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

Summary

Prescribing Information

The labeling 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.

- After 36 weeks of treatment, patients receiving FILSPARI achieved a mean reduction in UPCR from baseline of 45 percent, compared to a mean reduction in proteinuria from baseline of 15 percent for irbesartan-treated patients ($P<0.0001$). The treatment effect on UPCR at Week 36 was consistent across subgroups such as age, gender, race, and baseline eGFR and proteinuria levels[1]

Background

- The PROTECT study is a phase 3, global, randomized, multicenter, double-blind, parallel-arm, active-control study of the efficacy and safety of sparsentan compared to irbesartan for the treatment of IgA nephropathy[2]

Study Data

- Treatment with sparsentan resulted in a clinically meaningful difference compared to irbesartan in eGFR total slope (1.0 mL/min/1.73 m^2 per year; $P=0.058$) and eGFR chronic slope (1.1 mL/min/1.73 m^2 per year; $P=0.037$)[3]
- Over 2 years of treatment, patients treated with sparsentan experienced a slower rate of decrease in eGFR compared to patients taking irbesartan (−2.7 to −2.9 mL/min/1.73 m^2 per year)[3]
- 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 ($P<0.0001$)[4]
- At Week 110, proteinuria was 40% lower in the sparsentan group compared to the irbesartan group. Patients taking sparsentan experienced a mean reduction in UPCR from baseline of 42.8% compared to 4.4% for patients taking irbesartan[3]
- The composite kidney endpoint, defined as confirmed 40% reduction in eGFR, end-stage kidney disease, or all-cause mortality, was reached by 18 (9%) patients in the sparsentan group compared to 26 (13%) patients taking irbesartan[3]
- 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[3,5]

Prescribing Information

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After 36 weeks of treatment, patients receiving FILSPARI achieved a mean reduction in UPCR from baseline of 45 percent, compared to a mean reduction in proteinuria from baseline of 15 percent for irbesartan-treated patients (P<0.0001). The treatment effect on UPCR at Week 36 was consistent across subgroups such as age, gender, race, and baseline eGFR and proteinuria levels.[1]

For more information, 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.[6-8] 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.[9-11]

The PROTECT Study

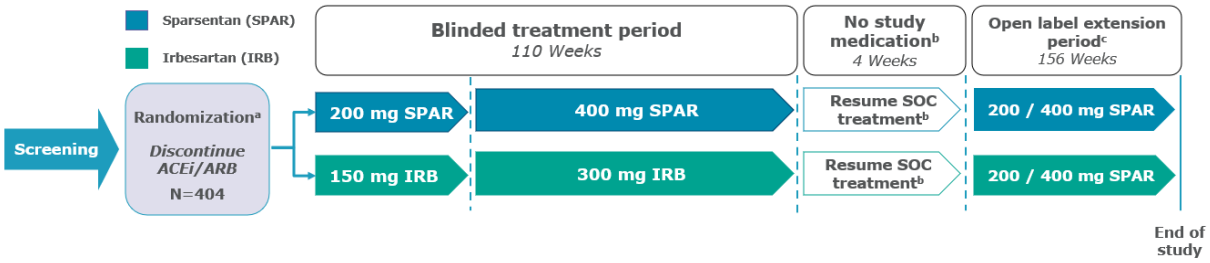
The PROTECT study (NCT03762850) is a phase 3, global, randomized, multicenter, double-blind, parallel-arm, active-controlled clinical trial evaluating long-term antiproteinuric and nephroprotective efficacy and safety of 400 mg of sparsentan in patients with IgA nephropathy compared to 300 mg of irbesartan.[12] 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. Patients with urine protein ≥1 g/day at screening, eGFR ≥30 mL/min/1.73 m^2, SBP ≤150 mm Hg, and DBP ≤100 mm Hg were eligible.[13] 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.[2,13] 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.[14] Reduction in proteinuria and decline in rate of eGFR are largely accepted as surrogate markers of treatment effect in studies of KF.[14,15]

Study Design

After the screening period, patients were randomized to receive either sparsentan or irbesartan, the active control, and subsequently dose titrated to the maximum dose of either 400 mg of sparsentan or 300 mg of irbesartan, as tolerated. The blinded treatment period was 110 weeks,

after which patients discontinued study medication and resumed SOC treatment for 4 weeks. Afterwards, patients had the option to participate in an open-label extension with sparsentan treatment if eligibility criteria were met (**Figure 1**).[16]

Figure 1. PROTECT Study Design



[a]On Day 1, patients will be randomized 1:1 to SPAR or IRB. [b]Patients will resume SOC treatment, including RAASi treatment. Where possible, the same treatment regimen the patient was on at study entry (ie, the same ACEi and/or ARB at the same dose[s]) should be used. [c]Starting dose of SPAR for the open-label extension will be 200 mg. Titration to 400 mg will be based on tolerability after 2 weeks of treatment in the open-label extension.

Endpoints

The PROTECT study endpoints are listed in **Table 1**.[16]

Table 1. PROTECT Study Endpoints

Key Endpoints	Safety Endpoints
Primary • Change in UPCR from baseline at Week 36 **Key secondary** • Rate of change in eGFR over 52-week period (from Week 6 to Week 58) • Rate of change in eGFR over 104-week period (from Week 6 to Week 110) • Rate of change in eGFR over 110-week period following initiation of randomized treatment	• Incidence of TEAEs • Changes from baseline in: o Body weight o Vital signs o Physical examinations o Peripheral edema o Clinical laboratory parameters

Study Data

Baseline Characteristics

A total of 404 patients were enrolled in the PROTECT study; 199 (98%) sparsentan patients and 191 (94%) irbesartan patients completed the double-blind study phase. Among these, 174 (86%) and 154 (76%) patients in the sparsentan and irbesartan groups, respectively, completed 110 weeks of treatment. The mean age of participants at time of diagnosis was 40.2 years (SD, 13.4) among patients randomized to the sparsentan group and 39.0 years (SD, 12.4) for those randomized to irbesartan. Median (IQR) time from initial kidney biopsy to informed consent for

study participation was 4.0 (1.0-10.0) years for both sparsentan and irbesartan groups. Mean eGFR was 56.8 mL/min/1.73 m^2 (SD, 24.3) and 57.1 mL/min/1.73 m^2 (SD, 23.6) in the sparsentan and irbesartan groups, respectively (**Table 2**).[3,17]

Table 2. Baseline Characteristics of Patients Enrolled in PROTECT

	Sparsentan (n=202)	Irbesartan (n=202)
Age at informed consent, mean (SD), years	46.6 (12.8)	45.4 (12.1)
Sex, n (%)		
Male	139 (69)	143 (71)
Female	63 (31)	59 (29)
Race, n (%)*		
Asian	67 (33)	48 (24)
Black or African American	1 (<1)	3 (1)
Native Hawaiian or Other Pacific Islander	0 (0)	1 (<1)
White	130 (64)	142 (70)
Other	4 (2)	9 (4)
Ethnicity, n (%)		
Hispanic or Latino	17 (8)	16 (8)
Not Hispanic or Latino	185 (92)	182 (91)
Not reported	0 (0)	3 (1)
Age at IgAN diagnosis, mean (SD), years†	40.2 (13.4)	39 (12.4)
Time from initial kidney biopsy to informed consent, median (IQR), years‡	4 (1-10)	4 (1-10)
History of hypertension, n (%)	146 (72)	144 (71)
Blood pressure, mean (SD), mm Hg		
Systolic	128 (14.4)	129.9 (12.4)
Diastolic	81.6 (10.6)	83.2 (10.6)
Urine protein excretion, median (IQR), g/d	1.8 (1.2-2.9)	1.8 (1.3-2.6)
UPCR, median (IQR), g/g	1.3 (0.8-1.8)	1.2 (0.9-1.7)
Hematuria, n (%)	111 (55)	114 (56)
eGFR, mean (SD), mL/min/1.73 m^2§	56.8 (24.3)	57.1 (23.6)
eGFR category, n (%)		
≥90 mL/min/1.73 m^2	26 (13)	25 (12)
≥60 to <90 mL/min/1.73 m^2	49 (24)	48 (24)
≥45 to <60 mL/min/1.73 m^2	45 (22)	49 (24)
≥30 to <45 mL/min/1.73 m^2	67 (33)	75 (37)
<30 mL/min/1.73 m^2¶	15 (7)	5 (2)
Serum albumin, mean (SD), g/L	41.2 (3.9)	41.7 (3.8)
ACEi or ARB at maximum labeled dose at screening, n (%)‖	130 (64)	125 (62)
Baseline concomitant medication use, n (%)**		
Antihypertensive medications††	90 (45)	88 (44)
Lipid lowering medications	114 (56)	116 (57)
eGFR, mean (SD), mL/min/1.73 m^2	56.8 (24.3)	57.1 (23.6)
Subgroups: baseline proteinuria quartiles		
UPCR <0.80 g/g	57.3 (24.0)	61.9 (27.3)
UPCR ≥0.80 to <1.25 g/g	60.6 (25.0)	59.3 (25.2)
UPCR ≥1.25 to <1.80 g/g	55.9 (24.0)	55.1 (21.9)
UPCR ≥1.80 g/g	53.6 (24.5)	52.1 (18.8)

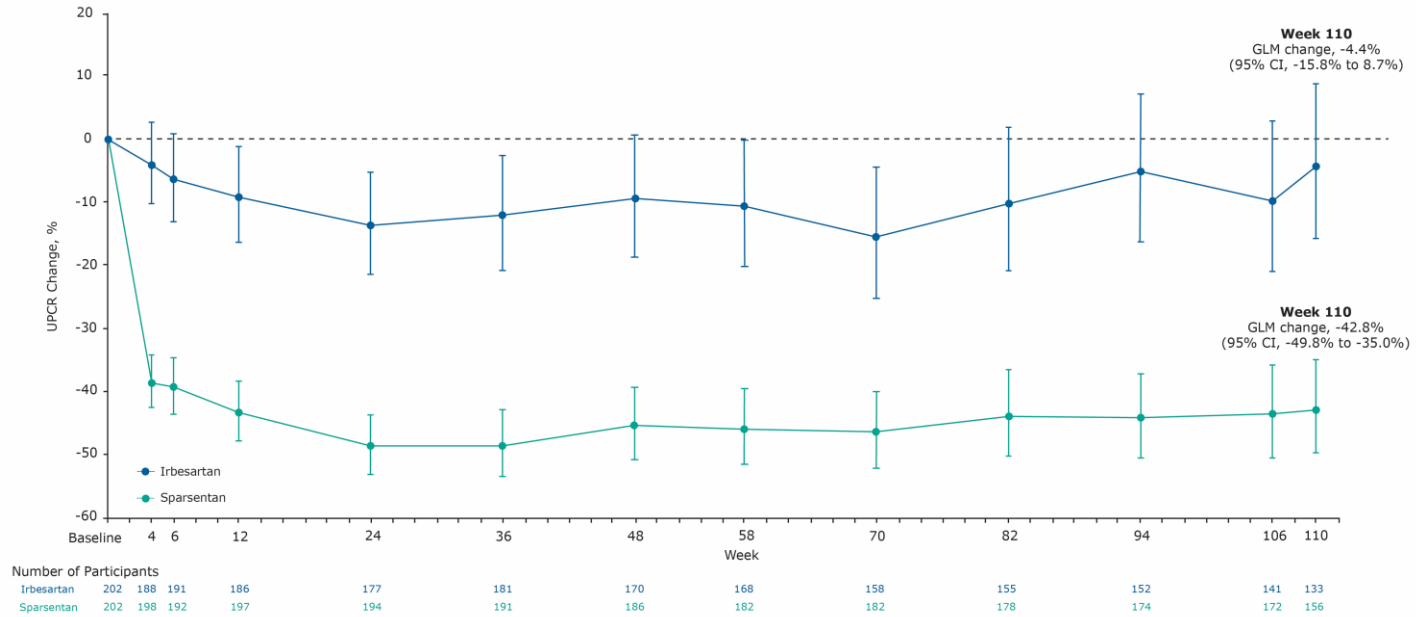
Data are mean (SD), n (%), or median (IQR). Percentages might not sum to 100 as a result of rounding.
*Patients might have selected more than one race. †Age at IgA nephropathy diagnosis is derived based on the year of diagnosis and year of birth. ‡Time from initial biopsy is derived based on the year of the initial kidney biopsy and year of signed informed consent. §eGFR was determined using the Chronic Kidney Disease Epidemiology Collaboration equation.[18] ¶Patients progressed from chronic kidney disease stage 3 to 4 between randomization and first dose of study drug. ‖ACEi and ARB treatment at screening; RAASis were prohibited during the study. **Baseline concomitant medications were started before and continued after the initial dose of study medication. ††Antihypertensive medications exclude ACEi, ARBs, aldosterone blockers, and aliskiren.

Titration to maximum labeled dose was achieved by 192 (95%) patients taking sparsentan and 196 (97%) patients taking irbesartan.[5]

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 ($P<0.0001$). 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.[14] Reduction in proteinuria was maintained over the course of treatment. At Week 110, patients taking sparsentan experienced a mean reduction in UPCR from baseline of 42.8% compared to 4.4% for patients taking irbesartan (**Figure 2**). The relative reduction in UPCR was 40% lower in sparsentan vs irbesartan-treated patients, comparable to a 41% relative reduction between treatments at Week 36.[3]

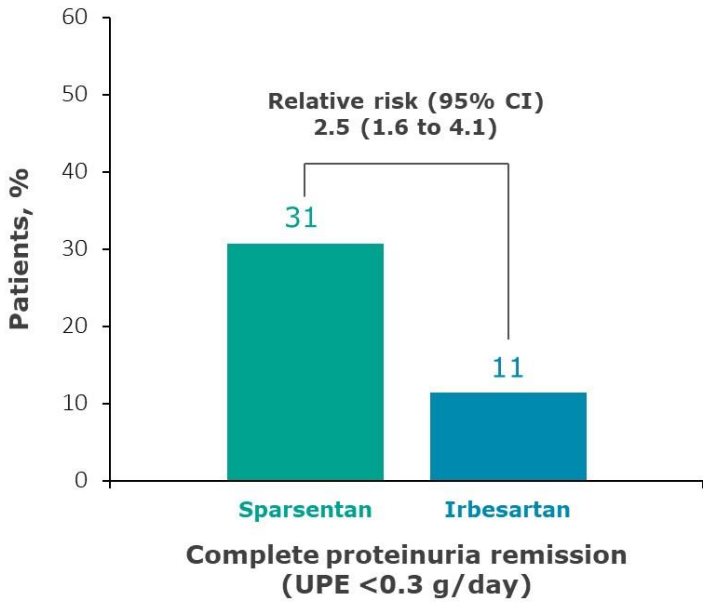
Figure 2. Sustained Reduction in Proteinuria Over 110 Weeks



Error bars indicate 95% CIs.

Relative risk to achieve complete proteinuria remission for sparsentan and irbesartan groups is described in **Figure 3**.[17]

Figure 3. Relative Risk in Complete Proteinuria Remission



The proteinuria-lowering effect was unlikely to be attributed to the modest reduction in blood pressure. Treatment with sparsentan resulted in a large difference in proteinuria reduction compared to irbesartan, despite minimal differences in blood pressure changes between the groups.[14]

Combined interim and confirmatory PROTECT study results demonstrated that sparsentan has a rapid and durable effect on proteinuria after 2 years of treatment.[19]

Key Secondary Efficacy Endpoint

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.[19]

- 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

Efficacy endpoints assessing preservation of kidney function favored sparsentan over irbesartan following 2 years of treatment (**Table 3**). 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 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).[3]

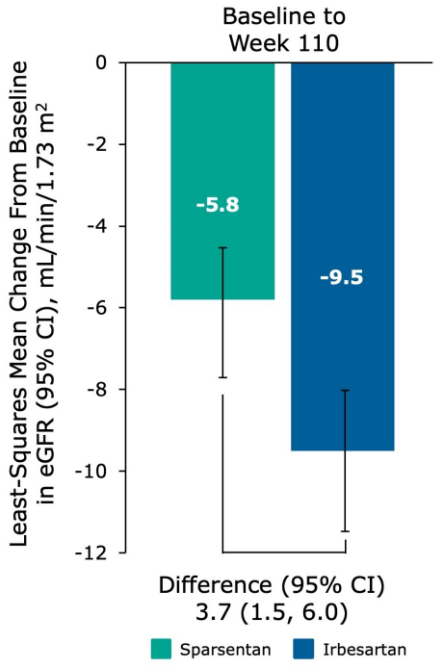
Table 3. Treatment With Sparsentan Demonstrated Long-Term Kidney Function Preservation

Key Secondary Efficacy Endpoints*	Sparsentan Group (n=202)	Irbesartan Group (n=202)	Between-Group Difference (95% CI)	p-value
Chronic slope from Week 6 to Week 110, mL/min/1.73 m² per year	-2.7 (-3.4, -2.1)	-3.8 (-4.6, -3.1)	1.1 (0.1, 2.1)	0.037
Total slope from Day 1 to Week 110, mL/min/1.73 m² per year	-2.9 (-3.6, -2.2)	-3.9 (-4.6, -3.1)	1.0 (-0.03, 1.94)	0.058

Data are geometric least-squares mean (95% CI) change in proteinuria from baseline to Week 110 unless otherwise stated.
*Assessed in the full analysis set.

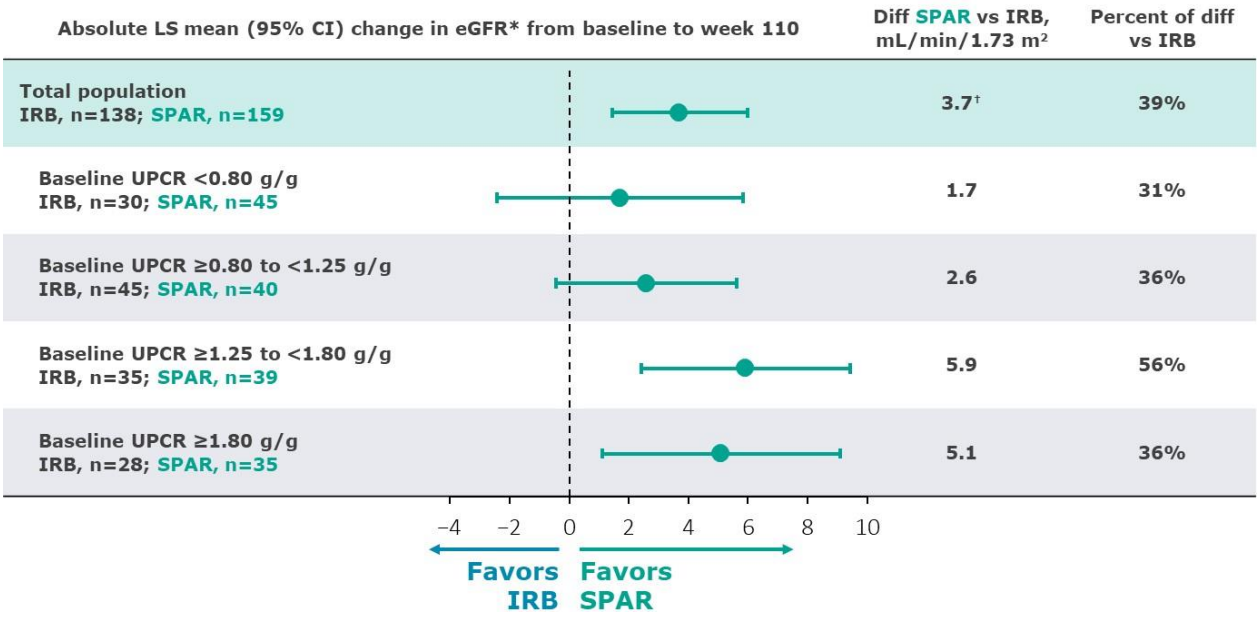
Least-squares mean absolute change in eGFR from baseline to Week 6 was similar between sparsentan and irbesartan (−1.2 mL/min/1.73 m^2 and −1.6 mL/min/1.73 m^2, respectively; difference=0.4). Least-squares mean absolute change in eGFR from baseline to Week 110 was lower with sparsentan versus irbesartan (−5.8 mL/min/1.73 m^2 and −9.5 mL/min/1.73 m^2, respectively; difference=3.7) (**Figure 4**). This effect was maintained 4 weeks after stopping study treatment and resuming SOC; change from baseline to Week 114 was −6.1 mL/min/1.73 m^2 with sparsentan and −9.0 mL/min/1.73 m^2 with irbesartan (difference=2.9).[3]

Figure 4. Change in eGFR From Baseline to Week 110



The sustained effect of sparsentan on eGFR at Week 110 was observed across all UPCR subgroups (**Figure 5**). [17]

Figure 5. eGFR Reduction per Baseline UPCR Subgroups

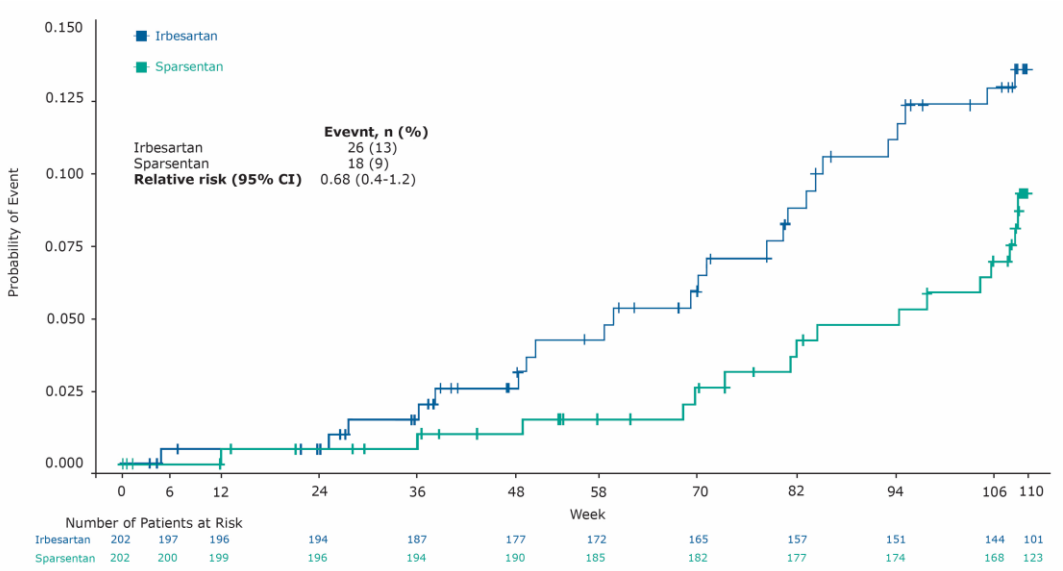


*On-treatment eGFR. †*P*=.001

Composite Endpoint

Secondary endpoints included a composite of kidney failure, defined as confirmed 40% eGFR reduction, kidney failure, or all-cause mortality. The composite endpoint was reached by 18 (9%) patients taking sparsentan and 26 (13%) patients taking irbesartan (**Figure 6**). Among these patients, 18 (9%) sparsentan-treated patients and 22 (11%) irbesartan-treated patients had confirmed 40% reduction in eGFR. In the sparsentan group, 9 (4%) patients reached kidney failure and no patient deaths occurred, compared to 11 (5%) patients who reached kidney failure and 1 patient who died in the irbesartan group.[3]

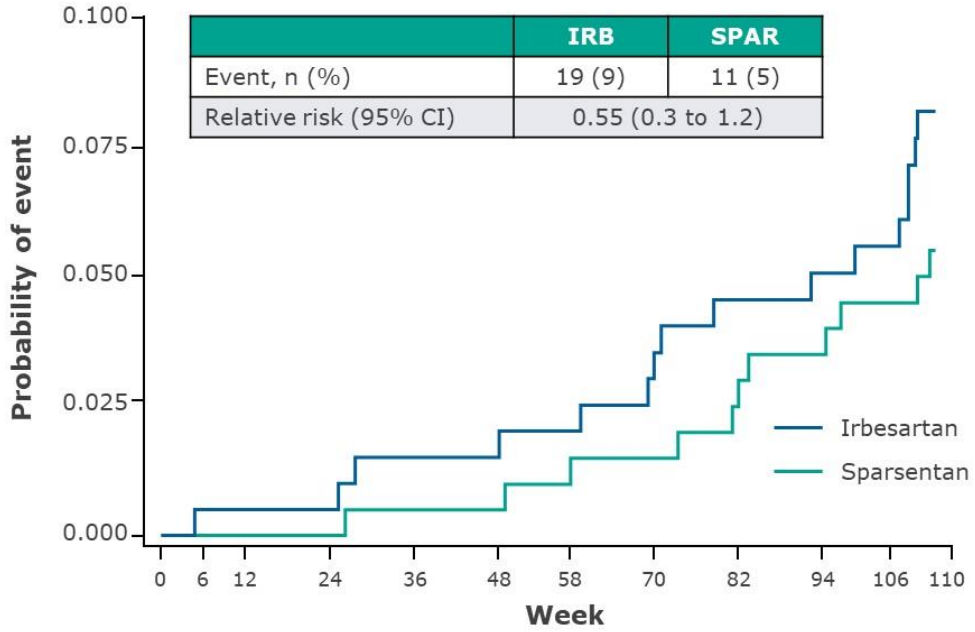
Figure 6. Time to Reach Composite Endpoint



Vertical bars indicate censored patients.

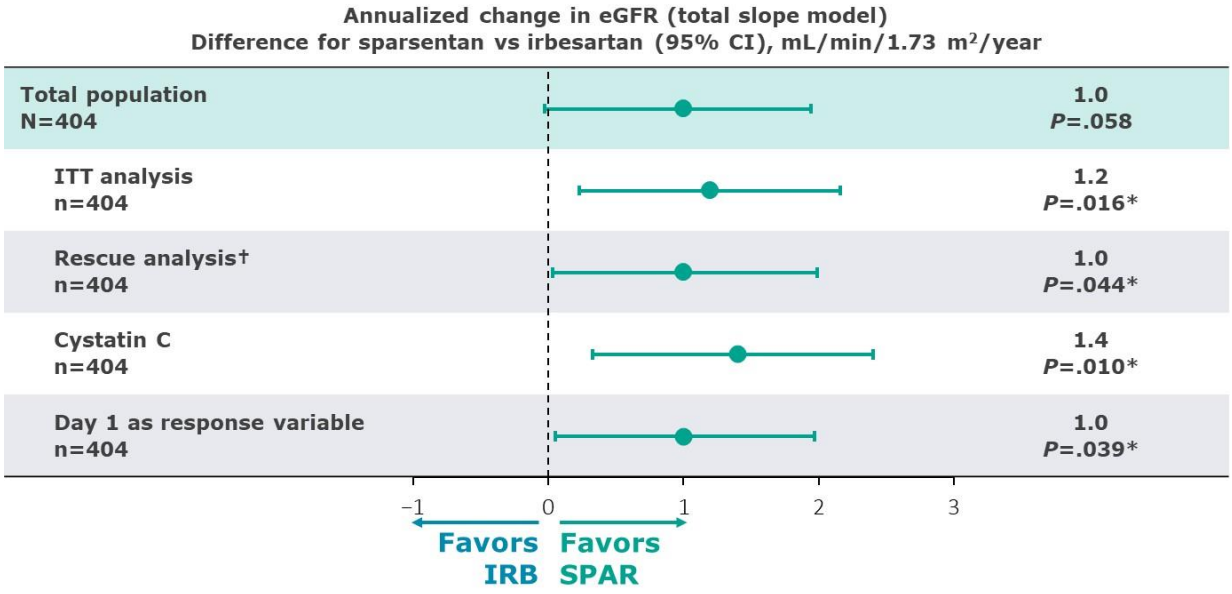
Time to reach 50% eGFR reduction, ESKD, or death was also evaluation (**Figure 7**).[17]

Figure 7. Confirmed 50% eGFR Reduction, ESKD, or Death



Long-term benefit of sparsentan and preservation of kidney function was further confirmed by eGFR sensitivity analysis (**Figure 8**). ITT analysis including all eGFR measurements through study end regardless of premature treatment discontinuations found an annualized difference (95% CI) between sparsentan and irbesartan in eGFR chronic slope of 1.3 (0.36 to 2.32) mL/min/1.73 m^2 per year. The difference between treatment groups in eGFR total slope was 1.2 (0.23 to 2.16) mL/min/1.73 m^2 per year. Rescue analysis excluded all eGFR measurements taken after initiation of rescue immunosuppression for renal diseases, which was initiated sooner and more frequently in the irbesartan group (n=16; 8%) than with sparsentan treatment (n=6; 3%).[3,5] The difference (95% CI) between treatment groups was 1.2 (0.16 to 2.15) mL/min/1.73 m^2 per year for chronic slope and 1.0 (0.03 to 1.99) mL/min/1.73 m^2 per year for total slope.[5,17]

Figure 8. Confirmed Long-term Effect of Sparsentan vs Irbesartan Treatment on eGFR



*Nominal *P* values. †Rescue analysis excludes eGFR measurements after initiation of rescue immunosuppression for renal disease.

Delay to Kidney Failure

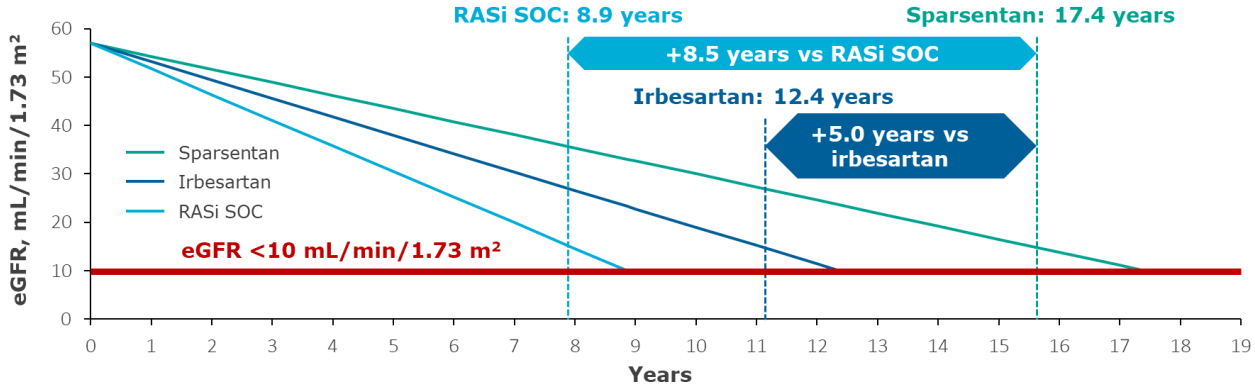
Treatment with sparsentan was associated with projected delay in time to KF, related to change in eGFR slope (**Figure 9**). Baseline eGFR was 57 mL/min/1.73 m^2, based on mean eGFR of the sparsentan group in the PROTECT study interim analysis. eGFR for SOC (maximized ACEi/ARB) equaled the mean of observed 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 17.4 years, 12.4 years, and 8.9 years for sparsentan, irbesartan, and SOC, respectively.[17]

- Compared to patients utilizing SOC, patients taking sparsentan experienced a mean 8.5years longer delay to KF

- Compared to patients taking irbesartan, sparsentan-treated patients experienced a mean 5.0years longer delay to KF

Figure 9. Treatment With Sparsentan Is Associated With Projected Delay in Time to Kidney Failure

	Sparsentan	Irbesartan	RASi SOC (ACEi/ARB)
eGFR chronic slope, mL/min/1.73 m²/year	−2.7	−3.8	−5.3*
Difference in eGFR slope vs sparsentan		1.1	2.6



Baseline (0 years) eGFR = 57 mL/min/1.73 m² based on the mean eGFR of all patients (N=404) reported in this study.
*Mean of observed slopes for maximized ACEi/ARB as reported in 5 clinical trials.

Safety

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. TEAEs were reported in 187 (93%) patients taking sparsentan and 177 (88%) irbesartan-treated patients. SAEs were reported by 75 (37%) patients taking sparsentan and 71 (35%) patients taking irbesartan.[3]

Peripheral edema was similar in both groups, with no increases in body weight. Change from no edema at baseline to severe edema occurred in 0 sparsentan-treated patients and 2 irbesartan-treated patients. Change from no edema to moderate edema occurred in 2 patients taking sparsentan and none taking irbesartan. Diuretic use initiated on or after beginning study drug was reported in 49 (24%) sparsentan patients and 54 (27%) irbesartan patients. The most frequently used class of diuretics was thiazides, utilized by 35 (17%) and 42 (21%) sparsentan and irbesartan patients, respectively. Hepatic TEAEs of interest of ALT or AST increasing >3× the ULN occurred in 5 (2%) patients in the sparsentan group and 7 (3%) patients in the irbesartan group. No cases of drug-induced liver injury occurred in either group.[3]

Additional safety data is reported in **Table 4**.

Table 4. TEAEs Over 2 Years of Sparsentan Treatment

	Sparsentan (n=202)	Irbesartan (n=202)
Any TEAE, n (%)	187 (93)	177 (88)
TEAEs in ≥5% of patients in ≥1 group		
COVID-19	53 (26)	46 (23)
Hyperkalemia	32 (16)	26 (13)
Peripheral edema	31 (15)	24 (12)
Dizziness	30 (15)	13 (6)
Headache	27 (13)	26 (13)
Hypotension	26 (13)	8 (4)
Hypertension	22 (11)	28 (14)
Upper respiratory tract infection	18 (9)	18 (9)
Fatigue	17 (8)	11 (5)
Anemia	16 (8)	9 (4)
Nasopharyngitis	15 (7)	16 (8)
Blood creatinine phosphokinase increased	15 (7)	10 (5)
Cough	15 (7)	7 (3)
Muscle spasms	14 (7)	17 (8)
Arthralgia	14 (7)	13 (6)
Proteinuria	13 (6)	15 (7)
Backpain	12 (6)	16 (8)
Lipase increased	12 (6)	9 (4)
Acute kidney injury	12 (6)	5 (2)
Gout	11 (5)	10 (5)
Pruritus	11 (5)	8 (4)
Diarrhea	10 (5)	19 (9)
Blood creatinine increased	10 (5)	14 (7)
ALT increased	10 (5)	8 (4)
Gastroesophageal reflux disease	10 (5)	8 (4)
Nausea	10 (5)	5 (2)
Myalgia	10 (5)	4 (2)
Renal impairment	7 (3)	12 (6)
Urinary tract infection	7 (3)	12 (6)
Hyperuricemia	7 (3)	11 (5)
Pain in extremity	6 (3)	12 (6)
Transaminase elevations,* n (%)	5 (2)	7 (3)
Serious TEAEs, n (%)	75 (37)	71 (35)
Serious TEAEs in ≥2 patients in ≥1 group, n (%)		
COVID-19	42 (21)	38 (19)
Chronic kidney disease	6 (3)	6 (3)
Acute kidney injury	4 (2)	1 (<1)
Dizziness	2 (1)	1 (<1)
Proteinuria	2 (1)	1 (<1)
Malaise	2 (1)	0 (0)
Appendicitis	1 (<1)	2 (1)
Cellulitis	1 (<1)	2 (1)
COVID-19 pneumonia	1 (<1)	2 (1)
IgAN	1 (<1)	2 (1)
Meniscus injury	1 (<1)	2 (1)
TEAEs leading to treatment discontinuation in ≥2 patients in ≥1 group, n (%)	21 (10)	18 (9)
Chronic kidney disease	3 (1)	3 (1)
Acute kidney injury	3 (1)	0 (0)
ALT increased	3 (1)	0 (0)
Hypotension	2 (1)	0 (0)
Lipase increased	2 (1)	0 (0)
Renal impairment	1 (<1)	4 (2)
TEAEs leading to death, n (%)	0 (0)	1 (<1)†

* Abnormal liver function test results that met the following criteria: (1) new elevation in ALT or AST of >3× ULN with or without elevation of total serum bilirubin of >2× ULN and (2) two-fold increase in ALT or AST above the baseline value in patients who had elevated values before taking study medication.

† One patient in the irbesartan group died due to a severe AE of cardiorespiratory arrest that was considered not related to study drug.

Abbreviations

ACEi, angiotensin-converting enzyme inhibitor; AE, adverse event; ALT, alanine aminotransferase; ARB, angiotensin receptor blocker; AST, aspartate aminotransferase; AT_1, angiotensin II type 1; CI, confidence interval; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; ET_A, endothelin-1 type A; EU, European Union; GLM, geometric least squares mean; IgA, immunoglobulin A; IgAN, immunoglobulin A nephropathy; IQR, interquartile range; IRB, irbesartan; ITT, intention-to-treat; KF, kidney failure; KRT, kidney replacement therapy; LS, least squares; RAASi, renin-angiotensin-aldosterone system inhibitor; RASI, renin-angiotensin system inhibitor; SAE, serious adverse event; SBP, systolic blood pressure; SD, standard deviation; SOC, standard of care; SPAR, sparsentan; 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.

References

1. FILSPARI. Prescribing information. Travere Therapeutics Inc; February 2023.
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