FILSPARI® (sparsentan)
DUPLEX (Phase 3 Study): Study Design & Results

Summary

Prescribing Information

- FILSPARI is indicated to reduce proteinuria in adults with primary immunoglobulin A nephropathy (IgAN) at risk of rapid disease progression, generally a urine protein-to-creatinine ratio (UPCR) ≥1.5 g/g[1]

Background

- Sparsentan is an investigational therapeutic candidate for the treatment of FSGS[2,3]

Study Data

- 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[4]
- 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[4]
- At Week 112, mean change in eGFR from baseline was −10.4 mL/min/1.73 m^2 with sparsentan and −12.1 mL/min/1.73 m^2 with irbesartan[4]
- At 108 weeks, the least-squares geometric mean reduction in UPCR from baseline was 50% for sparsentan compared to 32.3% for irbesartan[4]
- 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%)[4]
- Sparsentan had a comparable safety profile to irbesartan, and heart failure and liver injury were not identified as safety concerns[4]

Prescribing Information

FILSPARI is indicated to reduce proteinuria in adults with primary immunoglobulin A nephropathy (IgAN) at risk of rapid disease progression, generally a urine protein-to-creatinine ratio (UPCR) ≥1.5 g/g.[1]

For more information, please refer to the attached Prescribing Information.

Background

Sparsentan is an investigational therapeutic candidate for the treatment of FSGS.[2,3]

Sparsentan is a novel, first-in-class, and the only single molecule antagonist of the ET_A and AT_1 receptors.[3,5,6] 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.[7-9]

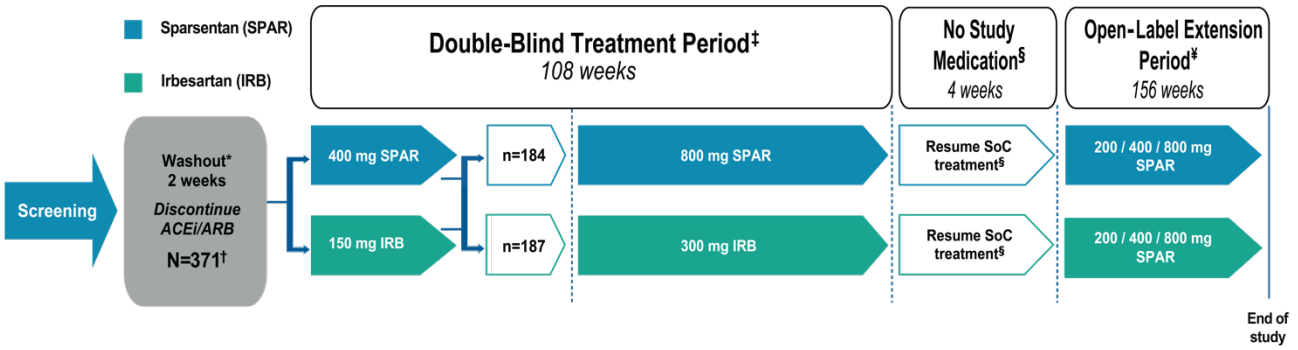
The DUPLEX Study

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.[2,4] 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.[4] 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.[2,4]

Study Design

Following the 2-week washout period from RAASi, 371 patients were randomized to receive either sparsentan (n=184) or irbesartan (n=187) and subsequently dose titrated to the maximum dose of either 800 mg of sparsentan or 300 mg of irbesartan, as tolerated. The double-blind treatment period continued for 108 weeks, after which patients discontinued study medication and resumed standard of care treatment for 4 weeks.[2,10] Eligible patients then had the option to participate in an open-label extension with sparsentan treatment.[10,11] Study details are presented in **Figure 1**.[2,10,11]

Figure 1. DUPLEX Study Design



*For patients who are undergoing washout from RAASi; †Patients randomized 1:1 to SPAR or IRB; ‡Patients whose body weight ≤50 kg at screening will receive half the otherwise specified dose of either SPAR or IRB; §Patients will resume SoC treatment including RAASi with the exception of IRB; ¥Starting dose and maximum maintenance dose of SPAR for the open-label extension will be based on the percentage of target dose at the end of the blinded treatment period.

Endpoints

The DUPLEX study endpoints are listed in **Table 1**. The study protocol provided for an unblinded analysis of at least 190 patients to be performed after 36 weeks of treatment to evaluate the interim efficacy endpoint: proportion of patients achieving FPRE, defined as UPCR ≤1.5 g/g and a >40% reduction in UPCR from baseline at Week 36.[2,10]

Table 1. DUPLEX Study Endpoints

Efficacy Endpoints	Safety Endpoints

Primary
• Rate of change in eGFR over 108 weeks of treatment
• Interim efficacy endpoint: proportion of patients achieving a UPCR ≤1.5 g/g and a >40% reduction from baseline in UPCR (*modified definition of partial remission*) at Week 36
Key secondary
• Percent change in eGFR from baseline to 4 weeks post-cessation of randomized treatment at Week 112
	• Incidence of TEAEs
	• Change from baseline in:
	  ○ Body weight
	  ○ Vital signs
	  ○ Physical examinations
	  ○ Peripheral edema
	  ○ 12-lead electrocardiogram
	  ○ Clinical laboratory parameters

Study Data

Baseline Characteristics

A total of 371 patients (336 adult, 35 pediatric aged <18 years) from 22 countries were randomized and received at least one dose of study drug. The majority of patients were male (53.9%), White (73.0%), and from North America (38.8%) and Europe (36.1%). Median age was 42.0 (IQR, 27.0-56.0) years. At baseline, 30.2% of patients presented with a history of nephrotic

syndrome, and 64.2% of patients had a history of hypertension. Mean systolic/diastolic blood pressure was 131.9/83.8 mm Hg at baseline after a 2-week RAASi washout period. Edema was present in 38.0% of patients. In total, 73.0% of patients received a RAASi before the 2-week washout period. Medications taken by patients from baseline into the double-blind treatment period included non-RAASi antihypertensive medications (59.0%), lipid-lowering medications (58.5%), and immunosuppressants (24.8%). Additional baseline demographic information is available in **Table 2**.[12]

Table 2. Patient Baseline Characteristics in the DUPLEX Study

	All Patients (N=371)	Adult Patients (n=336)	Pediatric Patients (n=35)
Age at informed consent, years			
Median (IQR)	42.0 (27.0-56.0)	44.0 (33.0-57.0)	14.0 (12.0-16.0)
Mean ± SD	41.6 ± 16.9	44.5 ± 15.1	14.1 ± 2.3
Sex, n (%)			
Male	200 (53.9)	188 (56.0)	12 (34.3)
Female	171 (46.1)	148 (44.0)	23 (65.7)
Race, n (%)[a]			
White	271 (73.0)	246 (73.2)	25 (71.4)
Asian	49 (13.2)	48 (14.3)	1 (2.9)
Black or African American	25 (6.7)	21 (6.3)	4 (11.4)
Other	26 (7.0)	21 (6.3)	5 (14.3)
Ethnicity, n (%)			
Not Hispanic or Latino	281 (75.7)	260 (77.4)	21 (60.0)
Hispanic or Latino	79 (21.3)	65 (19.3)	14 (40.0)
Not reported	7 (1.9)	7 (2.1)	0 (0.0)
Unknown	4 (1.1)	4 (1.2)	0 (0.0)
Age at FSGS diagnosis, median (IQR), years[b]	37.0 (23.0-51.0)	40.0 (27.0-53.0)	12.5 (10.0-15.0)
Time from FSGS diagnosis to informed consent, years[c]	2.0 (1.0-6.0)	2.0 (1.0-6.0)	2.0 (1.0-5.0)
History of diabetes and impaired fasting glucose, n (%)	58 (15.6)	58 (17.3)	0 (0.0)
HbA1c, all patients, mean ± SD	5.5 ± 0.6	5.5 ± 0.6	5.1 ± 0.4
HbA1c, patients with diabetes or impaired fasting glucose, mean ± SD	6.4 ± 0.8	6.4 ± 0.8	n/a
History of hypertension, n (%)	238 (64.2)	227 (67.6)	11 (31.4)
Blood pressure, mm Hg, mean ± SD			
Systolic	131.9 ± 14.9	133.4 ± 14.4	117.4 ± 12.5
Diastolic	83.8 ± 10.5	84.7 ± 10.2	75.7 ± 10.4
BMI, kg/m^2, mean ± SD	27.7 ± 5.9	28.0 ± 5.7	24.9 ± 7.3
Documented history of nephrotic syndrome, n (%)[d]	112 (30.2)	91 (27.1)	21 (60.0)
Baseline nephrotic syndrome, n (%)[e]	54 (14.6)	41 (12.2)	13 (37.1)

Data are given as n (%) or median (IQR) unless otherwise noted.
[a]Patients who selected more than 1 race are included in Other. "Other" race included American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, and Other.
[b]Age at FSGS diagnosis is derived based on the year of FSGS diagnosis and year of birth.
[c]Time from FSGS diagnosis is derived based on the year of FSGS diagnosis and year of signed informed consent.
[d]A patient was considered to have documented history of nephrotic syndrome if the term "Nephrotic syndrome" was present in their medical history or if all of the following conditions were met at any of the visits before the first dose of randomized treatment: UPCR >3.5 g/g (adults) or UPCR >2 g/g (pediatrics), serum albumin <3.0 g/dL, and abnormal edema from physical examination.
[e]Defined as patients with all of the following before first dose: UPCR >3.5 g/g (adults) or >2 g/g (pediatrics); serum albumin <3.0 g/dL; and abnormal edema from physical examination.

Median UPCR was 3.0 g/g at baseline, with 42.6% of patients within nephrotic range. Mean eGFR at baseline was 63.8 mL/min/1.73 m^2, with patients broadly distributed across eGFR categories corresponding to CKD stage (**Table 3**). Of 352 evaluated patients, 33 (9%) had pathogenic or likely pathogenic genetic variants associated with monogenic forms of genetic FSGS.[12]

Table 3. Patient eGFR Categories at Baseline

eGFR	All Patients (N=371)	Adult Patients (n=336)	Pediatric Patients (n=35)
≥90 mL/min/1.73 m²	70 (18.9)	58 (17.3)	12 (34.3)
≥60 to <90 mL/min/1.73 m²	98 (26.4)	86 (25.6)	12 (34.3)
≥45 to <60 mL/min/1.73 m²	79 (21.3)	74 (22.0)	5 (14.3)
≥30 to <45 mL/min/1.73 m²	101 (27.2)	95 (28.3)	6 (17.1)
≥15 to <30 mL/min/1.73 m²	23 (6.2)	23 (6.8)	0 (0.0)

Data are given as n (%).

Efficacy

Primary Efficacy Endpoint

Sparsentan did not achieve the primary efficacy eGFR slope endpoint over 108 weeks of treatment.[4]

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**).[4]

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).

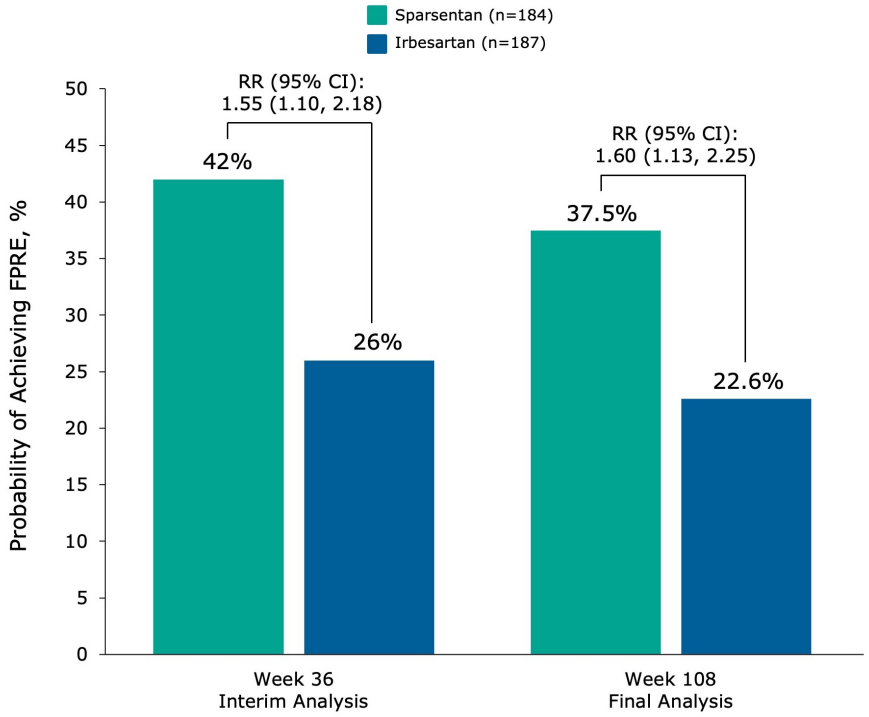
Secondary and Exploratory Endpoints

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

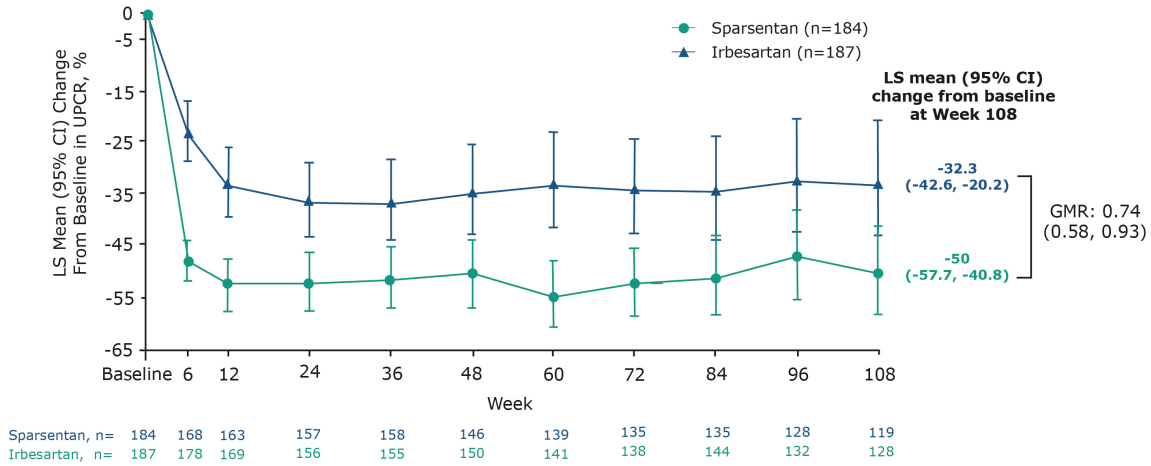
Analysis included an interim efficacy endpoint, the proportion of patients achieving FPRE, defined as UPCR ≤1.5 g/g and a >40% reduction in UPCR from baseline at Week 36 (**Figure 2**). Sparsentan achieved a statistically significant response on the interim proteinuria endpoint at Week 36 compared to irbesartan, with 42% of patients receiving sparsentan experiencing FPRE vs 26% of irbesartan-treated patients (*P*=0.009).[4,13] 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.[4]

Figure 2. 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 3**).[4]

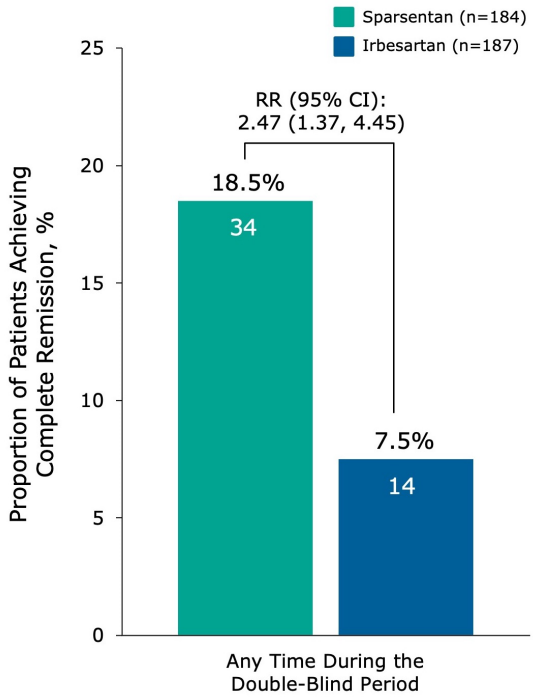
Figure 3. Decline in UPCR Through 108 Weeks of Sparsentan Treatment



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 4**).[4]

Figure 4. Proportion of Patients Achieving Complete Remission of Proteinuria



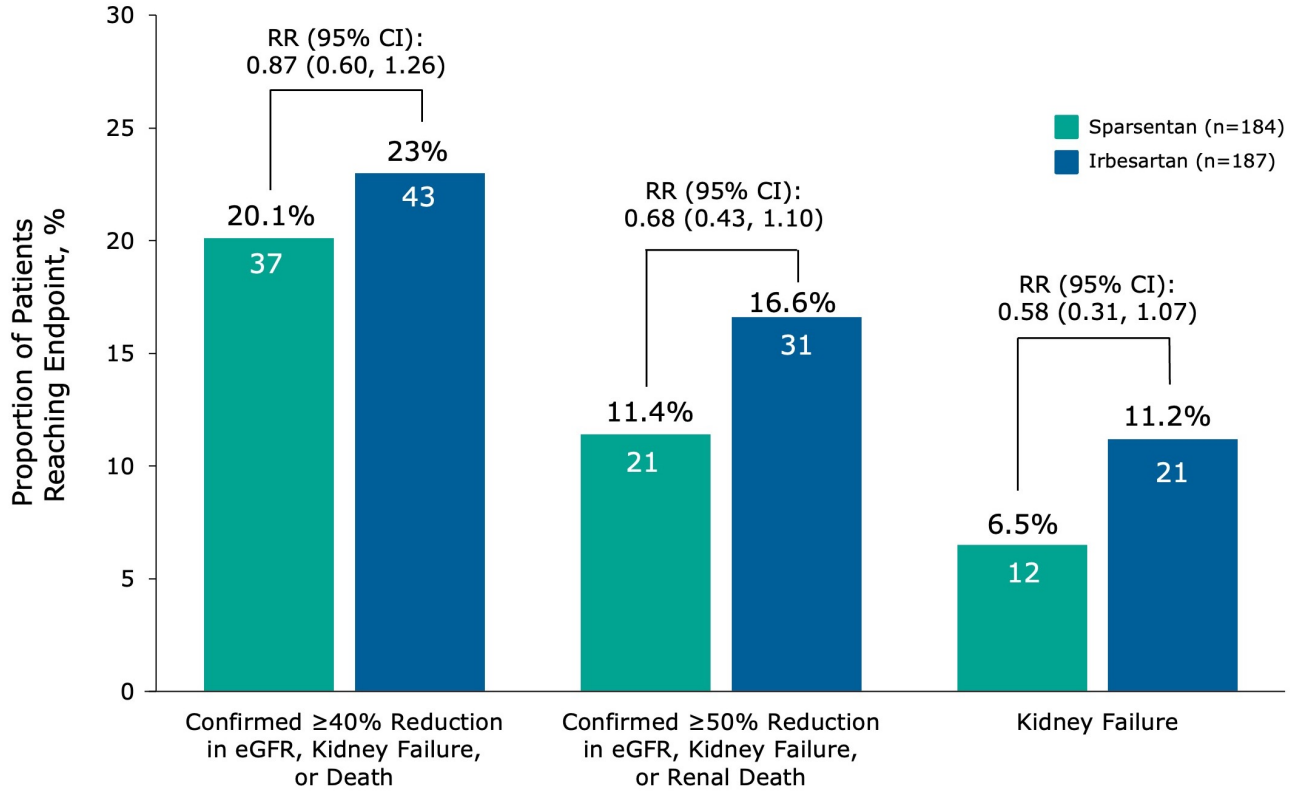
Complete remission defined as UPCR <0.3 g/g.

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).[4,14]

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 5**.[4]

Figure 5. 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. Additional safety data is presented in **Table 5**.[4]

Table 5. Summary of TEAEs in the DUPLEX Study

Variable	Sparsentan (n=184)	Irbesartan (n=187)
	n (%)	
Any AE	172 (93.5)	174 (93)
TEAE*	88 (47.8)	88 (47.1)
SAE	68 (37)	82 (43.9)
AE leading to treatment discontinuation	26 (14.1)	22 (11.8)
AE leading to death†	4 (2.2)	3 (1.6)
AEs reported in ≥10% of patients‡		
COVID-19	41 (22.3)	50 (26.7)
Diarrhea	25 (13.6)	27 (14.4)
Nausea	10 (5.4)	18 (9.6)
Hyperkalemia	31 (16.8)	20 (10.7)
Peripheral edema	36 (19.6)	41 (21.9)
Blood creatine kinase increased	19 (10.3)	8 (4.3)
Muscle spasms	25 (13.6)	15 (8)
Back pain	15 (8.2)	20 (10.7)
Hypotension	33 (17.9)	21 (11.2)
Hypertension	20 (10.9)	24 (12.8)
Chronic kidney disease	13 (7.1)	22 (11.8)
Dizziness	23 (12.5)	21 (11.2)
Headache	20 (10.9)	23 (12.3)
Anemia	24 (13)	10 (5.3)

* Treatment-related adverse events were defined as events that were considered to be "related" or "possibly related" to the trial drug by the investigator. Events with missing relationship information were counted as treatment-related events.
† Adverse events that led to death included neuroendocrine carcinoma, subdural hematoma, coronavirus disease 2019 (COVID-19), and suicide (in 1 patient each) in the sparsentan group; and COVID-19 pneumonia, COVID-19, and respiratory distress (in 1 patient each) in the irbesartan group.
‡ If a patient had more than one event with a given preferred term, the patient was counted only once for that term.

Abbreviations

ACEi, angiotensin-converting enzyme inhibitor; AE, adverse event; ALT, alanine transaminase; ARB, angiotensin receptor blocker; AST, aspartate aminotransferase; AT_1, angiotensin II type 1; BMI, body mass index; BP, blood pressure; CI, confidence interval; CKD, chronic kidney disease; 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 mean ratio; HbA1c, hemoglobin A1c; IgAN, immunoglobulin A nephropathy; IQR, interquartile range; IRB, irbesartan; LS, least squares; n/a, not applicable; RAASi, renin-

angiotensin-aldosterone system inhibitor; RR, relative risk; SAE, serious adverse event; SD, standard deviation; SoC, standard of care; SPAR, sparsentan; TEAE, treatment-emergent adverse event; ULN, upper limit of normal; UPCR, urine protein-to-creatinine ratio; US, United States.

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