FILSPARI® (sparsentan)

Pediatric Patients in Sparsentan FSGS Studies

Summary

Background

- Sparsentan is an investigational therapeutic candidate for the treatment of FSGS[1]
- Sparsentan is a novel, first-in-class, and the only single molecule antagonist of the ET_A and AT_1 receptors[1-3]
- 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 FSGS[1]
- 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[4,5]
- 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 FSGS[6]

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 period[7]
- 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 years[7]
- In pediatric patients with a range of proteinuric glomerular diseases, sparsentan treatment resulted in reductions in proteinuria over the initial 12 weeks of treatment[4]
- The DUPLEX study includes 35 patients aged 9 to <18 years. Analyses specific to this subgroup have not been conducted[6]
- Sparsentan appeared to be safe and well-tolerated[4]

Background

Sparsentan is a novel, first-in-class, and the only single molecule antagonist of the ET_A and AT_1 receptors.[1-3] 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.[8-10]

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.[1]

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.[5] 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.[4,5]

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 m^2, and mean seated BP ≥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.[11,12] 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.[11] 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.[11,12]

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 m^2 (range: 30-212 mL/min/1.73 m^2).[7]

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

	All Sparsentan (n=26)
Age, years, mean±SD/median (min, max)	15.0±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±SD	
Systolic	124.8±13.3
Diastolic	78.4±9.2
UPCR, g/g, mean±SD/median (min, max)	4.9±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 m^2, mean±SD/median (min, max)	91.4±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±SD/median (IQR)	12.2±5.6 / 14.5 (8.0, 16.8)
Time from FSGS diagnosis to informed consent, years, mean±SD/median (IQR)	3.2±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.

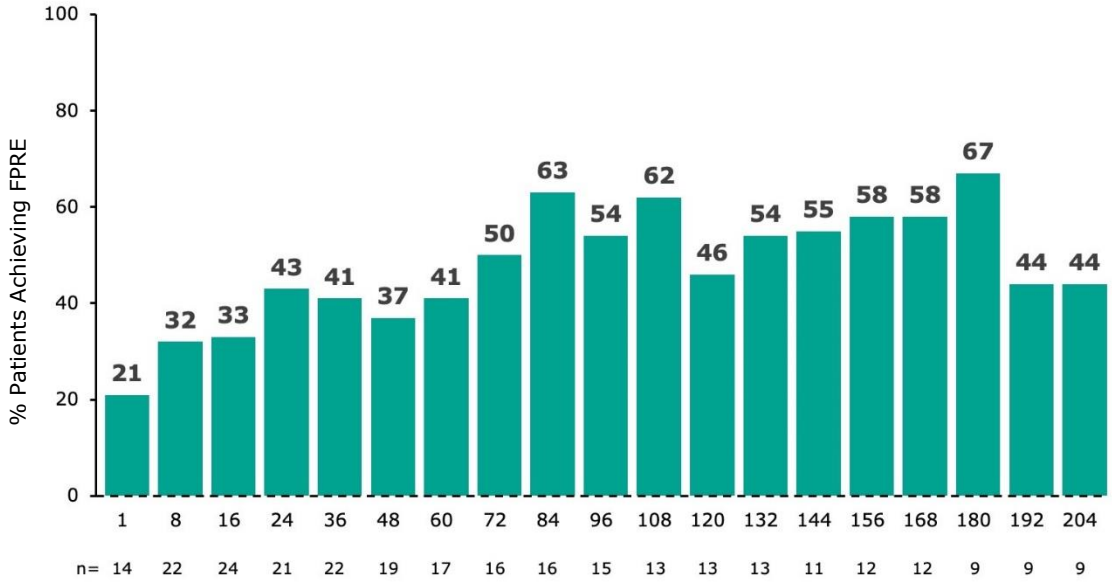
Among the 26 young patients, 10 (38%) experienced at least one complete remission of proteinuria, defined as UPCR ≤0.3 g/g, during the study period. Mean UPCR and change from baseline at 24-week timepoints is presented in **Table 2**. FPRE was achieved by 37% of patients at 1 year, 62% at 2 years, 58% at 3 years, and 44% at 4 years (**Figure 1**).[7]

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 FPRE divided by the number of patients with available FPRE results at the visit.

Sparsentan appeared safe and 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.[7]

The EPPIK Study

Patient Selection

Key eligibility criteria for the EPPIK study are provided in **Table 3**.[5]

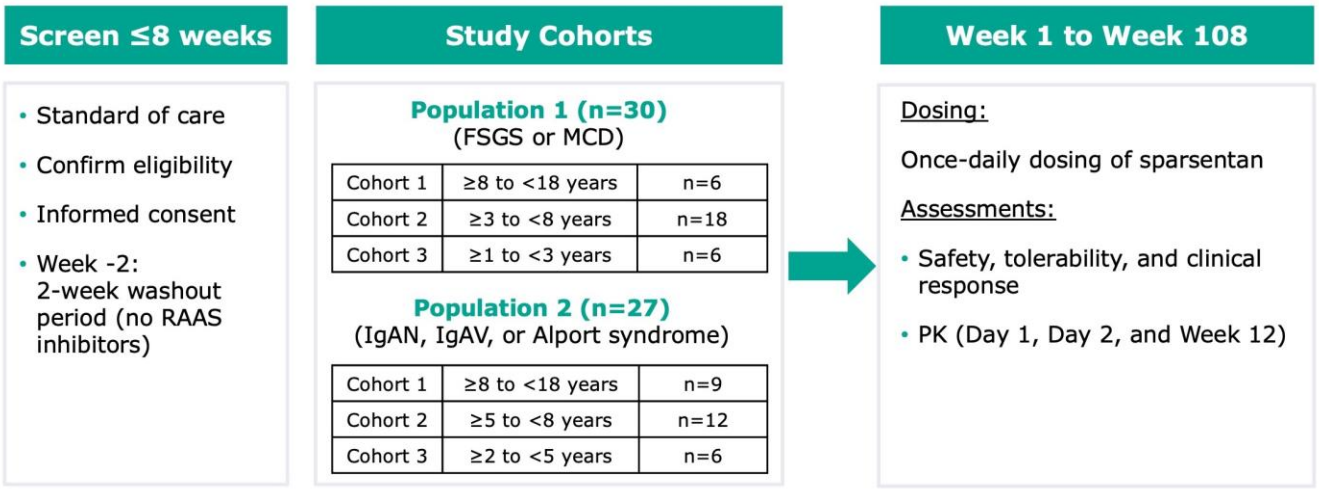
Table 3. EPPIK Study Inclusion and Exclusion Criteria

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 2**).[4,5]

Figure 2. 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.[5]

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.[5]

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				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.

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.[4,5] Safety and efficacy were assessed over 12 weeks of treatment.[4]

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 5**.[4]

Table 5. EPPIK Patient Baseline Characteristics

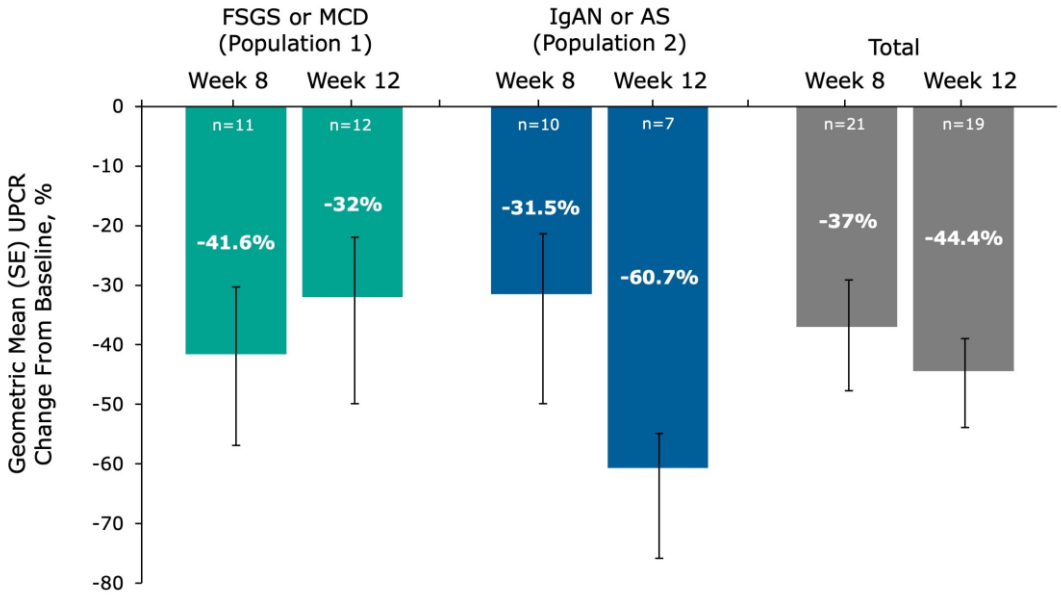
Characteristic	Population 1 MCD or FSGS (n=13)	Population 2 IgAN or Alport Syndrome (n=10)	Total (N=23)
Diagnosis, n (%)			
MCD	8 (61.5)	0	8 (34.8)
FSGS	5 (38.5)	0	5 (21.7)
IgAN	0	3 (30)	3 (13)
Alport syndrome	0	7 (70)	7 (30.4)
IgAVN	0	0	0
Male sex, n (%)	8 (61.5)	8 (80)	16 (69.6)
Age, years*, median (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 3**).[4]

Figure 3. UPCR Reduction Over 12 Weeks of Sparsentan Treatment



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

Figure 4. eGFR During 12 Weeks of Sparsentan Treatment

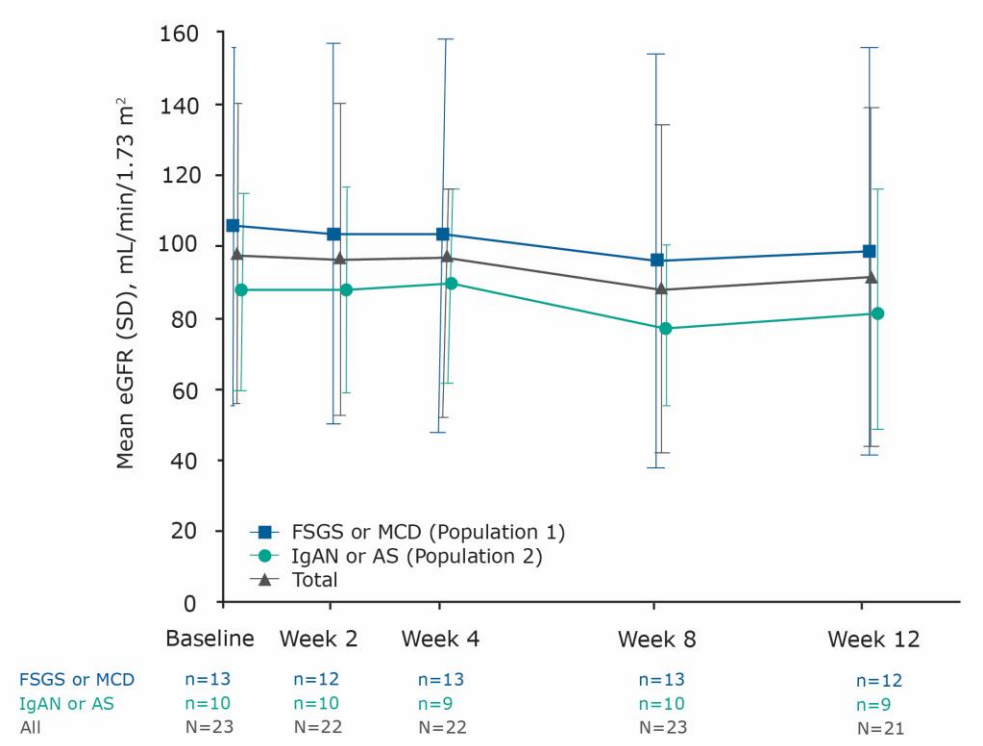
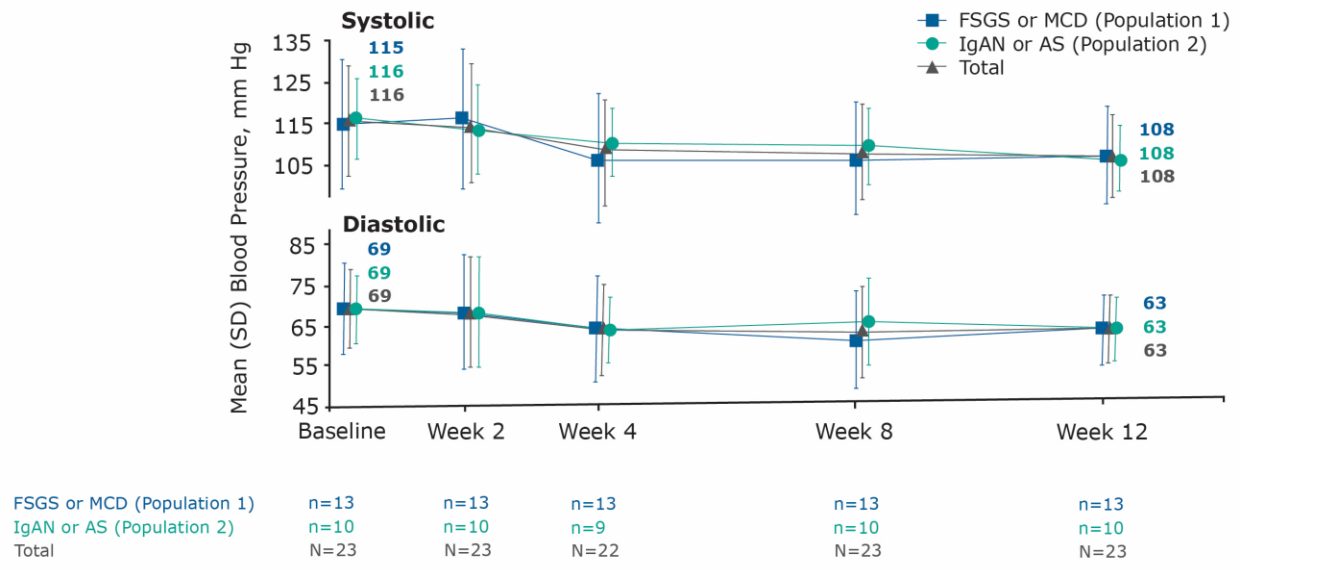


Figure 5. Effect of Sparsentan on Blood Pressure During 12 Weeks of Treatment



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.[4,13]

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.[11]

Analyses specific to this subgroup have not been conducted.

Abbreviations

ACEi, angiotensin-converting enzyme inhibitor; AE, adverse event; ARB, angiotensin receptor blocker; AT_1, angiotensin II type 1; 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; TEAE, treatment-emergent adverse event; UACR, urine albumin-to-creatinine ratio; UPCR, urine protein-to-creatinine ratio.

References

1. Trachtman H, Nelson P, Adler S, et al. DUET: A phase 2 study evaluating the efficacy and safety of sparsentan in patients with FSGS. *J Am Soc Nephrol*. 2018;29(11):2745-2754. doi:10.1681/ASN.2018010091
2. Komers R, Gipson DS, Nelson P, et al. Efficacy and safety of sparsentan compared with irbesartan in patients with primary focal segmental glomerulosclerosis: Randomized, controlled trial design (DUET). *Kidney Int Rep*. 2017;2(4):654-664. doi:10.1016/j.ekir.2017.02.019
3. Raczynska A, Pawlowicz-Szlarska E, Nowicki M. Sparsentan–a dual antagonist–literature review on endothelin and endothelin antagonists. *Nephrol Dial Pol*. 2021;25:77-82.
4. 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.
5. 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.
6. Data on file. Travere Therapeutics Inc; 2023.

7. Lieberman K, Paredes A, Srivastava T, Komers R, Murphy E, Trachtman H. Long-term efficacy and safety of sparsentan in young patients with FSGS: 240-week analysis of the DUET open-label extension (OLE). Poster presented at: World Congress of Nephrology; March 30-April 2, 2023; Bangkok, Thailand.
8. 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. Abstract presented at: ERA-EDTA Congress; May 19-22, 2022; Paris, France.
9. 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.
10. Bedard P, Jenkinson C, Komers R. Sparsentan protects the glomerular basement membrane and glycocalyx, and attenuates proteinuria in a rat model of focal segmental glomerulosclerosis (FSGS). Abstract presented at: ERA-EDTA Congress; May 19-22, 2022; Paris, France.
11. Rheault MN, Alpers CE, Barratt J, et al. Sparsentan versus irbesartan in focal segmental glomerulosclerosis. *N Engl J Med*. Published online November 3, 2023;doi:10.1056/NEJMoa2308550
12. Komers R, Diva U, Inrig JK, Loewen A, Trachtman H, Rote WE. Study design of the phase 3 sparsentan versus irbesartan (DUPLEX) study in patients with focal segmental glomerulosclerosis. *Kidney Int Rep*. 2020;5(4):494-502. doi:10.1016/j.ekir.2019.12.017
13. 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.