Sparsentan for Treatment of Pediatric Patients With Selected Proteinuric Glomerular Diseases: Design of the Phase 2 EPPIK Study

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METHODS

Study participants

- Enrollment of approximately 57 pediatric patients aged ≥1 to <18 years is planned, including ~30 patients with FSGS and/or treatment-resistant MCD (Population 1) and ~27 patients with IgAN, IgAV, or AS (Population 2)

Table 1. Key patient inclusion criteria for EPPIK

	Key Inclusion Criteria
All Patients	eGFR ≥30 mL/min/1.73 m² at screening
	Mean seated blood pressure 5th to 95th percentile for age, sex, height
Population 1	Male or female age ≥1 at screening and <18 years of age at Day 1
	UP/C ≥1.5 g/g at screening despite history of or ongoing corticosteroid or immunosuppressive drugs
	Biopsy-proven FSGS or MCD or documentation of a genetic mutation in a podocyte protein associated with FSGS or MCD (biopsy not required)
Population 2	Male or female age ≥2 and <18 years of age at screening
	UP/C ≥1.0 g/g at screening
	Biopsy-confirmed IgAN or IgAV nephritis or AS-associated genetic mutation

AS, Alport syndrome; eGFR, estimated glomerular filtration rate; FSGS, focal segmental glomerulosclerosis; IgAN, IgA nephropathy; IgAV, IgA vasculitis; MCD, minimal change disease; UP/C, urine protein/creatinine ratio.

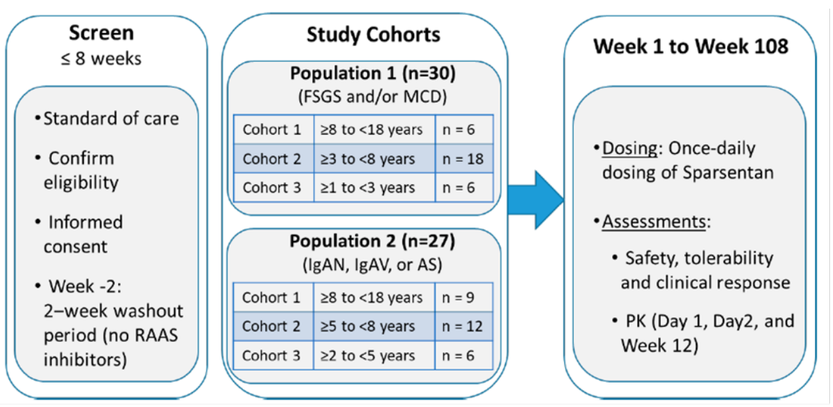
Table 2. Key patient exclusion criteria for EPPIK

Key Exclusion Criteria
Weighs <7.3 kg at screening
FSGS or MCD histological pattern secondary to viral infections, drug toxicities, or malignancies
IgA glomerular deposits not in the context of primary IgAN or IgAV (eg, secondary to systemic lupus erythematosus and liver cirrhosis)
Significant cardiovascular or hepatic conditions
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 therapy (including, but not limited to, systemic corticosteroids, calcineurin inhibitors and mycophenolate mofetil, abatacept, cyclophosphamide, rituximab, ofatumumab, and ocrelizumab) within 6 months before screening
Taking chronic immunosuppressive medications (including systemic steroids) and not on a stable dose for ≥1 month before screening
Any organ transplantation other than corneal transplants
History of malignancy within the past 2 years
Screening hematocrit <27% or a hemoglobin value <9 g/dL
Screening potassium value >5.5 mEq/L
Disqualifying laboratory abnormalities during a screening
History of allergic response to any angiotensin II antagonist or endothelin receptor antagonist

Study design

- EPPIK is a global, open-label, single-arm, multicenter, phase 2 cohort study of sparsentan in pediatric patients with selected proteinuric glomerular diseases
- EPPIK will evaluate the safety, efficacy, and PK of sparsentan in a novel liquid formulation in pediatric patients aged ≥1 to <18 years over 108 weeks (**Figure 1**)
  - Patients receiving renin-angiotensin-aldosterone system inhibitors (RAASI) will undergo a 2-week washout
  - Antihypertensive agents, except RAASI or endothelin inhibitors, are allowed to maintain blood pressure control in patients with hypertension
  - For each population, patients will be enrolled in 3 cohorts based on age ranges
  - PK assessments will occur at Day 1 (baseline; Visit 3), Day 2 (Visit 4), and Week 12 (Visit 9)

Figure 1. EPPIK study design



PK, pharmacokinetics; RAAS, renin-angiotensin-aldosterone system.

Table 3. Abbreviated schedule of clinic visits

	Screening	Washout[a]	Day 1 Baseline[b]	Treatment Period[c]	Treatment Period[d]	End of Study
Visit	1	2	3	5-8	9-16	17
Week	≤8 weeks before Day 1	Week -1	Week 1	Week 2 to 8	Week 12 to 96	Week 108
Inclusion/exclusion	•					
Physical examination	•	•	•	•	•	•
Vital signs	•	•	•	•	•	•
Clinical laboratory assessments	•	•	•	•	•	•
12-lead electrocardiogram[e]	•				•	
Quantitative urinalysis[f]	•		•	•	•	•
PK plasma levels[g]			•		•	
Palatability questionnaire[h]				•		
AE assessment	Continuous Monitoring					

[a]Patients taking RAASI at screening (Visit 1) will complete a 2-week (14-day) washout from these medications prior to Day 1 (baseline). [b]On Day 2 (Visit 4), pre-dose PK plasma levels are assessed at approximately 24 hours after the Day 1 dose. [c]From Week 2 to 8, assessments occur every 2 weeks with the exception that Week 6 only occurs for patients in Cohort 3. [d]Beginning at Week 12, assessments occur every 12 weeks through the end of the study. [e]Occurs at Visit 9/Week 12. [f]Occurs at Screening, Day 1, Visit 8/Week 8, and every visit thereafter. [g]PK plasma levels are assessed pre-dose on Day 1 (Visit 3) and Week 12 (Visit 9), and then at either 1 hour and 2 hours post-dose, 2 hours and 4 hours post-dose, or 4 hours and 6 hours post-dose based on the patient's randomly assigned PK sampling schedule. Additionally, pre-dose PK plasma levels are assessed on Day 2 (Visit 4) at approximately 24 hours after the Day 1 dose. [h]Occurs at Visit 5/Week 2.
AE, adverse event.

Study treatment

- Sparsentan 80 mg/mL oral suspension will be administered in a novel liquid formulation
  - Population 1 (FSGS and/or MCD) dose exposure will be similar to an adult equivalent dose of 800 mg/day
  - Population 2 (IgAN, IgAV, or AS) dose exposure will be similar to an adult equivalent dose of 400 mg/day
- The initiation dose and target dose of sparsentan will be determined based on patient age and weight (**Table 4**)
  - Patients ≥2 years old:
    - Sparsentan will be taken at 50% of the target dose up to Week 2, and if tolerated, increased to the target dose
  - Patients <2 years old:
    - Sparsentan will be taken at 25% of the target dose up to Week 2, and if tolerated, increased to 50% of the target dose through Week 4
    - If tolerated at Week 4, the dose will be increased to the target dose
- Allowed doses are 25%, 50%, and 100% of the target dose
- Doses may be modified, temporarily interrupted, or permanently discontinued at any time for safety and tolerability reasons

Table 4. Sparsentan dosage by age and weight of pediatric patients

Weight (kg)	Sparsentan 80 mg/mL					
	Population 1 (FSGS and/or MCD) Permitted Doses as % Target Dose			Population 2 (IgAN, IgAV, or AS) Permitted Doses as % Target Dose		
	25%	50%	100%	25%	50%	100%
≥2 years						
≥40	2.5 mL	**5 mL**	10 mL (800 mg)	1.25 mL	**2.5 mL**	5 mL (400 mg)
30 to <40	1.875 mL	**3.75 mL**	7.5 mL (600 mg)	0.938 mL	**1.875 mL**	3.75 mL (300 mg)
20 to <30	1.25 mL	**2.5 mL**	5 mL (400 mg)	0.625 mL	**1.25 mL**	2.5 mL (200 mg)
<20	0.625 mL	**1.25 mL**	2.5 mL (200 mg)	0.313 mL	**0.625 mL**	1.25 mL (100 mg)
<2 years				Not Applicable		
10 to <20	**0.625 mL**	1.25 mL	2.5 mL (200 mg)			
7 to <10	**0.313 mL**	0.625 mL	1.25 mL (100 mg)			

Bold indicates starting doses.

Study endpoints and assessments

Table 5. EPPIK endpoints

Primary Endpoints
Change from baseline in UP/C over the 108-week sparsentan treatment period
Incidence of TEAEs, SAEs, AEs leading to treatment discontinuation, AEs of interest
Secondary Endpoints
Observed plasma PK concentrations at scheduled timepoints and visits
Steady-state PK parameters
Change from baseline in UA/C over the 108-week sparsentan treatment period
Change from baseline in eGFR over the 108-week sparsentan treatment period
The proportion of patients with FSGS and/or MCD histological patterns achieving partial remission (FPRE[4]), defined as UP/C ≤1.5 g/g and >40% reduction in UP/C over the 108-week sparsentan treatment period
Exploratory Endpoints
Patients undergoing initiation/intensification in immunosuppressive medication
Patients undergoing reduction in immunosuppressive medication
Palatability and acceptability of sparsentan oral suspension
Other Safety Endpoints
Changes in vital signs, peripheral edema, and clinical laboratory tests

FPRE, FSGS partial remission endpoint; SAE, serious adverse events; TEAE, treatment-emergent adverse events; UA/C, urine albumin/creatinine ratio.

- Efficacy measures include urine protein/creatinine ratio (UP/C), urine albumin/creatinine ratio (UA/C), and eGFR
  - UP/C and UA/C quantitative urinalysis measures will use first morning void or Pediatric Urine Collector for patients using diapers
- Safety measures include treatment-emergent adverse events (TEAEs), serious AEs, AEs leading to treatment discontinuation, AEs of interest, vital signs, peripheral edema, and clinical laboratory parameters
- Steady-state PK measures include area under the plasma concentration-time curve during a dosing interval, maximum steady-state plasma drug concentration during a dosage interval, and minimum steady-state plasma drug concentration derived from population PK analysis

Data analysis

- The study has at least 80% probability to detect a relative reduction from baseline UP/C of at least 30% (ie, geometric mean ratio = 0.70) at the 1-sided α = 5% (ie, 10% 2-sided) in each population. This assumes that the SD of the change from baseline in log UP/C at a specific visit is 0.70.
  - Analyses will use mixed model repeated measures
- Safety data and PK parameters will be summarized using descriptive statistics

Strategies for achieving adequate participant enrollment

- If on-site visits are not feasible due to challenges related to COVID-19 or other unexpected circumstances, remote study visits (eg, conducted by telephone or video conference) are allowed
- To reduce the burden of clinical site visits for patients, home health agency home visits will be offered, for example, for collection of laboratory samples

SUMMARY

This Phase 2 study will evaluate the long-term safety, antiproteinuric, and nephroprotective effects of sparsentan in a novel liquid formulation in pediatric patients as young as 1 year of age with proteinuric glomerular diseases

DISCLOSURES

HT: Has received consultancy fees from Kaneka Inc., Otsuka, and ChemoCentryx and was previously a consultant to Genzyme and Optherion, is a consultant to Travere Therapeutics, Inc. through an agreement with NYU and has an agreement with Goldfinch Biopharma through NYU.

MS: Has consultant agreements receiving fees from Travere Therapeutics, Inc., Purespring Therapeutics, and Mission Therapeutics.

RC: Has consultant agreements receiving fees from Travere Therapeutics, Inc., AMGEN, Recordati, NOVARTIS, Argenx, Calliditas, Otsuka, Reata, and is under contract with UptoDate.

MNR: Is a site primary investigator for Travere Therapeutics, Inc., Advicenne, Reata, Genentech and has received research funding from Goldfinch Bio, Novartis, NIDDK, and Department of Defense.

PH, RK: Employees of Travere Therapeutics, Inc. and may have an equity or other financial interest in Travere Therapeutics, Inc.

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BACKGROUND

Sparsentan, a novel Dual Endothelin Angiotensin Receptor Antagonist (DEARA), is a dual acting, highly selective antagonist of both the endothelin A receptor (ET_AR) and the angiotensin II subtype 1 receptor (AT_1R) being investigated for the treatment of focal segmental glomerulosclerosis (FSGS) and IgA nephropathy (IgAN) in adults and for the treatment of FSGS in pediatric patients as young as 8 years old.[1-3] To understand the efficacy, pharmacokinetics (PK), and safety of sparsentan in pediatric patients, including very young children, the phase 2 open-label Evaluating Problematic Proteinuria in Kids (EPPIK) study is being conducted in patients as young as 1 year old with selected proteinuric glomerular diseases. This study is being conducted in alignment with the program's EMA assigned pediatric investigation plan (PiP) to support the regulatory process in Europe for potential submissions of sparsentan for the treatment of FSGS and IgAN.

AIMS AND OBJECTIVES

The EPPIK study will examine the long-term antiproteinuric and nephroprotective potential and safety of sparsentan in pediatric patients with FSGS, minimal change disease (MCD), IgAN, IgA vasculitis (IgAV), and Alport syndrome (AS). Here we describe the study design and methodology of the EPPIK study.

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