VX16-150-102 A Phase 2, Randomized, Double-blind, Placebo-controlled, 6-Week, Parallel-design Study of the Efficacy and Safety of VX-150 in Treating Subjects With Pain Caused by Small Fiber Neuropathy

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Primary Objective:To evaluate the efficacy of VX-150 for the treatment of pain caused by small fiber neuropathy.Secondary Objectives:* To evaluate the safety and tolerability of VX-150* To evaluate the pharmacokinetics (PK) of VRT-1207355 and the...

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

Summary

ID

NL-OMON46746

Source
ToetsingOnline

Brief title
VX16-150-102

Condition

- Peripheral neuropathies

Synonym
SFSN, small nerve fiber neuropathy

Research involving

Human

Sponsors and support

Primary sponsor: Vertex Pharmaceuticals
Source(s) of monetary or material Support: Vertex Pharmaceuticals Incorporated

Intervention

Keyword: Double-blind study, Pain, Parallel-design, Phase 2

Outcome measures

Primary outcome

Change from baseline in the weekly average of daily pain intensity on the

11-point numeric rating scale (NRS), as reported in the daily diary, at Week 6

Secondary outcome

* Proportion of subjects with *30% reduction in the weekly average of daily

pain intensity on the 11-point NRS, as reported in the daily diary, at Week 6

* Proportion of subjects with *50% reduction in the weekly average of daily

pain intensity on the 11-point NRS, as reported in the daily diary, at Week 6

* Change from baseline in the Daily Sleep Interference Scale (DSIS) at Week 6

* Proportion of subjects categorized as improved at Week 6 on the patient

global impression of change (PGIC) assessment

* Change from baseline in pain intensity on the 11-point NRS, as reported at

study visits, at Week 6

* Plasma PK parameters of VRT-1207355 and the metabolite VRT-1268114

* Safety and tolerability based on the Columbia Suicide Severity Rating Scale

(C- SSRS), incidence and type of adverse events (AEs), changes from baseline in

clinically significant laboratory test results, vital signs, and ECGs at each

visit

Study description

Background summary

Pain is the most common symptom for which patients seek medical attention. It is a protective mechanism designed to prevent tissue injury. When pain persists beyond its usefulness, it becomes pathological and can prove debilitating. Current pain therapies suffer from poor efficacy and have a high risk of adverse events (AEs). For example, lidocaine (a nonselective sodium channel blocker) may effectively reduce pain, but its utility is limited because of prominent side effects when given at dose levels required for pain relief. Opioid pain medications have a high abuse liability with approximately 16,000 annual deaths in the US and between 10,000 and 20,000 annual deaths in Europe due to overdose. In addition, opioid- induced hyperalgesia also limits the long-term use of opioids. While the incidence of opioid- induced hyperalgesia is not known, it is encountered regularly in clinical practice and creates significant challenges in pain management. The limited treatment options for pain, particularly chronic pain indications, combined with a growing awareness of the risks of the current standards of care underscore the need for new pain management therapies.

Voltage-gated sodium channels (Nav) play a critical role in pain signaling based on both nonclinical and clinical evidence. Evaluation of the role these channels play in normal physiology and the pathological states arising from mutations in sodium channel genes and animal models, as well as the pharmacology of known sodium channel modulating agents, all point to the critical role of Navs in pain sensation. The Nav1.8 channel is primarily restricted to peripheral neurons that sense pain (e.g., dorsal root ganglia) and is known to mediate pain sensation and chronic pain. For example, Nav1.8 gain-of-function mutations are thought to directly cause chronic pain in some patients with painful small fiber neuropathy. This channel has been identified as a target for analgesia and selective Nav1.8 blockers, which have the potential to treat pain indications where the primary mechanism for pain is nociceptor hyperexcitability.

VX-150, an orally bioavailable prodrug that rapidly converts in vivo to the active moiety
VRT-1207355, is being developed for the treatment of pain. VRT-1207355 is a Nav1.8 blocker that is highly selective for Nav1.8 relative to the other sodium channel subtypes.

To date, 4 Phase 1 clinical studies have been completed with VX-150.

VX14-150-001 (Study 001) was a first-in-human study which evaluated single-ascending and multiple-ascending doses of VX-150 in healthy subjects. Study VX15-150-002 (Study 002) evaluated the drug-drug interaction (DDI) between VX-150 and the proton-pump inhibitor esomeprazole, and Study VX15-150-003 (Study 003) evaluated the DDI between VX-150 and midazolam. Study VX15-150-004 (Study 004) evaluated the pharmacodynamics (PD) of VX-150 in a capsaicin pain model. A fifth Phase 1 study, Study VX16-150-005 (Study 005), is currently evaluating the PK of VX-150 after multiple doses of 1250 and 1750 mg daily (qd) with a capsule formulation in healthy subjects.

One Phase 2a study has completed dosing; Study VX15-150-101 (Study 101) is a proof of concept study to evaluate efficacy in patients with osteoarthritis pain. Overall, VX-150 has been well tolerated without any safety concerns. Additional details of the VX-150 development program are available in the VX-150 Investigator*s Brochure.

Small fiber neuropathy is a distinct clinical condition caused by diseases affecting peripheral small nerve fibers (A*- and C-fibers). Common symptoms include burning pain in the feet and evoked pain (e.g., pressure and touch allodynia). Diagnosis is defined as possible, probable, and definite based on the combination of symptoms, signs, evidence of large sensory nerve fiber function integrity by nerve conduction studies (NCS) and abnormal skin biopsy or quantitative sensory testing. By inhibiting Na 1.8 in the peripheral nerve fibers, VX-150 has the potential to treat pain caused by hyperexcitability of the damaged or diseased nerves.
Study VX16-150-102 is a proof of concept study that will evaluate the efficacy, safety, tolerability, and pharmacokinetics (PK) of VX-150 in the treatment of neuropathic pain in subjects with small fiber neuropathy.

Study objective

Primary Objective:
To evaluate the efficacy of VX-150 for the treatment of pain caused by small fiber neuropathy.

Secondary Objectives:
* To evaluate the safety and tolerability of VX-150
* To evaluate the pharmacokinetics (PK) of VRT-1207355 and the metabolite VRT-1268114

Study design

This is a Phase 2, randomized, double-blind, placebo-controlled, parallel-group, multicenter study. A total of approximately 114 subjects with small fiber neuropathy will be randomized 1:1 to VX-150 or placebo. Randomization will be stratified by sex and diagnosis of diabetes.Subjects with

diabetes will not exceed 60% of the total number of subjects. Subjects with diabetes and HbA1c
This study will include:
A 7-day Run-in Period to establish the baseline NRS pain score
A 6-week Treatment Period
A 28-day Safety Follow-up Period

Intervention

See section E4 of the ABR Form.

Study burden and risks

Risks of taking VX-150:

As of November 15, 2016 approximately 141 healthy subjects and 124 subjects with joint disease (osteoarthritis) have received at least one dose of VX-150. Based on limited experience so far, there are no known side effects for the study compound. Overall, the study medication has been well tolerated in humans. There were some adverse events that occurred in subjects taking the study compound or an inactive placebo, but we do not know whether they were due to the study compound or other conditions. Some of these adverse events included:
* Headache
* Muscle or joint aches
* Rash
* Dizziness
* Feeling tired
* Runny nose

Continued (blinded) analyses of the treatment of 124 patients with osteoarthritis are ongoing. Safety observations included 5 serious adverse events in 3 subjects (pain in jaw with dyspnea (shortness of breath), urinary tract infection, and urinary tract infection with sepsis (infection in the blood)), all of which were considered not related or unlikely related to Study Drug by the investigator. The most common adverse events that occurred in 4 or more subjects were headache (6 subjects), joint pain (6 subjects), dizziness (4 subjects), urinary tract infection (4 subjects), nasopharyngitis (common cold) (4 subjects), and rash (4 subjects).
The study compound has been studied in laboratory animals (rats, dogs and monkeys). There have been no harmful side effects or toxicities at any tested dose level. Decreased body weight and lower food consumption were observed in rats exposed to high doses of the study compound. The patient should be aware that these adverse effects and possibly others, still unknown, adverse effects may occur during the study.

Unknown adverse effects
All potential drugs may cause adverse effects; the extent to which this occurs differs. The patient should be aware that the aforementioned adverse effects and possibly other, still unknown adverse effects may occur during the study. The patient should notify the clinic staff if he/she thinks he/she is having any health problems at all, even if the patient does not believe the problems are related to study participation.
In addition, as with any drug including over-the-counter drugs, there is a small but significant risk of allergic reactions that, if severe, can be fatal. These types of reactions can start shortly after taking a drug and may appear in the form of itching or redness of the skin, swelling of the face, lips, tongue, throat, or difficulty breathing which may be severe in some cases. If the patient experiences any of these reactions, he/she must let the clinic nurse know immediately, and, if the patient is already discharged from the clinic, should go to the closest Emergency Department for treatment.

Risks of taking Acetaminophen (Paracetamol)
Adverse effects of acetaminophen (paracetamol) are rare. Very rare cases of serious skin reactions have been reported. There have been reports of blood abnormalities including platelet disorder causing decreased blood coagulation and therefore signs of skin bruising, inability of red blood cells to effectively deliver oxygen to body tissues and a decrease of white blood cells which fight against infections, but these adverse effects were not necessarily caused by acetaminophen (paracetamol). Damage to the liver can occur with very high/toxic doses of acetaminophen (paracetamol).

Drug Interaction Risks (medicines working with or against each other)
Almost all medicines can cause side effects. Many are mild, but some can sometimes become life threatening if they are not treated. The combination of the Study Drug and any other medications, dietary supplements, natural remedies, and vitamins could be harmful to you. The patient should tell your study doctor about every medicine, dietary supplement, natural remedy, and vitamin (or change) while he/she are in the study.

Unknown Risks
There may be side effects that are not yet known. The patient should call your study doctor if he/she thinks is having any of the problems listed above or even if the patient is having problems that are not on this list.

Contacts

Public
Vertex Pharmaceuticals

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US
Scientific
Vertex Pharmaceuticals

Northern Avenue 50
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US

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

1. Subject will sign and date an informed consent form (ICF)
2. Willing and able to comply with scheduled visits, treatment plan, study restrictions, laboratory tests, contraceptive guidelines, and other study procedures
3. Subjects (male and female) will be between the ages of 18 and 80 years, inclusive.
4. Body mass index (BMI) of >18.0 kg/m2
5. Diagnosis of small fiber neuropathy, as per European Federation Neurological Societies (EFNS)/American Academy of Neurology (AAN) guidelines, with pain for at least 3 months prior to screening
6. Reduction below the 5th percentile of sex and age-adjusted normal values in epidermal nerve fiber density on punch skin biopsy at the distal site of the leg performed at or within 6 months of screening
7. presence of sural response
8. Average NRS score between *4 and *9 reported in the daily diary on Days -7 through -1

Exclusion criteria

1. History in the past 10 years of malignancy except for squamous cell skin cancer, basal cell

skin cancer, and Stage 0 cervical carcinoma in situ (all 3 with no recurrence for the last 5 years)
2. Exposure to neurtoxic drugs (i.e., chemotherapy) since diagnosis of small fiber neuropathy.
Untreated or uncontrolled connective tissue disorders, sarcoidosis, Sjögren*s syndrome, amyloidosis, Fabry*s disease, celiac disease, Lyme disease, autoimmune disorders (i.e., as assessed by anti-nuclear antibodies, rheumatoid factor, sedimentation rate, and/or lupus anti-coagulant) including myasthenia gravis and Guillain-Barre syndrome, which in the opinion of the investigator makes the subject unsuitable for inclusion in this study.
3. A known or clinically suspected infection with human immunodeficiency virus or hepatitis B or C viruses
4. Current clinically significant liver or kidney dysfunction
5. Current uncontrolled thyroid dysfunction
6. Subjects with a diagnosis of diabetes who have any 1 of the following criteria:
- HbA1C >11% at screening
- are not stabilized on oral hypoglycemics and/or subcutaneous insulin or diet, in the opinion of the investigator
-evidence of ulcers or severe nephropathy resulting from their diabetes
-advanced retinopathy, defined as greater than State 3 (moderate non-proliferative diabetic retinopathy)
- history of a clinical atherosclerotic event, such as myocardial infarction or stroke
7. History of cardiac dysrhythmias requiring anti-arrhythmia treatment(s); or history or evidence of abnormal ECGs that in the opinion of the investigator or medical monitor would preclude the subject's participation in the study
8. Standard 12-lead ECG demonstrating QTc >450 msec at screening. If QTc exceeds 450 msec, the ECG will be repeated 2 more times, and the average of the 3 QTc values will be used to determine the subject*s eligibility.
9. Concomitant severe pain conditions (i.e., low back pain, radiculopathy, severe bone and musculoskeletal disorders) which may impair self-assessment of pain due to small fiber neuropathy
10. Abnormal laboratory results indicative of any significant medical disease that, in the opinion of the investigator, would preclude the subject's participation in the study
11. Other serious, acute, or chronic medical or psychiatric illness that, in the judgment of the investigator, could compromise subject safety, limit the subject*s ability to complete the study and/or compromise the objectives of the study
12. Female subjects who are pregnant, nursing, or planning to become pregnant during the study or within 90 days after the last study drug dose
13. Male subjects with a female partner who is pregnant, nursing, or planning to become pregnant during the study or within 90 days after the last study drug dose
14. Use of restricted medication or food within the specified duration before the first dose of study drug
15. Alcohol, analgesic/opioid, and/or illicit drug abuse as defined by the American Psychiatric Association Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, in the last 12 months before screening, or a positive test for drugs of abuse at screening
* A positive drug screen for a known concomitant medication that is not otherwise exclusionary (e.g., benzodiazepines) will not disqualify subjects; however, marijuana and marijuana derivatives will not be allowed
16. Subject, or close relative of the subject, is the investigator or a subinvestigator, research

assistant, pharmacist, study coordinator, or other staff directly involved with the conduct of the study at that site

Study design

Design

Study phase:	2
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):	05-03-2018
Enrollment:	4
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Placebo
Generic name:	Placebo
Product type:	Medicine
Brand name:	VX-150
Generic name:	VX-150

Ethics review

Approved WMO

Date:	04-07-2017

Application type:	First submission
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	06-12-2017
Application type:	First submission
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	23-01-2018
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	28-02-2018
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	17-05-2018
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	13-06-2018
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	17-07-2018
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	13-09-2018
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)

Approved WMO Date:	07-12-2018
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	06-02-2019
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)

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	EUCTR2017-001042-10-NL
CCMO	NL62086.068.17