FILSPARI® (sparsentan)
Continued Use

Summary

Prescribing Information

The efficacy data that follows is from the post-hoc analysis, which was limited to fewer patients (the first 281 randomized patients), with follow-up only to 36 weeks. It also includes patients who never started treatment and data after discontinuing treatment.

- In the PROTECT study, patients receiving FILSPARI achieved a mean reduction in UPCR from baseline of 45%, compared to a mean reduction in UPCR from baseline of 15% for irbesartan-treated patients ($P<0.0001$)[1]

Study Data

- In clinical trials, more than 1200 participants have taken sparsentan, including patients who have been on therapy for nearly 7 years[2]

PROTECT

The efficacy data that follows is from the pre-specified primary analysis reported at the interim assessment, which includes proteinuria data from all 404 randomized and treated patients in the PROTECT clinical trial at the time of the analysis.

- In the PROTECT study, after 36 weeks of treatment, patients receiving sparsentan achieved a mean reduction in proteinuria from baseline of 49.8%, compared to a 15.1% mean reduction for irbesartan-treated patients ($P<0.0001$).[3] Sparsentan was generally well tolerated, with no new safety signals emerging in the sparsentan group[3,4]

The efficacy and safety data that follows is from a 2-year confirmatory analysis including data from all 404 randomized and treated patients in the PROTECT clinical trial at the time of the analysis.

- Over 2 years of treatment, patients treated with sparsentan exhibited one of the slowest annual rates of kidney function decline seen in a clinical trial in IgA nephropathy (-2.7 to -2.9 mL/min/1.73 m^2 per year)[2]

DUET

- In the 240-week DUET OLE, patients with FSGS showed significant reduction in proteinuria, with a mean change in eGFR of -3.56 mL/min/1.73 m^2 per year after 108 weeks of treatment. No new safety signals emerged[5]

DUPLEX

- In the DUPLEX study, sparsentan showed a favorable difference on total eGFR slope of 0.3 mL/min/1.73 m^2 per year (95% CI, -1.7 to 2.4) and on eGFR chronic slope of 0.9 mL/min/1.73 m^2 per year (95% CI, -1.3 to 3.0) compared to irbesartan after 108 weeks of treatment (not statistically significant)[2]

Prescribing Information

To learn more about FILSPARI, 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.[4,6,7] 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 PROTECT Study

The PROTECT study (NCT03762850) is a phase 3, global, randomized, multicenter, double-blind, parallel-arm, active-controlled clinical trial evaluating long-term antiproteinuric and nephroprotective efficacy and safety of 400 mg of sparsentan compared to 300 mg of irbesartan.[11] The study includes 404 patients ages 18 years and older with biopsy proven IgA nephropathy who experience persistent proteinuria despite available ACEi or ARB therapy. The PROTECT study protocol provides for an unblinded interim analysis of at least 280 patients to be performed after 36 weeks of treatment to evaluate the primary efficacy endpoint, defined as change in proteinuria (UPCR) at Week 36 from baseline. Secondary efficacy endpoints include the rate of change in eGFR following the initiation of randomized treatment over 58-week and 110-week periods, as well as rate of change in eGFR over 52-week and 104-week periods following the first 6 weeks of randomized treatment.[12,13] The PROTECT study also examines change from baseline in UACR based on a 24-hour urine sample at Week 36, and prespecified exploratory endpoints of complete (urinary protein excretion <0.3 g/day) and partial (urinary protein excretion <1.0 g/day) proteinuria remission at least once at any time during the double-blind period. In addition, this study evaluates the proportion of patients in each group reaching a confirmed 40% reduction in eGFR from baseline, KF, or all-cause mortality. KF is defined as initiation of KRT or sustained eGFR value of <15 mL/min/1.73 m^2.[3] Reduction in proteinuria and decline in rate of eGFR are largely accepted as surrogate markers of treatment effect in studies of KF.[3,14]

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.[7]

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 with biopsy-proven FSGS. 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.[2] Patients remained on maintenance doses of sparsentan or irbesartan during a 108-week double-blind phase. 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). An additional interim endpoint was the proportion of patients achieving a 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.[2,15]

Study Data

Use of Sparsentan in IgA Nephropathy

The PROTECT Study

The efficacy and safety data that follows is from the pre-specified primary analysis reported at the interim assessment, which includes proteinuria data from all 404 randomized and treated patients in the PROTECT clinical trial at the time of the analysis.

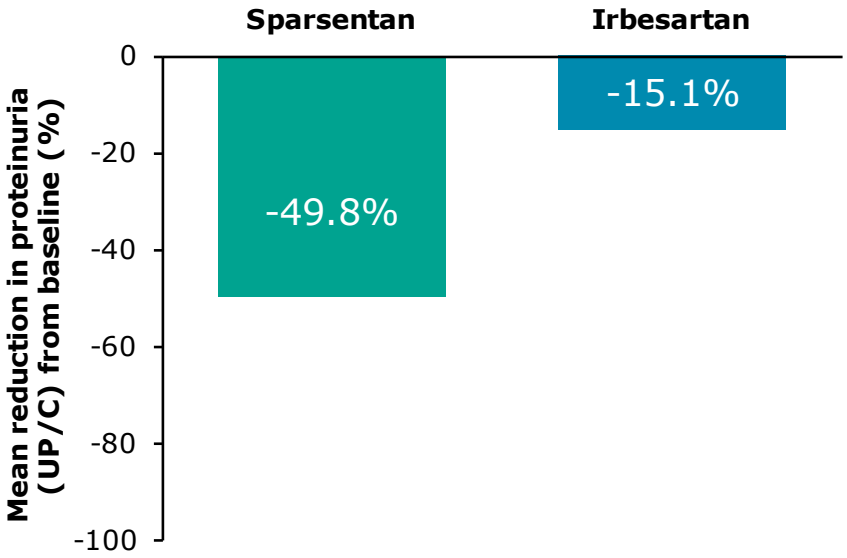
Interim Efficacy Results

The PROTECT study protocol provided for an unblinded interim analysis to evaluate the primary efficacy endpoint–the change in UPCR from baseline at Week 36–approximately 36 weeks following randomization of the first 280 patients.[16]

Primary Efficacy Endpoint

After 36 weeks of treatment, patients receiving sparsentan achieved a mean reduction in proteinuria from baseline of 49.8%, compared to a mean reduction in proteinuria from baseline of 15.1% for irbesartan-treated patients (P<0.0001) (**Figure 1**). Reduction in proteinuria was greater with sparsentan compared to irbesartan at the first post-randomization visit (Week 4), continued to Week 36 of the interim analysis, and was consistent across patient subgroups of baseline demographic and clinical characteristics. The robust effect of sparsentan on reduction of proteinuria was found to be both statistically significant and clinically meaningful.[3]

Figure 1. Mean Reduction in Proteinuria (UPCR) from Baseline at Week 36 of the PROTECT Study



The proteinuria-lowering effect of sparsentan is unlikely to be attributable to the modest reduction in blood pressure, especially considering the large difference in proteinuria reduction despite minimal differences in blood pressure changes between the sparsentan and irbesartan groups.[3]

2-Year Confirmatory Endpoint Analysis

The PROTECT study included a confirmatory endpoint analysis following 2 years of sparsentan treatment. The confirmatory endpoint was the eGFR slope of progression to KF, measured by total slope in the US and by chronic slope in the EU.[2]

- The slope of eGFR following initiation of randomized treatment, from Day 1 to Week 110, defined the eGFR total slope
- The slope of eGFR following the initial acute effect of randomized treatment, from Week 6 to Week 110, defined the eGFR chronic slope

Topline efficacy endpoints assessing preservation of kidney function favored sparsentan over irbesartan following 2 years of treatment (**Table 1**). Patients taking sparsentan experienced an eGFR total slope 1.0 mL/min/1.73 m^2 per year favorable and clinically meaningful difference as compared to irbesartan. The observed difference in eGFR total slope narrowly missed statistical significance (P=0.058). For patients taking sparsentan, eGFR chronic slope showed a clinically meaningful and statistically significant difference of 1.1 mL/min/1.73 m^2 per year as compared to irbesartan (P=0.037).[2]

Table 1. Treatment With Sparsentan Demonstrated Long-Term Kidney Function Preservation

eGFR Slope	Sparsentan (n=202)	Irbesartan (n=202)	Difference (Sparsentan – Irbesartan) (95% CI)
eGFR total slope, mL/min/1.73 m² per year[a]	**-2.9**	**-3.9**	**1.0,** *P*=0.058 (-0.03, 1.94)
eGFR chronic slope, mL/min/1.73 m² per year[b]	**-2.7**	**-3.8**	**1.1,** *P*=0.037 (0.07, 2.12)

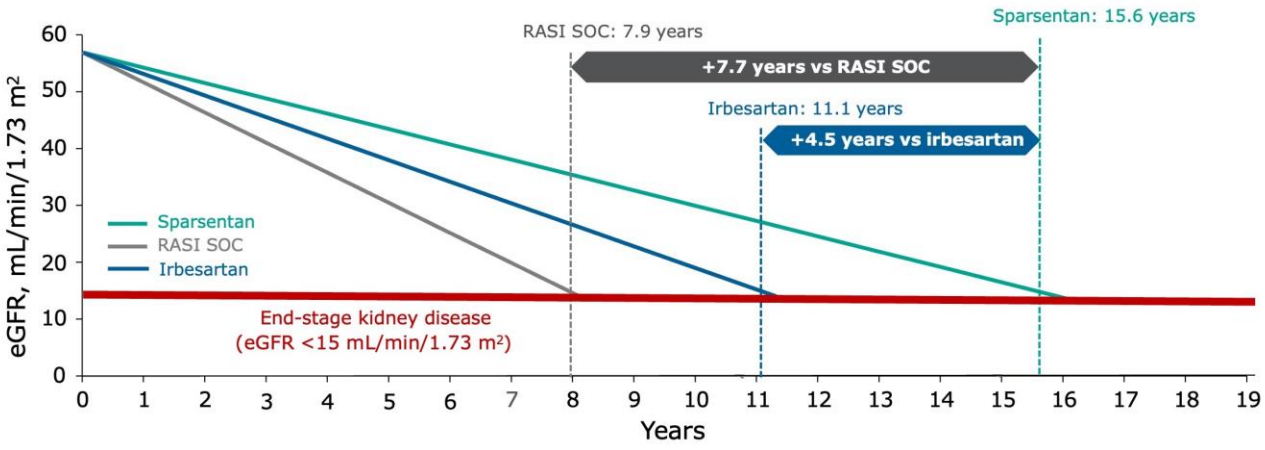
[a]LS mean and 95% CI from a random coefficient analysis including available on-treatment eGFR data from Week 6 through Week 110 with multiple imputation.
[b]LS mean and 95% CI from a random coefficient analysis including available on-treatment eGFR data through Week 110 with multiple imputation.

eGFR Slope

Treatment with sparsentan was associated with projected delay in time to KF, related to change in eGFR slope (**Figure 2**). Baseline eGFR was 57 mL/min/1.73 m^2, based on mean eGFR of the sparsentan group in the PROTECT study interim analysis. eGFR for SOC (maximized ACEi/ARB) equaled the mean of observed slopes reported in previous clinical trials. Observed eGFR chronic slope was -2.7 mL/min/1.73 m^2 per year for sparsentan, -3.8 mL/min/1.73 m^2 per year for irbesartan, and -5.3 mL/min/1.73 m^2 per year for SOC treatment. Corresponding time to KF was reported as 15.6 years, 11.1 years, and 7.9 years for sparsentan, irbesartan, and SOC, respectively.[2]

- Compared to patients utilizing SOC, patients taking sparsentan-treated experienced a mean 7.7 years longer delay to KF
- Compared to patients taking irbesartan, sparsentan-treated patients experienced a mean 4.5 years longer delay to KF

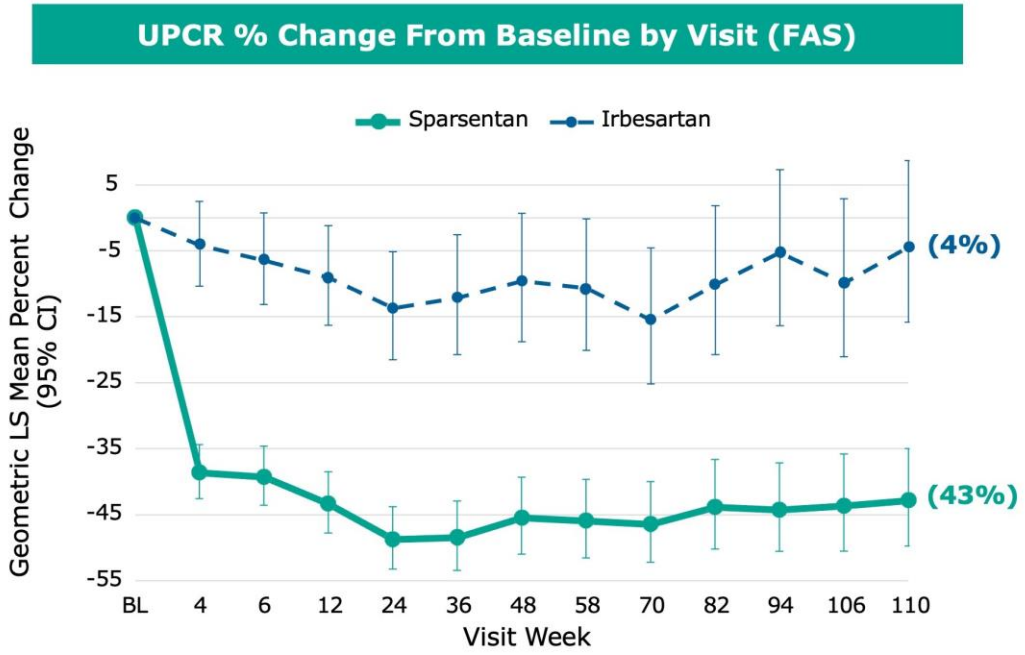
Figure 2. Treatment With Sparsentan Is Associated With Projected Delay in Time to Kidney Failure



Reduction in UPCR

Treatment with sparsentan resulted in a rapid and sustained antiproteinuric effect as demonstrated by proteinuria reduction. Following 2 years of treatment, patients taking sparsentan experienced a 43% proteinuria reduction from baseline compared to 4% for patients taking irbesartan (**Figure 3**).[2]

Figure 3. Sparsentan Provided Rapid and Sustained Antiproteinuric Effects After 2 Years of Treatment



Safety

2-Year Safety Results

Additional safety data from the 2-year confirmatory analysis showed sparsentan to be well-tolerated, with a consistent safety profile comparable to irbesartan and no new safety signals. Among patients taking sparsentan, 187 (93%) reported TEAEs. Among patients taking irbesartan, 177 (88%) reported TEAEs. SAEs were reported by 75 (37%) patients taking sparsentan and 71 (35%) patients taking irbesartan. TEAEs leading to discontinuation occurred in 21 (10%) patients taking sparsentan and 18 (9%) patients taking irbesartan. There was 1 TEAE leading to death in the irbesartan group and none in the sparsentan group (**Table 2**).[2]

Abnormal liver function tests were found in 5 (2%) patients taking sparsentan and 7 (3%) patients taking irbesartan. No new AEs of interest of 3× ULN AST or ALT, cases of Hy's law, or drug-induced liver injury occurred with sparsentan.[2]

Table 2. Adverse Events Reported After 2 Years of Sparsentan Treatment

Adverse Reactions	Sparsentan (n=202), n (%)	Irbesartan (n=202), n (%)	Total (N=404), n (%)
Any TEAEs[a]	187 (93)	177 (88)	364 (90)
Any related TEAEs[b]	93 (46)	70 (35)	163 (40)
Any severe TEAEs	24 (12)	29 (14)	53 (13)
Any SAEs	75 (37)	71 (35)	146 (36)
Any AEOIs: Abnormal liver function tests[c]	5 (2)	7 (3)	12 (3)
Any TEAEs leading to treatment discontinuation	21 (10)	18 (9)	39 (10)
Any TEAEs leading to death	0 (0)	1 (<1)	1 (<1)

[a]TEAE is defined as any AE that newly appear, increase in frequency, or worsens in severity following initiation of study medication.
[b]Related TEAEs are defined as TEAEs that are deemed to be 'possibly related' or 'related' to the study medication by the investigator.
[c]AEOI are those abnormal liver function tests that meet the following criteria: (1) new elevation in ALT or AST >3x ULN with or without elevation of total serum bilirubin >2x ULN; (2) 2-fold increase in ALT or AST above the baseline value in patients who had elevated values prior to starting study medication.

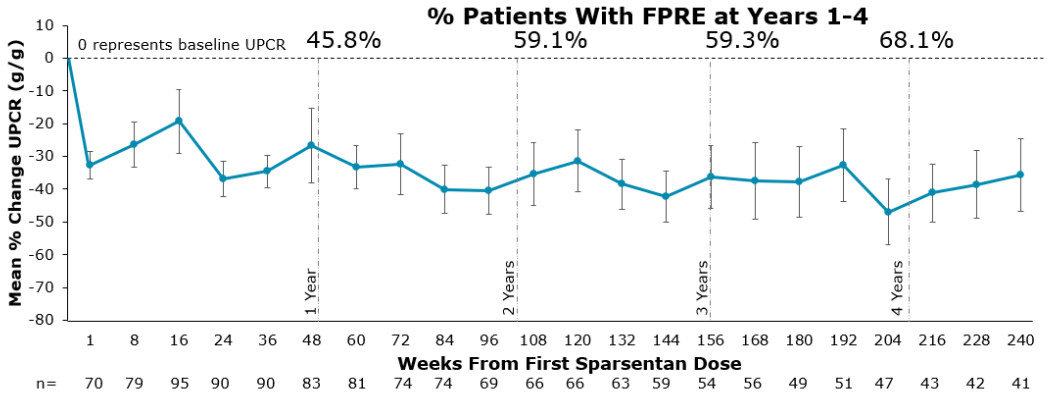
Sparsentan in FSGS

The DUET Study

In the phase 2 DUET study, 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). 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.[7]

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 4**).[5] Previous research in patients with steroid-resistant FSGS found that over 26 weeks of treatment, changes in proteinuria were significantly associated with eGFR slope, with lower proteinuria related to a less steep slope and slower decline in eGFR. Reductions in proteinuria were associated with slower decline in kidney function and lower incidence of death in the study sample.[17]

Figure 4. 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)

Analysis of OLE data found no new or unexpected safety signals. The most common TEAEs were headache, peripheral edema, upper respiratory tract infection, and hyperkalemia (**Table 3**).[5]

Table 3. Most Common TEAEs by Year and Cases Per 100 Patient-Years for Total Study Duration in the DUET OLE Study

	n (%) Within Each Year					Total Study Duration Cases Per 100 Patient-Years, Cases/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
Edema peripheral	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	6.3
Blood creatinine increased	11 (10.2)	1 (1.1)	4 (5.6)	0	1 (1.9)	5.5
Blood creatine phosphokinase increased	8 (7.4)	2 (2.3)	0	3 (5.0)	2 (3.7)	4.9
Anemia	11 (10.2)	1 (1.1)	0	2 (3.3)	1 (1.9)	4.1

The DUPLEX Study

Efficacy

Primary Efficacy Endpoint

Sparsentan did not achieve the primary efficacy eGFR slope endpoint over 108 weeks of treatment.[2]

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). At the end of the 108-week double-blind period, sparsentan

showed favorable differences in eGFR total slope, chronic slope and acute effect compared to irbesartan, which were not statistically significant (**Table 4**).[2]

Table 4. Sparsentan Shows Activity on eGFR Slopes – Did Not Achieve Primary Endpoints

	Irbesartan (n=187)	Sparsentan (n=184)	Difference (Sparsentan – Irbesartan)
Total slope,	**-5.7**	**-5.4**	**0.3,** p=0.7491
mL/min/1.73 m^2 per year[a] (95% CI)	(-7.2, -4.3)	(-6.9, -3.9)	(-1.7, 2.4)
Chronic slope,	**-5.7**	**-4.8**	**0.9,** p=0.4203
mL/min/1.73 m^2 per year[b] (95% CI)	(-7.2, -4.2)	(-6.3, -3.3)	(-1.3, 3.0)
Acute effect[c]	**-0.8**	**-4.1**	**-3.3**
Change from baseline at week 6 (95% CI)	(-2.5, 0.9)	(-5.8, -2.4)	(-5.7, -0.9)

[a]Random coefficient analysis with 1 slope including available on-treatment eGFR data through Week 108; mL/min/1.73 m^2 per year.
[b]Random coefficient analysis with 2 slopes (change point at Week 6) including available on-treatment eGFR through Week 108; mL/min/1.73 m^2 per year.
[c]MMRM analysis including data through Week 108; mL/min/1.73 m^2.
Results are LS Means and 95% CI.

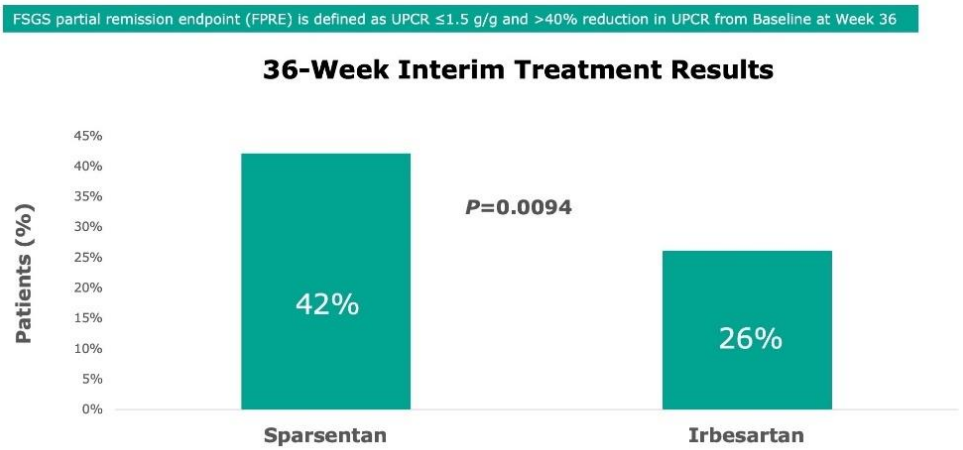
Secondary and Exploratory Endpoints

Secondary and topline exploratory endpoints in the study trended favorably for sparsentan at both the 36-week interim analysis and analysis after 108 weeks of treatment.[2]

UPCR and FPRE

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. Sparsentan achieved a statistically significant response on the interim proteinuria endpoint compared to irbesartan, with 42% of patients receiving sparsentan experiencing FPRE vs 26% of irbesartan-treated patients (*P*=0.0094) (**Figure 5**).[18]

Figure 5. DUPLEX Study: Proportion of Patients Achieving FPRE



Analysis of the full data set at 108 weeks showed that change from baseline UPCR was 50% for sparsentan compared to 32.3% for irbesartan, and 38% of patients on sparsentan achieved FPRE compared with 22.6% on irbesartan (**Table 5**).[2]

Table 5. Treatment With Sparsentan Reduces Proteinuria

	Week	Irbesartan (n=187)	Sparsentan (n=184)
UPCR			
% change from baseline by visit week (95% CI)	36	**-36.2** (43.44, -28.03)	**-51.0** (-56.61, -44.67)
	108	**-32.3** (42.56, -20.21)	**-50.0** (-57.73, -40.81)
FPRE			
UPCR ≤1.5 g/g and a >40% reduction from baseline (95% CI)	36	**26.8** (19.70, 38.87)	**45.9** (38.32, 53.54)
	108	**22.6** (15.31, 29.94)	**37.5** (29.14, 45.82)

Complete Remission of Proteinuria

After 108 weeks of treatment, patients on sparsentan were 2× more likely to achieve complete remission. In the sparsentan treatment group, 34 patients (18%) achieved complete remission of proteinuria (UPCR <0.3 g/g) at any time in the double-blind period, compared to 14 patients (7%) in the irbesartan group.[2]

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, ESRD, or death and of a confirmed 50% reduction in eGFR, ESRD, or renal death are presented in **Table 6**.[2]

Table 6. Composite Renal Endpoints Trended Favorably for Sparsentan

	Irbesartan (n=187), n (%)	Sparsentan (n=184), n (%)	Sparsentan vs. Irbesartan
Confirmed 40% Reduction in eGFR, ESRD, or Death During the Study - Events	**43** (23.0)	**37** (20.1)	**RR: 0.87** (0.60, 1.26)[a]
Confirmed 50% Reduction in eGFR, ESRD, or Renal Death During the Study - Events	**31** (16.6)	**21** (11.4)	**RR: 0.68** (0.43, 1.10)[a]
End-Stage Renal Disease (ESRD)	21 (11)	12 (7)	**RR: 0.58** (0.31, 1.07)
Confirmed eGFR <15 mL/min/1.73 m^2	11 (6)	5 (3)	
Renal Replacement Therapy	13 (7)	10 (5)	
Death	3 (2)	4 (2)	
Renal Death	0 (0)	0 (0)	

[a]Relative risk of events and 95% CI from CMH Test.

Safety

Data at 36 weeks of treatment indicated that sparsentan was generally well-tolerated and no new safety signals emerged. Overall tolerability was comparable to the active control irbesartan.[2]

Over 108 weeks of treatment, TEAEs were reported with similar frequency in the sparsentan (n=172, 93%) and irbesartan (n=174, 93%) treatment groups. Serious TEAEs occurred in 44 (24%) sparsentan-treated patients and 41 (22%) irbesartan-treated patients. There was a total of 12 (3%) events of abnormal liver function tests in the study, with 7 (4%) events in the sparsentan arm and 5 (3%) events in the irbesartan arm. There were no reports of Hy's law or drug-induced liver injury with sparsentan. SAEs due to peripheral edema occurred in 3% of patients treated with irbesartan and none in the sparsentan group and there were no SAEs due to CHF. No new safety signals emerged.[2]

To date, sparsentan was well-tolerated with a consistent safety profile across all clinical trials and comparable to irbesartan.[2]

Abbreviations

ACEi, angiotensin-converting enzyme inhibitor; AE, adverse event; AEOI, adverse events of interest; ALT, alanine transaminase; ARB, angiotensin receptor blocker; AST, aspartate aminotransferase; AT_1, angiotensin II type 1; BL, baseline; CHF, congestive heart failure; CI, confidence interval; CMH, Cochran-Mantel-Haenszel; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; ET_A, endothelin-1 type A; EU, European Union; FAS, full analysis set; FPRE, FSGS partial remission endpoint; FSGS, focal segmental glomerulosclerosis; IgA, immunoglobulin A; KF, kidney failure, KRT, kidney replacement therapy; LS, least squares; MMRM, mixed model repeated measures; OLE, open-label extension; RASI, renin-angiotensin system inhibitor; RR, relative risk; SAE, serious adverse event; SE, standard error; SOC, standard of care;

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

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