FILSPARI® (sparsentan)
Effect on Proteinuria in IgA Nephropathy

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

- 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 ($P<0.0001$)[3]
- 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[4]
- 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[4,5]

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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 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 (1.0-10.00) 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 m^2 (SD, 24.3) and 57.1 mL/min/1.73 m^2 (SD, 23.6) in the sparsentan and irbesartan groups, respectively.[4,16]

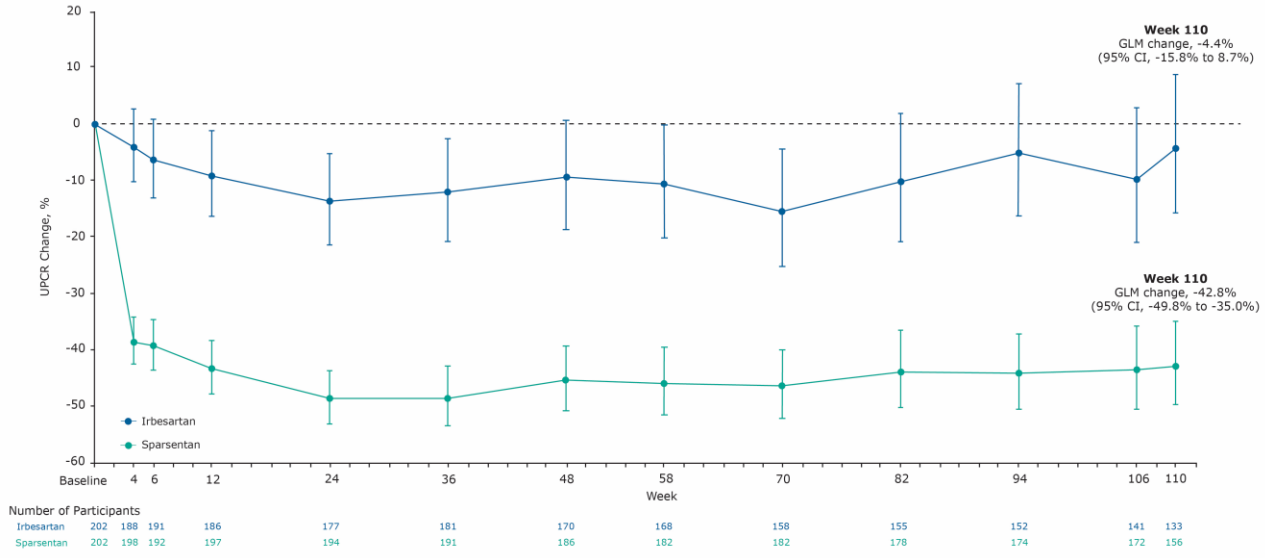
Mean (SD) eGFR measures were further assessed in subgroups based on baseline UPCR values.[16]

- 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

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 1**). 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.[4]

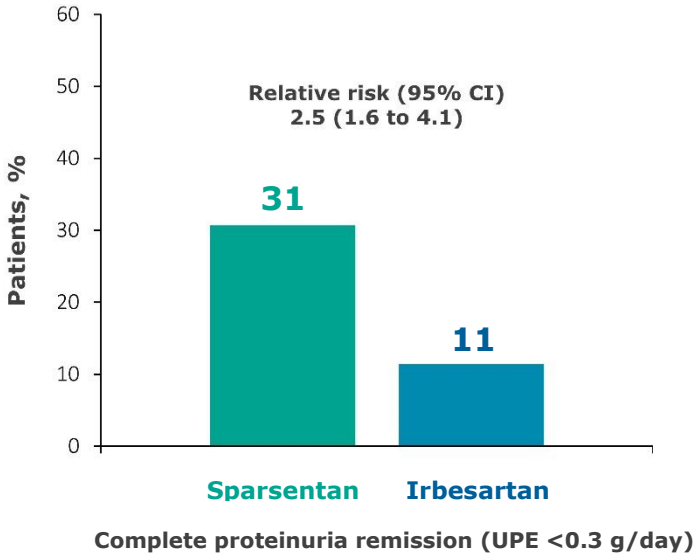
Figure 1. Sustained Reduction in Proteinuria Over 110 Weeks



Error bars indicate 95% CIs.

Relative risk to achieve complete proteinuria remission for sparsentan and irbesartan groups is described in **Figure 2**.

Figure 2. 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.[17]

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.[4]

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. Rescue immunosuppression therapy was initiated sooner and more frequently in the irbesartan group (n=16; 8%) than with sparsentan treatment (n=6; 3%).[4,5] 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.[4]

Abbreviations

ACEi, angiotensin-converting enzyme inhibitor; 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; GLM, geometric least squares mean; IgA, immunoglobulin A; IQR, interquartile range; KF, kidney failure; KRT, kidney replacement therapy; SAE, serious adverse event; SBP, systolic blood pressure; SD, standard deviation; TEAE, treatment-emergent adverse event; UACR, urine albumin-to-creatinine ratio; ULN, upper limit of normal; UPCR, urine protein-to-creatinine ratio.

References

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