ISRCTN30672343 https://doi.org/10.1186/ISRCTN30672343

A study to investigate the effects of two painkillers as a combination treatment for pain

Submission date
25/03/2022

Recruitment status
No longer recruiting

Registration date
01/04/2022

Overall study status
Completed

Last Edited
01/04/2022

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
Chronic pain is one of the most prevalent and complex medical conditions in the Western world. In general, around 20% of the population in Europe experiences chronic pain, resulting in a large social as well as an economic burden, including the effect on the patient's environment and health care system.
The current pain treatment includes mostly opioids, anti-depressants, antiepileptics, benzodiazepines and nonsteroidal anti-inflammatory drugs (NSAIDs). 60% of patients treated for chronic pain respond poorly to the above-mentioned therapies.

Prescription of opioids is currently the most effective class of painkillers for moderate to severe chronic pain. However, opioids are well knowing for their side effects including sedation, cognitive side-effects and addiction. A solution for this may be by adding a non-opioid analgesic to treatment with an opioid, which may lead to an improved balance of therapeutic benefit and adverse effects, resulting in an opioid-sparing effect.

To obtain a better understanding of combination pain therapies a consortium was established through a Horizon 2020 European Union grant: QSPainRelief (H2020-SC1-BHC-2018-2020). The consortium will investigate alternative novel drug combinations with improved analgesic- and reduced adverse effects. Please refer to qspainrelief.eu for further details.

For example, morphine and pregabalin are two commonly used analgesic compounds that are separately used as treatment for patients with chronic pain. A combination of both compounds may result in an improved analgesic effect and reduced adverse effects.

The Centre of Human Drug Research (CHDR, Leiden, NL) will run this European Union-funded study as part of the QSPainRelief project.

Who can participate?
Healthy subjects, 18 to 65 years of age

What does the study involve?
The study consists of 4 identical study periods where two analgesics (morphine and pregabalin)

are tested in combination, separately and compared to placebo. Pharmacodynamic testing will inform on both the beneficial (analgesic) effects and side effect profile (cognitive functioning and related biomarkers).

What are the possible benefits and risks of participating?
There are no direct health benefits for the participating volunteers, but results will help in developing in the treatment for chronic pain. Possible side effects or risks that can occur during the study are; side effects of the administered treatments, inconveniences of the invasive measurements, in-house stays and lifestyle restrictions.

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 2022 to September 2022

Who is funding the study?
EU Horizon 2020

Who is the main contact?
clintrials@chdr.nl

Contact information

Type(s)
Principal investigator

Contact name
Prof Geert Jan Groeneveld

ORCID ID
https://orcid.org/0000-0002-4655-6667

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

Type(s)
Public

Contact name
Mr Wouter Bakker

Contact details
Zernikedreef 8
Leiden
Netherlands

2333 CL
+31 71 5246 400
WBakker@chdr.nl

Additional identifiers

Clinical Trials Information System (CTIS)
2021-005826-39

ClinicalTrials.gov (NCT)
Nil known

Protocol serial number
CHDR2009

Study information

Scientific Title
A randomized, double-blind, double dummy, placebo-controlled, four-way cross-over study to investigate the analgesic effects and CNS effects of morphine and pregabalin in healthy subjects.

Study objectives
The aim of this experimental pain study, the QSPainRelief-novel Atrial, is to investigate the analgesic effects and effects on CNS functioning of morphine and pregabalin as an analgesic combination in healthy subjects, compared to each of the two analgesics alone and to placebo.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 13/01/2022, Stichting Beoordeling Ethiek Biomedisch Onderzoek (METC Assen, Dr. Nassaulaan 10, 9401HK Assen, Netherlands; +31 592 405 871; info@stbebo.nl), ref: CHDR2009, NL79589.056.21

Study design
Randomized double-blind double-dummy placebo-controlled four-way cross-over study

Primary study design
Interventional

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Novel treatment combination for neuropathic pain in healthy male volunteers

Interventions
The study consists of four identical study periods, Day -1 up to Day 2, each separated by a 1-week wash-out
Each study period, subjects will receive one of the four treatment options in randomized order

Option A: Placebo (oral) that looks like pregabalin, intravenous injection morphine of 3 mg, and intravenous injection morphine of 7mg
Option B: Pregabalin 300 mg oral, and two intravenous injections with placebo that will look like morphine
Option C: Pregabalin 300 mg oral, intravenous injections morphine of 3 mg, and intravenous injection morphine of 7 mg
Option D: placebo (oral) that looks like pregabalin, and two intravenous injections with placebo that will look like morphine

Intervention Type
Drug

Phase
Phase I

Drug/device/biological/vaccine name(s)
Pregabalin (Lyrica), morphine hydrochloride (HCl)

Primary outcome(s)
Analgesic effects measured using the following pre-dose up to 9 h post-dose:
1. Pressure Pain: Pain Detection Threshold (PDT), Pain Tolerance Threshold (PTT), Area Under the Curve (AUC), post-test Visual Analogue Scale (VAS)
2. Heat pain (pre-cold pressor: unexposed/normal and UVB-exposed skin, the latter only for subjects with MED lower than 355 mJ/cm² at screening): PDT, and post-test VAS.
3. Cold Pressor: PDT, PTT, Area Above the Curve (AAC), post-test VAS
4. Electrical Stair test: PDT, PTT, AUC, post-test VAS
5. Electrical burst test: PDT, PTT, AUC, post-test VAS
6. Conditioned Pain Modulation (CPM) Response (change from heat pain pre-and post-cold pressor): PDT
7. Short Form McGill Pain Questionnaire (SFMPQ) for pressure pain, heat pain, cold pressor, electrical stair test and electrical burst test.

Key secondary outcome(s))
To evaluate the drug-sensitive central nervous system (CNS) functioning of morphine, pregabalin and the two drugs as combination by biomarker profiling and the NeuroCart at pre-dose up to 9 h post-dose:
1. Body sway: antero-posterior sway (mm);
2. Visual Analog Scales (VAS) according to Bond and Lader to assess:
2.1. mood (mm),
2.2. alertness (mm), and
2.3. calmness (mm).
3. Visual Analog Scales (VAS) according to Bowdle to assess:
3.1. Feeling high (mm)
3.2. Internal perception (mm)
3.3. External perception(mm)
4. N-back
4.1. Average reaction time (ms) (zero-, one-, two-back)
4.2. Number of correct targets (zero-, one-, two-back)
4.3. Number of incorrect targets (zero-, one-, two-back)
4.4. Number of faulty non-target responses (zero-, one-, two-back)
5. Adaptive Tracking: Average performance (%);

6. Visual Verbal Learning Test (VVLT) memory testing
6.1. Immediate recall trial 3 (number correct)
6.2. Delayed recall (number correct)
6.3. Delayed recognition (number correct)
6.4. Delayed recognition (reaction time correct) (msec)
7. Electroencephalography: Frequency ranges for spectral analysis, Delta, Theta, Alpha, Beta, Gamma
8. Simple Reaction Time Task (SRT): Reaction time (ms) Questionnaires:
9. State-Trait Anxiety Inventory (STAI): State anxiety score
10. Brief Symptom Inventory (BSI)
10.1 General somatic symptoms
10.2 Cognitive symptom so Inter personal sensitivity
10.3 Depressed mood
10.4 Anxiety
10.5 Hostility
10.6 Phobic anxiety
10.7 Paranoid thoughts
10.8 Psychoticism
10.9 Global severity index

To evaluate the blood pharmacokinetic parameters of morphine, pregabalin and the two drugs as a combination at pre-dose up to 24h post-dose:
11. PK parameters of morphine (and metabolitemorphine-6-glucuronide), pregabalin by noncompartmental analysis of the plasma concentration-time data: AUCinf, AUClast, CL(/F), Cmax, t1/2, tlag, tmax, Vz(/F)

To evaluate the safety and tolerability of morphine, pregabalin and the two drugs as combination at Day-1 up to the follow-up visit:
12. Treatment-emergent (serious) adverse events ((S)AEs)throughout the study at every study visit
13. Concomitant medication throughout the study at every study visit
14. Vital signs (Pulse Rate (bpm), Systolic blood pressure (mmHg),Oxygen saturation, Diastolic blood pressure (mmHg)) as per assessment schedule
15. Clinical laboratory tests(Hematology, blood chemistry, glucose, and urinalysis)as per assessment schedule
16. ECG parameters (Heart Rate (HR) (bpm), PR, QRS, QT, QTcF) as per assessment schedule

Completion date
30/09/2022

Eligibility

Key inclusion criteria
1. Healthy subjects, 18 to 65 years of age, inclusive. Healthy status is defined by absence of evidence of any active or chronic disease following a detailed medical and surgical history, a complete physical examination including vital signs, 12-lead ECG, haematology, blood chemistry, and urinalysis
2. Body mass index (BMI) between 18 and 30 kg/m2, inclusive, and with a minimum weight of 50 kg and a maximum weight of 100 kg.
3. Able to participate and willing to give written informed consent and to comply with the study restrictions

Participant type(s)
Healthy volunteer

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 years

Sex
All

Key exclusion criteria
1. Evidence of any active or chronic disease or condition that could interfere with, or for which the treatment of might interfere with, the conduct of the study, or that would pose an unacceptable risk to the subject in the opinion of the investigator (following a detailed medical history, physical examination, vital signs (systolic and diastolic blood pressure, pulse rate, body temperature) and 12-lead electrocardiogram (ECG)). Minor deviations from the normal range may be accepted, if judged by the Investigator to have no clinical relevance.
2. Clinically significant abnormalities, as judged by the investigator, in laboratory test results (including hepatic and renal panels, complete blood count, chemistry panel and urinalysis). In the case of uncertain or questionable results, tests performed during screening may be repeated before randomization to confirm eligibility or judged to be clinically irrelevant for healthy subjects.
3. Positive Hepatitis B surface antigen (HBsAg), Hepatitis C antibody (HCV Ab), or human immunodeficiency virus antibody (HIV Ab) at screening.
4. Systolic blood pressure (SBP) greater than 140 or less than 90 mm Hg, and diastolic blood pressure (DBP) greater than 90 or less than 50 mm Hg at screening.
5. Abnormal findings in the resting ECG at screening defined as:
a. QTcF> 450 or < 300 msec for men and QTcF> 470 or < 300 msec for women
b. Notable resting bradycardia (HR < 45 bpm) or tachycardia (HR > 100 bpm)
c. Personal or family history of congenital long QT syndrome or sudden death;
d. ECG with QRS and/or T wave judged to be unfavourable for a consistently accurate QT measurement (e.g., neuromuscular artefact that cannot be readily eliminated, arrhythmias, indistinct QRS onset, low amplitude T wave, merged T- and U-waves, prominent U waves);
e. Evidence of atrial fibrillation, atrial flutter, complete branch block, Wolf-Parkinson-White Syndrome, or cardiac pacemaker
6. Use of any medications (prescription or over-the-counter [OTC]), within 14 days of study drug administration, or less than 5 half-lives (whichever is longer). Exceptions are paracetamol (up to 4 g/day) and ibuprofen (up to 1g/day), which are allowed up to 2 days before screening and 2 days before each study drug administration. Other exceptions will only be made if the rationale is clearly documented by the investigator.
7. Use of any vitamin, mineral, herbal, and dietary supplements within 7 days of study drug administration, or less than 5 half-lives (whichever is longer). Exceptions will only be made if the rationale is clearly documented by the investigator.
8. Participation in an investigational drug or device study (last dosing of previous study was within 90 days prior to first dosing of this study).
9. History of abuse of addictive substances (alcohol, illegal substances) or current use of more

than 21 units (for males) or 14 units (for females) of alcohol per week, drug abuse, or regular user of sedatives, hypnotics, tranquilizers, or any other addictive agent
10. Positive test for drugs of abuse at screening or pre-dose.
11. Alcohol will not be allowed from at least 24 hours before screening or each admission.
12. Current use of tobacco or nicotine products and unable to abstain from use of these products within the previous 3 months before the first dose administration.
13. Is demonstrating excess in caffeine consumption (more than eight cups of coffee or equivalent per day).
14. Any confirmed significant allergic reactions (urticaria or anaphylaxis) against any drug, or multiple drug allergies (non-active hay fever is acceptable).
15. Loss or donation of blood over 500 mL within three months (males) or four months (females) prior to screening or intention to donate blood or blood products during the study.
16. If a woman, pregnant, or breast-feeding, or planning to become pregnant during the study.
17. Not willing to practice effective contraception during the study and not willing and able to continue contraception for at least 90 days after their last dose of study treatment.
18. Any known factor, condition, or disease that might interfere with treatment compliance, study conduct or interpretation of the results such as drug or alcohol dependence or psychiatric disease.
19. Known hypersensitivity to the investigational drug or comparative drug or drugs of the same class, or any of their excipients.
20. Fitzpatrick skin type IV, V and VI, wide-spread acne, tattoos or scarring interfering with the area of interest (i.e. upper back).
21. Any current, clinically significant, known medical condition in particular any existing conditions that could have affected sensitivity to cold (such as atherosclerosis, Raynaud's disease, urticaria, hypothyroidism) or pain (paraesthesia, etc.).
22. Subjects who indicated nociceptive tests intolerable at screening or who achieved tolerance at >80% of maximum input intensity for the cold pressor or electrical pain tasks.

Date of first enrolment
30/03/2022

Date of final enrolment
15/08/2022

Locations

Countries of recruitment
Netherlands

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

Sponsor information

Organisation
Centre for Human Drug Research

ROR
https://ror.org/044hshx49

Funder(s)

Funder type
Government

Funder Name
Horizon 2020

Alternative Name(s)
EU Framework Programme for Research and Innovation, Horizon 2020 - Research and Innovation Framework Programme, European Union Framework Programme for Research and Innovation

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location

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