FILSPARI® (sparsentan)

EPPIK (Phase 2 Study): Treatment in Pediatric Patients With Proteinuric Glomerular Diseases

Summary

Prescribing Information

- FILSPARI is an endothelin and angiotensin II receptor antagonist indicated to slow kidney function decline in adults with primary immunoglobulin A nephropathy (IgAN) who are at risk for disease progression[1]
- The safety and efficacy of FILSPARI in pediatric patients have not been established[1]

Background

- Sparsentan is a novel, first-in-class, and the only single molecule antagonist of the ET_A and AT_1 receptors[2-4]
- The EPPIK study is an open-label, single-arm, multicenter trial evaluating the safety, efficacy, and PK of liquid sparsentan in patients aged ≥1 to <18 years with FSGS or MCD and aged ≥2 to <18 years with IgAN, IgAV, or Alport syndrome[5,6]

Study Data

- In pediatric patients with a range of proteinuric glomerular diseases, sparsentan treatment resulted in reductions in proteinuria over the initial 12 weeks of treatment[5]
- Sparsentan appeared to be safe and well-tolerated[5]

Prescribing Information

The safety and efficacy of FILSPARI in pediatric patients have not been established.[1]

For more information, please refer to the attached Prescribing Information.

Background

Sparsentan is a novel, first-in-class, and the only single molecule antagonist of the ET_A and AT_1 receptors.[2-4] Preclinical studies in rodent models of chronic kidney disease have shown that blockade of both ET_A and AT_1 pathways reduces proteinuria, protects podocytes, and prevents glomerulosclerosis and mesangial cell proliferation.[7-9]

The EPPIK Study

The EPPIK study (NCT05003986) is a phase 2, global, open-label, single-arm, multicenter cohort study to evaluate the safety, efficacy, and PK of a liquid formulation of sparsentan in pediatric patients with selected proteinuric glomerular diseases. The primary objective of the EPPIK study is to examine long-term antiproteinuric and nephroprotective potential and safety in this pediatric population.[6] Approximately 57 pediatric patients aged ≥1 to <18 years will be enrolled. EPPIK Population 1 will include ~30 patients aged 1 to <18 years with FSGS or treatment-resistant MCD. Population 2 will include ~27 patients aged 2 to <18 years with IgAN, IgAV, or Alport syndrome. Primary endpoints are the change from baseline in UPCR over a 108-week treatment period, incidence of TEAEs, SAEs, AEs leading to treatment discontinuation, and AEs of interest. Secondary endpoints include observed plasma PK concentration, steady-state PK parameters, change from baseline in UACR and eGFR over 108 weeks of treatment, and proportion of patients with FSGS or MCD histological patterns achieving partial remission (FPRE) in UPCR. Partial remission is defined as UPCR ≤1.5 g/g and >40% reduction in UPCR. Safety parameters are monitored throughout the duration of the study.[5,6]

Patient Selection

Key eligibility criteria for the EPPIK study are provided in **Table 1**.[6]

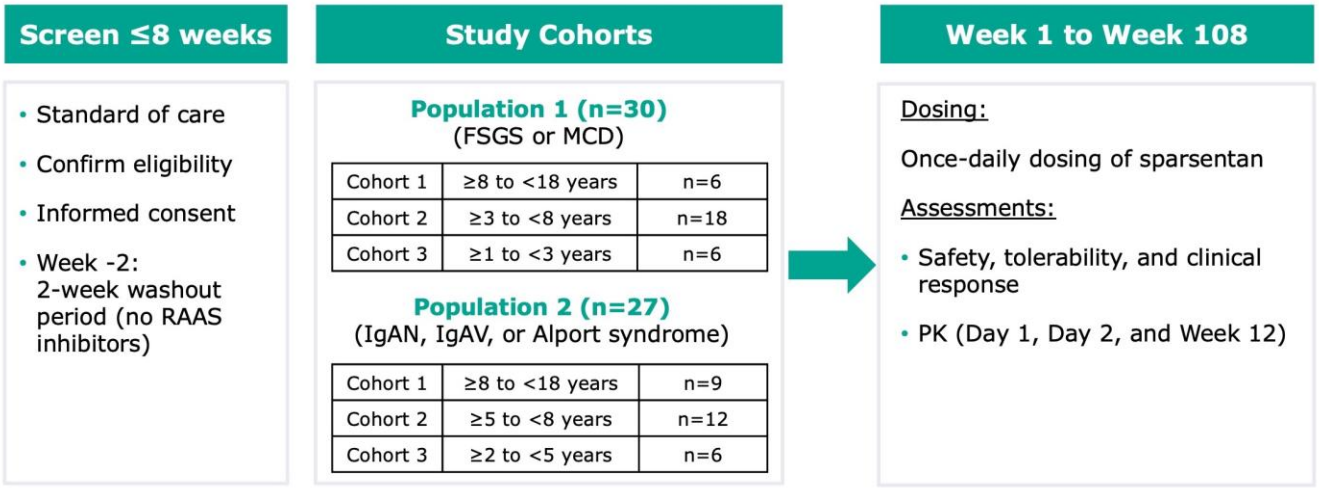
Table 1. EPPIK Study Inclusion and Exclusion Criteria

Key Inclusion Criteria	
All Patients	eGFR ≥30 mL/min/1.73 m^2 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
	UPCR ≥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
	UPCR ≥1.0 g/g at screening
	Biopsy-confirmed IgAN or IgAV nephritis or Alport syndrome-associated genetic mutation
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

Prior to enrollment, patients taking RAASi will undergo a 2-week washout period. Other antihypertensive medications, except endothelin inhibitors, are allowed for treatment of patients with hypertension. Following enrollment into Population 1 or 2, patients are further stratified into cohorts according to age. Patients are evaluated over 108 weeks and treated with once-daily dosing of liquid sparsentan. Patients are then returned to SOC for 4 weeks of follow-up. Safety, tolerability, and clinical response are assessed throughout the study (**Figure 1**).[5,6]

Figure 1. EPPIK Study Design



Patients are randomly assigned to a PK assessment schedule. For all patients, PK plasma levels are assessed pre-dose on Day 1 and Week 12; an additional pre-dose PK plasma level measurement occurs on Day 2, ~24 hours after the first sparsentan dose on Day 1. At clinic visits following Week 12, plasma PK is assessed at either 1 hour and 2 hours post-dose, 2 hours and 4 hours post-dose, or 4 hours and 6 hours post-dose, depending upon the patient's assigned PK sampling schedule.[6]

Study Treatment

Sparsentan 80 mg/mL oral suspension is administered in a novel liquid formulation; starting and target doses are determined based on patient age and weight (**Table 2**). For patients in Population 1 (FSGS or MCD), dose exposure is similar to an adult equivalent dose of 800 mg/day. For patients in Population 2 (IgAN, IgAV, or Alport syndrome), dose exposure is similar to an adult equivalent of 400 mg/day. Dosing titration is determined by patient age. Patients aged ≥2 years begin with 50% of the target dose and continue to Week 2; if tolerated, dose is increased to target. Patients aged <2 years begin with 25% of target dose up to Week 2; if tolerated, dose is increased to 50% target to Week 4. If tolerated at 50%, dose is increased to target. If necessary, doses may be modified, temporarily halted, or discontinued.[6]

Table 2. Sparsentan Dosing

Weight (kg)	Sparsentan 80 mg/mL					
	Population 1 (FSGS or MCD) Permitted Doses as % Target Dose			Population 2 (IgAN, IgAV, or Alport Syndrome) 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 Data

Preliminary Study Results

At data cutoff (April 5, 2023), 23 pediatric patients enrolled in the EPPIK study have received ≥1 dose of sparsentan oral suspension.[5,6] Safety and efficacy were assessed over 12 weeks of treatment.[5]

Baseline Characteristics

In this preliminary analysis, Population 1 included 13 patients, 8 (61.5%) with MCD and 5 (38.5%) with FSGS. Median age at time of screening was 8 years (IQR, 6-13 years). Population 2 included 10 patients, 3 (30%) with IgAN and 7 (70%) with Alport syndrome. Median age at screening was 13 years (IQR, 12-14 years). Additional baseline characteristics are presented in **Table 3**.[5]

Table 3. EPPIK Patient Baseline Characteristics

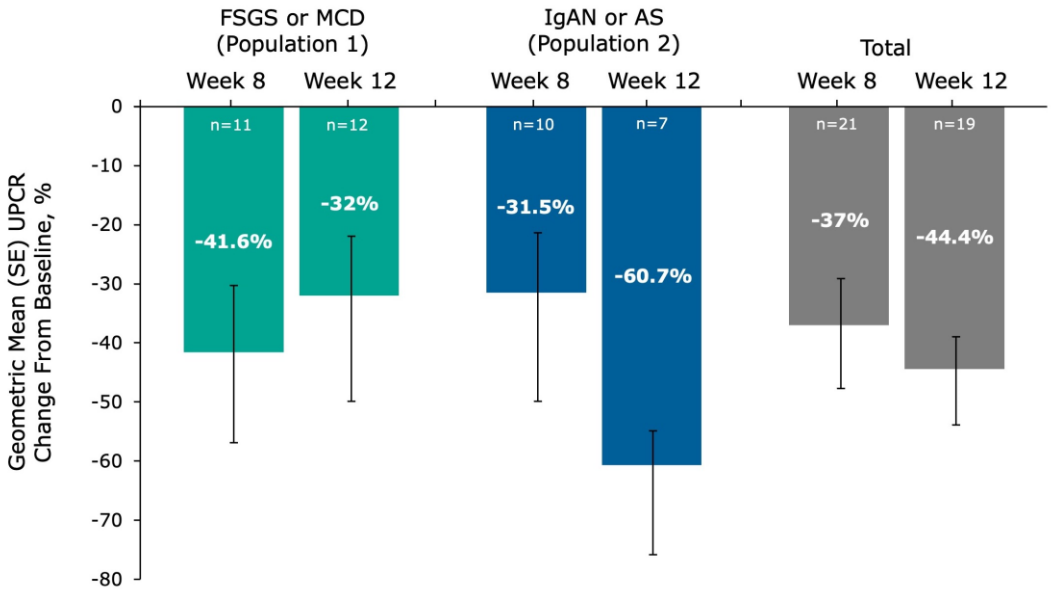
Characteristic	Population 1 MCD or FSGS (n=13)	Population 2 IgAN or Alport Syndrome (n=10)	Total (N=23)
Diagnosis, n (%)			
MCD	8 (61.5)	0	8 (34.8)
FSGS	5 (38.5)	0	5 (21.7)
IgAN	0	3 (30)	3 (13)
Alport syndrome	0	7 (70)	7 (30.4)
IgAVN	0	0	0
Male sex, n (%)	8 (61.5)	8 (80)	16 (69.6)
Age, years*, median (IQR)	8 (6, 13)	13 (12, 14)	12 (7, 14)
White race, n (%)	12 (92.3)	6 (60)	18 (78.3)
UPCR, g/g, median (IQR)	3 (2.5, 5.7)	2.5 (2.1, 3.2)	2.8 (2.3, 5)
Nephrotic-range proteinuria (UPCR ≥2 g/g), n (%)	12 (92.3)	8 (80)	20 (87)
eGFR, mean (SD), mL/min/1.73 m²	106.1 (50)	87.3 (27.4)	97.9 (42)
Immunosuppression at baseline, n (%)	8 (61.5)	1 (10)	9 (39.1)
Blood pressure, systolic/diastolic, mean (SD), mm Hg	115 (16.1) / 69.3 (11.3)	116.2 (10) / 69.1 (8.4)	115.5 (13.5) / 69.2 (9.9)

*At screening.

Efficacy

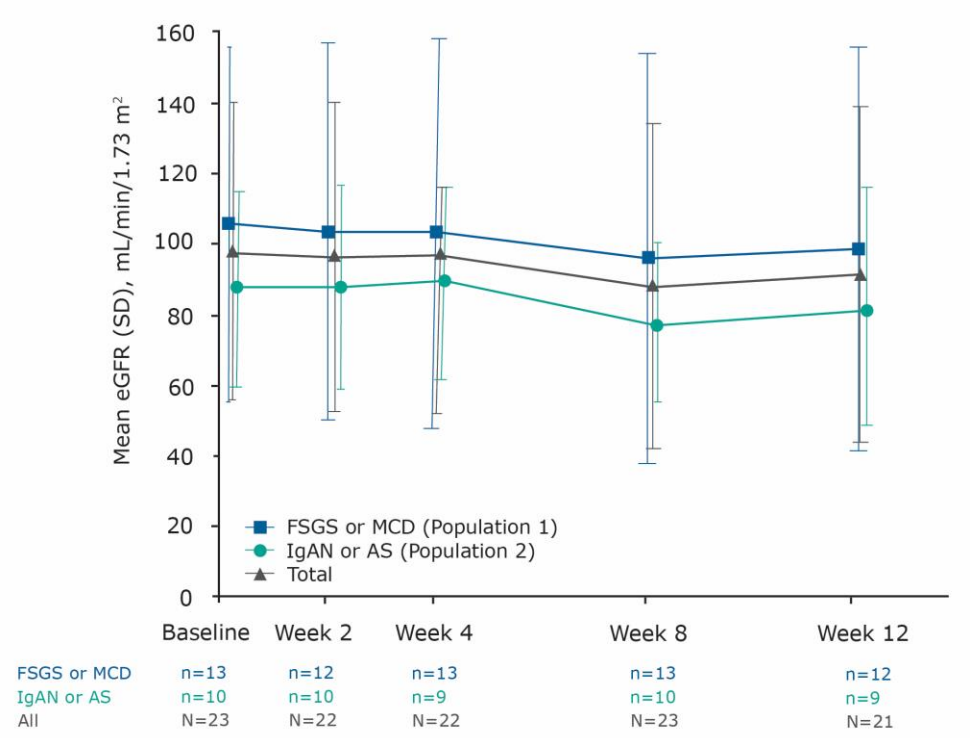
In pediatric patients with a range of proteinuric glomerular diseases, sparsentan treatment resulted in reductions in proteinuria over the initial 12 weeks of treatment (**Figure 2**).[5,10]

Figure 2. UPCR Reduction Over 12 Weeks of Sparsentan Treatment



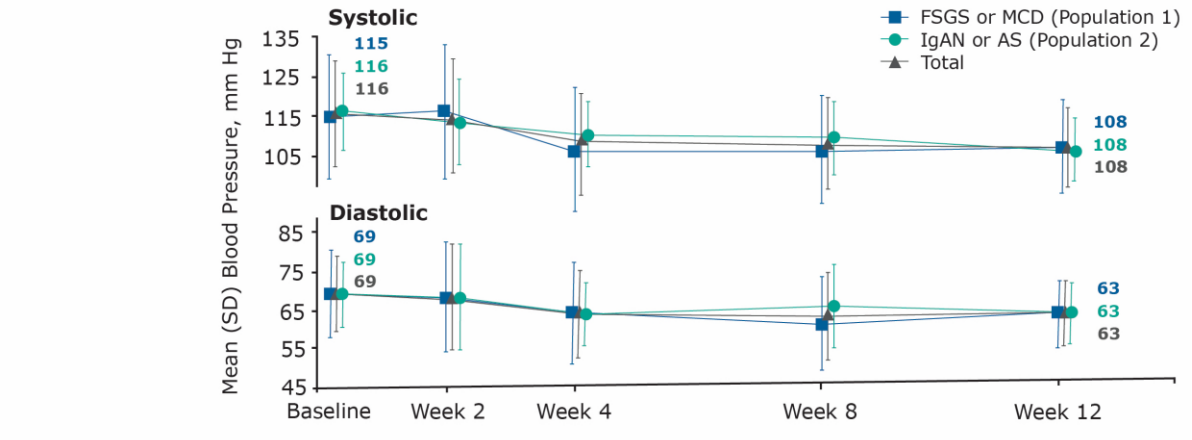
eGFR remained fairly stable throughout the 12-week treatment period (**Figure 3**). The effect of sparsentan on blood pressure is presented in **Figure 4**.[5]

Figure 3. eGFR During 12 Weeks of Sparsentan Treatment



FSGS or MCD	n=13	n=12	n=13	n=13	n=12
IgAN or AS	n=10	n=10	n=9	n=10	n=9
All	N=23	N=22	N=22	N=23	N=21

Figure 4. Effect of Sparsentan on Blood Pressure During 12 Weeks of Treatment



FSGS or MCD (Population 1)	n=13	n=13	n=13	n=13	n=13
IgAN or AS (Population 2)	n=10	n=10	n=9	n=10	n=10
Total	N=23	N=23	N=22	N=23	N=23

Safety

Sparsentan appeared to be safe and well-tolerated by pediatric patients in the EPPIK study. One patient discontinued study treatment due to worsening of nephrotic symptoms. The observed safety profile was consistent with that seen in adult FSGS and IgAN trials. Additional safety information is presented in **Table 4**.[5,10]

Table 4. TEAEs Reported in the EPPIK Study

Patients, n (%)	FSGS or MCD Population 1 (n=13)	IgAN or AS Population 2 (n=10)	Total (N=23)
Any TEAE	**11 (85)**	**7 (70)**	**18 (78)**
Most common TEAEs (≥3 patients in either population)			
Pyrexia	3 (23)	1 (10)	4 (17)
Vomiting	3 (23)	1 (10)	4 (17)
Headache	3 (23)	1 (10)	4 (17)
Blood creatinine increase	3 (23)	–	3 (13)
Any serious TEAE	**4 (31)**	**2 (20)**	**6 (26)**
AKI	0	1 (10)	1 (4)
Nephrotic syndrome	1 (8)	0	1 (4)
Hypotension	1 (8)	0	1 (4)
Fluid retention	1 (8)	0	1 (4)

Abbreviations

AE, adverse event; AKI, acute kidney injury; AT_1, angiotensin II type 1; AS, Alport syndrome; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; ET_A, endothelin-1 type A; FPRE, FSGS partial remission of proteinuria endpoint; FSGS, focal segmental glomerulosclerosis; IgAN, immunoglobulin A nephropathy; IgAV, immunoglobulin A-associated vasculitis; IgAVN, immunoglobulin A-associated vasculitis nephritis; IQR, interquartile range; MCD, minimal change disease; PK, pharmacokinetics; RAAS, renin-angiotensin-aldosterone system; RAASi, renin-angiotensin-aldosterone system inhibitor; SAE, serious adverse event; SD, standard deviation; SBP, systolic blood pressure; SOC, standard of care; TEAE, treatment-emergent adverse event; UACR, urine albumin-to-creatinine ratio; UPCR, urine protein-to-creatinine ratio.

References

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5. Trachtman H, Coppo R, He P, et al. Preliminary findings from the phase 2 EPPIK study of sparsentan in pediatric patients with selected proteinuric glomerular diseases. Oral presentation presented at: ASN Kidney Week; November 2-5, 2023; Philadelphia, PA.
6. Trachtman H, Saleem M, Coppo R, Rheault MN, He P, Komers R. Sparsentan for treatment of pediatric patients with selected proteinuric glomerular diseases: Design of the phase 2 EPPIK study. Poster presented at: American Society of Nephrology Kidney Week; November 4-7, 2021; San Diego, California.
7. Nagasawa H, Suzuki H, Jenkinson C, et al. Sparsentan, the dual endothelin angiotensin receptor antagonist (DEARA), attenuates albuminuria and protects from the development of renal injury to a greater extent than losartan in the gddY mouse model of IgA nephropathy: A 16-week study. Mini oral presented at: ERA-EDTA Congress; May 19-22, 2022; Paris, France.
8. Nagasawa H, Suzuki H, Jenkinson C, et al. The dual endothelin type A receptor (ET_AR) and angiotensin II type 1 receptor (AT_1R) antagonist, sparsentan, protects against the development of albuminuria and glomerulosclerosis in the gddY mouse model of IgA nephropathy. Poster presented at: ERA-EDTA Virtual Congress; June 6-9, 2020; Virtual Meeting.
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10. Trachtman H, Coppo R, He P, et al. Preliminary findings from the phase 2 EPPIK study of sparsentan in pediatric patients with selected proteinuric glomerular diseases. Abstract presented at: ASN Kidney Week; November 2-5, 2023; Philadelphia, PA.