A Phase 1, Randomized, Double-Blind, Placebo-Controlled, Single and Multiple Ascending Dose Ranging Study in Healthy Volunteers to Assess Safety, Tolerability, and Evaluate the Pharmacokinetics and Pharmacodynamics of R2R01

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In this study we will investigate how safe the new compound R2R01 is and how well it is tolerated when it is used by healthy participants.We also investigate how quickly and to what extent R2R01 is absorbed and eliminated from the body. In addition...

Ethical review	Approved WMO
Status	Completed
Health condition type	Renal disorders (excl nephropathies)
Study type	Interventional

Summary

ID

NL-OMON51081

Source
ToetsingOnline

Brief title
Placebo-controlled SAD/MAD of R2R01

Condition

- Renal disorders (excl nephropathies)

Synonym
Kidney failure

Research involving
Human

Sponsors and support

Primary sponsor: River 2 Renal Corporation
Source(s) of monetary or material Support: Pharmaceutical Industry

Intervention

Keyword: MAD, R2R01, SAD, Safety

Outcome measures

Primary outcome

To evaluate the tolerability and safety of ascending single and multiple doses of R2R01 in healthy volunteers.

Secondary outcome

- To determine the pharmacokinetic (PK) parameters of R2R01.

- To compare the PK of a single 4-mg subcutaneous (SC) dose with a single 4-mg intravenous (IV) dose.

- To establish a dose concentration-response relationship for tolerability and pharmacodynamic (PD) parameters over a range of R2R01 doses in order to select a dose to be studied in patients after single and multiple dose administrations have been completed in healthy volunteers.

- To assess the potential immunogenicity of R2R01 after multiple dose administrations in healthy volunteers.

Study description

Background summary

R2R01 is a new compound that may be used for the treatment of kidney failure in patients with acute and chronic liver disease.
R2R01 is a small protein that binds to a receptor (proteins on the outside or inside of cells) called RXFP1. This RXFP1 receptor is involved in several processes in the body, including the relaxation of blood vessels, anti inflammatory processes, cell protection and preventing scar formation in tissues.

Study objective

In this study we will investigate how safe the new compound R2R01 is and how well it is tolerated when it is used by healthy participants.

We also investigate how quickly and to what extent R2R01 is absorbed and eliminated from the body. In addition, we look at the effect of R2R01 on the levels of 2 biomarkers in the blood. In addition in Part B we look at the effect of R2R01 on kidney blood flow.

We compare the effects of R2R01 with the effects of a placebo. R2R01 has not been administered to humans before. It has been extensively tested in the laboratory and on animals. R2R01 will be tested at various dose levels.

Part B only
During the study subjects will also receive p-aminohippurate and/or iohexol at 3 occasions. This is to study the effect of R2R01 on the kidney blood flow. P-aminohippurate and iohexol are both registered agents used for diagnostics.

Study design

Part A

Group A1, A3, A4 and A5:
Total duration: 9 weeks

Screening > Day -28 up to Day -2

Treatment Period - Arrival Day > Day -1
Treatment Period - In-house stay > Day -1 to Day 6
Treatment Period - Study drug administration > Day 1
Treatment Period - Departure > Day 6

Follow-up (phone call) > Day 36

Group A2
Total duration: 12 weeks

Screening > Day -28 up to Day -2 prior to the first period

Treatment Period 1 and 2 - Arrival Day > Day -1 of each period
Treatment Period 1 and 2 - In-house stay > Day -1 to Day 6 of each period
Treatment Period 1 and 2 - Study drug administration > Day 1 of each period
Treatment Period 1 and 2 - Departure > Day 6 of each period

Follow-up (phone call) > Day 36 of last period
There will be at least 2 weeks between Day 1 of Period 1 and Day 1 of Period 2.

Part B
Total duration: 11 weeks

Screening > Day -28 up to Day -3 (screening tests)

Treatment Period - In-house stay > Day -2 up to Day 19
Treatment Period - Arrival > Day -2
Treatment Period - Administration of p-aminohippurate and iohexol > Day -1
Treatment Period - Administration of study compound > Day 1 to Day 11
Treatment Period - Administration of iohexol and study compound > Day 12
Treatment Period - Administration of p-aminohippurate and study compound > Day 13
Treatment Period - Administration of study compound > Day 14
Treatment Period - Departure > Day 19

Follow-up (phone call) > Day 49

Intervention

Part A
Groups A1, A3, A4, A5
Subjects will be given R2R01 or placebo once as an injection under the skin (subcutaneous).

Group A2
Subjects will be given R2R01 or placebo once as an injection under the skin (subcutaneous) in Period 1 and once given directly in a blood vessel as a 15-minute infusion in Period 2.

In the table below the planned dose levels for each group are shown. The doses of Groups A3 to A5 can be adjusted, for example because the study compound had more or less effect than was expected. However, the dose will not be lower than 1.0 mg and not higher than 48.0 mg. The dose for the next group will only be increased if the lower dose of the previous group was found to be well tolerated and in case of no objection by the Medical Research Ethics Committee. The study will be discontinued or the dose will be decreased if, in the opinion of the investigators, unacceptable side effects appear.

The planned dose levels for the study are as follows:

Group | Day | Treatment | Dosing | Form | How often
A1 | Day 1 | R2R01 1.0 mg or placebo | Subcutaneous injection | Once
A2 | Day 1 of Period 1 | R2R01 4.0 mg or placebo | Subcutaneous injection | Once
A2 | Day 1 of Period 2 | R2R01 4.0 mg or placebo | 15-minute infusion | Once
A3 | Day 1 | R2R01 12.0 mg or placebo | Subcutaneous injection | Once
A4| Day 1 | R2R01 24.0 mg or placebo | Subcutaneous injection | Once
A5 | Day 1 | R2R01 48.0 mg or placebo | Subcutaneous injection | Once
* In case the dose level will be lower or higher than planned, you will be informed verbally.

Part B
Subjects will be given R2R01 or placebo for 14 days as an injection under the skin (subcutaneous).

In the table below the planned dose levels for each group are shown. The doses of Groups B1 to B3 can be adjusted. for example because the study compound had more or less effect than was expected. However, the dose will not be lower than 5.0 mg and not higher than 30.0 mg. The dose for the next group will only be increased if the lower dose of the previous group was found to be well tolerated and in case of no objection by the Medical Research Ethics Committee. The study will be discontinued or the dose will be decreased if, in the opinion of the investigators, unacceptable side effects appear.
Subjects will receive p-aminohippurate on Days 1 and Day 13 as an intravenous infusion with a duration of 2 hours in total. P aminohippurate is a registered diagnostic agent that is given to investigate whether R2R01 affects renal blood flow.
Subjects will receive iohexol on Day -1 and Day 12 as an intravenous infusion with a maximum duration of 5 minutes. Iohexol is a registered diagnostic agent that is given before R2R01 administration to investigate whether R2R01 affects kidney function.

The planned dose levels for the study are as follows:

Group | Day | Treatment* | Dosing Form | How often
B1 | Day -1 | p-aminohippurate and iohexol (5 mL containing 3.236 g) | intravenous infusion | once
B1 | Day 12 | iohexol (5 mL containing 3.236 g) | intravenous infusion | once
B1 | Day 13 | p-aminohippurate** | intravenous infusion | twice daily
B1 | Days 1 to 14 | R2R01 5.0 mg or placebo | subcutaneous injection | once daily for 14 days

B2 | Day -1 | p-aminohippurate and iohexol (5 mL containing 3.236 g) | intravenous infusion | once
B2 | Day 12 | iohexol (5 mL containing 3.236 g) | intravenous infusion | once

B2 | Day 13 | p-aminohippurate** | intravenous infusion | twice daily
B2 | Days 1 to 14 | R2R01 15.0 mg or placebo | subcutaneous injection | once daily for 14 days

B3 | Day -1 | p-aminohippurate and iohexol (5 mL containing 3.236 g) | intravenous infusion | once
B3 | Day 12 | iohexol (5 mL containing 3.236 g) | intravenous infusion | once
B3 | Day 13 | p-aminohippurate** | intravenous infusion | twice daily
B3 | Days 1 to 14 | R2R01 30.0 mg or placebo | subcutaneous injection | once daily for 14 days

* In case the dose level will be lower or higher than planned, subjects will be informed verbally.
** The actual dose will depend on body weight.

Study burden and risks

Blood draw/intravenous infusion
Drawing blood may be painful or cause some bruising. The use of the indwelling cannula or an intravenous infusion can sometimes lead to inflammation, swelling, hardening of the vein, blood clotting, and bleeding in the environment (bruising) of the puncture site. In some individuals, a blood draw can sometimes cause pallor, nausea, seating, low heart rate, or drop in blood pressure with dizziness or fainting.

In part A we will take about 125 milliliters (mL) (for Groups A1, A3, A4, and A5) or 255 mL (for Group A2) of blood in total.
In part B we will take about 283 milliliters (mL) (for Groups B1 and B3) or 403 mL (for Group B2) of blood in total. For Group B2 more blood will be drawn to measure the concentration of a breakdown product of the study compound.

These amounts do not cause any problems in adults. To compare: a blood donation involves 500 mL of blood being taken each time. If the investigator thinks it is necessary for the safety of a participant, extra samples might be taken for possible additional testing. If this happens, the total amount of blood drawn will be more than the amount indicated above.

Heart tracing
To make a heart tracing, electrodes will be placed on arms, chest and legs. Prolonged use of these electrodes can cause skin irritation.

Fasting
If subjects have to fast for a prolonged time during the study, this may lead to symptoms such as dizziness, headache, stomach upset, or fainting.

Subcutaneous injection
Subcutaneous injections might cause a local reaction, such as swelling,

redness, or itching.

Coronavirus test
Samples for the coronavirus test will be taken from the back of the nose and throat using swabs. Taking the samples only takes a few seconds, but can cause discomfort and can give an unpleasant feeling. Taking a sample from the back of the throat may cause subjects to gag. When the sample is taken from the back of the nose, they may experience a stinging sensation and the eyes may become watery.

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. Sex: male or female; for the SAD part and the first cohort in the MAD part,

females must be of nonchildbearing potential, or postmenopausal. Women of childbearing potential will be excluded from all cohorts in the SAD part and from the first MAD cohort for reasons outlined in Section 3.2.4 of the protocol. If no ADAs are observed in the first MAD cohort (5.0 mg), inclusion of WOCBP may be permitted in subsequent MAD cohorts.
2. Age: 18 to 55 years, inclusive, at screening.
3. Body mass index (BMI): 18.0 to 30.0 kg/m2, inclusive, at screening.
4. Weight: 50 to 110 kg, inclusive, at screening.
5. Status: healthy subjects.

Exclusion criteria

1. Previous participation in the current study.
2. Employee of PRA or the Sponsor.
3. History of a serious adverse reaction or significant hypersensitivity to any drug, has a known clinically significant allergy to anti-inflammatory drugs or chemically related compounds or has a clinically significant allergy to drugs, foods or other materials (in the opinion of the Investigator).
4. Using tobacco products within 3 months prior to (the first) drug administration.
5. History of alcohol abuse or drug addiction (including soft drugs like cannabis products).

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:	Completed
Start date (anticipated):	30-04-2021

Enrollment:	64
Type:	Actual

Ethics review

Approved WMO Date:	01-04-2021
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	23-04-2021
Application type:	First submission
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	EUCTR2021-000882-33-NL
CCMO	NL77141.056.21

Study results

Date completed:	25-12-2021

Results posted: 30-06-2022

First publication
18-05-2022