A randomized, double-blind, placebo-controlled, serial-cohort, single ascending dose of Xen2174 PK/PD study administered intrathecally in healthy volunteers.

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The objectives of the study are:To determine the pharmacokinetic profile of Xen2174 in plasma and CSF when administered intrathecally to healthy volunteersTo determine which modalities of pain are affected by treatment with Xen2174 when administered...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Tissue disorders NEC
Study type	Interventional

Summary

ID

NL-OMON35658

Source
ToetsingOnline

Brief title
Single Ascending Dose of Xen2174 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)

24 hour EEG data

Pharmacokinetics:

-CSF Xen2174 PK

-Plasma Xen2174 PK

Exploratory

-Tolerability of intrathecal catheter

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 profile of Xen2174 in plasma and CSF when administered intrathecally to healthy volunteers

To determine which modalities of pain are affected by treatment with Xen2174 when administered to healthy volunteers.

To assess the effect of a single administration of Xen2174 in different dosages on safety and tolerability in healthy subjects;

to assess the effect of a single administration of Xen2174 in different dosages on EEG in healthy subjects;

to determine the dose of Xen2174 at which the anti-nociceptive or anti-allodynic effect is maximal in multiple pain paradigms in healthy volunteers;

to assess tolerability of CSF sampling by using an intrathecal catheter

Study design

This will be a randomized, double-blind, placebo-controlled, serial-cohort, single ascending dose of Xen2174 or placebo PK/PD study, administered intrathecally in healthy volunteers. Three doses will be examined. (Xen2174

0.50 mg, 1.00 mg and 2.50 mg)

Intervention

There will be 3 treatment cohorts. Cohort 1 and cohort 2 consist of 11 subjects, 8 subjects on an ascending dose of Xen2174 and 3 subjects on placebo. Cohort 3 consists of 10 subjects, 8 subjects on Xen2174 and 2 subjects on placebo.

Treatment cohorts N=32
1. Xen2174 0.50 mg (n=8), placebo (n=3)
2. Xen2174 1.00 mg (n=8), placebo (n=3)
3. Xen2174 2.50 mg (n=8), placebo (n=2)

Study burden and risks

Across studies. the majority of adverse events were mild or moderate. Side effects that are reported after use of Xen217 4
are: nausea, blood creatine phosphokinase increased. dizziness, (post punctional) headache, hypotension and vomiting.
No exceptional severe adverse drug reactions are expected and burdenlinconvenience for the subjects are considered
relatively mild. Development of Xen2174 ooutd constitute an additional therapeutic tool for the treatment of postoperative
pain.

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. 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 35.0ºC and 37.5ºC
•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/m2(inclusive). BMI = weight (kg)/height2 (m2).
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.
35. Subjects having complaints of low back pain.

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:	Recruitment stopped
Start date (anticipated):	28-12-2011
Enrollment:	32
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Xen2174
Generic name:	Xen2174

Ethics review

Approved WMO

Date:	07-12-2011

Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	19-12-2011
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	21-12-2011
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	09-02-2012
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	16-02-2012
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	08-03-2012
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	22-03-2012
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	17-04-2012
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	EUCTR2011-005768-73-NL
CCMO	NL38941.056.11