A phase 1, randomized, double blind, placebo-controlled, single ascending dose study to assess safety, tolerability and pharmacokinetics of cRGD-ZW800-1 intravenous injection in healthy volunteers

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Primary objective- To determine safety and tolerability of a single dose of cRGD-ZW800-1 in healthy volunteers.Secondary objectives- To determine the pharmacokinetics of a single dose of cRGD-ZW800-1 by measuring the fluorescence of blood and urine...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Miscellaneous and site unspecified neoplasms malignant and unspecified
Study type	Observational invasive

Summary

ID

NL-OMON43465

Source
ToetsingOnline

Brief title
A phase 1 study of cRGD-ZW800-1 in healthy volunteers

Condition

- Miscellaneous and site unspecified neoplasms malignant and unspecified

Synonym
Cancer, Malignant tumors

Research involving
Human

Sponsors and support

Primary sponsor: Centre for Human Drug Research
Source(s) of monetary or material Support: The CHDR is the sponsor of the study and is funding the study

Intervention

Keyword: cRGD-ZW800-1, Pharmacokinetics, Safety, Tolerability

Outcome measures

Primary outcome

Safety and tolerability is the primary endpoint of the study. This will be

assessed from data on the occurrence of treatment-emergent adverse events

(TEAEs) from the time of administration throughout the study period, and

changes in serum biochemistry, hematology, urinalysis, vital signs, ECG,

injection site status, and physical examination findings. In addition, analysis

of the PK of cRGD-ZW800-1 will be conducted.

Secondary outcome

Not Applicable

Study description

Background summary

Accurate and real-time detection of tumors during surgery remains challenging. Sensitivity of available imaging modalities is often inadequate with respect to margin or metastasis detection. Following SPECT and PET agents, tumor targeted ligands can also be conjugated to NIR (near-infrared, 700-900 nm) fluorophores and being visualized using specific intraoperative near-infrared imaging systems. Traditionally, NIR fluorophores have been developed for a variety of preclinical applications, including labeling to specific ligands, and can be

used to understand the fate of intravenously administered anticancer therapeutics, in determining biodistribution, tissue penetration and cellular localization. Currently, NIR fluorescent labeled vehicles are also being used as a diagnostic tool for accurate localization of cancer cells in real-time during surgery.
Here we study cRGD-ZW800-1, a cyclic pentapeptide (cRGD) conjugated to the 800 nm NIR fluorophore ZW800-1. The cyclic 3-amino acid sequence (RGD) is clinically a well-known peptide that binds to various integrins (αvβ1, αVβ3, αvβ5, αvβ6, αvβ8, α5β1, α8β1 and αIIbβ3), mostly associated with neoangiogenesis. Tumors larger than 1-2 mm depend on the formation of new blood vessels to acquire sufficient amounts of oxygen and nutrients. Some of these integrins are therefore overexpressed on malignant cells and in tumor stroma, for example in breast, colorectal, pancreas and lung cancer. RGD based molecules have already been investigated in various phase I and phase II imaging studies using PET and SPECT and in a phase III study as an anticancer therapy (cilengitide).
Extensive preliminary work on the cRGD-ZW800-1 agent has been performed by our group and showed clear delineation of melanomas and colorectal, liver, pancreatic, lung, and head and neck tumors in xenograft mouse models while due to its renal clearance route also ureters could be recognized.
As there is no clinical experience with cRGD-ZW800-1, this will be the first in human study in which cRGD-ZW800-1 will be investigated in healthy volunteers. In this study, two single ascending i.v. doses of cRGD-ZW800-1 or placebo will be administrated to healthy volunteers.

Study objective

Primary objective
- To determine safety and tolerability of a single dose of cRGD-ZW800-1 in healthy volunteers.

Secondary objectives
- To determine the pharmacokinetics of a single dose of cRGD-ZW800-1 by measuring the fluorescence of blood and urine.
- To describe the temporal relationship of any fluorescence of superficial tissues (skin, veins) to the administration of cRGD-ZW800-1.

Study design

This is a single ascending dose, randomized, placebo-controlled design in healthy volunteers. Two ascending dose levels of cRGD-ZW800-1 will be investigated in two cohorts. Within the first cohort a sentinel approach will be used: on the first day 2 subjects will be administered study drug in a 1:1 ratio for active and placebo. The other subjects in this cohort will be randomized to active:placebo in a 3:1 ratio. In the second cohort 5 subjects will be randomized in a ratio of 4:1 active:placebo.

Study burden and risks

Burden: The burden for participants consists of a time investment of 1 full day and 2 1-hour visits, possible side effects and compliance with lifestyle restriction.

Risks: The risks to subjects related to cRGD-ZW800-1 are unknown at this time; safety is therefore a primary study objective in the current study. Other risks to subjects mainly relate to the i.v. injection and venous blood sampling. Intravenous injection and the use of cannulas (1 cannula for i.v. injection and 1 cannula for venous blood sampling) are known to carry a small risk of infection and hematoma. Based on consistent observations in the preclinical efficacy and safety pharmacology studies, it is expected that discoloration of the skin and urine may occur. Based on experience with other fluorescent probes, it cannot be excluded that hypersensitivity reactions may occur, although there are no indications for cRGD-ZW800-1.

Benefits: There are no expected direct benefits to subjects who participate in this trial, but participants may help others prospectively by contributing to the knowledge base for designing future studies in cancer patients.

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. The subject is 18-65 years old at screening.
2. The subject is able and willing to comply with study procedures, and signed and dated informed consent is obtained before any study-related procedure is performed.
3. Female subjects need to be either surgically sterile, post-menopausal or pre-menopausal with a negative urine pregnancy test at screening and just before administration of cRGD-ZW800-1. Pre-menopausal female subjects who are not surgically sterile should also employ an effective method of birth control for at least 90 days post dosing when it consists of a hormonal contraceptive method or IUD. For other contraceptive methods premenopausal females who are not surgically sterile have to agree to use an effective method of contraception.
4. The subject*s body weight is <=90 kg and the body mass index is <=30 kg/m2.
5. The subject has a normal or clinically acceptable medical history, physical examination, and vital signs findings at screening (within 21 days before administration of study drug).
6. The 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.
7. The subject has negative screening test results for hepatitis B, hepatitis C, and human immunodeficiency virus.
8. The subject has negative test results for drug and alcohol screening.
9. Absence of any psychological, familial, sociological or geographical condition potentially hampering compliance with the study protocol and follow-up schedule; those conditions should be discussed with the patient before registration in the trial.
10. Before patient registration, written informed consent must be given according to ICH/GCP, and national/local regulations.

Exclusion criteria

1. Female subjects that are lactating or pregnant.
2. Unacceptable known diagnoses or diseases at baseline, e.g., known cardiovascular or pulmonary disease, renal or liver dysfunction, ECG or laboratory abnormalities, etc.
3. Use of prescription drugs, with the exception of contraceptive drugs.
4. Previous inclusion in this study.
5. Participation in a clinical trial within 90 days of screening or more than 4 times in the previous year.
6. History of anaphylactic reactions.

Study design

Design

Study type:	Observational invasive
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):	03-04-2017
Enrollment:	11
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	cRGD-ZW800-1
Generic name:	n.a.

Ethics review

Approved WMO Date:	25-02-2016
Application type:	First submission
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	06-07-2016
Application type:	First submission
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	29-03-2017

Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	20-06-2017
Application type:	Amendment
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	EUCTR2016-000397-38-NL
CCMO	NL56621.058.16