A phase 2, open-label, single-arm, cohort study to evaluate the safety, efficacy, and pharmacokinetics of sparsentan treatment in pediatric subjects with selected proteinuric glomerular diseases (EPPIK)

Published: 14-12-2021
Last updated: 30-11-2024

This study has been transitioned to CTIS with ID 2023-505497-14-00 check the CTIS register for the current data. Primary Objectives:• Evaluate the safety and tolerability of sparsentan oral suspension (Population 1 and Population 2) and tablets (...

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

Summary

ID

NL-OMON52074

Source
ToetsingOnline

Brief title
EPPIK

Condition

- Renal disorders (excl nephropathies)

Synonym
kidney disorders

Research involving

Human

Sponsors and support

Primary sponsor: Travere Therapeutics, Inc.
Source(s) of monetary or material Support: Travere Therapeutics;Inc.

Intervention

Keyword: Pediatric study, Phase 2, proteinuric glomerular diseases, Sparsentan

Outcome measures

Primary outcome

Primary Endpoints:

• The incidence of treatment-emergent adverse events (TEAEs), serious adverse events (SAEs), adverse events (AEs) leading to treatment discontinuation, and adverse events of interest (AEOIs)

• Change from baseline in urine protein/creatinine ratio (UP/C) over 108 weeks

Secondary outcome

Secondary Endpoints:

• Observed plasma PK concentrations at scheduled timepoints and visits

• Relevant steady-state PK parameters (area under the plasma concentration-time curve during a dosing interval [AUC*], maximum steady-state plasma drug concentration [Cmax_ss], and minimum steady-state plasma drug concentration [Cmin_ss])

• Change from baseline in urine albumin/creatinine ratio (UA/C) and eGFR over 108 weeks

• The proportion of subjects achieving complete remission of proteinuria, defined as UP/C <0.3 g/g, over 108 weeks

• The proportion of subjects with focal segmental glomerulosclerosis (FSGS)

and/or minimal change disease (MCD) histological patterns achieving partial

remission, defined as UP/C <=1.5 g/g and >40% reduction in UP/C over 108 weeks

• The proportion of subjects who discontinue study medication due to inability

to tolerate the smell, taste, aftertaste, volume of administration, or method

of administration of the oral suspension (Population 1 and Population 2)

Study description

Background summary

This is a multicenter, open-label, 112-week study of sparsentan in approximately 67 pediatric subjects aged >=1 year to <18 years with selected proteinuric glomerular diseases, divided into three populations, defined as follows:
• Population 1: Subjects with selected proteinuric glomerular diseases associated with FSGS and MCD histological patterns
• Population 2: Subjects with kidney biopsy-confirmed immunoglobulin A nephropathy (IgAN), immunoglobulin A vasculitis (IgAV), or Alport syndrome (AS)
• Population 3: Subjects with kidney biopsy-confirmed IgAN
The study will evaluate long term safety, tolerability, and efficacy in all the tree populations with PK evaluations at Day 1 (Baseline), Day 2 (Visit 4), and Week 12 (visit 9) in population 1 and population 2. In population 3, PK values (Cmin, SS) are evaluated at Day 1 (Baseline), at Weeks 4, 8, 12, 24, 36 and then every 12 weeks until Week 96.

Study objective

This study has been transitioned to CTIS with ID 2023-505497-14-00 check the CTIS register for the current data.

Primary Objectives:
• Evaluate the safety and tolerability of sparsentan oral suspension (Population 1 and Population 2) and tablets (Population 3)
• Assess changes in proteinuria after once-daily dosing of sparsentan oral suspension and tablets over 108 weeks
Secondary Objectives:
• Assess the pharmacokinetics (PK) of sparsentan oral suspension and tablets in a pediatric population

• Assess changes in estimated glomerular filtration rate (eGFR) after once-daily dosing of sparsentan oral suspension and tablets over 108 weeks
• Assess the palatability and acceptability of sparsentan oral suspension

Study design

Population 1 and 2:
Enrollment will initially start for all subjects aged >=2 years and who are >=10 kg at screening and Day 1. For subjects aged <2 years (Population 1 only) or <10 kg (Population 1 and Population 2), the Data Monitoring Committee will recommend enrollment to proceed based on exposure and safety data from subjects already enrolled in the study. The 10 kg limit will be determined as *dry weight* by the Investigator*s judgement based on body weight when the child is free of edema or ascites and taking into account most recent premorbid or remission body weight, preferably as the last weight recorded within 3 months of the onset of the nephrotic syndrome. Subjects who meet screening eligibility criteria for enrolment who are taking inhibitors of the renin angiotensin aldosterone system (RAAS inhibitors), will undergo a 2 week washout period from these agents prior to Day 1/Randomization.
After screening, subjects (including the washout subjects) meeting the eligibility criteria will undergo comprehensive baseline evaluations and clinical laboratory tests and will then be randomly assigned in a 1:1:1 ratio to 1 of the 3 PK sampling schemes.

Population 3:
Subjects aged >=8 years to <18 years and who are >=40 kg at screening and Day 1 will be enrolled. To be eligible for Population 3, subjects are required to be on angiotensin-converting enzyme inhibitor (ACEIs) and/or angiotensin receptor blocker (ARBs) for at least 12 weeks prior to screening. Subjects will remain on ACEIs and/or ARBs throughout the screening period until start of study medication (no washout). The final dose of an ACEIs and/or ARBs should be taken on the day before the Day 1 (Baseline) visit, the visit at which study medication is initiated.
Pre dose (Cmin_ss) samples will be collected on Day 1 (Baseline), and at Weeks 4, 8, 12, 24, 36, 48, 60, 72, 84, and 96. The date and time of dosing of the subject, the day preceding the PK visit must be recorded.

The safety and tolerability of sparsentan will be evaluated by AEs, vital signs, physical examinations, clinical laboratory parameters, and 12-lead electrocardiograms.
Maximum blood volumes for blood sample collection for all ages will be based on body weight according to World Health Organization (WHO) guidance (WHO blood sample volumes in child health research: review of safe limits [https://www.who.int/bulletin/volumes/89/1/10-080010/en/] unless superseded by local requirements.
Periodic safety and efficacy assessments will be performed, respectively. Adverse events and concomitant medications/therapies will be monitored and

recorded from the time of informed consent/assent through study completion (ie, Week 112). Ongoing SAEs after completion of the last scheduled visit will continue to be followed to determine the final outcome.
For subjects with hypertension, additional antihypertensive agents or adjustments to current antihypertensive treatment are strongly recommended during the study to achieve and maintain blood pressure within the normal range for age, with the exception of those that inhibit the RAAS or endothelin system.

Intervention

The study medication will be supplied as an oral suspension containing 80 mg/mL of sparsentan for Population 1, Population 2 and tablets (200 mg or 400 mg) for Population 3.

Population 1 and Population 2:
Sparsentan suspension should not be taken on an empty stomach. On the days of study site visits, subjects will take their dose with or within 30 minutes after starting a meal at the study site. At visits with PK sample collection, the daily dose will be administered at the clinic after the predose PK sample has been obtained. On all other days, the daily dose should be taken with or within 30 minutes after starting the first meal of the day. Subjects will be instructed to avoid drinking or eating anything that contains grapefruit, Seville oranges (bitter oranges often used as marmalade), starfruit (carambola), or pomelo/shaddock throughout the study.
The intent is to achieve exposure similar to an adult equivalent dose of 800 mg (Population 1) and 400 mg (Population 2) in the pediatric populations planned for inclusion in this study and willrequire weight-based dosing.
The starting dose will be determined based on age, dry weight and blood pressure at baseline.
For subjects starting on 25% of the target dose
Sparsentan administration will be initiated at 25% of the target dose on Day 1 (Visit 3). If the initial starting dose of sparsentan is tolerated up to Week 2 (Visit 5), the dose will be increased up to 50% of the target dose. Subjects who do not tolerate the initial 25% dose for any reason will be discontinued from the study. At Week 4 (Visit 6), if 50% of the target dose is tolerated, the sparsentan dose will be increased up to the target dose, and the target dose will be maintained through Week 108 (Visit 17). Note that the target dose may change during the course of the study if the subject gains or loses weight. An additional visit at Week 6 will be required for subjects who achieve the target dose (ie, 100% dose).
For subjects starting on 50% of the Target Dose
Sparsentan administration will be initiated and continued at 50% of the target dose up to Week 2 (Visit 5). If the initial starting dose of sparsentan is tolerated up to Week 2 (Visit 5), the dose will be increased up to the target dose (ie. 100% dose), and the target dose will be maintained through Week 108 (Visit 17) based on the subject's weight.

Population 3
For Population 3 study medication will be supplied as 200 mg or 400 mg tablets to subjects. Sparsentan tablets should be taken whole on an empty stomach and subjects will be instructed to take the appropriate number of tablets for their assigned oral dose at approximately the same time each day, preferably prior to the morning meal (please note that this is different from the suspension formulation), except on the day of a study visit. On the day of each study visit, subjects will take their study medication at the clinic. Subjects will be instructed to avoid drinking or eating anything that contains grapefruit, Seville oranges (bitter oranges often used as marmalade), starfruit (carambola), or pomelo/shaddock throughout the study
The permitted target dose is 400 mg. The intent is to achieve exposure similar to an adult equivalent dose of 400 mg in the pediatric populations planned for inclusion in this study. Sparsentan administration will be initiated and continued at 50% of the target dose up to Week 2 (Visit 3).
If the initial starting dose of sparsentan is tolerated up to Week 2 (Visit 3), the dose will be increased up to the target dose (ie, 100% dose), and the target dose will be maintained through Week 108 (Visit 14). In Population 3, if weight of the subject falls below 40 kg during the study, subject may be dosed with 200 mg or 400 mg at the investigator*s discretion based on tolerability.

During treatment, the Investigator will evaluate the subject for intolerance, allowing for dose up-titration, dose maintenance, dose reduction, dose interruption (ie, temporary discontinuation), or permanent discontinuation. The permitted doses are 25%, 50%, and 100% of the target dose for Population 1 and Population 2. For Population 3 permitted doses are 50% and 100% of the target dose.
Doses may be modified, temporarily interrupted, or permanently discontinued at any time throughout the study for safety and tolerability reasons at the Investigator*s discretion. If subjects permanently discontinue treatment before Week 12 or a Week 12 PK is not obtained (Population 1 and Population 2 only), additional subjects may be enrolled.
Subjects who permanently discontinue the treatment before Week 108 will be withdrawn from the study following a safety follow-up visit, 4 weeks after the last dose of the study medication.

Study burden and risks

We do not know all the possible side effects of the study drug. Like all medicines, the study drug can cause side effects, although not everybody gets them. Most side effects are mild to moderate. However, some people may experience serious side effects and may require treatment.

The following side effects have been experienced by other people who have taken the study drug:

Side effects experienced in up to 5% of people
• Abdominal distension (swollen belly)
• Abdominal pain (belly pain)
• Abdominal pain upper (pain in upper area of belly)
• Acute kidney injury (sudden or short-term decrease in kidney function)
• Asthenia (loss of energy or weakness)
• Blood creatine phosphokinase increased (may represent muscle injury)
• Chronic Kidney Disease (long term kidney disease)
• Diarrhea (loose or watery stool)
• Dizziness postural (feeling of spinning)
• Eructation (burping)
• Fatigue
• Hemoglobin decreased (a decrease in substance in red blood cells which transports oxygen)
• Hypokalemia (low blood potassium)
• Orthostatic hypotension (low blood pressure on standing up)
• Rash
• Syncope (fainting)

Side effects experienced in more than 5% of people
• Anemia (low red blood cell count)
• Blood creatinine increased (a sign of reduced kidney function)
• Dizziness
• Glomerular filtration rate decreased (a sign of reduced kidney function)
• Headache
• Hyperkalemia (high blood potassium)
• Hypotension (low blood pressure)
• Nausea
• Peripheral edema (swelling, usually seen in the legs and feet)
• Vomiting

In addition to the risks above, the following were reported as serious and possibly related to the study drug use in a previous study:
• Acute kidney injury (sudden decrease in kidney function)
• Anemia (low red blood cell count)
• Hyperaldosteronism (too much aldosterone (a hormone), produced by the body)
• Hyperkalemia (high levels of potassium in the blood)
• Hypokalemia (low levels of potassium in the blood)
• Liver injury (damage to the liver)
• Melena (blood in stool)
• Syncope (fainting)
• Spontaneous abortion (miscarriage)
The study drug can also have side effects that we do not know about at the moment.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adolescents (12-15 years)
Adolescents (16-17 years)
Children (2-11 years)
Babies and toddlers (28 days-23 months)

Inclusion criteria

Inclusion Criteria for All Subjects (All Three Populations):
A subject must meet all of the following criteria to be eligible for participation in this study:
1. The subject or parent/legal guardian (as appropriate) is willing and able to provide signed informed consent/assent, and where required, the subject is willing to provide assent before any screening procedures per local requirements.
2. The subject has an eGFR >=30 mL/min/1.73 m2 at screening.
3. The subject has a mean seated blood pressure between the 5th and 95th percentile for sex and height.

Inclusion Criteria for Population 1:
1. The subject is male or female >=1 year at screening and <18 years of age at Day 1 (Baseline).
2. The subject has a UP/C >=1.5 g/g (170 mg/mmol) at screening AND one of the following:
• Kidney biopsy-proven FSGS or MCD histological patterns and clinical presentation consistent with primary FSGS or MCD and qualifying proteinuria at screening despite history or ongoing treatment with corticosteroids and/or other immunosuppressive disease-modifying agents.
• Documentation of a genetic mutation in a podocyte protein associated with FSGS or MCD. Subjects with a documented podocytic mutation do not require kidney biopsy.
• Kidney biopsy-proven FSGS histological pattern with medical history and clinical presentation consistent with maladaptive cause of the lesion.
Note: The kidney biopsy may have been performed at any time in the past but must include light microscopy and electron microscopy characteristics and/or immunofluorescence findings consistent with FSGS or MCD.
Inclusion Criteria for Population 2:
1. The subject is male or female >=2 years at screening and <18 years of age at Day 1 (Baseline).
2. The subject has UP/C >=0.6 g/g (68 mg/mmol) at screening AND one of the following diagnoses:
• Kidney biopsy-confirmed IgAN, IgAV or AS
• Diagnosis of AS by genetic testing (pathogenic X-linked COL4A5 mutation OR autosomal-recessive mutations in both alleles of COL4A3 and/or COL4A4 OR autosomal-dominant COL4A3 and/or COL4A4 and digenic mutations [ie, simultaneous mutations in 2 of the COL4A3, COL4A4, and COL4A5 genes])
Inclusion Criteria for Population 3:
1. The subject is male or female >=8 years at screening and <18 years of age at Day 1 (Baseline).
2. The subject has UP/C >=1.0 g/g (113 mg/mmol) at screening AND has kidney biopsy confirmed IgAN
3. Subject weighs >=40 kg
4. The subject has been on ACEI and/or ARB therapy for at least 12 weeks prior to screening.
Subjects diagnosed with IgAN will be assessed for Population 3 (in US and UK only) after it is determined that enrollment to Population 2 is no longer possible (ie, enrollment to the applicable population cohort is completed).

Exclusion criteria

Exclusion Criteria for All Subjects (All Three Populations):
A subject who meets any of the following will be excluded from this study:
1. The subject weighs <7.3 kg at screening.
2. The subject has FSGS or MCD histological pattern secondary to viral

infections, drug toxicities, or malignancies.
3. The subject has immunoglobulin A (IgA) glomerular deposits not in the context of primary IgAN or IgAV (ie, secondary to another condition eg, systemic lupus erythematosus and liver cirrhosis).
4. The subject has had an acute onset or presentation of glomerular disease or a diagnostic biopsy or a relapse of glomerular disease requiring new or different class of immunosuppressive treatment (including, but not limited to, systemic corticosteroids, calcineurin inhibitors and mycophenolate mofetil, abatacept, cyclophosphamide, rituximab, ofatumumab, and ocrelizumab) within 6 months before screening.
5. Subjects taking chronic immunosuppressive medications (including systemic steroids) not on a stable dose for >=1 month before screening.
6. The subject requires any of the prohibited concomitant medications as defined in the study protocol.
7. The subject has undergone any organ transplantation, with the exception of corneal transplants.
8. The subject has a documented history of congenital or acquired heart failure (modified Ross heart failure classification for children Class II to Class IV) and/or previous hospitalization for heart failure or unexplained dyspnea, orthopnea, paroxysmal nocturnal dyspnea, ascites, and/or peripheral edema.
9. The subject has hemodynamically significant cardiac valvular disease.
10. The subject has clinically significant congenital vascular disease.
11. The subject has jaundice, hepatitis, or known hepatobiliary disease, or alanine aminotransferase and/or aspartate aminotransferase >2 times the upper limit of the normal range at screening.
12. The subject has a history of malignancy within the past 2 years.
13. The subject has a screening hematocrit <27% (0.27 L/L) or a hemoglobin value <9 g/dL (90 g/L).
14. The subject has a screening potassium value >5.5 mEq/L (5.5 mmol/L).
15. The subject has any abnormal clinical laboratory screening values that are considered by the Investigator to be clinically significant.
16. The subject has a history of allergic response to any angiotensin II antagonist or endothelin receptor antagonist, including sparsentan, or has a hypersensitivity to any of the excipients in the study medication.
17. The female subject is pregnant, plans to become pregnant during the course of the study, or is breastfeeding.
18. Female subjects of childbearing potential, beginning at menarche, who do not agree to use 1 highly reliable (ie, can achieve a failure rate of <1% per year) method of contraception from 7 days before the first dose of the study medication until 28 days after the last dose of study medication. Examples of highly reliable contraception methods include stable oral, implanted, transdermal, or injected contraceptive hormones associated with the inhibition of ovulation or an intrauterine device. One additional barrier method must also be used during vaginal sexual activity, such as a diaphragm, diaphragm with spermicide (preferred), or male partner*s use of male condom or male condom with spermicide (preferred), from Day 1/Randomization until 28 days after the last dose of study medication. Female subjects of childbearing potential are

defined as those who are fertile after menarche, unless permanently sterile; permanent sterilization methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy. All female subjects of childbearing potential must have a negative serum pregnancy test result at screening (Visit 1) and a negative urine pregnancy test result, with positive results confirmed by serum, at every study visit from Day 1 (Visit 3) and after.
Note: Before menarche, pregnancy testing and contraceptive use are not required. However, subjects and their parents/legal guardians must be advised that, immediately upon menarche, subjects will be required to begin pregnancy testing and initiate contraceptive use. This requirement cannot be waived.
19. The subject has participated in a study of another study medication within 28 days before screening or plans to participate in such a study during the course of this study.
20. The subject has had prior exposure to sparsentan.
21. The subject or parent/legal guardian (as appropriate), in the opinion of the Investigator, are unable to adhere to the requirements of the study including but not limited to, a history of noncompliance and/or any other reason that causes the Investigator to believe the subject would not be a good candidate for the study.
22. For Population 3 - The subject is unable to swallow the study medication tablets whole.

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):	09-11-2023
Enrollment:	2
Type:	Actual

Medical products/devices used

Registration:	No
Product type:	Medicine
Brand name:	Sparsentan
Generic name:	Sparsentan

Ethics review

Approved WMO Date:	14-12-2021
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	22-03-2022
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	05-08-2022
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	20-08-2022
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	31-08-2022
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	06-04-2023
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	08-05-2023
Application type:	Amendment

Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	02-07-2023
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	21-02-2024
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	11-03-2024
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)

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	CTIS2023-505497-14-00
EudraCT	EUCTR2021-000621-27-NL
CCMO	NL78694.091.21