FILSPARI® (sparsentan)

Effect on Estimated Glomerular Filtration Rate (eGFR) in IgA Nephropathy

Summary

Prescribing Information

- FILSPARI is and endothelin and angiotensin II receptor antagonist indicated to reduce proteinuria in adults with primary immunoglobulin A nephropathy (IgAN) at risk for rapid disease progression, generally a urine protein-to-creatinine ratio (UPCR) ≥1.5 g/g[1]
- This indication is approved under accelerated approval based on reduction of proteinuria. It has not been established whether FILSPRI slows kidney function decline in patients with IgAN. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory clinical trial[1]

Background

- Sparsentan is a novel, first-in-class, and the only single molecule antagonist of the ET_A and AT_1 receptors[2-4]

Study Data

The PROTECT Study

- 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)[5]
- Least-squares mean absolute change in eGFR from baseline to Week 110 was lower with sparsentan vs irbesartan (−5.8 mL/min/1.73 m^2 and −9.5 mL/min/1.73 m^2, respectively; difference=3.7)[5]

Prescribing Information

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This indication is approved under accelerated approval based on reduction of proteinuria. It has not been established whether FILSPRI slows kidney function decline in patients with IgAN. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory clinical trial[1]

Laboratory Tests

In the PROTECT study, laboratory tests showed that initiation of FILSPARI may cause an initial small decrease in eGFR that occurs within the first 4 weeks of starting therapy and then stabilizes.[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.[2-4] 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.[6-8]

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.[9] 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.[10] 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.[10,11] 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.[12] Reduction in proteinuria and decline in rate of eGFR are largely accepted as surrogate markers of treatment effect in studies of KF.[12,13]

Study Data

The PROTECT Study

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 (86.1%) and 154 (76.2%) 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 participants was 4.0 (1.0-10.0) years for both sparsentan and irbesartan groups. Median urine protein excretion was 1.8 (IQR, 1.2-2.9) g/day in the sparsentan group and 1.8 (IQR, 1.3-2.6) g/day in the irbesartan group. The median UPCR was 1.3 (IQR, 0.8-1.8) g/g for sparsentan-treated patients and 1.2 (IQR, 0.9-1.7) g/g for patients treated with irbesartan. Mean eGFR was 56.8 mL/min/1.73 m² (SD, 24.3) and 57.1 mL/min/1.73 m² (SD, 23.6) in the sparsentan and irbesartan groups, respectively.[5,14]

Mean (SD) eGFR measures were further assessed in subgroups based on baseline UPCR values.[14]

- UPCR <0.80 g/g: sparsentan 57.3 (24.0), irbesartan 61.9 (27.3) mL/min/1.73 m^2
- UPCR ≥0.80 to <1.25 g/g: sparsentan 60.6 (25.0), irbesartan 59.3 (25.2) mL/min/1.73 m^2
- UPCR ≥1.25 to <1.80 g/g: sparsentan 55.9 (24.0), irbesartan 55.1 (21.9) mL/min/1.73 m^2
- UPCR ≥1.80 g/g: sparsentan 53.6 (24.5), irbesartan 52.1 (18.8) mL/min/1.73 m^2

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.[15]

- 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 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 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).[5]

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

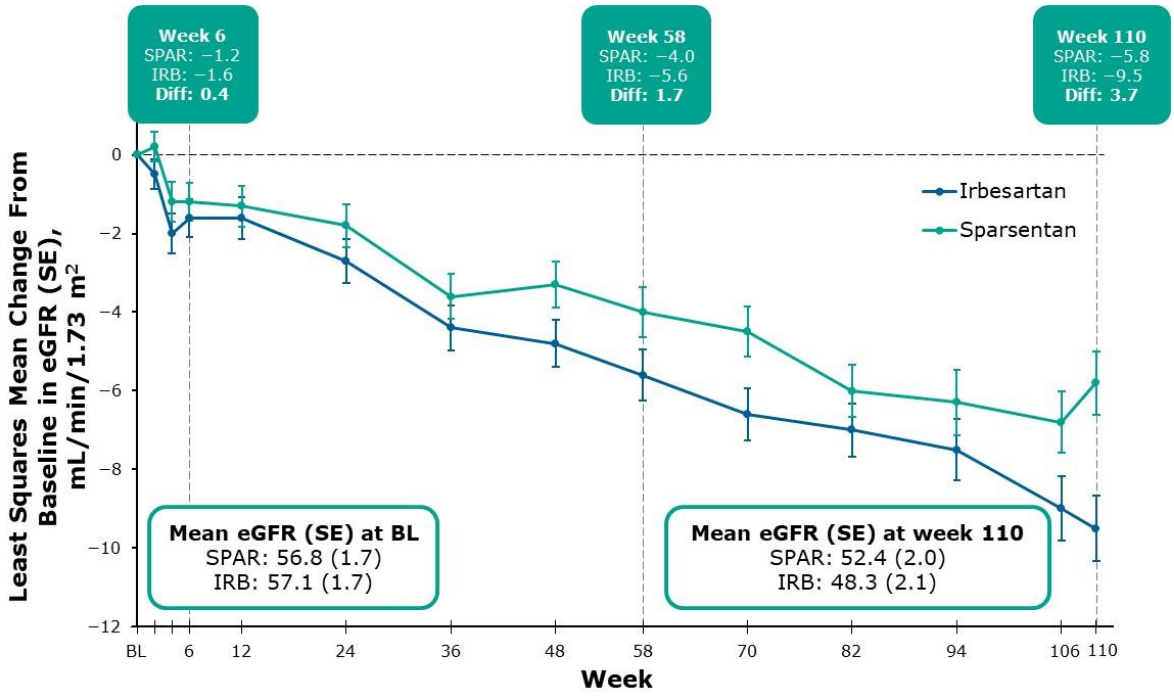
Key Secondary Efficacy Endpoints*	Sparsentan Group (n=202)	Irbesartan Group (n=202)	Between-Group Difference (95% CI)	p-value
Chronic slope from Week 6 to Week 110, mL/min/1.73 m² per year	-2.7 (-3.4, -2.1)	-3.8 (-4.6, -3.1)	1.1 (0.1, 2.1)	0.037
Total slope from Day 1 to Week 110, mL/min/1.73 m² per 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 vs irbesartan (−5.8 mL/min/1.73 m^2 and −9.5 mL/min/1.73 m^2, respectively; difference=3.7) (**Figure 1**).[14] 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).[5]

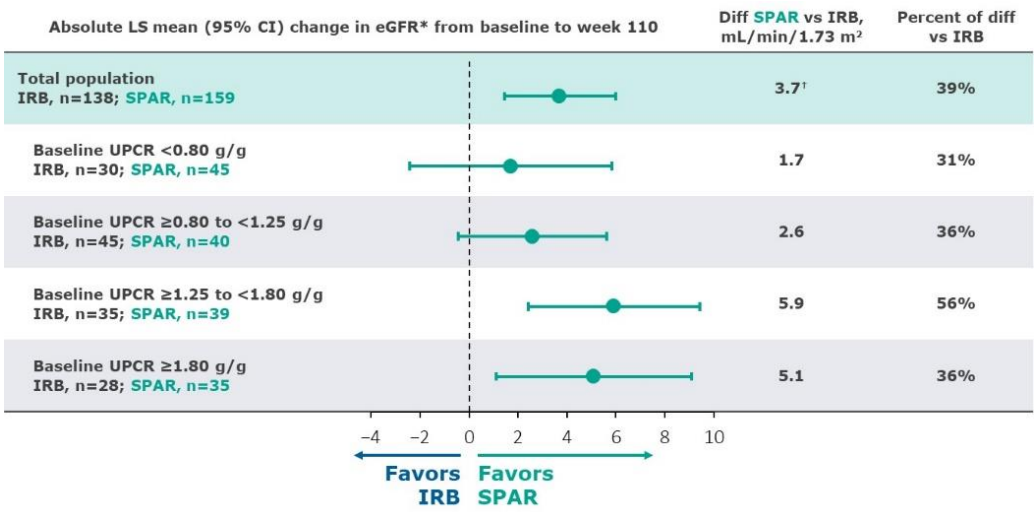
Figure 1. Preservation of Kidney Function with Sparsentan vs Irbesartan



Abbreviations: BL, baseline; diff, difference; IRB, irbesartan; SE, standard error; SPAR, sparsentan

The sustained effect of sparsentan on eGFR at Week 110 was observed across all UPCR subgroups (**Figure 2**).[14]

Figure 2. eGFR Reduction per Baseline UPCR Subgroups

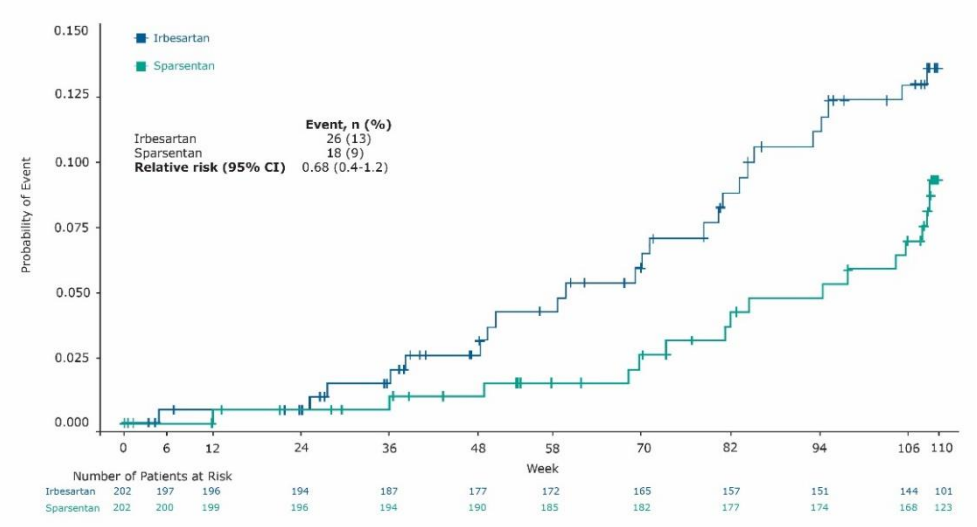


Abbreviations: CI, confidence interval; diff, difference; eGFR, estimated glomerular filtration rate; IRB, irbesartan; LS, least squares; SPAR, sparsentan; UPCR, urine protein-to-creatinine ratio
*On-treatment eGFR
†*P*=0.001

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 3**). 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.[5]

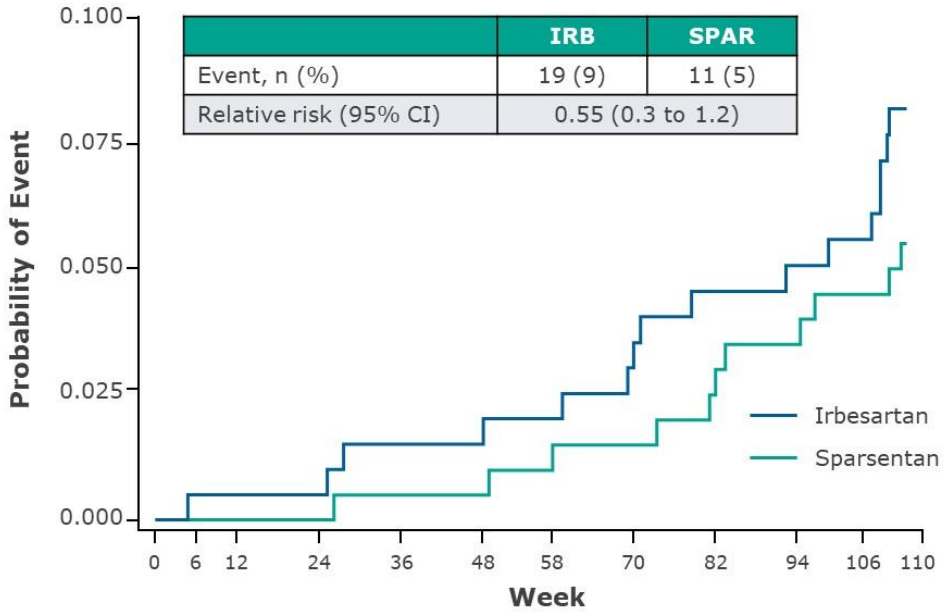
Figure 3. Time to Reach Composite Endpoint



Vertical bars indicate censored patients.

A confirmed 50% reduction in eGFR, ESKD, or death was also observed in more patients taking sparsentan than those taking irbesartan (19 vs 11 patients, respectively; **Figure 4**).[14]

Figure 4. Confirmed 50% eGFR Reduction, ESKD, or Death



Additional sensitivity analyses examined long-term preservation of kidney function. 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%).[5,16] 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 (**Table 2**).[16] Sparsentan patients also consistently maintained greater kidney function over time as compared to irbesartan (**Table 3**).[5]

Table 2. Pre-specified Sensitivity Analyses

All Randomized Patients (Irrespective of Early Treatment Discontinuations – mITT Analysis)	Sparsentan (n=202)	Irbesartan (n=202)	Treatment Difference (Sparsentan – Irbesartan) (95% CI)
eGFR total slope, mL/min/1.73 m^2 per year	**-3.0**	**-4.2**	**1.2** (0.23, 2.16)
eGFR chronic slope, mL/min/1.73 m^2 per year	**-2.9**	**-4.2**	**1.3** (0.36, 2.32)
Exclusion of Assessments After Initiation of Immunosuppression for Renal Disease	**Sparsentan (n=202)**	**Irbesartan (n=202)**	**Treatment Difference (Sparsentan – Irbesartan) (95% CI)**
eGFR total slope, mL/min/1.73 m^2 per year	**-2.9**	**-3.9**	**1.0** (0.03, 1.99)
eGFR chronic slope, mL/min/1.73 m^2 per year	**-2.8**	**-3.9**	**1.2** (0.16, 2.15)

Results obtained using the same models as the main analyses without multiple imputation.

Table 3. Sparsentan Demonstrated Treatment Benefit on Kidney Function Endpoints

Absolute Overall Change in Kidney Function	Sparsentan (n=202)	Irbesartan (n=202)	Difference (Sparsentan – Irbesartan) (N=404)
Absolute change in eGFR Mean change from baseline at week 110[a]	**-5.8**	**-9.5**	**3.7** (1.5, 6.0)
Absolute change in eGFR Mean change from baseline to 4 weeks post-cessation of randomized treatment week 114[b] (Patients who completed the blinded treatment period)	**(n=174)**	**(n=154)**	
	-6.1	**-9.0**	**2.9** (0.5, 5.3)
	Sparsentan (n=202)	**Irbesartan (n=202)**	**Difference (Sparsentan – Irbesartan)**
Confirmed 40% reduction in eGFR, ESRD, or death during the study, n (%)	**18** (9.0)	**26** (13.0)	**RR: 0.68** (0.4, 1.2)[c]

[a]LS mean and 95% CI from MMRM analysis including on-treatment data through Week 110; mL/min/1.73 m^2.
[b]LS mean and 95% CI from ANCOVA adjusted for eGFR at baseline; mL/min/1.73 m^2.
[c]RR of events and 95% CI from Poisson regression model.

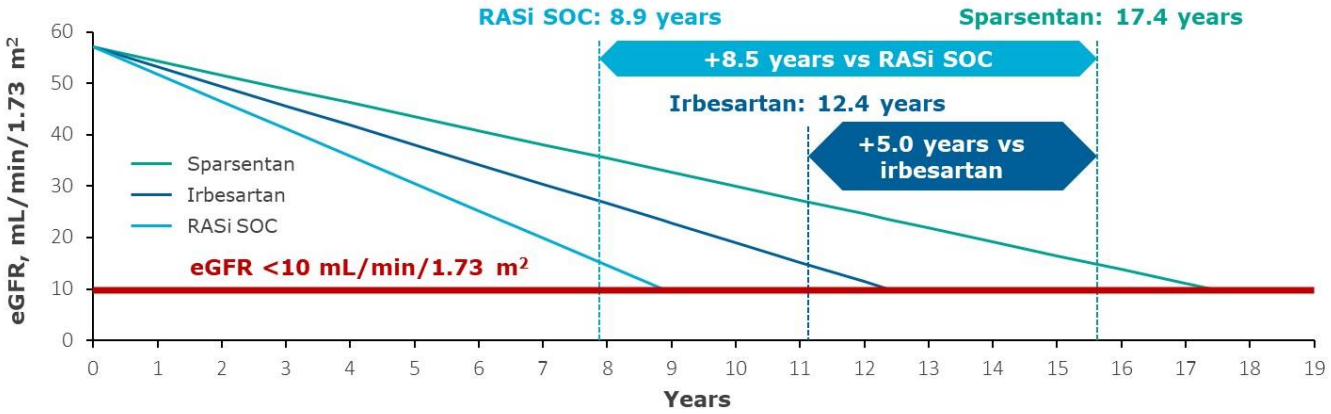
Delay to Kidney Failure

Treatment with sparsentan was associated with projected delay in time to KF, related to change in eGFR slope (**Figure 5**). Baseline eGFR was 56.8 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.[14]

- Compared to patients utilizing SOC, patients taking sparsentan experienced a mean 8.5 years longer delay to KF
- Compared to patients taking irbesartan, sparsentan-treated patients experienced a mean 5.0 years longer delay to KF

Figure 5. 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 m^2/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 m^2 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.[5]

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.[5]

Abbreviations

ACEi, angiotensin-converting enzyme inhibitor; ALT, alanine aminotransferase; ANCOVA, analysis of covariance; ARB, angiotensin receptor blocker; AST, aspartate aminotransferase; AT_1, angiotensin II type 1; CI, confidence interval; DBP, diastolic blood pressure; diff, difference; eGFR, estimated glomerular filtration rate; ET_A, endothelin-1 type A; EU, European Union; IgA, immunoglobulin A; IgAN, immunoglobulin A nephropathy; IRB, irbesartan; ITT, intention-to-treat; KF, kidney failure; KRT, kidney replacement therapy; LS, least squares; mITT, modified intention-to-treat; MMRM, mixed model for repeated measures; RASI, renin-angiotensin system inhibitor; RR, relative risk; SAE, serious adverse event; SBP, systolic blood pressure; 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.

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