Supplemental document 1 to:

Neurocognitive effect of biased μ-opioid receptor agonist oliceridine, a utility function analysis and comparison with morphine

Laurence Moss MD,[1] Hemme Hijma PhD,[1] Mark Demitrack MD,[2] Jessica Kim MSc,[2] Geert Jan Groeneveld MD PhD,[1,3] Monique van Velzen PhD,[3] Marieke Niesters MD PhD,[3] Albert Dahan MD PhD,[3,4] Erik Olofsen PhD[3]

1. Centre for Human Drug Research, Leiden, the Netherlands; 2. Trevena Inc., Chesterbrook, Pennsylvania, USA; 3. Department of Anesthesiology, Leiden University Medical Center, Leiden, the Netherlands; 4. PainLess Foundation, Leiden, the Netherlands

Supplemental materials: inclusion and exclusion criteria

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 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.

Exclusion criteria

1. Poor metabolizers 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, hypesthesia, hyperalgesia, allodynia, paresthesia, 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, hematological 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 ms in females) demonstrated on ECG at screening or baseline.

9. A history of risk factors for torsade de pointes (e.g., heart failure, hypokalemia, family history of long QT syndrome). A history of myocardial infarction, ischemic 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, 5th 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 behavior 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. A subject employed by the sponsor (Trevena), the contract research organization (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.