

Sparsentan

Pediatric Patients in Sparsentan FSGS Studies

Summary

- Sparsentan is an investigational therapeutic candidate for the treatment of FSGS^{1,2}

Prescribing Information

- FILSPARI (sparsentan) 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 progression³
- The safety and efficacy of FILSPARI in pediatric patients have not been established³

Background

- Sparsentan is a novel, first-in-class, and the only single molecule antagonist of the ET_A and AT₁ receptors^{2,4,5}
- The DUET study is a phase 2, randomized, multicenter, double-blind, active-control trial examining the safety and efficacy of sparsentan compared to irbesartan in patients aged 8 to 75 years with FSGS²
- The DUPLEX study is a global, randomized, multicenter, double-blind, active-controlled, phase 3 trial assessing the efficacy and safety of sparsentan as compared to irbesartan in 371 patients, ages 8 to 75 years, with primary and genetic FSGS⁶
- The EPPIK study is an open-label, single-arm, multicenter phase 2 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 syndrome⁷

Study Data

- Among 26 patients aged <21 years in the DUET OLE, 10 (38%) experienced at least one complete remission of proteinuria, defined as UPCR ≤0.3 g/g, during the study period⁸
- In the DUET OLE, FPRE was achieved by 37% of young patients at 1 year, 62% at 2 years, 58% at 3 years, and 44% at 4 years⁸
- The DUPLEX study includes 35 patients aged 9 to <18 years. Analyses specific to this subgroup have not been conducted⁶
- In the EPPIK study, over 12 weeks of sparsentan treatment, pediatric patients with FSGS (n=6) experienced a 27.3% mean change from baseline in proteinuria⁷
- Sparsentan appeared to be well tolerated⁹

Prescribing Information

The safety and efficacy of FILSPARI in pediatric patients have not been established.³

For more information, please refer to the [Prescribing Information](#), including Boxed Warning.

Background

Sparsentan is a novel, first-in-class, and the only single molecule antagonist of the ET_A and AT₁ receptors.^{2,4,5} Preclinical studies in rodent models of chronic kidney disease have shown that blockade of both ET_A and AT₁ pathways reduces proteinuria, protects podocytes, and prevents glomerulosclerosis and mesangial cell proliferation.¹⁰⁻¹²

The DUET Study

The DUET study ([NCT01613118](#)) is a phase 2, randomized, multicenter, double-blind, active-control trial in patients aged 8 to 75 years with biopsy-proven FSGS. Patients were randomized to 1 of 3 doses (200, 400, or 800 mg/day) of sparsentan or irbesartan (300 mg/day) and maintained through an 8-week double-blind phase. The primary endpoint was defined as reduction in UPCR after 8 weeks of treatment. The proportion of patients who achieved partial FSGS remission was evaluated as a secondary endpoint. Following the double-blind phase, patients had the option to continue into a 144-week OLE of treatment with sparsentan.²

The DUPLEX Study

The DUPLEX study ([NCT03493685](#)) is a global, randomized, multicenter, double-blind, active-controlled, phase 3 trial examining the safety and efficacy of sparsentan as compared to irbesartan in patients aged 8 to 75 years with biopsy-proven FSGS. Patients with UPCR ≥ 1.5 g/g at screening, eGFR ≥ 30 mL/min/1.73 m², and mean seated BP $\geq 100/60$ mm Hg (patients ≥ 18 years) or above the 5th percentile for sex and height (< 18 years) were eligible. After a 2-week washout period, 371 patients were randomized to receive either sparsentan or irbesartan, and subsequently dose titrated over 2 weeks to the maximum dose of either 800 mg/day sparsentan or 300 mg/day irbesartan, as tolerated.^{1,13} Patients remained on maintenance doses of sparsentan or irbesartan during a 108-week double blind phase. Standard-of-care treatment, including RAASi, was resumed in Weeks 108-112. The primary efficacy endpoint was eGFR slope over 108 weeks of treatment, defined as eGFR total slope from Day 1 to Week 108 of treatment and eGFR chronic slope from Week 6 to Week 108 (following the initial acute effect of randomized treatment). The key secondary endpoint was percent change in eGFR from baseline to 4 weeks post-cessation of randomized treatment at Week 112.¹³ An additional interim endpoint was the proportion of patients achieving partial remission of proteinuria, defined as UPCR ≤ 1.5 g/g and a $>40\%$ reduction (FPRE) at Week 36. Proportion of patients achieving complete remission of proteinuria (UPCR < 0.3 g/g) at any time in the double-blind period was also examined. Safety was assessed by double-blind monitoring of adverse events and safety endpoints.^{1,13}

The EPIIK Study

The EPIIK study ([NCT05003986](#)) is a phase 2, global, open-label, single-arm, multicenter cohort study to evaluate the safety, efficacy, and PK of a once-daily oral suspension of sparsentan in

pediatric patients with selected proteinuric glomerular diseases. The primary objective of the EPIIK study is to examine long-term antiproteinuric and nephroprotective potential and safety in this pediatric population.¹⁴ Approximately 57 pediatric patients aged ≥ 1 to < 18 years will be enrolled. EPIIK 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. Target exposure of sparsentan is equivalent to 800 mg in Population 1 and 400 mg in Population 2. 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.^{7,9,14}

Study Data

The DUET Study

The DUET OLE included 26 patients aged < 21 years who received at least one dose of sparsentan (**Table 1**). Of these, 23% had nephrotic syndrome in their medical history or at baseline and 73% had nephrotic range proteinuria at baseline, defined as UPCR ≥ 2.0 g/g in patients age < 18 years and ≥ 3.5 g/g in patients aged 18-21 years. Baseline mean eGFR was 91.4 mL/min/1.73 m² (range: 30-212 mL/min/1.73 m²).⁸

Table 1. Demographics and Disease Characteristics at Baseline in Patients Age ≤ 21 Years

	All Sparsentan (n=26)
Age, years, mean\pmSD/median (min, max)	15.0 \pm 4.0 / 16.0 (8, 21)
Female, n (%)	14 (54)
Race, n (%)	
White	19 (73)
Black or African American	5 (19)
Other	2 (8)
Blood pressure, mmHg, mean\pmSD	
Systolic	124.8 \pm 13.3
Diastolic	78.4 \pm 9.2
UPCR, g/g, mean\pmSD/median (min, max)	4.9 \pm 3.9 / 3.6 (1.0, 14.0)
Documented nephrotic syndrome in medical history or at baseline, n (%)	6 (23)
Nephrotic range proteinuria*, n (%)	19 (73)
eGFR, mL/min/1.73 m², mean\pmSD/median (min, max)	91.4 \pm 55.1 / 74.7 (30, 212)
Any immunosuppressive treatment for renal indications at baseline, n (%)	12 (46)
Steroids	5 (19)
CNI	9 (35)
MMF	4 (15)
ACEi or ARB use before washout, n (%)	20 (77)
≥ 1 diuretic or antihypertensive agent, n (%)	11 (42)
Diuretic use, n (%)	9 (35)
Additional antihypertensive treatments (not RAASi), n (%)	6 (23)
Age at FSGS diagnosis, years, mean\pmSD/median (IQR)	12.2 \pm 5.6 / 14.5 (8.0, 16.8)
Time from FSGS diagnosis to informed consent, years, mean\pmSD/median (IQR)	3.2 \pm 3.9 / 1.9 (0.8, 4.6)

UPCR measured in first morning void samples. eGFR derived using the Modified Schwartz formula for patients age < 18 years and the Modification of Diet in Renal Disease Formula for patients aged 18-21 years.

*UPCR > 2.0 g/g in patients aged < 18 years; 3.5 g/g in patients aged 18-21 years.

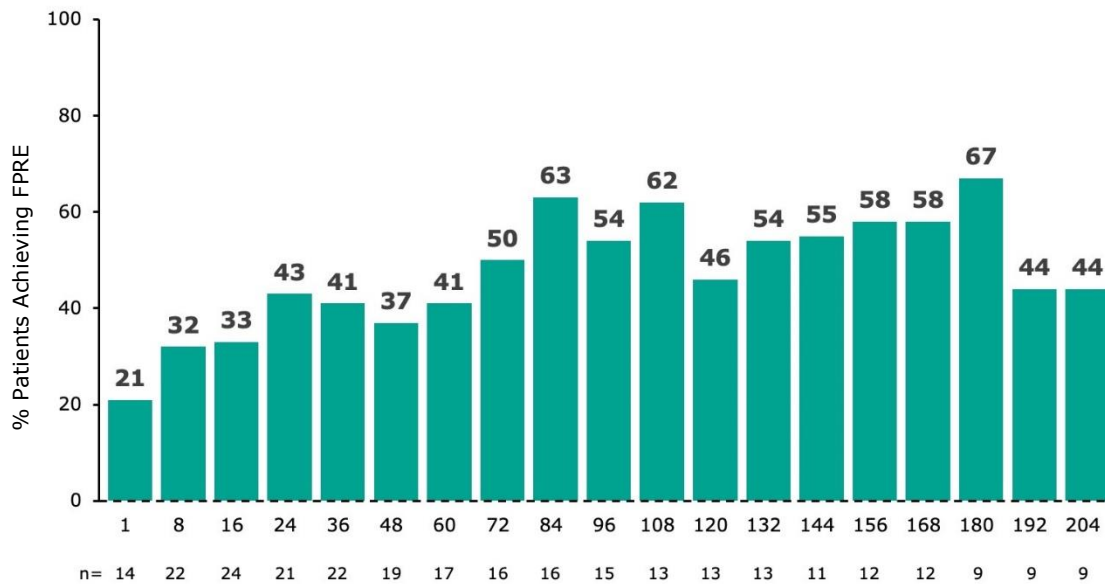
Among the 26 young patients, 10 (38%) experienced at least one complete remission of proteinuria, defined as UPCR ≤ 0.3 g/g, during the study period. Mean UPCR and change from baseline at 24-week timepoints is presented in **Table 2**. FPRE was achieved by 37% of patients at 1 year, 62% at 2 years, 58% at 3 years, and 44% at 4 years (**Figure 1**).⁸

Table 2. Median UPCR and Change From Baseline in UPCR Every 24 Weeks in Patients Age ≤ 21 Years

Study Week	n	UPCR, g/g		Median (IQR) % Change From Baseline
		Median (IQR)	Median (IQR) Change From Baseline	
Baseline	26	2.9 (1.7, 5.1)	-	-
24	21	1.5 (0.6, 2.6)	-0.8 (-1.4, -0.3)	-42.1 (-72.1, -8.72)
72	16	0.9 (0.4, 2.9)	-1.1 (-2.4, -0.3)	-68.0 (-87.0, -21.6)
96	15	1.4 (0.4, 3.3)	-1.2 (-2.4, -0.5)	-57.3 (-72.6, -15.5)
120	13	1.5 (0.4, 2.3)	-1.3 (-2.6, -0.8)	-58.2 (-85.4, -25.1)
144	11	1.5 (0.1, 1.9)	-1.3 (-2.5, -0.8)	-62.6 (-91.5, -31.9)
168	12	1.2 (0.2, 2.9)	-1.3 (-1.5, -0.3)	-47.4 (-91.8, -7.3)
192	9	1.3 (0.8, 2.3)	-1.2 (-1.5, -0.4)	-54.8 (-72.9, -12.0)

UPCR measured in first morning void samples.

Figure 1. Percentage of Patients Achieving FPRE by Visit in Patients Age ≤ 21 Years



Percentage of patients achieving the FSGS partial remission endpoint (FPRE; UPCR ≤ 1.5 g/g and $>40\%$ reduction in UPCR from baseline) by assessment of UPCR at a given visit. Only on-treatment observations (defined as occurring within 1 day of last sparsentan dose) are included. Percentage is calculated as the number of patients achieving FPPE divided by the number of patients with available FPPE results at the visit.

Sparsentan appeared to be well tolerated over 240 weeks of treatment in young patients with FSGS. The most common TEAEs were hyperkalemia, vomiting, and nausea. No deaths occurred during sparsentan treatment.⁸

Summary	PI	Background	Study Data	Abbreviations	References
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The DUPLEX Study

A total of 371 patients enrolled in the DUPLEX study. The study population included 35 pediatric patients aged 8 to <18 years.¹³

Analyses specific to this subgroup have not been conducted.

The EPIIK Study

Patient Selection

Key eligibility criteria for the EPIIK study are provided in **Table 3**.¹⁴

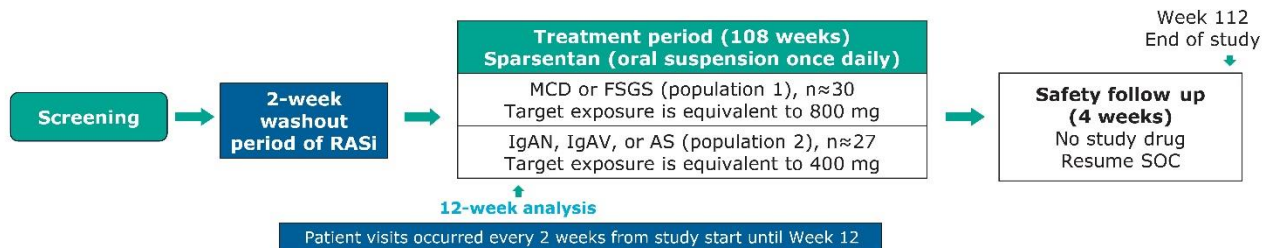
Table 3. EPIIK Study Inclusion and Exclusion Criteria

Key Inclusion Criteria	
All Patients	eGFR ≥ 30 mL/min/1.73 m ² at screening
	Mean seated blood pressure 5 th to 95 th 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 2**).^{7,14}

Figure 2. EPIK 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.¹⁴

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 4**). 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.¹⁴

Table 4. 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						
10 to <20	0.625 mL	1.25 mL	2.5 mL (200 mg)	Not Applicable		
7 to <10	0.313 mL	0.625 mL	1.25 mL (100 mg)			

Bold indicates starting doses.

Preliminary Study Results

Baseline Characteristics

At data cutoff (February 15, 2024), 34 pediatric patients enrolled in the EPIK study have received ≥ 1 dose of sparsentan oral suspension. Safety and efficacy were assessed over 12 weeks of treatment. Population 1 included 10 patients with MCD and 11 patients with FSGS; Population 2 included 4 patients with IgAN/IgAV and 9 patients with Alport syndrome. Additional baseline characteristics are presented in [Table 5](#).⁷

Table 5. EPIK Baseline Characteristics Per Patient Population

Characteristic	Population 1		Population 2		Total (n=34)
	MCD (n=10)	FSGS (n=11)	IgAN/IgAV* (n=4)	AS (n=9)	
Male sex, n (%)	5 (50.0)	3 (27.3)	2 (50.0)	8 (88.9)	18 (52.9)
Age [†] , median (IQR), years	7.5 (6.0-11.0)	5.0 (3.0-14.0)	13.0 (9.5-13.5)	12.0 (11.0-14.0)	8.5 (6.0-13.0)
White, n (%)	9 (90.0)	9 (81.8)	3 (75.0)	4 (44.4)	25 (73.5)
UPCR, median (IQR), g/g	2.75 (2.13-3.61)	4.91 (4.33-11.28)	2.27 (0.67-3.18)	2.61 (2.30-3.74)	3.08 (2.36-4.98)
Nephrotic-range proteinuria (UPCR >2 g/g), n (%)	8 (80.0)	10 (90.9)	2 (50.0)	8 (88.9)	28 (82.4)
eGFR, mean (SE), mL/min/1.73 m ²	149.2 (14.95)	73.9 (6.14)	127.0 (22.66)	89.3 (10.42)	106.4 (8.04)
Immunosuppressant use at baseline, n (%)	5 (50.0)	6 (54.5)	2 (50.0)	0 (0.0)	13 (38.2)
Blood pressure systolic/diastolic, mean (SE), mm Hg	110.4 (4.52)/66.1 (2.92)	114.3 (4.08)/75.0 (9.78)	117.5 (9.90)/68.0 (2.55)	110.4 (1.98)/67.9 (3.27)	112.5 (2.18)/69.7 (1.62)

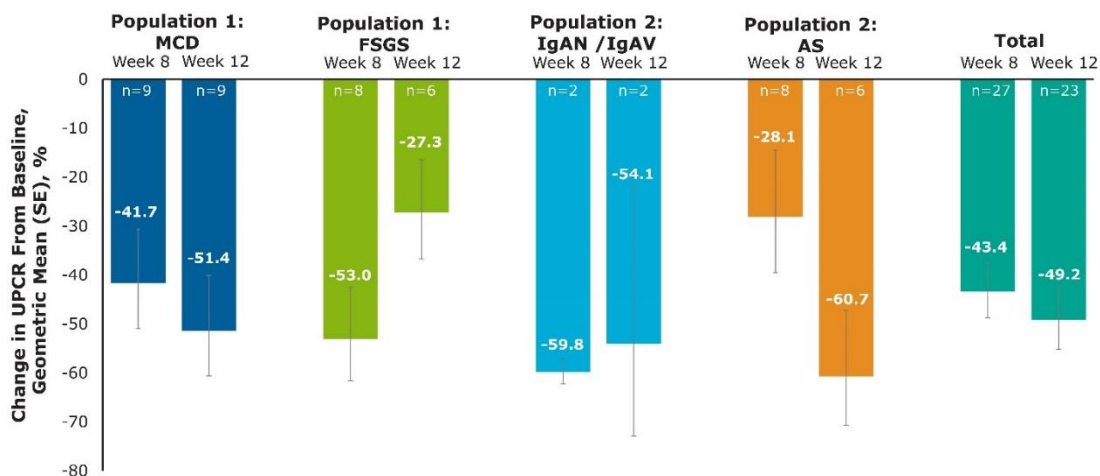
*One patient with IgAV.

[†]At screening.

Efficacy

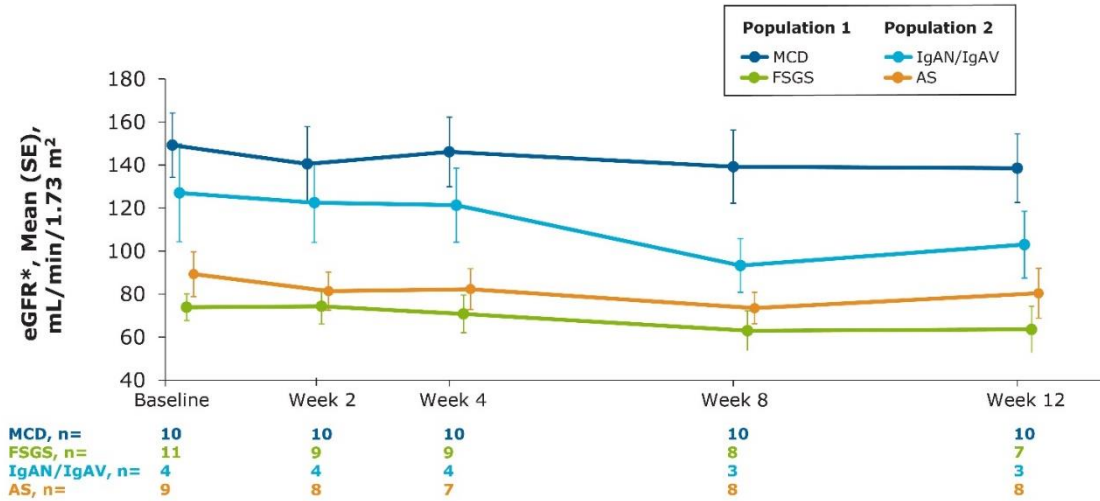
Over 12 weeks of sparsentan treatment, UPCR from baseline was decreased in all subpopulations. In patients with FSGS (n=6), mean reduction in UPCR from baseline at 12 weeks was 27.3% ([Figure 3](#)).⁷

Figure 3. UPCR Reduction Over 12 Weeks of Sparsentan Treatment



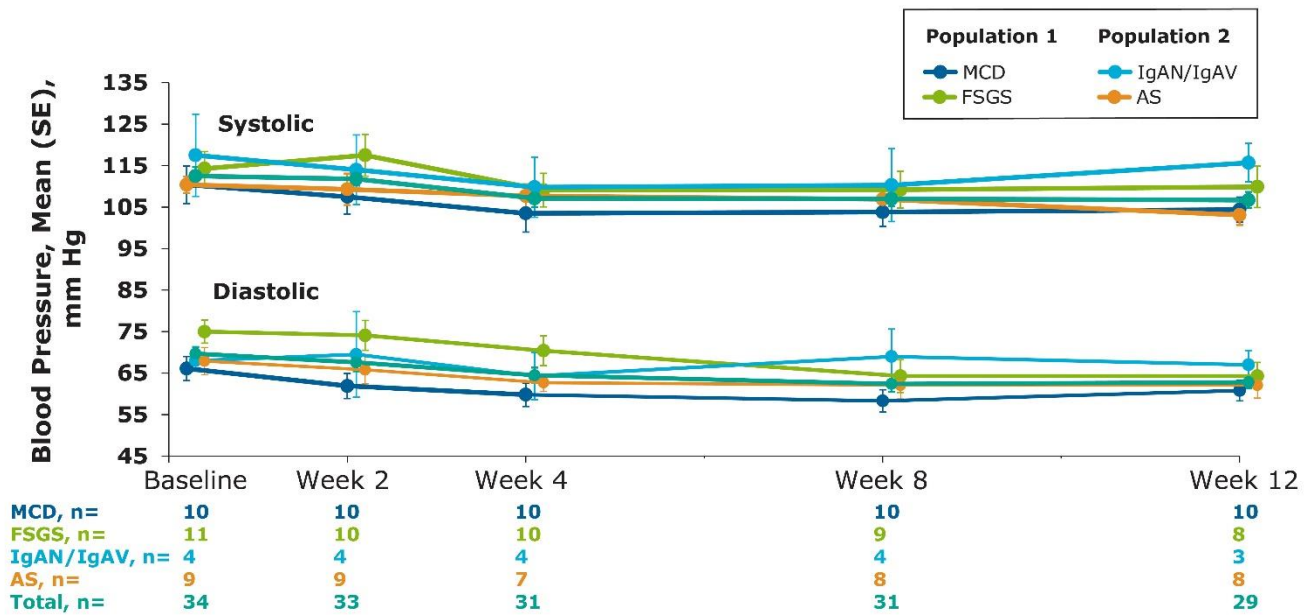
Both eGFR and blood pressure remained fairly stable throughout the 12-week treatment period (Figure 4; Figure 5).⁷

Figure 4. eGFR During 12 Weeks of Sparsentan Treatment



*eGFR determined using the modified Schwartz formula.

Figure 5. Mean Blood Pressure Change From Baseline



Safety

Sparsentan oral formulation appeared to be well tolerated by pediatric patients in the EPPIK study. Ten serious TEAEs were reported in 6 patients, and 1 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.^{7,9}

Abbreviations

ACEi, angiotensin-converting enzyme inhibitor; AE, adverse event; ARB, angiotensin receptor blocker; AS, Alport syndrome; AT₁, angiotensin II type 1; BP, blood pressure; CNI, calcineurin inhibitor; eGFR, estimated glomerular filtration rate; ET_A, endothelin-1 type A; FPRE, FSGS partial remission endpoint; FSGS, focal segmental glomerulosclerosis; IgA, immunoglobulin A; IgAN, immunoglobulin A nephropathy; IgAV, IgA vasculitis; IQR, interquartile range; MCD, minimal change disease; MMF, mycophenolate mofetil; OLE, open-label extension; PK, pharmacokinetics; RAAS, renin-angiotensin-aldosterone system; RAASi, renin-angiotensin-aldosterone system inhibitor; SAE, serious adverse event; SD, standard deviation; SE, standard error; SOC, standard of care; TEAE, treatment-emergent adverse event; UACR, urine albumin-to-creatinine ratio; UPCR, urine protein-to-creatinine ratio.

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