Double-blind, placebo-controlled phase 1 trial of nizaracianine administered in three divided doses to healthy volunteers

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Primary• To assess the safety and tolerability in healthy volunteers of nizaracianine administered IV in three divided dosesSecondary• To perform pharmacokinetic analyses of blood and urine• To determine if bolus injection of nizaracianine enables...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Urinary tract signs and symptoms
Study type	Interventional

Summary

ID

NL-OMON51504

Source
ToetsingOnline

Brief title
A phase 1 study of divided doses of nizaracianine in healthy volunteers

Condition

- Urinary tract signs and symptoms

Synonym
Preventing iatrogenic ureteral damage preventing unneccessary damage to urinary tract

Research involving
Human

Sponsors and support

Primary sponsor: Curadel Surgical Innovations, Inc.

Source(s) of monetary or material Support: Curadel Surgical Innovations;Inc.

Intervention

Keyword: Fluorescence, NIR, Nizaracianine, Ureters

Outcome measures

Primary outcome

• Treatment-emergent (serious) adverse events ((S)AEs) throughout the study at every study visit

• Concomitant medication throughout the study at every study visit

• Vital signs (pulse rate (bpm), systolic blood pressure (mmHg), diastolic blood pressure (mmHg)) as per assessment schedule

• Clinical laboratory tests (hematology, blood chemistry and urinalysis) as per assessment schedule

• ECG parameters (heart rate (HR) (bpm), PR, QRS, QT, QTcF) as per assessment schedule

Secondary outcome

• PK- parameters of nizaracianine by multi-compartmental analysis of the plasma concentration-time data and urine data:

* AUCinf, AUClast, CL/F, Cmax, t1/2, tlag, tmax, Vz/F

* Dose-normalized PK parameters: AUCinf, AUClast, Cmax

* Urine PK parameters: Aelast, Aelast%, CLR

• Analysis of continuous NIR fluorescence imaging of the vascular flush in the abdominal vasculature from 5 seconds prior to the injection until 1 minute after the injection. PD-parameters are:

* Fluorescent yes or no

* Signal-to-background ratio (SBR)

* Mean fluorescent intensity in the most prominent artery or vein

* Mean fluorescent intensity in the background

• Fluorescence intensity is reported as:

* Fluorescent yes or no

* Signal-to-background ratio (SBR)

* Mean fluorescent intensity in the Foley tubing

* Mean fluorescent intensity in the background

Study description

Background summary

Fluorescence imaging using near-infrared (NIR) light (i.e., 700-900 nm) can assist surgeons to recognize structures that need to be spared, e.g., blood vessels and ureters, and structures that need to be resected, e.g., sentinel lymph nodes and tumors. Currently, the only clinically available NIR fluorophores are methylene blue, 5-ALA and indocyanine green (ICG). However, the fluorescence emission intensity (i.e., the product of extinction coefficient and quantum yield) and peak (600 nm and 700 nm, respectively) of 5-ALA and methylene blue and the clearance route of ICG (primarily hepatic), are far from optimal. Nizaracianine (formerly ZW800-1) has improved in vivo properties compared to available NIR fluorophores, including low non-specific binding and uptake, a high extinction coefficient and quantum yield. Moreover, nizaracianine has exclusive renal clearance after intravenous administration, which allows intraoperative imaging of the ureters, and this could prevent damage to the ureter during surgery. Safety of nizaracianine administered as a single dose was tested in animal studies and a phase 1 human volunteer study. A phase 2 study in surgical patients showed that after a single low-dose intravenous injection, ureters were visible for 1-3 hours during abdominopelvic surgery. The purpose of this repeat phase 1 clinical trial is to assess the safety of nizaracianine in healthy volunteers when administered as three divided doses. Long surgeries are common with abdominopelvic procedures and

repeat dosing of nizaracianine should provide the surgeon with continuous visualization of the ureters during most common procedures.

Study objective

Primary
• To assess the safety and tolerability in healthy volunteers of nizaracianine administered IV in three divided doses

Secondary
• To perform pharmacokinetic analyses of blood and urine
• To determine if bolus injection of nizaracianine enables NIR fluorescence angiography
• To determine the fluorescence intensities in the tubing of the Foley catheter (a proximal surrogate for fluorescence intensity of the ureters)

Study design

This is an ascending dose, double-blind, randomized, placebo-controlled study in healthy volunteers.

Intervention

Nizaracianine or placebo

Study burden and risks

Adverse reactions, such as hypersensitivity reactions, may occur. However, the likelihood of a hypersensitivity reaction is low as no such toxicity was seen in the earlier studies. Nevertheless, study subjects will be monitored clinically (observation, vital signs, etc.) before, during, and after IMP administration in a dedicated research clinic. In the phase 1 and phase 2a administration of nizaracianine was well tolerated without relevant toxicity.

In the renal transplant patient pilot study unexplained rejection of the renal transplants were observed in two transplant recipients. A relationship to the nizaracianine administration cannot be excluded. Therefore, subjects will be monitored closely to identify potential adverse effects on renal function

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)

Inclusion criteria

1. Subject is 18-55 years old at screening (inclusive).
2. Subject is able and willing to comply with study procedures.
3. Subject is in good general health, according to the investigator*s judgement based on vital signs, medical history, physical examination, and laboratory tests performed.
4. Body mass index between 18-32 kg/m2 (inclusive) and with a minimum body weight of 50 kg at screening.
5. An estimated GFR >= 90.
6. Female subjects need to be surgically sterile, post-menopausal or pre-menopausal with a negative urine pregnancy test at screening and before administration of nizaracianine. Pre-menopausal female subjects who are not surgically sterile have to agree to use an effective method of contraception.
7. Subject*s screening ECG and clinical laboratory test results are within normal limits, or if any are outside of normal limits they are considered to be clinically insignificant.
8. Subject has negative test results for drug and alcohol screening.
9. Written informed consent must be given prior to any study activities, according to ICH/GCP and national/local regulations.

Exclusion criteria

1. (A history of) any clinically significant medical condition or abnormalities, as judged by the investigator, in physical examination, laboratory test results (including chemistry panel with hepatic and renal panels, complete blood count, and urine dipstick) or electrocardiography (ECG) at screening. In the case of uncertain or questionable results, tests performed during screening may be repeated to confirm eligibility or judged by the investigator to be clinically irrelevant for healthy subjects.
2. Female subjects that are lactating or pregnant.
3. The subject has a positive screening test for hepatitis B, hepatitis C, and human immunodeficiency virus.
4. Use of any prescription medication and any other substance that in the opinion of the investigators may influence the outcome of the study within 7 days prior to study drug administrations, or less than five half-lives (whichever is longer, and during the course of the study).
5. Previous inclusion in this study.
6. Participation in a clinical trial within 3 months or 5 half-lives, whichever is longer.
7. Use of alcohol during the 24 hours prior to screening and/or an unwillingness to abstain from alcohol consumption during the stay at the clinical unit, and for at least 24 hours prior to each study visit;
8. Positive urine drug screen or alcohol test at screening and/or at first study day.
9. History of anaphylactic reactions to a prescription drug, over-the-counter drug, or herbal supplement.
10. Prior organ transplant.
11. Signs of moderate or severe symptoms of prostate hypertrophy
12. Loss or donation of blood over 500 mL within four months prior to screening.
13. Any other condition that in the opinion of the investigator would complicate or compromise the study or the well-being of the subject.
14. History of AV blocks or any type of AV block on the ECG at the screening
15. History of syncope

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):	09-11-2022
Enrollment:	21
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	N.a.
Generic name:	Nizaracianine

Ethics review

Approved WMO Date:	19-04-2022
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	15-08-2022
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	24-11-2022
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	01-12-2022
Application type:	Amendment

Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	30-12-2022
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	04-01-2023
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	EUCTR2022□001457□23-NL
CCMO	NL81211.056.22