

# A randomized, double-blind, placebo-controlled, serial-cohort, single ascending dose of Xen2174 with bupivacaine interaction study administered intrathecally in healthy volunteers.

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<b>Ethical review</b>	Not approved
<b>Status</b>	Will not start
<b>Health condition type</b>	Tissue disorders NEC
<b>Study type</b>	Interventional

## Summary

### ID

NL-OMON35341

### Source

ToetsingOnline

### Brief title

Xen2174 and bupivacaine interaction study

### Condition

- Tissue disorders NEC

### Synonym

pain after surgery, Post operative pain

### Research involving

Human

## Sponsors and support

**Primary sponsor:** Xenome Ltd.

**Source(s) of monetary or material Support:** Xenome Ltd.

## Intervention

**Keyword:** Intrathecal, Norepinephrine transporter inhibitor, postoperative pain, Single ascending

## Outcome measures

### Primary outcome

Pharmacodynamics:

Pain threshold and tolerance levels for each nociceptive test:

- Pressure pain (muscle) (kPa),
- Electrical pain (skin) (mA) single stimulus
- Electrical pain (skin) (mA) repeated stimulus
- Cold pressor pain (seconds)
- Diffuse Noxious Inhibitory Control (difference of electrical pain before and after cold pressor task)

EEG data

Determination of the level and duration of sensory blockade due to bupivacaine

- Pin Prick/ Cold discrimination

Determination of the level and duration of motor blockade due to bupivacaine

- Modified Bromage scale

Pharmacokinetics:

- CSF Bupivacaine PK

-CSF Xen2174 PK

-Plasma bupivacaine PK

-Plasma Xen2174 PK

## **Secondary outcome**

Not applicable

# **Study description**

## **Background summary**

Xen2174 is a synthetic 13-amino acid peptide that is being developed by Xenome for the intrathecal treatment of moderate to severe pain. In nonclinical pharmacology studies, Xen2174 has effectively reduced nociceptive pain and postoperative pain in animal models. Data from the clinical studies to date have demonstrated that a single dose of Xen2174, administered intravenously at 10 to 200 µg/kg or intrathecally at 0.025 to 30 mg, is safe and well-tolerated. The current clinical development plan is to further investigate the use of Xen2174 for moderate to severe pain.

## **Study objective**

The objectives of the study are:

To determine the pharmacokinetic and pharmacodynamic interaction of a single ascending dose of Xen2174 with bupivacaine, and in one cohort of Xen2174 alone, when administered intrathecally to healthy volunteers and assess the effect of a single administration of Xen2174 in different dosages in conjunction to bupivacaine, and in one cohort of Xen2174 alone, on safety and tolerability in healthy subjects.

## **Study design**

This will be a randomized, double-blind, placebo-controlled, serial-cohort, single ascending dose, interaction study administered intrathecally that will examine 3 different doses. (Xen2174 0.25 mg, 1.00 mg and 2.50 mg together with bupivacaine 10 mg).

## **Intervention**

There will be 4 treatment cohorts. Cohorts 1 and 2 consist of 11 subjects; 8 subjects on an ascending dose of Xen2174 in combination with bupivacaine and 3 subjects on vehicle in combination with bupivacaine. Cohort 3 consists of 10 subjects: 8 subjects on the highest dose of Xen2174 in combination with bupivacaine and 2 subjects on vehicle in combination with bupivacaine. Cohort 4 consists of 12 subjects; 6 subjects on a dose of 2.5 mg Xen2174 and 6 vehicle-only subjects.

1. Xen2174 0.25 mg + bupivacaine 10 mg (n=8), bupivacaine 10 mg alone (n=3)
2. Xen2174 1.00 mg + bupivacaine 10 mg (n=8), bupivacaine 10mg alone (n=3)
3. Xen2174 2.50 mg + bupivacaine 10 mg (n=8), bupivacaine 10 mg alone (n=2)
4. Xen2174 2.50 mg (n=6), vehicle alone (n=6)

### **Study burden and risks**

Across studies, the majority of adverse events were mild or moderate. Side effects that are reported after use of Xen2174 are: nausea, blood creatine phosphokinase increased, dizziness, headache, hypotension and vomiting. No exceptional severe adverse drug reactions are expected and burden/inconvenience for the subjects are considered relatively mild. Development of Xen2174 could constitute an additional therapeutic tool for the treatment of postoperative pain.

## **Contacts**

### **Public**

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Australie

### **Scientific**

Xenome Ltd.

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Australie

## **Trial sites**

## Listed location countries

Netherlands

## Eligibility criteria

### Age

Adults (18-64 years)

Elderly (65 years and older)

### Inclusion criteria

1. Healthy subjects aged 18-50 years at the time of informed consent.
2. Voluntary provision of written informed consent prior to any study procedure, indicative of understanding the purpose of the study and willing to participate in the study and comply with the study procedures and restrictions.

### Exclusion criteria

1. Subject has or had, in the opinion of the investigator, clinical significant abnormalities as found in the medical history, physical examination, electrocardiogram (ECG), laboratory profile and/or blood and urine.
2. Vital sign measurements outside the following ranges: (Individuals with values outside of these ranges may be enrolled if clinically acceptable to the investigator and sponsor):
  - Body temperature, between 35.0°C and 37.5°C
  - Systolic blood pressure, 90 to 140 mm Hg
  - Diastolic blood pressure, 45 to 90 mm Hg
  - Pulse rate, 40 to 100 bpm
3. Women of childbearing potential who refuse to use a medically acceptable form of contraception throughout the study. (Acceptable methods of contraception are as follows: oral or injectable hormonal contraceptives, intrauterine devices, vaginal hormonal rings, and only in combination with a male condom, a vaginal diaphragm, or cervical caps. Men are advised to use male condoms in addition to having their partner use another acceptable method during the study and for 3 months after the last dose.)
4. Women who are pregnant or lactating, or have a positive pregnancy test within 72 hours prior to randomization.
5. Presence or history of clinically significant psychiatric diseases, as judged by the investigator.
6. Any clinically relevant acute or chronic diseases which according to the investigator could interfere with the subject's safety during the trial, or expose them to undue risk, or which could interfere with the study objectives.
7. Presence or history of clinically significant allergy or known hypersensitivity to any component of the investigational product.

8. Subjects having an abnormal EEG at screening.
9. Subjects who had ever had an abnormal EEG.
10. Subjects having a history or family history (first degree) of seizures or seizure disorder.
11. Subjects who had febrile seizure in childhood.
12. Subjects who had an episode of loss of consciousness for any reason other than a vasovagal reaction.
13. Subjects having a history of hydrocephalus, head injury or (repeated) blow(s) to the head, which in the opinion of the investigator might have resulted in an (undiagnosed) brain injury.
14. Subjects having a history of or presenting pseudo or psychogenic seizure;
15. Subjects having a history of meningitis/encephalitis or other infectious process affecting the brain, central, and/or peripheral nervous system;
16. Subjects having a history of haematological disorder such as leukaemia, lymphoma, purpura, clotting disorders, or conditions that affect bleeding or clotting time;
17. Subjects having a history or family history of ankylosing spondylitis, previous (lumbar) back surgery and/or spinal deformity;
18. Subjects having a local skin infection at the site of injection, or dermatological condition e.g. psoriasis that preclude aseptic preparation of the skin around the injection site;
19. Subjects indicating nociceptive tests intolerable at screening.
20. Has a body mass index (BMI) outside the following range: 18 to 30 kg/m<sup>2</sup>(inclusive). BMI = weight (kg)/height<sup>2</sup> (m<sup>2</sup>).
21. Has positive serology for HIV, hepatitis B (surface antigen), and/or hepatitis C antibodies.
22. Has planned medical treatments between screening and follow-up visit.
23. Enrolment in any investigational study or intake of an investigational drug within 3 months prior to the start of the study or more than 4 times a year.
24. Current regular user of any illicit drugs or history of drug abuse. Subjects who have a positive drug screen at screening will be excluded.
25. Donation of blood/plasma outside limits of Sanquin Blood Supply Foundation guidelines.
26. Is not likely to co-operate in the study, and/or has poor compliance as anticipated by the investigator, or not consistently reachable in case of emergency.
27. Daily consumption of xanthine-containing products more than 8 units. Unwilling or unable to refrain from consumption of xanthine-containing foods or drinks from 1 days prior to admission and during the stay in the research unit. One caffeine unit is contained in the following items: one cup of coffee, two cans of cola, one glass of tea, \* cup of energy drink (e.g., Red Bull) or three chocolate bars.
28. Unwilling or unable to refrain from intensive physical exercise from 48 hours prior to each study day until dismissal from CHDR.
29. History of alcohol abuse and/or excessive current use of alcohol (i.e., regular use of more than 21 units of alcohol/week for males and more than 14 units/week for females), and/or unwillingness or unable to refrain from products containing alcohol from 1 days before admission and during the stay in the research unit. Subjects who have a positive alcohol breath test at screening will be excluded.
30. Unwilling or unable to refrain from smoking during admission and the stay in the research unit.
31. Males who are unwilling to abstain from having unprotected sexual intercourse or donating sperm during the study and for 3 months after study.
32. Male\*s partner is planning pregnancy within 3 months of last dosing.
33. Subjects previously treated with Xen2174.

34. Is unsuitable, in the opinion of the investigator, to participate in the study for any other reason.

## Study design

### Design

Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

### Recruitment

NL	
Recruitment status:	Will not start
Enrollment:	44
Type:	Anticipated

### Medical products/devices used

Product type:	Medicine
Brand name:	Marcaine
Generic name:	Bupivacaine
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Xen2174
Generic name:	Xen2174

## Ethics review

Approved WMO	
Date:	16-08-2011
Application type:	First submission

Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Not approved	
Date:	10-11-2011
Application type:	First submission
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)

## 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	EUCTR2011-003776-37-NL
CCMO	NL37832.058.11