate family* of a Trevena, CHDR, investigator, or study site employee. * Immediate family is defined as a spouse, parent, sibling, or child, whether biological or legally adopted
21. Is currently enrolled in another clinical study or used any investigational drug or device

within 3 months prior to dosing or has participated in more than 4 investigational drug studies within 1 year prior to Screening.

Date of first enrolment
04/02/2022

Date of final enrolment
24/04/2022

Locations

Countries of recruitment
Netherlands

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

Sponsor information

Organisation
Trevena, Inc.

Funder(s)

Funder type
Industry

Funder Name
Trevena, 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?
Results article		01/09/2023	15/09/2023	Yes	No