FILSPARI® (sparsentan) Safety and Efficacy in Focal Segmental Glomerulosclerosis (FSGS)

Summary

Background

- Sparsentan is an investigational therapeutic candidate for the treatment of FSGS[1,2]

Study Data

The DUET Study

- During the 8-week double-blind period of the DUET study, patients treated with sparsentan achieved a significantly greater reduction in proteinuria than those treated with irbesartan (44.8% vs 18.5%, respectively; *P*=0.006)[2]
- At the 240-week analysis of the OLE, patients who continued treatment with sparsentan achieved a sustained decrease in UPCR and blood pressure over 240 weeks. An increasing proportion of patients achieved FPRE with ongoing sparsentan treatment in the OLE[3]
- No new or unexpected TEAEs were observed; the most common TEAEs (>4 cases per 100 patient years) related to sparsentan treatment were hyperkalemia, hypotension, and dizziness. TEAEs were similar in pediatric and adult patients.[3,4]

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[5]
- After 108 weeks of treatment, sparsentan showed a favorable (not statistically significant) difference on total eGFR slope of 0.3 mL/min/1.73 m^2 per year (95% CI, −1.7 to 2.4; *P*=0.75) and on eGFR chronic slope of 0.9 mL/min/1.73 m^2 per year (95% CI, −1.3 to 3.0; *P*=0.42) compared to irbesartan[5]
- 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%)[5]
- Sparsentan had a comparable safety profile to irbesartan, and heart failure and liver injury were not identified as safety concerns[5]

The EPPIK Study

- Over 12 weeks of treatment, pediatric patients (n=23) experienced a mean overall decrease in UPCR of 35%[6]
- Sparsentan appeared to be safe and well-tolerated[7]

Background

Sparsentan is an investigational therapeutic candidate for the treatment of FSGS.[1,2]

Sparsentan is a novel, first-in-class, and the only single molecule antagonist of the ET_A and AT_1 receptors.[2,8,9] 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.[2]

Following the double-blind phase, patients had the option to continue into a 144-week OLE of treatment with sparsentan.[2] Patients initially randomized to receive sparsentan continued on the dose taken on the last day of the double-blind period. Patients who received irbesartan during the double-blind period transitioned to sparsentan at the beginning of the OLE, without a washout period. Initial sparsentan dose corresponded to each patient's original dose cohort and was titrated up to 800 mg/day.[4]

Throughout the OLE, vital signs, laboratory parameters, and efficacy evaluations of eGFR and proteinuria were performed approximately every 12 weeks. Assessment of efficacy included achievement of FSGS partial remission, defined as UPCR ≤1.5 g/g and >40% decrease in UPCR and number of patients reaching 40% reduction in eGFR from the first sparsentan dose or KF. KF parameters included ESKD, consecutive eGFR <15 mL/min/1.73 m^2 ≥14 days apart, or dialysis.[4]

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.[1,5] 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.[5] 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. The key secondary endpoint was percent change in eGFR from baseline to 4 weeks post-cessation of randomized treatment at Week 112.[5] 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.[1,5]

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 and/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 and/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

Baseline Characteristics

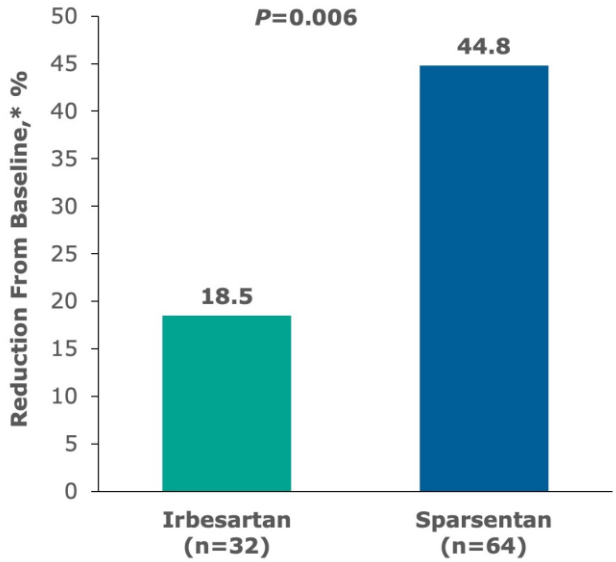
A total of 109 patients were enrolled in the DUET study. At baseline, of the 73 patients in the sparsentan group, 18% (n=13) were pediatric patients (≥8 to ≤18 years) and 82% (n=60) were adult patients (>18-75 years). The sparsentan group was 44% female, mean (SD) eGFR was 74.4 mL/min/1.73 m^2 (37.3), and median (range) UPCR ratio was 3.61 g/g (0.4-18.7).[2]

8-Week Double-Blind Phase

Primary Endpoint

During the 8-week double-blind period patients taking sparsentan experienced significantly greater reduction in proteinuria after 8 weeks of treatment than patients taking irbesartan (44.8% vs 18.5%; *P*=0.006, **Figure 1**). Safety assessments during the double-blind phase showed that, compared with patients taking irbesartan, patients treated with sparsentan reported more frequent hypotension (16.4% vs 8.3%), dizziness (13.7% vs 11.1%), edema (12.3% vs 2.8%), and gastrointestinal TEAEs (nausea, 12.3% vs 8.3%; diarrhea, 8.2% vs 2.8%; vomiting, 8.2% vs 2.8%). Overall, incidence of TEAEs, drug-related TEAEs, serious TEAEs, and the number of study withdrawals were similar between the two groups.[2]

Figure 1. Reduction in UPCR From Baseline at Week 8 of the DUET Study



*Geometric least squares mean reduction.

Open-Label Extension

Of 109 patients enrolled in the DUET study, 68 patients initially randomized to sparsentan and 35 patients initially randomized to irbesartan continued into the OLE. At time of data cutoff (February 5, 2021), 45 patients were receiving sparsentan. Median time to treatment discontinuation was 3.9 years. Yearly dispositions of patients in the OLE are presented in **Table 1**.[4]

Table 1. Patient Disposition by Year of Sparsentan Treatment

	All Sparsentan (N=108)				
	Year 0 to <1	Year 1 to <2	Year 2 to <3	Year 3 to <4	Year 4 to <5
Ongoing	85 (78.7%)	72 (66.7%)	60 (55.6%)	54 (50.0%)	47 (43.5%)[a]
Discontinued	23 (21.3%)	13 (12.0%)	12 (11.1%)	6 (5.6%)	7 (6.5%)
Adverse event	10 (9.3%)	2 (1.9%)	2 (1.9%)	3 (2.8%)	3 (2.8%)
Lost to follow-up	3 (2.8%)	1 (0.9%)	0 (0%)	0 (0%)	0 (0%)
Other	2 (1.9%)	2 (1.9%)	0 (0%)	0 (0%)	0 (0%)
Physician decision	2 (1.9%)	2 (1.9%)	5 (4.6%)	1 (0.9%)	0 (0%)
Pregnancy	2 (1.9%)	1 (0.9%)	0 (0%)	1 (0.9%)	0 (0%)
Protocol deviation	1 (0.9%)	0 (0%)	1 (0.9%)	0 (0%)	0 (0%)
Withdrawal by patient	3 (2.8%)	5 (4.6%)	3 (2.8%)	1 (0.9%)	2 (1.9%)
Noncompliance with study drug	0 (0%)	0 (0%)	1 (0.9%)	0 (0%)	1 (0.9%)
Missing	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (0.9%)

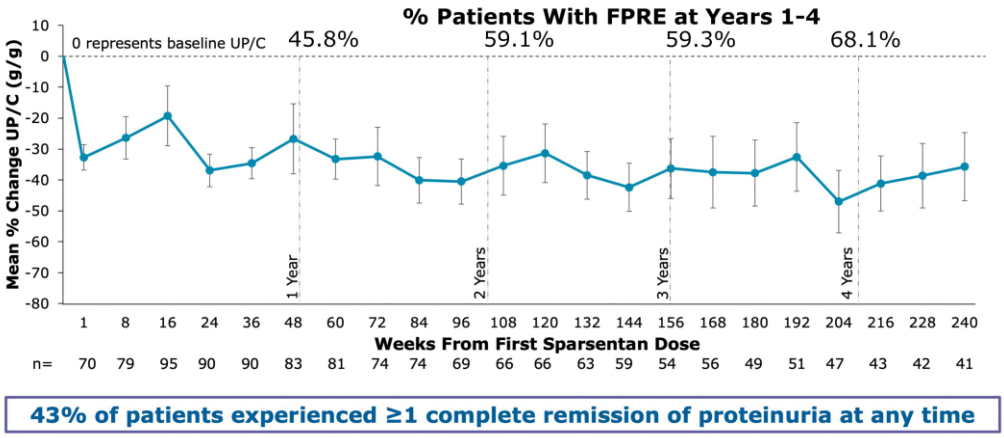
Data are given as n (%). Year 0 to <1 begins at DUET study baseline for patients initially randomized to sparsentan or at week 8 at the start of sparsentan treatment in the open-label extension for patients initially randomized to irbesartan during the double-blind period.
[a]Forty-five patients were ongoing at data cutoff at 4.6 years.

Long-term Efficacy

Treatment with sparsentan brought about rapid and sustained reduction in UPCR within 8 weeks of treatment initiation. This antiproteinuric effect occurred both in patients who were randomized to sparsentan treatment in the double-blind period and those who transitioned to sparsentan at the beginning of the OLE, without RAASi washout.[4]

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 2**).[3]

Figure 2. Reduction in UPCR Over 240 Weeks of Treatment in the DUET Study

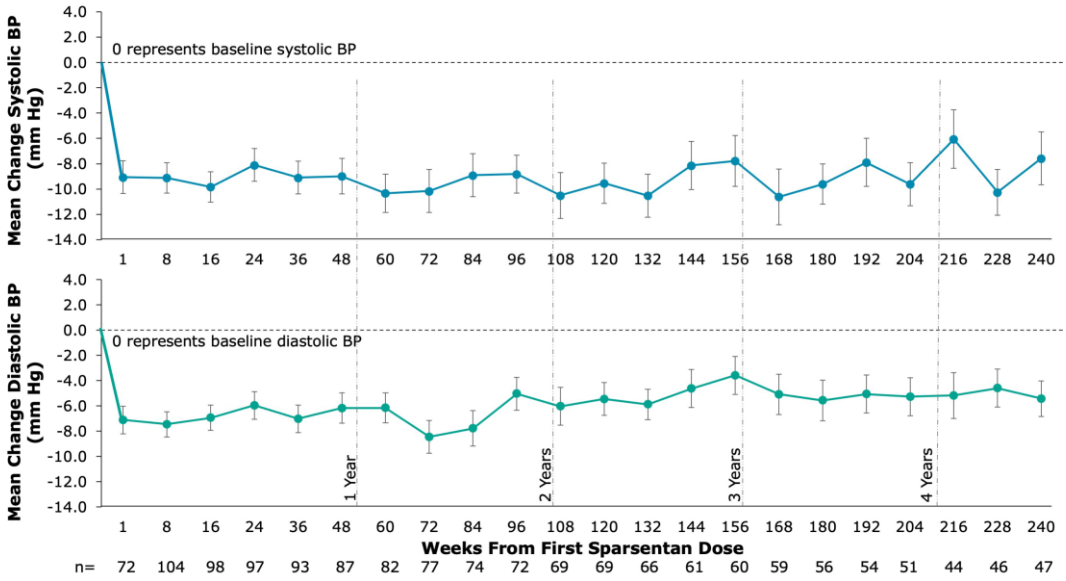


Error bars show SE. Only on-treatment observations (defined as occurring within 1 day of last sparsentan dose) are included. FPRE (UPCR ≤1.5 g/g and >40% reduction in UPCR from baseline).

FPRE was further assessed by comparing patients who achieved FPRE within 9 months of sparsentan treatment (n=57, 52.8%) vs those who did not (n=51, 47.2%). Patients who experienced FPRE within 9 months showed a significantly slower rate of eGFR decline. eGFR slope estimates during the first 2 years of treatment among patients who reached FPRE within 9 months was −1.69 mL/min/1.73 m^2 per year vs −6.46 mL/min/1.73 m^2 per year in patients who did not (*P*=0.03). Over the entire treatment period slope estimates in the 2 groups were −2.70 vs −6.56 mL/ min/1.73 m^2 per year (*P*=0.03), respectively. Over the follow-up period, the composite clinical endpoint was reached by 33 (30.6%) patients; 32 (29.6%) patients demonstrated a confirmed 40% reduction in eGFR and 12 (11.1%) patients reached KF.[4]

At the 240-week analysis of the OLE, patients who continued treatment with sparsentan achieved a sustained decrease in UPCR and blood pressure over 240 weeks (**Figure 3**).[3] Both SBP and DBP decreased within several weeks of sparsentan treatment; this decrease was greater in patients initially randomized to sparsentan after the 2-week RAASi washout vs patients who switched to sparsentan without washout. BP remained stable throughout the study follow-up period.[4]

Figure 3. Mean Change From Baseline in Blood Pressure Over 240 Weeks in the DUET Study



Error bars show SE. Only on-treatment observations (defined as occurring within 1 day of last sparsentan dose) are included.

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]

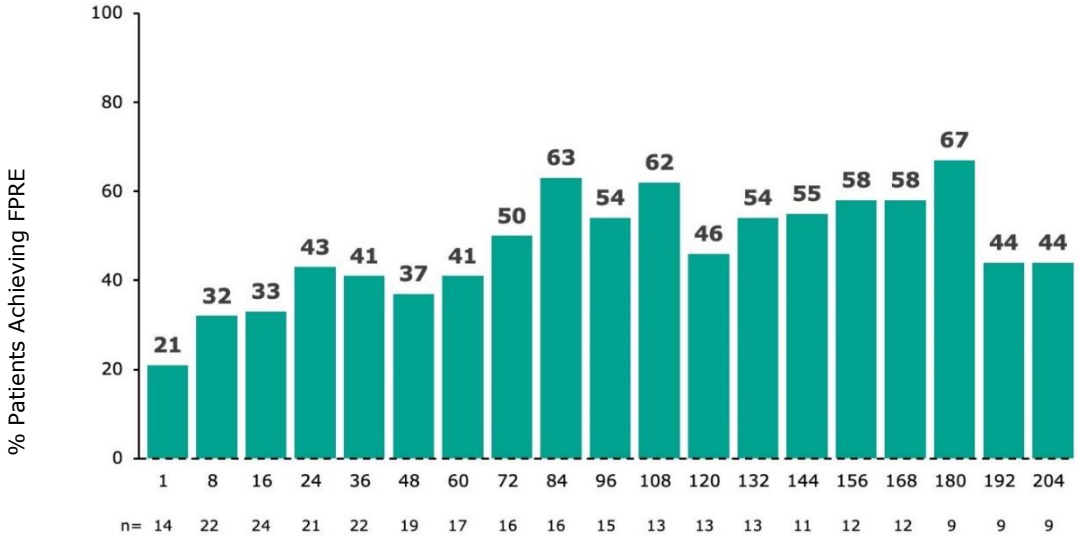
Among the 26 young patients, 10 (38%) experienced at least one complete remission of proteinuria, defined as UPCR ≤0.3 g/g, during the study period. Mean UPCR and change from baseline at 24-week timepoints is presented in **Table 2**. FPRE was achieved by 37% of patients at 1 year, 62% at 2 years, 58%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

Table 2. Median UPCR and Change From Baseline in UPCR Every 24 Weeks in Patients Aged ≤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 4. Percentage of Patients Achieving FPRE by Visit in Patients Aged ≤21 Years



Percentage of patients achieving the 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.

Long-term Safety

Analysis of OLE data found no new or unexpected safety signals. The most common TEAEs (>9 cases per 100 patient-years) were headache, peripheral edema, upper respiratory tract infection, hyperkalemia, and hypotension (**Table 3**). Sparsentan-related TEAEs that occurred in >4 cases per 100 patient years were hyperkalemia, hypotension, and dizziness. TEAEs did not differ between pediatric and adult patients.[3,4]

ALT and/or AST >3× ULN occurred in 4 patients; 2 patients discontinued sparsentan due to liver-related TEAEs, one of which was considered serious. No cases of heart failure were reported and no patients died. During follow-up, 27 (25.0%) patients had ≥1 hospitalization.[4]

Table 3. Most Common TEAEs by Year and Cases per 100 Patient-Years for the Total Study Duration

	Number Within Each Year					Total Study Duration Cases Per 100 Patient-Years
	Year 0 to <1 (n = 108)	Year 1 to <2 (n = 87)	Year 2 to <3 (n = 72)	Year 3 to <4 (n = 60)	Year 4 to <5 (n = 54)	
Headache	25 (23.1%)	5 (5.7%)	1 (1.4%)	4 (6.7%)	2 (3.7%)	11.7
Peripheral edema	15 (13.9%)	10 (11.5%)	3 (4.2%)	2 (3.3%)	2 (3.7%)	11.2
Upper respiratory tract infection	9 (8.3%)	5 (5.7%)	6 (8.3%)	5 (8.3%)	2 (3.7%)	10.6
Hyperkalemia	7 (6.5%)	9 (10.3%)	3 (4.2%)	6 (10.0%)	6 (11.1%)	10.4
Hypotension	17 (15.7%)	6 (6.9%)	3 (4.2%)	2 (3.3%)	1 (1.9%)	9.3
Nausea	17 (15.7%)	3 (3.4%)	2 (2.8%)	4 (6.7%)	1 (1.9%)	8.5
Hypertension	6 (5.6%)	7 (8.0%)	2 (2.8%)	3 (5.0%)	6 (11.1%)	7.6
Vomiting	12 (11.1%)	2 (2.3%)	5 (6.9%)	2 (3.3%)	1 (1.9%)	7.6
Diarrhea	14 (13.0%)	3 (3.4%)	3 (4.2%)	1 (1.7%)	4 (7.4%)	7.1
Dizziness	14 (13.0%)	3 (3.4%)	1 (1.4%)	2 (3.3%)	0 (0%)	6.3
Blood creatinine increased	11 (10.2%)	1 (1.1%)	4 (5.6%)	0 (0%)	1 (1.9%)	5.5
Blood creatine phosphokinase increased	8 (7.4%)	2 (2.3%)	0 (0%)	3 (5.0%)	2 (3.7%)	4.9
Anemia	11 (10.2%)	1 (1.1%)	0 (0%)	2 (3.3%)	1 (1.9%)	4.1

Note: Data are given as n (%).
Abbreviation: TEAE, treatment-emergent adverse event.

The DUPLEX Study

A total of 371 patients enrolled in the DUPLEX study; 184 patients received sparsentan and 187 patients received irbesartan. Male patients comprised 54.9% and 52.9% of the sparsentan and irbesartan groups, respectively. Mean (SD) eGFR at baseline was 63.3 (28.6) mL/min/1.73 m^2 in the sparsentan group and 64.1 (31.7) mL/min/1.73 m^2 for irbesartan patients. Median (IQR) UPCR for sparsentan patients was 3.1 (2.3-4.5) and 3.0 (2.1-4.7) in the irbesartan group.[5]

Efficacy

Primary Efficacy Endpoint

Sparsentan did not achieve the primary efficacy eGFR slope endpoint over 108 weeks of treatment.[5]

Primary efficacy endpoints were defined as eGFR total slope from Day 1 to Week 108 of treatment (US primary) and eGFR chronic slope from Week 6 to Week 108, following initial acute effect of randomized treatment (EU primary). A decrease from baseline in mean (95% CI) eGFR over the first 6 weeks of treatment was −4.1 (−5.8 to −2.4) mL/min/1.73 m^2 with sparsentan and −0.8 (−2.5 to 0.9) mL/min/1.73 m^2 with irbesartan (difference, −3.3 [−5.7 to −0.9] mL/min/1.73 m^2). After 108 weeks of treatment, sparsentan showed a favorable (not statistically significant) difference on total eGFR slope of 0.3 mL/min/1.73 m^2 per year (95% CI, −1.7 to 2.4; P=0.75) and on eGFR chronic slope of 0.9 mL/min/1.73 m^2 per year (95% CI, −1.3 to 3.0; P=0.42) compared to irbesartan (**Table 4**).[5]

Table 4. The eGFR Slope and Change in eGFR

Variable	Sparsentan (n=184)	Irbesartan (n=187)	Difference
Least-squares mean eGFR slope (95% CI), mL/min/1.73 m² per year			
eGFR total slope*	**-5.4** (-6.9, -3.9)	**-5.7** (-7.2, -4.3)	**0.3,** *P*=0.75 (-1.7, 2.4)
eGFR chronic slope†	**-4.8** (-6.3, -3.3)	**-5.7** (-7.2, -4.2)	**0.9,** *P*=0.42 (-1.3, 3)
Least-squares mean change in eGFR from baseline to Week 112 (95% CI), mL/min/1.73 m²‡	**-10.4** (-12.6, 8.1)	**-12.1** (-14.4, -9.9)	**1.8** (-1.4, 4.9)

* The eGFR total slope was the slope from Day 1 to Week 108.
† The eGFR chronic slope was the slope from Week 6 to Week 108.
‡ Data are for patients who completed the double-blind treatment period (129 patients in the sparsentan group and 136 patients in the irbesartan group).

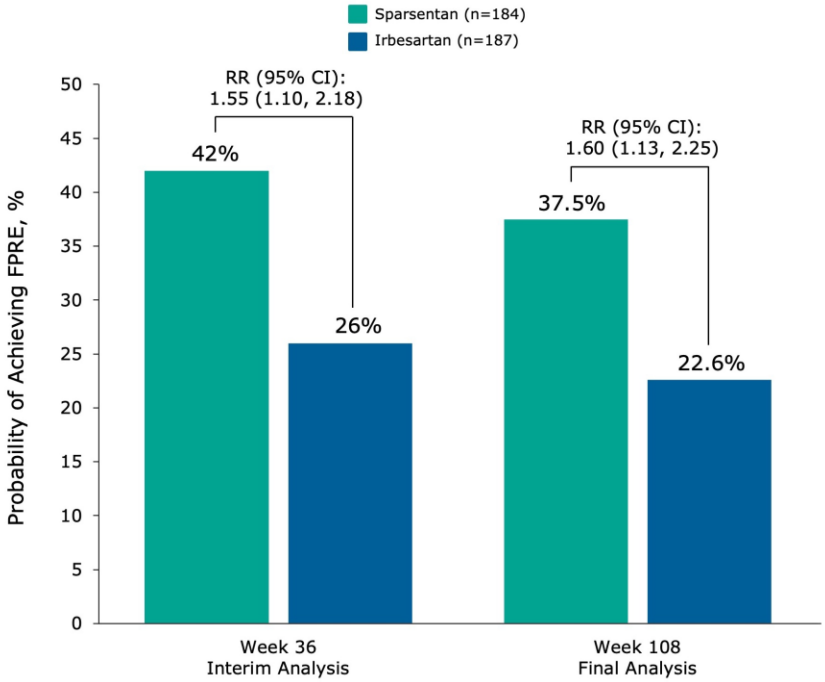
Secondary and Exploratory Endpoints

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

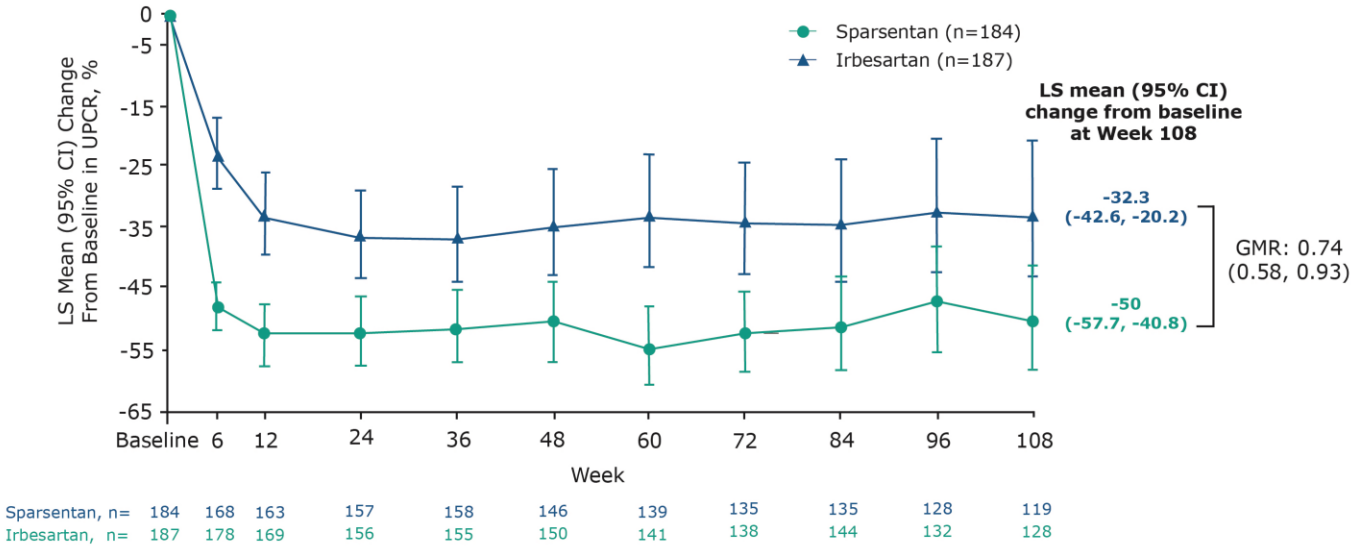
Analysis included an interim efficacy endpoint, the proportion of patients achieving FPRE, defined as UPCR ≤1.5 g/g and a >40% reduction in UPCR from baseline at Week 36 (**Figure 5**). Sparsentan achieved a statistically significant response on the interim proteinuria endpoint at Week 36 compared to irbesartan, with 42% of patients receiving sparsentan experiencing FPRE vs 26% of irbesartan-treated patients (*P*=0.009).[5,15] 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.[5]

Figure 5. 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 6**).[5]

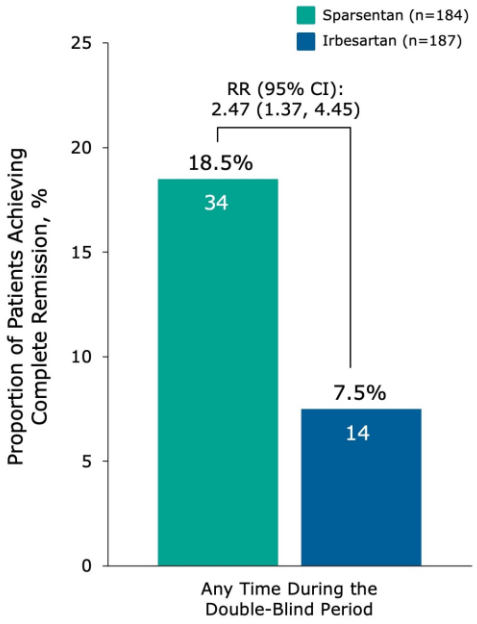
Figure 6. Decline in UPCR Through 108 Weeks of Sparsentan Treatment



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 7**).[5]

Figure 7. Proportion of Patients Achieving Complete Remission of Proteinuria



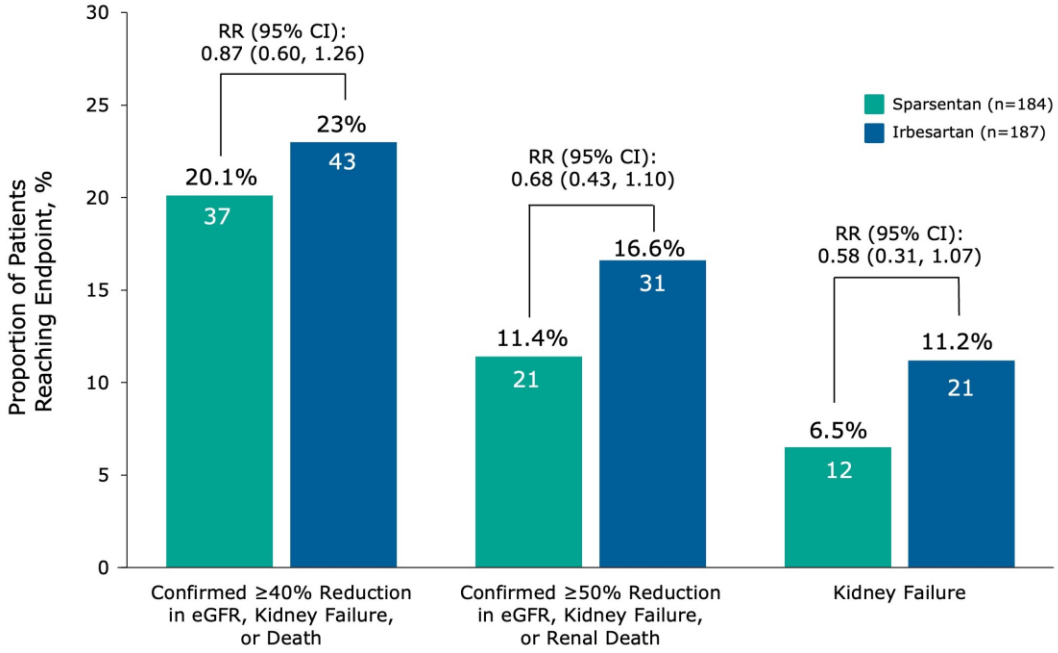
Complete remission defined as UPCR <0.3 g/g.

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).[5,16]

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 8**.[5]

Figure 8. 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. ALT or AST elevations >3× ULN occurred in 5 (2.7%) patients taking sparsentan and 4 (2.2%) taking irbesartan; no cases were concurrent with elevated bilirubin levels ≥1.5× ULN. There were no drug-induced liver injuries with sparsentan; 1 was reported in the irbesartan group.[5]

The EPPIK Study

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]

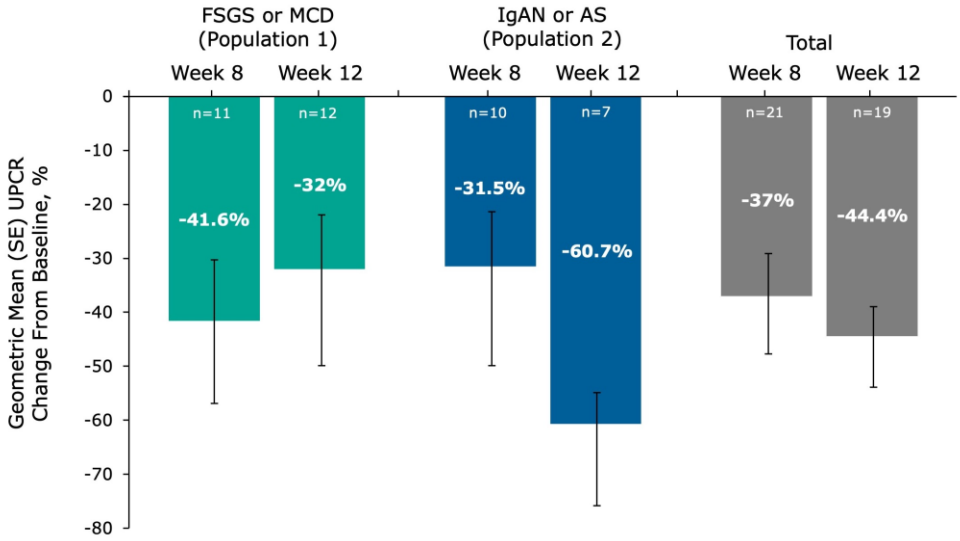
Baseline Characteristics

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). Among patients with FSGS or MCD, mean (SD) eGFR was 106.1 (50) mL/min/1.73 m^2; median (IQR) UPCR was 3.0 (2.5-5.7) g/g.[7]

Efficacy

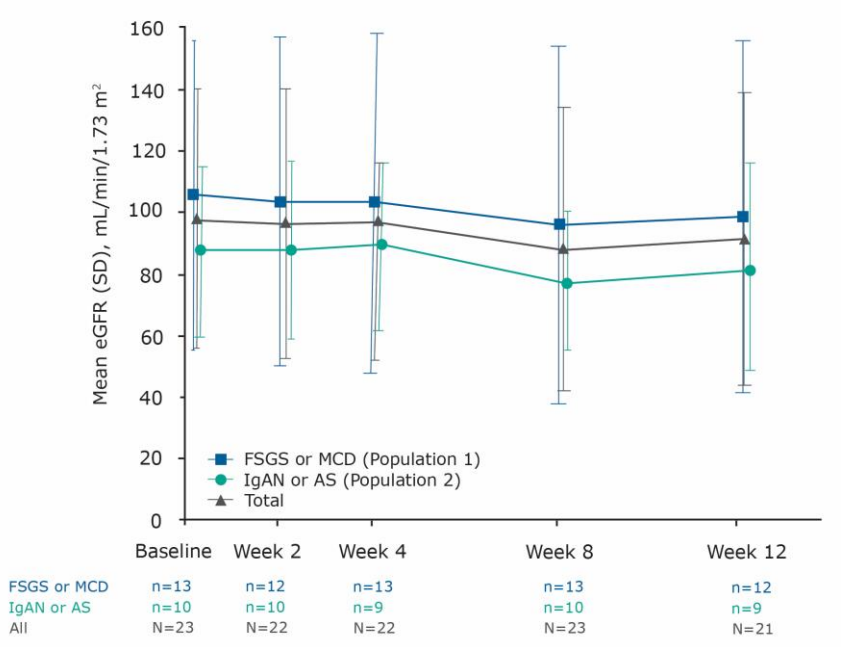
In pediatric patients with a range of proteinuric glomerular diseases, sparsentan treatment resulted in reductions in proteinuria over the initial 12 weeks of treatment (**Figure 9**).[6,7]

Figure 9. UPCR Reduction Over 12 Weeks of Sparsentan Treatment



eGFR remained fairly stable throughout the 12-week treatment period (**Figure 10**).[7]

Figure 10. eGFR During 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.[6,7]

Abbreviations

AE, adverse event; ALT, alanine transaminase; AS, Alport syndrome; AST, aspartate aminotransferase; AT_1, angiotensin II type 1; BP, blood pressure; CI, confidence interval; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; ESKD, end stage kidney disease; ET_A, endothelin-1 type A; EU, European Union; FPRE, FSGS partial remission of proteinuria endpoint; FSGS, focal segmental glomerulosclerosis; GMR, geometric mean ratio; IgAN, immunoglobulin A nephropathy; IgAV, immunoglobulin A-associated vasculitis; IQR, interquartile range; KF, kidney failure; LS, least squares; MCD, minimal change disease; OLE, open-label extension; PK, pharmacokinetics; RAASi, renin-angiotensin-aldosterone system inhibitor; RR, relative risk; SAE, serious adverse event; SBP, systolic blood pressure; SD, standard deviation; SE, standard error; TEAE, treatment-emergent adverse event; ULN, upper limit of normal; UPCR, urine protein-to-creatinine ratio; US, United States.

References

1. 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
2. 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
3. Srivastava T, Tesar V, Campbell KN, et al. Long-term efficacy and safety of sparsentan in FSGS: 240-week analysis of the DUET open-label extension (OLE). Abstract presented at: ASN Kidney Week; November 3-6 2022; Orlando, FL.
4. Campbell KN, Gesualdo L, Murphy E, et al. Sparsentan for focal segmental glomerulosclerosis in the DUET open-label extension: Long-term efficacy and safety. *Kidney Medicine*. 2024;6(6):1-12. doi:10.1016/j.xkme.2024.100833
5. Rheault MN, Alpers CE, Barratt J, et al. Sparsentan versus irbesartan in focal segmental glomerulosclerosis. *N Engl J Med*. 2023;389(26):2436-2445. doi:10.1056/NEJMoa2308550
6. 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.
7. 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.

8. 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
9. 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.
10. 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.
11. 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.
12. 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.
13. 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.
14. 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.
15. Rheault MN, Trachtman H, Diva U, Komers R. Sparsentan vs irbesartan in patients with focal segmental glomerularsclerosis (FSGS): Results from the phase 3 DUPLEX trial. Oral presentation presented at: ASN Kidney Week; November 2-5, 2023; Philadelphia, PA.
16. Rheault MN, Alpers CE, Barratt J, et al. Sparsentan versus irbesartan in focal segmental glomerulosclerosis, supplement. *N Engl J Med*. 2023;389(26):2436-2445. doi:10.1056/NEJMoa2308550