A Phase I study assessing the safety, tolerability, pharmacokinetics and pharmacodynamics of single ascending doses of HTX-011-19 (a long acting formulation of 5% bupivacaine and 0.15% meloxicam) and HTX-011-49 (a long acting formulation of 2.5% bupivacaine and 0.075% meloxicam) after subcutaneous administration in healthy subjects.

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

Summary

ID

NL-OMON41936

Source
ToetsingOnline

Brief title
HTX C2014-02

Condition

- Other condition

Synonym
analgesics, post-operative pain

Health condition

post-operative pain

Research involving
Human

Sponsors and support

Primary sponsor: Heron Therapeutics, Inc.
Source(s) of monetary or material Support: Heron Therapeutics;Inc.

Intervention

Keyword: Pharmacodynamics, Pharmacokinetics, Safety, Tolerability

Outcome measures

Primary outcome

Part I

• To assess the pharmacokinetics of bupivacaine and meloxicam after single

ascending, subcutaneous doses of HTX-011

Part II

• To assess and compare the analgesic and anesthetic effects of three

different, single, subcutaneous doses of HTX-011

Part III

• To assess the pharmacokinetics of bupivacaine and meloxicam after single

ascending, subcutaneous doses of HTX-011-49

Secondary outcome

Part I

• To assess the safety and (local) tolerability of single ascending

subcutaneous doses of HTX-011

• To assess the pharmacodynamics of HTX-011 after single ascending subcutaneous

doses of HTX-011

Part II

• To compare the pharmacokinetics, safety and tolerability of three different

single, subcutaneous doses of HTX-011

Part III

• To assess the safety and (local) tolerability of single ascending

subcutaneous doses of HTX-011-49.

• To assess the pharmacodynamics of HTX-011-49 after single ascending

subcutaneous doses of HTX-011-49

Study description

Background summary

HTX-011 has the potential to offer substantive clinical improvement over bupivacaine in the treatment of post-operative pain by adding the NSAID meloxicam and by having a potentially much longer effect than currently available local anesthetics. The study is primarily designed to investigate the pharmacokinetics and safety/tolerability of HTX-011 in part I of this study and to investigate the pharmacodynamic (analgesic and anesthetic) effect of

different doses of HTX-011 using the UVB burn analgesia model in part II of the study. Although this study will be the first use of HTX-011 in humans, there is already a lot of experience with both bupivacaine and meloxicam in clinical practice. Non-clinical evaluations of HTX-011 demonstrated shared but more pronounced and longer lasting pharmacologic properties than bupivacaine alone. Pre-clinical results with HTX-011 suggest that no previously unidentified adverse effects should be anticipated with the use of the combined treatment of bupivacaine and meloxicam beyond those individually reported with bupivacaine or meloxicam.

Study objective

The primary objective for part I of the study is the investigation of the pharmacokinetics. Although there is substantial clinical experience with all components of HTX-011, the formulation itself and the route of administration is new, which explains the ascending dose design. This design permits careful evaluation of safety and tolerability at each dose level before escalation to the next dose. As systemic toxicity associated with bupivacaine has rarely been reported with blood levels of 1000ng/mlor less, we will discontinue any further dose escalation if we see PK data of bupivacaine with a Cmax at or near 1000 ng/ml.

One placebo (saline) per cohort is included to collect background information about the subcutaneous administration itself such is mechanical trauma of injection. In order to collect preliminary information about the onset, magnitude and duration of pharmacodynamics effects of HTX-011, two elements of the quantitative sensory testing (QST) test battery (see below) will be applied in part I, i.e. mechanical detection threshold (MDT) and mechanical pain threshold (MPD).

In part II of the study, the pharmacodynamic effects as well as the pharmacokinetics of bupivacaine and meloxicam of different single doses of HTX-011 will be further investigated. As a pharmacodynamic pain model, the UVB sunburn model will be incorporated. This is a method, well described in literature (ref 8, 9, 10) and widely applied. Briefly, UVB irradiation causes skin inflammation which is noxious and elicits pronounced inflammation-related heat and mechanical hyperalgesia at the UVB-irradiated site. This hyperalgesia peaks at about 20-24 h post irradiation after which it slowly subsides. Quantitative sensory testing (QST) assesses characteristic sensory patterns in pain models. The QST battery assembles a comprehensive list of robust and validated short form tests representing measures of all relevant sub-modalities of the somatosensory system (ref 11). In the applied model for this part of the study, the test battery of QST consists of MDT, MPT and cold and heat pain threshold (CPT and HPT).

The purpose of part III of this trial is:
• to study how HTX-011-49 (the study drug) is absorbed, broken-down and

excreted by the body (pharmacokinetics).
• to investigate the safety and tolerability of the study drug HTX-011-49.
• to investigate the effect of the study drug HTX-011-49 on the body (pharmacodynamics)

Study design

Part I.
In part I, 4 cohorts of 6 subjects each will be dosed sequentially. The subsequent ascending dose will be confirmed or determined based on the safety and tolerability data collected during at least the first 72 hours after the previous dosing. The interim safety report following each cohort must be approved by the independent ethics committee (IEC) prior to dosing of the next subsequent cohort. After assessing eligibility during a 21 day screening period, it is planned that in total 24 subjects will participate in this part of the study. Subjects will enter the study center on the day before dosing (Day -1), for baseline assessments and to (re*)confirm eligibility. Subjects will remain in the study center through day 5 (96 hour assessment) and will return to the study center on Day 6 (120 hour blood draw and assessments), Day 7 (144 hour blood draw and assessments) and Day 12 (± 2 days).

On Day 1, all subjects will receive a single subcutaneous dose of HTX-011 or placebo (saline) in the upper part of the right leg. The assigned total volume will be infiltrated as a number of smaller volumes (minimum and maximum volumes to be administered per location will be 0.43 and 0.86 mL in the superficial part of the subcutis). For cohort 1, volumes of 0.43 mL each will be administered in each of the 4 corners of a marked square of approximately 2 x 2 cm. The volumes per location, number of locations and the size of the marked square for each next cohort will be determined based on the results of the previous cohort. These details will be documented in the interim safety report to be submitted to the Ethics Committee prior to proceeding with the next cohort. Blood samples for the determination of bupivacaine and meloxicam will be collected pre*dose and at specified time points up through Day 7 (144 h). The mechanical detection threshold (MDT) and mechanical pain threshold (MPT) for assessing pharmacodynamic effects of HTX-011 will be assessed pre-dose on Day 1 and at specified time points up through Day 7 (144 h) on the square where HTX-011 has been administered.

Safety and tolerability will be assessed throughout the study by adverse event reporting, local tolerability assessments, vital signs and ECG recordings and clinical safety laboratory assessments. For each subject, a follow-up examination will be conducted on Day 12 (± 2 days). All AEs will be followed to resolution or Day 28 after dosing.

Part II.
In part II, 3 cohorts of 8 subjects each will be dosed sequentially. After assessing eligibility during a 21 day screening period during which time each

subject*s own minimal erythema dose (MED) of UVB light will be determined, it is planned that 24 subjects will participate in this part of the study. Subjects will enter the study center on the day before dosing (Day -1) for baseline assessments and to (re*)confirm eligibility. In addition, 20 hours before each dosing, the subject will be exposed to three times the minimal erythema dose (MED) of UVB light on an approximately 3 x 3 cm area on the upper part of the right leg. Subjects will remain in the study center through day 5 (96 hour assessment) and will return to the study center on Day 6 (120 hour blood draw and assessments), Day 7 (144 hour blood draw and assessments) and Day 12 (± 2 days). On Day 1 all subjects will receive a single subcutaneous dose of HTX-011 or placebo (saline) by injection in the upper part of the right leg. The doses of HTX-011 will be selected during the course of part I. One quarter of the assigned total volume will be administered subcutaneously in the superficial part of the subcutis from each of the 4 corners of UVB irradiated marked square of approximately 3 x 3 cm. Blood samples for the determination of bupivacaine and meloxicam levels will be collected pre*dose and at specified time points up through Day 7 (144 h). MDT, MPT, cold and heat pain thresholds (CPT and HPT) for assessing the pharmacodynamics effects will be assessed prior to the UVB irradiation on Day -1, pre-dose on Day 1 and at specified time points up through Day 7 (144 h) on the UVB irradiated area. Safety and tolerability will be assessed throughout the study by adverse event reporting, local tolerability assessments, vital signs and ECG recordings and clinical safety laboratory assessments. For each subject, a follow-up examination will be conducted on Day 12 (± 2 days). All AEs will be followed to resolution or Day 28 after dosing.

Part III
In total 12 healthy female and male subjects will participate in Part 3 of the trial. The subjects will be divided into 2 cohorts of 6 subjects. Within each cohort, 5 subjects will receive a single dose of HTX-011-49 and 1 subject will receive a placebo. In this trial saline will be used as a placebo. Cohort 9 will receive a single dose of 3.44 mL HTX-011-49 or placebo and Cohort 10 will receive a single dose of 6.88 mL HTX-011-49 or placebo. The dose of HTX-011-49 in Cohort 9 is selected based on the results in Part 1 and 2 of this trial

Intervention

The study will start with a screening visit. During the screening visit standard medical assessments including safety laboratory tests (blood draw, urine collection), an alcohol breath test, urine drug screen, a physical examination, ECG and a vital signs measurement will be performed. In addition all subjects will have a UVB test, women will be tested for pregnancy and post-menopausal women will also have their FSH analyzed.

After the subject passes all above mentioned tests, the subject will be enrolled in the study. During study the subjects will enter the clinic, will receive either HTX-011 or placebo , will be asked on a regular basis for

possible side effects, blood will be drawn for safety / PK / PD measurements and the vital signs / ECG will be checked regularly during the confinement period. In addition local tolerability and MDT, MPT, CPT and HPT testing will be perform.

Finally a follow-up examination will be performed. During this visit the subjects will be asked for possible side effects, blood will be drawn for safety, the vital signs/ECG will be checked, local tolerability will be tested, women will be tested for pregnancy and a physical examination will be conducted..

Study burden and risks

HTX*011
The study drug HTX*011 has not been tested before in humans. HTX*011 has been tested in animals by giving it as an injection under the skin. The side*effects in these studies that were likely related to the study drug included subcutaneous acute inflammation and congestion/hemorrhage.

Bupivacaine
High plasma concentrations have been associated with adverse neurologic and cardiovascular events. Signs and symptoms of neurotoxicity can include those associated with both central nervous system (CNS) excitation and depression such as anxiety, restlessness, dizziness, tinnitus, blurred vision, tremors and convulsion. Cardiovascular events may include cardiac conduction abnormalities, hypotension, arrhythmias and cardiac arrest.

Meloxicam
In animal studies, meloxicam resulted in slight increases in systolic or mean arterial pressure, respiratory minute volume or heart rate.

Active polymer
Finally, some studies have been performed with other drugs containing the same active polymer as is used in HTX*011. The polymer in HTX*011 is the matrix in which bupivacaine and meloxicam are loaded. This matrix slowly releases bupivacaine and meloxicam, which causes the effects of bupivacaine and meloxicam to last so long. Studies with the same polymer as in HTX*011 but with other drugs have been performed in over 4000 healthy volunteers and cancer patients. The side*effects reported in these studies included bruising, erythema, nodule and pain at the injection site. These side*effects were generally mild, likely related to the study drug/formulation and were resolved at the time of completion of the study. In rare cases, more serious side*effects occurred: 1% reported injection site hemorrhage, injection site pruritus, induration and discoloration; less than 1% reported tenderness, scab, irritation, and hypersensitivity at the injection site. One patient was withdrawn from the study prematurely because of side*effects at the injection site.

The dose levels of bupivacaine and meloxicam for this study were selected based on research results in animals. The risk to health at these dose levels is limited but you may experience one of the above*mentioned side*effects or other symptoms not previously reported. Your health will be closely monitored during the trial to minimize these risks.

In total, if the subject receives the study drug, 42 blood samples will be drawn and the total blood volume will be approximately 237 mL. If the subject receives placebo, 9 blood samples will be drawn and the total blood volume will be approximately 69 mL. The blood collection procedure is not dangerous, but may cause discomfort or bruising. Occasionally, fainting or an infection at the blood sampling site can occur.

The effects of the study drug on an unborn child are unknown. Subjects will be instructed to use reliable methods of contraception for the duration of the trial and for three months afterwards, to prevent pregnancy.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

1. Subject has signed the informed consent form prior to study participation.
2. Subject is a healthy male or female volunteer between 18 and 55 years old (extremes inclusive).
3. Subject has a body weight between 55 kg and 100 kg and a BMI between 18 and 30 kg/m2 (extremes inclusive).
4. Subject can stay in study center for 6 days and return to study center for 2 consecutive days thereafter, and again on Day 12 (± 2 days).
5. Subject has the ability to lie in a semi-recumbent position for at least 1.5 hours.
6. Subject is appropriate for the study in the judgment of the investigator, based on physical examination, laboratory tests, and subject*s interview.
7. Subject has a skin-type I or II (Fitzpatrick).
8. Subject is willing to use adequate contraception from the time of dosing until 90 days after the follow-up visit. o For male subjects: subjects with female partner of childbearing potential must agree to use a highly effective form of birth control, which entails the use of oral, injected or implanted hormonal methods of contraception or intra-uterine device/system by the female partner, in combination with a barrier method (e.g. condom, diaphragm, cervical cap with spermicide) during the study and for 90 days after discontinuation of treatment. Furthermore male subjects must agree not to donate sperm during participation in the trial and for 90 days after discontinuation of treatment; For female subjects: confirmed post-menopausal women, or female subjects agreeing to use a highly effective form of birth control, which entails the use of oral, injected or implanted hormonal methods of contraception or intra-uterine device/system in combination with a barrier method (e.g. condom, diaphragm, cervical cap with spermicide) during the study and for 90 days after discontinuation of treatment

Exclusion criteria

1. Subject has a medical history of allergies including hypersensitivity against drug or clinically significant allergies, incl. asthma, urticaria, or allergic-type reactions after taking aspirin or other NSAIDs.
2. Subject has clinically significant abnormalities of hepatic, renal, respiratory system, endocrine system, nervous system, immune system, hematologic, psychiatric, cardiovascular system, cancer or has a history of cancer.
3. Subject has an abnormal laboratory result judged by the investigator as being clinically significant.
4. Subject has a positive urinary drug screen (incl. amphetamine, barbiturates, benzodiazepines, cocaine, marijuana, methadone, methamphetamine, morphine, phencyclidine, and tricyclic antidepressants).

5. Subject has a positive test for HIV antibody, HBsAg, or HCV antibody.
6. Subject has a QTc (Bazet) prolongation greater than or equal to 450 ms, or has significant electrocardiogram (ECG) abnormalities.
7. Subject is a heavy smoker (> 10 cigarettes or equivalents per day).
8. Subject is unwilling or unable to refrain from smoking while in the clinical research unit.
9. Subject has tattoos on the skin areas to be treated.
10. Subject has a history of hypersensitivity reactions for any IMP constituent including bupivacaine and other amide-type local anesthetics, and meloxicam.
11. Subject has a supine SBP < 90mmHg or supine SBP > 140mmHg, or supine DBP < 55mmHg or supine DBP > 90mmHg, or Pulse rate > 100 per/min.
12. Subject has used any prescription drug or herbal medicine within 14 days, OTC or vitamin supplements within 7 days prior to Day 1 of any study period.
13. Subject participated in a previous clinical trial with administered IMP within 90 days prior to Day 1 of the first study period.
14. Subject is a heavy alcohol consumer (alcohol > 23 units/week) or cannot stop drinking while in the clinical research unit.
15. Subject lost a volume of blood, including through blood donation, of more than 400 mL within 8 weeks prior to Day 1.
16. Subject is unwilling or unable to adhere to any specific protocol restriction as mentioned in Section 8.3.3 of the protocol.
17. For females: Subject is currently pregnant, breast feeding, or disagrees to avoid getting pregnant during the clinical study.
18. Subject is legally incapable or has limited legal capacity at screening.

Study design

Design

Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	06-10-2014
Enrollment:	46

Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	-
Generic name:	bupivacaine / meloxicam

Ethics review

Approved WMO Date:	23-10-2014
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	31-10-2014
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	07-05-2015
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	11-05-2015
Application type:	Amendment
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	EUCTR2014-003094-41-NL
CCMO	NL50985.056.14