A phase 1, randomized, double blind, placebo-controlled, single and repeated ascending dose study to assess safety, tolerability and pharmacokinetics of ZW800-1 injected intravenously into healthy volunteers

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

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

Summary

ID

NL-OMON45587

Source
ToetsingOnline

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

Condition

- Miscellaneous and site unspecified neoplasms malignant and unspecified
- Renal and urinary tract therapeutic procedures

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: Pharmacokinetics, Safety, Tolerability, ZW800-1

Outcome measures

Primary outcome

Safety and tolerability endpoints

- Treatment-emergent (serious) adverse events ((S)AEs).

- Clinical laboratory tests (urinalysis, serum biochemistry, hematology) Vital

signs

o Pulse Rate (bpm)

o Systolic blood pressure (mmHg)

o Diastolic blood pressure (mmHg)

- ECG (heart rate (bpm), PR, QRS, QT, QTcB, QTcF)

- Injection site status

- Physical examination findings

PK endpoints

- The following endpoints will be determined for ZW800-1 following each

treatment. They will be derived by non-compartmental analysis of the serum

concentration-time data:

o The area under the plasma concentration-time curve from zero to infinity

(AUC0-inf);

o The maximum plasma concentration (Cmax);

o The area under the plasma concentration-time curve from zero to t of the last

measured concentration above the limit of quantification (AUC0-last);

o The time to reach maximum plasma concentration (tmax);

o The terminal disposition rate constant (*z) with the respective half-life

(t*).

o Other parameters, including Vz, CL, and other parameters as appropriate, as

well as dose adjusted parameters, may be determined.

o Urinary excretion of ZW800-1 at specific time points (see table 1).

- Fluorescence intensity of the skin over time

Secondary outcome

N.A.

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. For tumor-targeted NIR fluorescence imaging, a NIR fluorophore needs to be conjugated to a targeting ligand, such as an antibody or peptide. Currently, the only clinically available NIR fluorophores are methylene blue, 5-ALA and indocyanine green (ICG), but these fluorophores cannot easily be conjugated covalently to other molecules. Moreover, 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. Therefore, new fluorophores need to be developed. ZW800-1 has improved

in vivo properties, including low non-specific binding and uptake, high extinction coefficient and quantum yield, and exclusive renal clearance of intravenously injected drug. We believe that this first-in-class molecule will form the foundation for the next generation of targeted NIR fluorophores; however, the focus of this Phase 1 study will be ZW800-1 alone injected intravenously.

Study objective

Primary Objective
- To determine safety and tolerability of a single dose of ZW800-1 in healthy volunteers.
Secondary Objectives
- To determine the pharmacokinetics of a single dose of ZW800-1 by measuring the fluorescence of blood and urine.
- To describe the relationship of any fluorescence of skin to the administration of ZW800-1.

Study design

This is a single ascending dose, randomized, placebo-controlled study in healthy volunteers. Three ascending dose levels of ZW800-1 will be investigated in three non-overlapping 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 following cohorts 5 subjects will be randomized in a ratio of 4:1 active:placebo.

Intervention

Intravenous administration of ZW800-1 and fluorescence imaging.

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 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 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.
3. Female subjects need to be surgically sterile, post-menopausal or pre-menopausal with a

negative urine pregnancy test at screening and just before administration of 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 has a normal or clinically acceptable medical history, physical examination, and vital signs findings at screening (within 21 days before administration of study drug).
5. 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.
6. The subject has negative screening test results for hepatitis B, hepatitis C, and human immunodeficiency virus.
7. The subject has negative test results for drug and alcohol screening.
8. 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.
9. 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:	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):	15-02-2017
Enrollment:	16
Type:	Actual

Medical products/devices used

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

Ethics review

Approved WMO Date:	17-01-2017
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	06-02-2017
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	13-02-2017
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	20-02-2017
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	24-02-2017

Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	17-03-2017
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	27-03-2017
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	11-04-2017
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	EUCTR2016-003919-35-NL
CCMO	NL59365.056.16