A Phase II, Multi-center, Open-Label Study to Assess Safety, Tolerability, Efficacy and Pharmacokinetics of R3R01 in Alport Syndrome Patients with Uncontrolled Proteinuria on ACE/ARB Inhibition and in Patients with Primary Steroid-Resistant Focal Segmental Glomerulosclerosis.

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Ethical review	Approved WMO
Status	Recruiting
Health condition type	Other condition
Study type	Interventional

Summary

ID

NL-OMON56035

Source
ToetsingOnline

Brief title
R3R01 study

Condition

- Other condition

Synonym
Renal disease

Health condition

Alport Syndrome (AS) and Primary Steroid-Resistent Focal Segmental Glomerulosclerosis (FSGS)

Research involving
Human

Sponsors and support

Primary sponsor: River 3Renal Corporation
Source(s) of monetary or material Support: River 3 Renal;Corporation

Intervention

Keyword: AS, FSGS, Renal

Outcome measures

Primary outcome

For all patients:

• To evaluate the tolerability and safety of R3R01 administered orally for 12

weeks.

For AS patients:

• To evaluate the efficacy of R3R01 in reducing proteinuria at 12 weeks in the

whole AS group.

For FSGS patients:

• To evaluate the efficacy of R3R01 in reducing proteinuria at 12 weeks in the

whole FSGS group.

Secondary outcome

For all patients:

• To evaluate improvement in quality of life as measured by the Short Form

SF-36 for adults or the pediatric quality of life inventory (PedsQL) for children (ages 12-18) and their parents/ legal quardians, by assessing the change from baseline to end of treatment (Day 84) and end of the follow-up period (Day 168).

• To evaluate the pharmacokinetics of R3R01.

For AS patients:

• To evaluate proteinuria complete response (UPCR <0.3g/g) at all timepoints proteinuria is measured.

• To evaluate proteinuria partial response (decrease in proteinuria from baseline of >=50%) at all timepoints proteinuria is measured.

For FSGS patients:

• To evaluate proteinuria complete remission (UPCR <0.3g/g) at all timepoints proteinuria is measured.

• To evaluate proteinuria partial remission (decrease in proteinuria from baseline of >=50% and an absolute value of UPCR < 3.0g/g) at all timepoints proteinuria is measured.

• To evaluate proteinuria modified partial remission (decrease of >=40% and UPCR < 1.5g/g) at all timepoints proteinuria is measured.

Study description

Background summary

There are currently no approved therapies for AS. The only definitive treatment for the renal signs and symptoms is kidney transplant. Current standard of care is angiotensin converting enzyme inhibitors (ACEi) or angiotensin II receptor blockers (ARB) to control renal blood flow, with the goal to slow disease

progression. Bardoxolone, a drug that induces sustained increases in GFR, is in late-stage development. However, bardoxolone does not improve proteinuria, and there are concerns over long-term exacerbation of disease progression. There is clear unmet medical need to treat AS.

Study objective

This study has been transitioned to CTIS with ID 2024-512964-73-00 check the CTIS register for the current data.

The overall objective is to investigate the safety, tolerability, efficacy and pharmacokinetics of R3R01 administered daily for 3 months in 2 cohorts of patients. Cohort 1 will be AS patients with uncontrolled proteinuria on a maximum tolerated dose of ACEi or ARB therapy, and Cohort 2 will be FSGS patients with primary steroid-resistant FSGS.

Study design

This is a multicenter study with an open-label design testing one dose of the investigational compound R3R01 in 2-cohorts.

Intervention

Dose and timing of administration: All patients will receive 200 mg (two 100 mg tablets) BID for the 84 days. Study drug must be taken with food (after breakfast and after dinner). Study drug administration will begin the morning after the baseline visit when drug is dispensed.

Study burden and risks

Blood tests
During the collection of blood samples, you may experience pain and/or bruising at the needle injection site. Although rare, localized clot formation and infections may occur. Light-headedness and/or fainting may also occur during or shortly after the blood draw.

Electrocardiogram (ECG)
ECG patches may cause a skin reaction such as redness or itching. You may also experience skin discomforts and/or hair loss associated with the removal of the patches.

Eye exams (only for people with AS)
In some of the eye exams, you may need to put drops of another medication in your eyes, which can be uncomfortable.

Contacts

Public
River 3Renal Corporation

7550 Purple Sage
Park City UT 84098
US
Scientific
River 3Renal Corporation

7550 Purple Sage
Park City UT 84098
US

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

All Patients:
1. Patient is able to communicate well with the investigator, understands and is willing to comply with all requirements of the study, and understands and signs the written informed consent form (ICF).
2. For children to be eligible, one or both parents/legal guardians must sign a parental permission form which provides information contained in the ICF. Children capable of assent must express their willingness to participate by signing an assent form.
3. If patient has received a COVID vaccination, the baseline visit must occur at least one week or more after the second/booster vaccination.
4. Patients who have had active symptoms of COVID within 3 months prior to screening and are now asymptomatic for the last 2 weeks but have tested COVID

PCR positive. If a patient is asymptomatic at screening but is COVID positive, then rescreening can occur after a minimum of two weeks.
5. Both female patients, as well as female partners of male patients who are of child-bearing potential must be willing to not become pregnant for the complete duration of the study (>180 days) (90 days after the last dose of study medication).
6. Males (including sterilized subjects) whose female partners have child-bearing potential, must agree to use male contraception (condoms) during the period from the time of signing the informed consent form (ICF) through 90 days after the last dose of study drug. They must agree to immediately inform the investigator if their partner becomes pregnant during the study.

AS Inclusion Criteria (in addition):
7. Males and females with X-Linked AS and males and females with autosomal inherited AS.
a. For countries that are enrolling pediatric patients: patients from age 12 years and older.
b. For countries that are not enrolling pediatric patients: patients from age 18 years and older.
8. Confirmed diagnosis of AS by genetic testing and /or kidney biopsy. For patients enrolled in the US who meet all inclusion and exclusion criteria but have not had their diagnosis confirmed by genetic testing or kidney biopsy, the Sponsor will provide for patient*s genetic testing.
9. UPCR >=1.0 g/g.
10. eGFR >= 45 mL/min/1.73m2 (using CKD-EPI equation for adults and Bedside Schwartz equation for children).
11. ACEi/ARB therapy at maximum tolerated dose stable for at least 4 weeks prior to screening. ACEi/ARB dose should remain stable over the course of the study.

FSGS Inclusion Criteria (in addition):
12. Male or female patients,
a. For countries that are enrolling pediatric patients: 12 to 75 years old at the time of signing the informed consent
b. For countries that are not enrolling pediatric patients: 18 to 75 years old at the time of signing the informed consent
13. Primary FSGS (without any identifiable cause, and where the FSGS is confirmed by renal biopsy) or FSGS where there is documentation of a genetic mutation in a podocyte protein associated with FSGS.
14. Steroid-resistance defined as failure to achieve partial or complete remission, or experienced adverse events without acceptable clinical benefit after at least 8 weeks of adequate corticosteroid therapy for children and 12 weeks for adults.
15. UPCR between 3.5g/g and 12.0g/g.
16. eGFR > 45 mL/min/1.73m2 (using CKD-EPI equation for adults and Bedside Schwartz equation for children).
17. If taking concomitant ACEi and/or ARB treatment, it should remain at a

stable dose for a minimum of 28 days prior to enrollment and during the course of the study.

Exclusion criteria

All Patients:
1. Uncontrolled diabetes mellitus as evidenced by an HbA1c >= 11%. For Germany: HbA1c >= 8.5%.
2. Uncontrolled hypertension
a. Adults: (SBP >= 180mmHg and/or DBP >= 100mmHg). For Germany: (SBP >= 140mmHg and/or DBP >= 100mmHg).
b. Children: >= 95th percentile or >= 130/80 mm Hg, whichever is lower, as defined in Appendix 13.8.
3. Moderate or severe hepatic impairment as per Child Pugh score (See Section 9.5.4.7), except if (a) decreased serum albumin is directly related to the renal disease (resulting in a Child Pugh score of 7), and (b) no other Child-Pugh Score parameters are increased and (c) patient has no liver pathology in medical history.
4. Presence of any active (i.e., with symptoms) and/or uncontrolled infection (including COVID).
5. Presence of Human immunodeficiency virus (HIV).
6. BMI > 40. For Germany: BMI > 35 (Obesity Class II).
7. History of malignancy other than treated basal cell or squamous cell skin cancer within the past 5 years.
8. History of alcohol abuse in the last 5 years or currently drinks in excess of 21 and 14 units per week for males and females, respectively.
9. Received an investigational agent within 30 days or 5 half-lives prior to screening (whichever is longer).
10. History of non-compliance such that patient is unlikely to be compliant with study visits, procedures or drug administration.
11. Patient has had an organ transplant, is currently on an organ transplant waiting list or there is a reasonable possibility that the patient will have an organ transplant in the 6 months after screening.
12. Participation in an interventional trial within the previous 3 months prior to screening or concurrent participation in a research trial.
13. Patient is not suitable to participate in the study for any reason (including, but not limited to co-morbidities, history of non-compliance with study visits, procedures, or drug administration) in the opinion of the investigator.
14. Females of childbearing potential (those who are not surgically sterilized or post-menopausal for at least 1 year) are excluded from participation in the study unless they agree to use highly effective contraception as described in Section 13.3.
15. Females that are lactating.
16. History of hypersensitivity to study drug and/or any of its excipients.

17. Patients with hereditary galactose intolerance, total lactase deficiency or glucose-galactose malabsorption.
18. Required concomitant use of bardoxolone, rituximab, cyclo-phosphamide, abatacept or sparsentan.
AS Exclusion Criteria (in addition):
19. Kidney disease apart from AS, e.g., diabetic nephropathy or lupus nephritis.
20. Use of Bardoxolone or sparsentan treatment in the 30 days prior to screening. SGLT2 inhibitors are allowed if the patient is on a stable dose for at least 3 months prior to screening.
FSGS Exclusion Criteria (in addition):
21. Patient has collapsing variant of FSGS on renal biopsy.
22. Patient has FSGS secondary to another condition (e.g., obesity, cardiovascular, infectious, or autoimmune disorder).
23. Use of Rituximab, cyclophosphamide or abatacept treatment in the 120 days prior to screening. If taking other chronic immune-modulatory medications that are small molecules, the dosage must be stable for 4 weeks prior to screening.
24. If previous Rituximab treatment is greater than 120 days from screening, CD20 cell count should be within normal limits.
25. If previous other antibody treatment on a stable dose is greater than 120 days from screening, the investigator must deem administration of study drug to be safe.
26. Use of sparsentan in the 30 days prior to screening. SGLT2 inhibitors are allowed if the patient is on a stable dose for at least 3 months prior to screening.

Study design

Design

Study phase:	2
Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	07-06-2023
Enrollment:	10

Type:	Actual

Medical products/devices used

Registration:	No

Ethics review

Approved WMO Date:	06-07-2022
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	27-09-2022
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	25-11-2022
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	20-01-2023
Application type:	Amendment
Review commission:	MEC Academisch Medisch Centrum (Amsterdam) Kamer G4-214 Postbus 22660 1100 DD Amsterdam 020 566 7389 mecamc@amsterdamumc.nl
Approved WMO Date:	21-02-2023
Application type:	Amendment
Review commission:	MEC Academisch Medisch Centrum (Amsterdam)

	Kamer G4-214 Postbus 22660 1100 DD Amsterdam 020 566 7389 mecamc@amsterdamumc.nl
Approved WMO Date:	03-04-2023
Application type:	Amendment
Review commission:	MEC Academisch Medisch Centrum (Amsterdam) Kamer G4-214 Postbus 22660 1100 DD Amsterdam 020 566 7389 mecamc@amsterdamumc.nl
Approved WMO Date:	19-12-2023
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	22-01-2024
Application type:	Amendment
Review commission:	METC Amsterdam UMC

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
EU-CTR	CTIS2024-512964-73-00
EudraCT	EUCTR2021-004192-13-NL
ClinicalTrials.gov	NCT05267262
CCMO	NL80975.018.22