FILSPARI® (sparsentan)

Effect on Proteinuria in Focal Segmental Glomerulosclerosis

Summary

Background

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

Study Data

The DUET Study

- In the phase 2 DUET study, patients taking sparsentan experienced significantly greater reduction in proteinuria after 8 weeks of double-blind treatment than patients taking irbesartan (44.8% vs 18.5%; *P*=0.006)[3]
- In the DUET OLE, the clinically meaningful endpoint FPRE (UPCR ≤1.5 g/g and >40% reduction in UPCR from baseline) was observed in 45.8% of patients after year 1, 59.1% after year 2, 59.3% after year 3, and 68.1% after year 4. Additionally, 43% of OLE patients experienced complete remission of proteinuria, defined as UPCR ≤0.3 g/g, at least one time over 240 weeks[5]

The DUPLEX Study

- At 36 weeks, 42% of patients on sparsentan achieved FPRE (defined as UPCR ≤1.5 g/g and a >40% reduction in UPCR) compared with 26% on irbesartan. This effect was maintained through 108 weeks as 37.5% of patients on sparsentan achieved FPRE compared with 22.6% on irbesartan[6]
- At 108 weeks, the least-squares geometric mean reduction in UPCR from baseline was 50% for sparsentan compared to 32.3% for irbesartan[6]
- Complete remission of proteinuria (UPCR <0.3 g/g at any time during the double-blind period) was achieved more frequently with sparsentan (18.5%) than with irbesartan (7.5%)[6]

The EPPIK Study

- In pediatric patients with a range of proteinuric glomerular diseases, sparsentan treatment resulted in reductions in proteinuria over the initial 12 weeks of treatment[7]

Safety

- Sparsentan has been generally well-tolerated in clinical trials, with a safety profile comparable to irbesartan[8,9]

Background

Sparsentan is an investigational therapeutic candidate for the treatment of FSGS[3,4]

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.[10-12]

The DUET Study

The DUET study (NCT01613118) is a phase 2, randomized, multicenter, double-blind, active-control trial in patients 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.[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.[4,6] 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.[6] 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.[4,6]

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.[13] 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.[7,13]

Study Data

The DUET Study

Efficacy

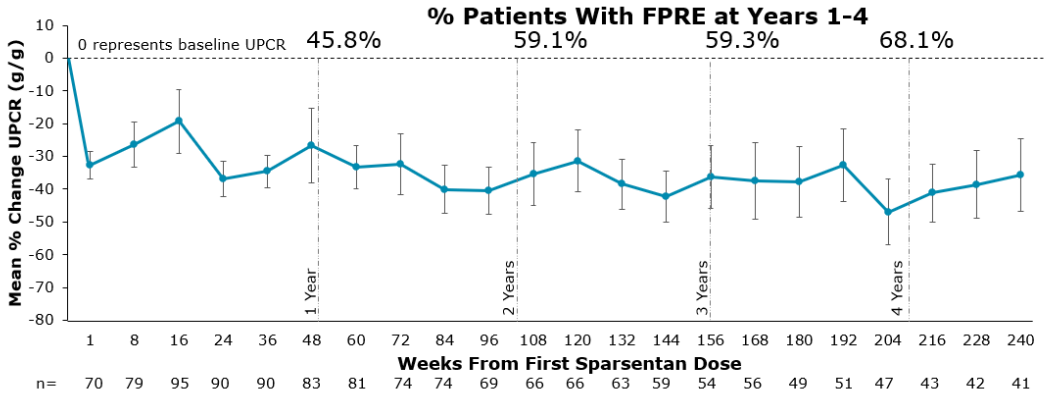
Primary Endpoint

In the phase 2 DUET study, patients taking sparsentan experienced significantly greater reduction in proteinuria after 8 weeks of double-blind treatment than patients taking irbesartan (44.8% vs 18.5%; *P*=0.006).[3]

Open-label Extension

In the OLE, FPRE (UPCR ≤1.5 g/g and >40% reduction in UPCR from baseline) was observed in 45.8% of patients after year 1, 59.1% after year 2, 59.3% after year 3, and 68.1% after year 4, demonstrating sustained proteinuria reduction among patients enrolled in the OLE. Additionally, 43% of OLE patients experienced complete remission of proteinuria, defined as UPCR ≤0.3 g/g, at least one time over 240 weeks (**Figure 1**).[5]

Figure 1. DUET OLE: Mean Percent Change From Baseline in UPCR by Visit



43% of patients experienced ≥1 complete remission of proteinuria at any time

Error bars show SE. Only on-treatment observations (defined as occurring within 1 day of last sparsentan dose) are included. FPRE (UPCR ≤1.5 g/g and >40% reduction in UPCR from baseline).

Pediatric Patients

The DUET OLE included 26 patients aged <21 years who received at least one dose of sparsentan. 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).[14]

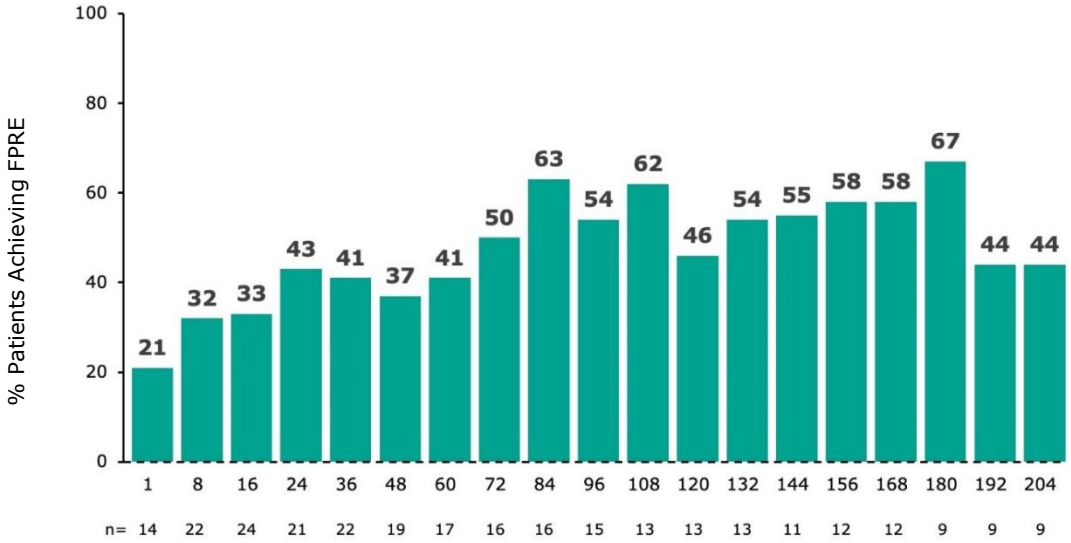
Among the 26 young patients, 10 (38%) experienced at least one complete remission of proteinuria, defined as UPCR <0.3 g/g, during the study period. Median UPCR and change from baseline at 24-week timepoints is presented in **Table 1**. FPRE was achieved by 37% of patients at 1 year, 62% at 2 years, 58% at 3 years, and 44% at 4 years (**Figure 2**).[14]

Table 1. 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 2. 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.

Safety

Overall, incidence of TEAEs, drug-related TEAEs, serious TEAEs, and the number of study withdrawals were similar between the sparsentan and irbesartan groups.[3] Analysis of OLE data found no new or unexpected safety signals.[5]

The DUPLEX Study

Efficacy

Primary Efficacy Endpoint

Sparsentan did not achieve the primary efficacy eGFR slope endpoint over 108 weeks of treatment.[6]

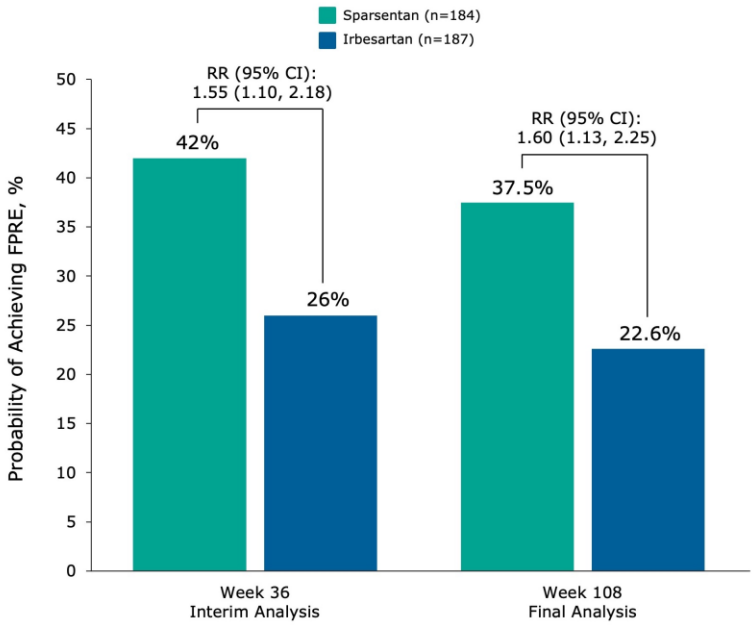
Secondary and Exploratory Endpoints

Secondary and exploratory endpoints in the study trended favorably for sparsentan at both the 36-week interim analysis and analysis after 108 weeks of treatment.

FPRE and UPCR

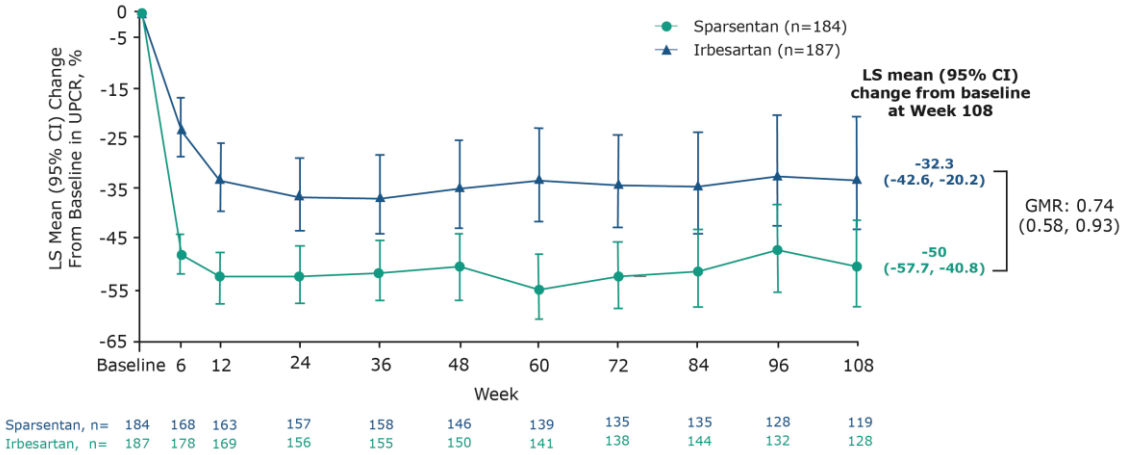
Analysis included an interim efficacy endpoint, the proportion of patients achieving FPRE, defined as UPCR ≤1.5 g/g and a >40% reduction in UPCR from baseline at Week 36 (**Figure 3**). Sparsentan achieved a statistically significant response on the interim proteinuria endpoint at Week 36 compared to irbesartan, with 42% of patients receiving sparsentan experiencing FPRE vs 26% of irbesartan-treated patients (P=0.009).[6,15] Analysis of the full data set at 108 weeks showed that the response was sustained, as 37.5% of patients on sparsentan achieved FPRE compared with 22.6% on irbesartan (RR, 1.60; 95% CI, 1.13 to 2.25). In the 112 week analysis, median time to first achieving FPRE was 14.1 weeks with sparsentan and 109.0 weeks with irbesartan.[6]

Figure 3. More Patients Taking Sparsentan Achieved FPRE



The least-squares geometric mean reduction in UPCR from baseline was 50% for sparsentan compared to 32.3% for irbesartan (ratio of percent reduction, 0.74; 95% CI, 0.58 to 0.93) (**Figure 4**).[6]

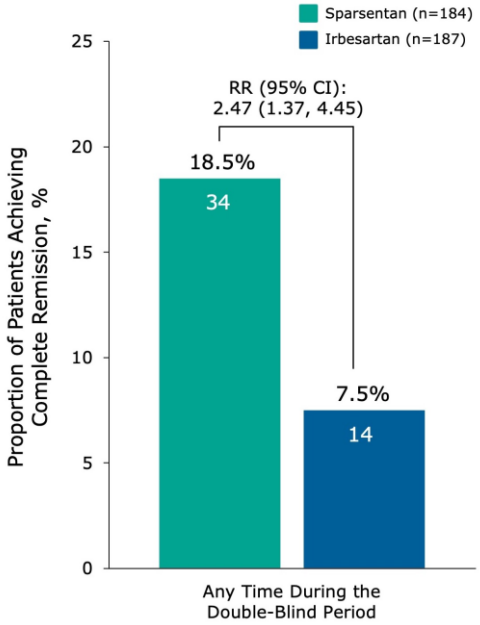
Figure 4. Decline in UPCR Through 108 Weeks of Sparsentan Treatment



Complete Remission of Proteinuria

After 108 weeks of treatment, 34 patients (18.5%) in the sparsentan group achieved complete remission of proteinuria (UPCR <0.3 g/g) at any time in the double-blind period, compared to 14 patients (7.5%) in the irbesartan group (**Figure 5**).[6]

Figure 5. Proportion of Patients Achieving Complete Remission of Proteinuria



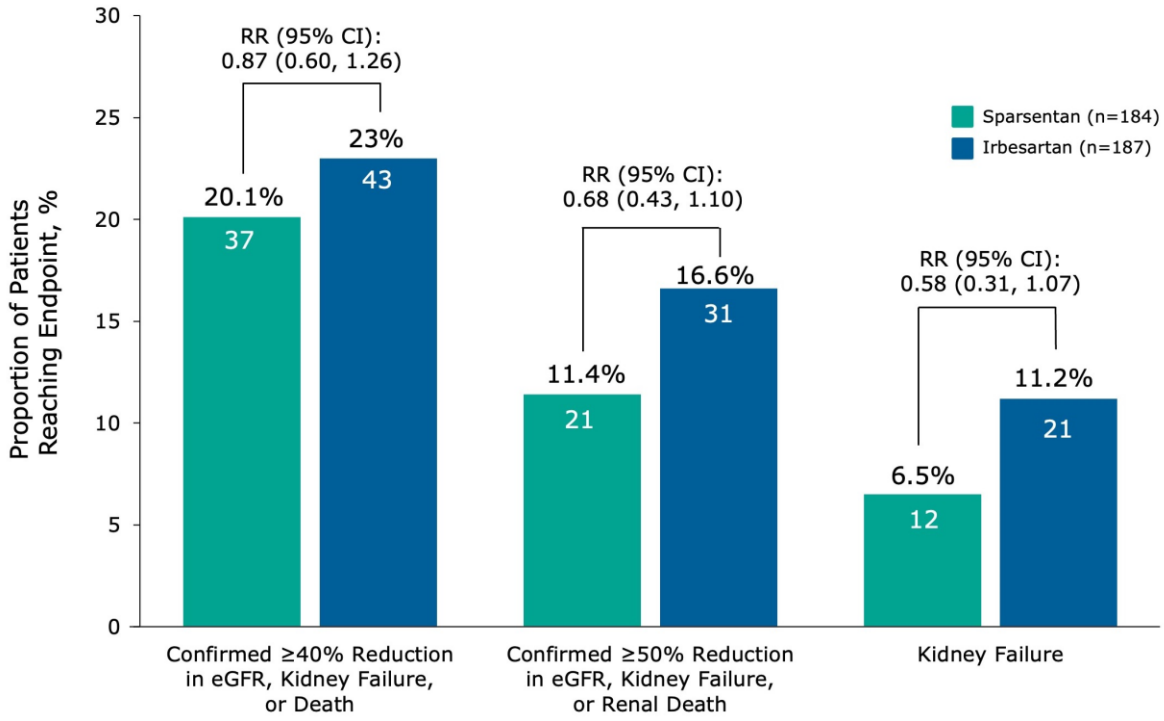
Complete remission defined as UPCR <0.3 g/g.

Patients taking sparsentan achieved complete remission earlier in the course of treatment than patients taking irbesartan. With sparsentan treatment, 29 (85.3%) patients who achieved complete remission maintained remission without returning to baseline UPCR. Median time to first UPCR greater than baseline was 29.1 weeks for sparsentan and 17.7 weeks for irbesartan, indicating that complete remission was maintained longer with sparsentan treatment. Additionally, more patients achieved UPCR <0.5, <1.0, or <1.5 g/g at any time during the double-blind period with sparsentan compared to irbesartan (31%, 53.3%, and 69%, respectively for sparsentan-treated patients vs 14.4%, 35.8%, and 50.8% for irbesartan-treated patients).[6,16]

Composite Endpoints

Composite renal endpoints were also favorable for sparsentan. The number of events for the composite endpoints of a confirmed ≥40% reduction in eGFR, kidney failure, or death and of a confirmed ≥50% reduction in eGFR, kidney failure, or renal death are presented in **Figure 6**.[6]

Figure 6. Composite Renal Endpoints Trended Favorably for Sparsentan



Safety

Over 108 weeks of treatment, TEAEs were reported with similar frequency in the sparsentan (n=172; 93.5%) and irbesartan (n=174; 93%) treatment groups. Serious TEAEs occurred in 68 (37%) sparsentan-treated patients and 82 (43.9%) irbesartan-treated patients.[6]

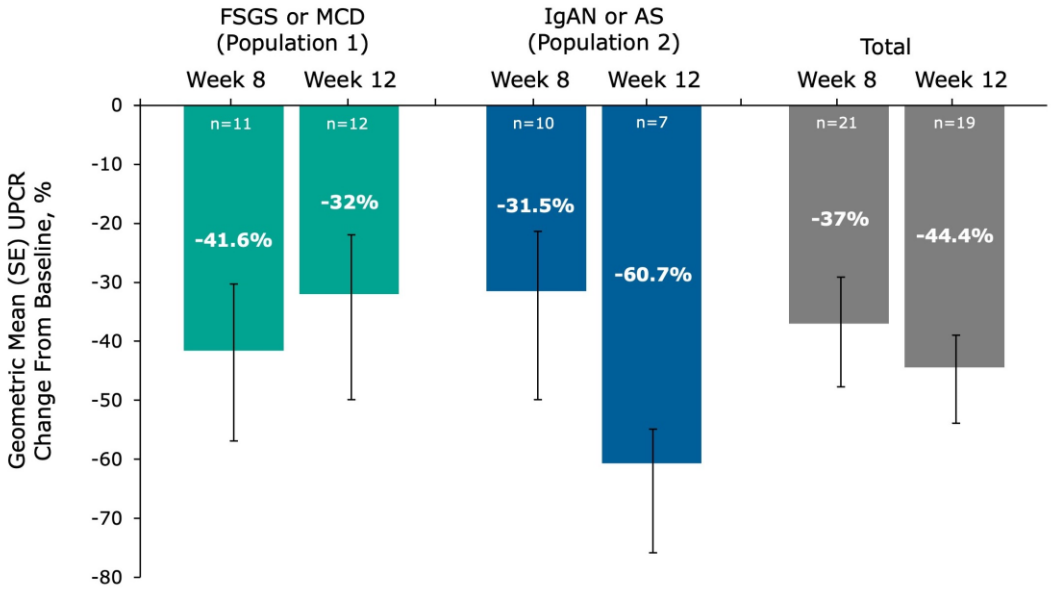
The EPPIK Study

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.[7,13] Safety and efficacy were assessed over 12 weeks of treatment.[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 (**Figure 7**).[7]

Figure 7. UPCR Reduction Over 12 Weeks of Sparsentan 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.[7,17]

Abbreviations

AE, adverse event; AS, Alport syndrome; AT_1, angiotensin II type 1; BP, blood pressure; CI, confidence interval; eGFR, estimated glomerular filtration rate; ET_A, endothelin-1 type A; EU, European Union; FPRE, FSGS partial remission of proteinuria endpoint; FSGS, focal segmental glomerulosclerosis; GMR, geometric least squares mean ratio; IgAN, immunoglobulin A nephropathy; IgAV, immunoglobulin A-associated vasculitis; IQR, interquartile range; LS, least squares; MCD, minimal change disease; OLE, open-label extension; PK, pharmacokinetics; RAASi, renin-angiotensin-aldosterone system inhibitor; RR, relative risk; SE, standard error; SAE, serious

adverse event; TEAE, treatment-emergent adverse event; UACR, urine albumin-to-creatinine ratio; UPCR, urine protein-to-creatinine ratio; US, United States.

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