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.

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Primaryo To evaluate the effects of oliceridine following IV bolus dose administration on neurocognitive functioning, when compared to morphine and placeboSecondaryo To evaluate the effects of oliceridine following IV bolus dose administration on...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Other condition
Study type	Interventional

Summary

ID

NL-OMON50676

Source
ToetsingOnline

Brief title
Oliceridine effects on CNS and Pain

Condition

- Other condition

Synonym
Acute pain, pain

Health condition

Acute Pain

Research involving
Human

Sponsors and support

Primary sponsor: Trevena Inc.
Source(s) of monetary or material Support: Trevena Inc.

Intervention

Keyword: CNS functioning, Oliceridine, Pharmacodynamics, Pharmacokinetics

Outcome measures

Primary outcome

o Saccadic eye movement: peak velocity (°/s)

Secondary outcome

o Saccadic eye movement: reaction time (s), inaccuracy (%)

o Smooth pursuit eye movement: percentage of time the eyes of the subjects are

in smooth pursuit of the target (%)

o Pupillometry (pupil/iris ratio): pupil constriction compared to baseline (mm)

o Adaptive tracking: average performance (%)

o Body sway: antero-posterior sway (mm)

o Symbol-digit substitution test (SDST): total number of correct and incorrect

responses, average reaction time for 1st SDST trial until 36th SDST trial (s)

o Visual analogue scale (VAS) Bond & Lader (Alertness, mood, calmness) (mm)

o VAS Bowdle (internal perception, external perception, *feeling high*) (mm)

o Cold pressor test

* Pain Detection Threshold (PDT) (s)

* Pain Tolerance Threshold (PTT) (s)

* Area above the curve (AAC) (s*mm)

* Post-test VAS (mm)

o The maximum plasma concentration observed (Cmax)

o Time to reach Cmax (tmax)

o The area under the concentration*time curve from time zero to time of last quantifiable concentration (AUClast)

o The area under the concentration*time curve from time zero to 12 hours (AUC0-12)

o The area under the concentration*time curve from time zero and extrapolated from the time of last quantifiable concentration to infinity (AUCinf)

o The half-life (t1/2)

o Other parameters, including volume of distribution (Vz), clearance (CL), and other parameters as appropriate, as well as dose adjusted parameters, may be determined

o EC50 and Emax for oliceridine and morphine effects on NeuroCart measurements and the cold pressor test as determined by PK/PD models

o Treatment-emergent AEs (TEAEs)

o Clinical laboratory evaluations: haematology, biochemistry including glucose, coagulation, and urinalysis

o Vital signs: systolic and diastolic blood pressure, pulse rate, respiratory rate, and body temperature

o Safety 12-lead ECG: Heart rate (bpm), PR, RR, QRS, QT, QTcF

o Specific assessments for opioid effects:

* Pasero Opioid-Induced Sedation Scale (POSS)

* Pulse oximetry

Study description

Background summary

TRV130, registered as oliceridine injection or Olinvyk®, 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 *-arrestin2 to the MOR. These findings define oliceridine as a *G protein-biased ligand*, a novel class of G protein coupled receptor (GPCR) ligands that stimulate only a subset of the normal repertoire of receptor coupling mechanisms.

Twelve Phase 1 studies (nine in healthy subjects and three in special populations), two Phase 2 studies, one pilot Phase 2 study, two Phase 3 pivotal efficacy and safety studies, and a Phase 3 open-label safety study have been completed. Oliceridine has been approved by the FDA for use in adults for the management of acute pain severe enough to require an intravenous opioid analgesic, and alternative treatments are inadequate or not expected to be tolerated.

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.

Study objective

Primary
o To evaluate the effects of oliceridine following IV bolus dose administration on neurocognitive functioning, when compared to morphine and placebo

Secondary
o To evaluate the effects of oliceridine following IV bolus dose administration on neurocognitive functioning, when compared to morphine and placebo
o To evaluate the analgesic activity of oliceridine and morphine following IV bolus dose administration
o To assess pharmacokinetics of oliceridine, morphine, and morphine*s metabolite M6G after IV bolus dose administration
o To assess the pharmacokinetic/ pharmacodynamic (PK/PD) relationships of

oliceridine following IV bolus dose administration
o To assess the CNS effect:nociception ratio and compare between oliceridine and morphine using utility functions
o To assess safety and tolerability to IV bolus dose administration of oliceridine and morphine

Study design

This single-centre, randomised, double-blind, placebo-controlled, 3-way partial crossover study will investigate the effects of IV oliceridine on CNS functions, opioid related parameters, and evoked pain tests in approximately 20 healthy male and female volunteers, aged 18-55. Each subject will have 3 study periods of 26 hours (evening Day -1 to evening Day 1) with treatment administered on Day 1 and PD tests performed throughout the day.

Intervention

Oliceridine 1 mg
Oliceridine 3 mg
Morphine HCl 5 mg
Morphine HCl 10 mg
Matching placebo

Study burden and risks

Opioids are effective treatments commonly prescribed for pain. However, opioid pain medications are associated with serious risks including overdose, respiratory depression, constipation, sedation, and opioid use disorder. As such, there is an unmet need for well-tolerated and effective therapies, including opioids with improved safety characteristics, for the management of pain
Commonly reported adverse events (AEs) for opioid agonists include constipation, nausea, vomiting, sedation, headache, and pruritus. Molecules with a preference toward G-protein coupled intracellular signalling with low levels of *-arrestin recruitment, such as oliceridine, are thought to retain analgesic efficacy and reduce the risk of key side effects of opioids.
Morphine, the drug used as reference therapy in this study, could elicit these symptoms. The total maximum dose of 10 mg of morphine IV on one day was chosen because it is expected to provide adequate analgesic properties and possibly measurable effects on neurocognitive tests, while having manageable adverse effects.
The clinical data available for oliceridine and morphine are considered in the risk assessment of this study, including the study inclusion/exclusion criteria, as well as planned safety monitoring of participating subjects. All study drug administrations will be performed in the clinic under medical supervision. The subjects receiving any study drug will remain in the clinic

for at least 12 hours after first administration of study drug on each day of dosing and will be closely monitored by medically qualified staff for any adverse events during the treatment period(s), with adequate rescue therapies available (e.g., supplemental oxygen, naloxone as antidote). Medical monitoring will include peripheral oxygen saturation (SpO2), respiratory rate, sedation, and ECG. Subjects will be discharged by a physician only if their medical condition allows. The assessment of alertness according to the Pasero Opioid Sedation Scale (POSS), which is also be scheduled for the 12-hour post-dose time point, will be documented, and taken into account when the decision is made to discharge a subject. Therefore, careful observation and medical management will minimize any associated risk in this study.

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 included in this study:
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 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.

Exclusion criteria

1. Poor metabolisers of CYP 2D6 substrates, as defined after genotyping assessment at screening.
2. Use of prescription or 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.

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:	Recruitment stopped
Start date (anticipated):	04-02-2022
Enrollment:	20
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Morphine HCl
Generic name:	Morphinehydrochloride

Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	16-12-2021
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	21-01-2022
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	EUCTR2021-006334-39-NL
CCMO	NL79823.056.21