A randomized, double blind, four-period, six-treatment, double-dummy, placebo controlled, partial-crossover study to explore and compare the ventilatory response to hypercapnia (VRH) of cebranopadol, oxycodone, and placebo in healthy subjects

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Primary • To evaluate the effects of cebranopadol and oxycodone on respiratory drive.Secondary• To evaluate the pupil response/ pupillometry following single oral doses of cebranopadol and oxycodone• To evaluate the effects of single oral doses of…

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

Summary

ID

NL-OMON51788

Source
ToetsingOnline

Brief title
Cebranopadol effects on ventilatory drive, CNS and pain

Condition

- Other condition

Synonym
Acute and chronic pain, pain

Health condition

Acute and chronic pain

Research involving
Human

Sponsors and support

Primary sponsor: Park Therapeutics Inc
Source(s) of monetary or material Support: Park Therapeutics Inc

Intervention

Keyword: Cebranopadol, Hypercapnia, Oxycodone, Ventilatory response

Outcome measures

Primary outcome

• Ventilatory response to hypercapnia (VRH) by maximum decrease in minute

ventilation (L)

Secondary outcome

• pupil constriction compared to baseline (mm)• Minute ventilation (expired

minute volume; L)

• Respiratory rate (breaths/min)

• Flow rates (peak expired flow; L/min)

• Tidal volume (expired tidal volume; mL)

• End tidal CO2 (partial pressure)• O2 Saturation peripheral (%)

• Analgesic effects will be assessed by:

o Electrical and pressure pain tests measuring the mean:

o Pain Detection Threshold (PDT) o Pain Tolerance Threshold (PTT - only for

electrical pain test)o Area under the curve (AUC)

• adverse event (AE) reporting,

• clinical observations,

• 12-lead electrocardiograms (ECGs) (Heart rate (bpm), PR, RR, QRS, QT, QTcF),

• vital signs (blood pressure, heart rate,• respiratory rate, oxygen

saturation, and

• body temperature), oxygen saturation, and safety laboratory tests

Study description

Background summary

Cebranopadol is a first-in-class investigational drug to treat patients with acute and chronic pain. The molecule dually activates the Nociceptin/Orphanin FQ peptide (NOP) receptor and the classical μ-opioid peptide (MOP) receptor. This is a unique mechanism of action (MOA) and has demonstrated efficacy in multiple Phase 2 and Phase 3 clinical studies across several nociceptive and neuropathic indications as well as a superior safety profile, low potential for abuse and minimal risk of physical dependence. Cebranopadol could provide a safer and less addictive option for many pain patients than approved opioids and the Sponsor intends to develop it broadly for multiple indications.

In animal studies, cebranopadol produced considerably less respiratory depression at comparable doses of oxycodone and fentanyl and appeared to have a ceiling to its respiratory effects. Preliminary clinical trials have suggested that these results will also be present in people.

The present study is designed to investigate if:
1. cebranopadol produces less respiratory depression than oxycodone
2. cebranopadol respiratory effects have a ceiling at supratherapeutic doses and
3. cebranopadol does not produce significant respiratory depression, as measured in this study design with 30 subjects, at any dose in the VRH model

Study objective

Primary
• To evaluate the effects of cebranopadol and oxycodone on respiratory drive.

Secondary

• To evaluate the pupil response/ pupillometry following single oral doses of cebranopadol and oxycodone
• To evaluate the effects of single oral doses of cebranopadol and oxycodone on the sensitivity of the ventilatory response to hypercapnia
• To evaluate the analgesic effects of single oral doses of cebranopadol and oxycodone
• To assess safety and tolerability of single oral doses of cebranopadol and oxycodone

Study design

This randomized, double-blind-placebo-controlled multiple ascending dose four-way partial cross-over study will investigate the effects of cebranopadol on the ventilatory response to hypercapnia, nociceptive thresholds, pharmacokinetics (PK) and safety.

Intervention

- Cebranopadol tablets (strength: 200 µg); single oral doses of 600 µg, 800 µg, and 1000 µg
- Oxycodone IR capsules(strengths: 10 mg and 20 mg); single oral doses of 30 mg and 60 mg
- Matching placebo for cebranopadol, and matching placebo for oxycodone (double-dummy).

all interventions will be over-encapsulated to maintain the blind.

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 drug reactions for Cebranopadol are sedation, dizziness, somnolence, nausea and vomiting. Cebranopadol may cause some degree of respiratory depression. The planned doses are within the therapeutic range and have previously been safely administered to similar patient populations in trials.

Commonly reported adverse events for oxycodone are sedation, dizziness, sleep, miosis, hypoventilation, nausea, vomiting, bradycardia and headache. Hallucinations and other psychotomimetic effects can occur although more rarely. Hypotension leading to syncope or shock can occur. Oxycodone may cause

significant respiratory depression. The planned doses are within the therapeutic range and have previously been safely administered to similar patient populations both in trials and in clinical practice.

For both opioids used in this study, the occurrence of respiratory depression is dose- and mu opioid receptor related and can be reversed by a mu opioid receptor antagonist such as naloxone. Multiple doses of naloxone may be necessary because the respiratory depression will last longer than the duration of action of the opioid. Subjects will remain under appropriate surveillance. Resuscitation equipment and opioid antagonists will be readily available. Adequate spontaneous breathing must be established and maintained before discharge.

Nausea and vomiting are expected problems with anesthetic agents and hypercapnia. Antiemetics are commonly used as pretreatment and treatment during surgical/medical procedures to healthy individuals and patients. Ondansetron and metoclopramide have been characterized under conditions of continuous opioid infusion under hypercapnic clamp. Neither compound interfered with respiratory assessments or PK when used in conjunction with opioids (Derschwitz 1992, Egan 1996). Therefore, subjects that are screened successfully will be pretreated with ondansetron 4mg IV prior to IMP dose and approximately 2 h post-IMP dose. During the study, additional doses of antiemetics may be provided according to standard on-label dose and dose intervals. Other than inhibiting opioid-induced nausea and/or vomiting as intended, no significant interaction is expected between ondansetron and cebranopadol, or ondansetron and oxycodone.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)

Inclusion criteria

1. Signed informed consent prior to any study-mandated procedure.
2. Subject is able to speak, read, and understand Dutch and voluntarily provide written informed consent to participate in the study.
3. Adult men or women aged 18 to 45 years, inclusive.
4. Subjects are in good health as indicated by medical history, physical examination, vital signs, oxygen saturation, clinical laboratory tests, and 12-lead ECG.
5. Body mass index between 18.0 kg/m2 and 32.0 kg/m2 and body weight greater than 50 kg, inclusive.
6. Adequate contraception is being used or women of nonchildbearing potential may be enrolled if surgically sterile (i.e., after hysterectomy) or postmenopausal for at least 2 years (based on subject*s report). • For women of childbearing potential:
o A medically acceptable and highly effective method of birth control is defined as any form of contraception with a low failure rate defined as <1% per year.
o For example:
• Hormonal contraceptives for at least 8 weeks prior to screening and at least until 4 weeks after the Follow-up visit.
• An intra-uterine device.
• Additional barrier contraception should be used by the partner for the duration of the trial, defined as from the time of screening until 4 weeks after the follow-up visit. A single barrier method alone is not acceptable.
• For men:
o Subjects must be willing to use medically acceptable and highly effective methods of birth control. Subjects must be willing to use barrier contraception (condom) during sexual intercourse with females from the first administration of IMP until 4 weeks after the Follow-up visit.
o Subjects must be willing to take care that their female sexual partner uses at least 1 additional method of contraception with a low failure rate defined

as <1% per year (e.g., hormonal contraceptives, diaphragm) during this time.

Exclusion criteria

1. History or presence of clinically significant cardiovascular (incl. a history of risk factors for torsade de pointes e.g., heart failure, hypokalaemia, family history of long QT syndrome, history of myocardial infarction, ischaemic heart disease, clinically significant arrhythmia or uncontrolled arrhythmia or cardiac failure), pulmonary, hepatic, renal, hematologic, gastrointestinal, endocrine, immunologic, dermatologic, neurologic, oncologic, or psychiatric disease(e.g., anxiety); or any other condition (e.g., hyperventilation disorder), which, in the opinion of the Investigator, would jeopardize the safety of the subject or the validity of the study results.
2. History of known difficult airway access or uncontrolled gastroesophageal reflux disease (GERD), gastric motility disorders, or delayed gastric emptying
3. Has clinically significant abnormalities on ECG at screening or Day -1, as defined by the following:
a) prolonged corrected QT interval (Fridericia-corrected QT interval [QTcF] >450 ms in males and >470 in females) demonstrated on ECG;
b) Left bundle branch block at Screening or Baseline
4. Systolic blood pressure (BP) >150 or <90 mmHg or diastolic BP >95 or <50 mmHg at Screening or Baseline, or history of clinically significant orthostatic hypotension.
5. Heart rate (HR) <40 beats per minute (bpm) or >100 bpm at Screening.
6. 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.
7. Has any condition in which an opioid is contraindicated (e.g., significant respiratory depression, acute or severe bronchial asthma or hypercarbia, or has or is suspected of having paralytic ileus).
8. Have a history of chronic obstructive pulmonary disease or any other lung disease (e.g., asthma, bronchitis, obstructive sleep apnoea, exercise-induced asthma) that would cause CO2 retention.
9. 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 (excluding nicotine and caffeine) within the last 5 years before Screening, which, in the opinion of the Investigator, would jeopardize the safety of the subject or the validity of the study results
10. Has a positive alcohol test or urine drug screen for drugs of abuse (amphetamines, methamphetamines, barbiturates, benzodiazepines, cocaine, and opioids) at Screening or Day -1.
11. Use of nicotine-containing products within 4 weeks before the Screening visit and not able to withhold from smoking during the study.
12. Pregnant or breastfeeding.

13. Subjects indicating pain test intolerability at Screening or achieving pain tolerance at >80% of maximum input intensity for the pain tests.
14. 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.
15. 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.
16. Use of prescription, non-prescription medications or herbal preparations containing St. John*s Wort, within 14days or 5 half-lives prior to dosing, whichever is longer. An exception is made for contraceptives and 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.
17. No vitamin, mineral, herbal, and dietary supplements will be permitted within 7 days prior to study drug administrations, or less than 5 half-lives (whichever is longer, and during the course of the study.
18. Any clinically significant lifetime history of suicidal behaviour or ideation and/or poses a current (within the past12 months) 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 Tris, Park, 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 Tris, Park, CHDR, Investigator, or study site employee. * Immediate family is defined as a spouse, parent, sibling, or child, whether biological or legally adopted

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):	29-07-2022
Enrollment:	30
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	N.A.
Generic name:	cebranopadol
Product type:	Medicine
Brand name:	N.A.
Generic name:	Oxycodone hydrochloride
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO

Date:	19-04-2022
Application type:	First submission
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO

Date:	15-07-2022
Application type:	First submission
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO

Date:	03-10-2022
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)

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Approved WMO Date:	17-10-2022
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
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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	EUCTR2021-006701-30-NL
CCMO	NL81080.058.22