FILSPARI® (sparsentan)

Changes in Blood Pressure and Hypotensive Events in IgA Nephropathy

Summary

Prescribing Information

The 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.

- In the PROTECT trial, hypotensive events (including orthostatic hypotension) occurred in 28 (14%) patients taking FILSPARI compared to 12 (6%) patients taking irbesartan[1]
- FILSPARI should not be coadministered with ARBs, ERAs, or aliskiren. Combined use of these agents is associated with increased risks of hypotension, syncope, hyperkalemia, and changes in renal function (including acute renal failure)[1]
- Overdose of FILSPARI may result in decreased blood pressure[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

- In a phase 2 study of sparsentan as treatment for hypertension, 1 patient taking the 800 mg dose withdrew due to hypotension[5]
- Data from the PROTECT study showed little difference in SBP and a small difference in DBP between sparsentan and irbesartan groups over 2 years of treatment[6]
- In the SPARTAN study, after an initial decrease, BP remained stable during the rest of follow-up[7]

Prescribing Information

- Overdose of FILSPARI may result in decreased blood pressure. In the event of an overdose, standard supportive measures should be taken, as required[1]
- Hypotension has been observed in patients treated with ARBs and ERAs and was observed in clinical studies with FILSPARI. In the PROTECT trial, there was a greater incidence of hypotension-associated adverse events, some serious, including dizziness, in patients treated with FILSPARI compared to irbesartan[1]
- In patients at risk for hypotension, consider eliminating or adjusting other antihypertensive medications and maintaining appropriate volume status[1]

- If hypotension develops, despite elimination or reduction of other antihypertensive medications, consider a dose reduction or dose interruption of FILSPARI. A transient hypotensive response is not a contraindication to further dosing of FILSPARI, which can be given once blood pressure has stabilized[1]
- In the PROTECT trial, hypotension (including orthostatic hypotension) occurred in 28 (14%) patients taking FILSPARI compared to 12 (6%) patients taking irbesartan[1]
- FILSPARI should not be coadministered with ARBs, ERAs, or aliskiren. Combined use of these agents is associated with increased risks of hypotension, syncope, hyperkalemia, and changes in renal function (including acute renal failure)[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.[8-10]

Studies of Sparsentan in Hypertensive Patients

Two phase 2, double-blind, placebo-controlled studies examined antihypertensive effects of sparsentan in patients with stage 1 or stage 2 hypertension.[5]

In study 1, patients aged 30 to 80 years with mean seated SBP ≥150 and ≤179 mm Hg and mean seated DBP ≤110 mm Hg, and mean daytime SBP ≥140 and ≤179 mm Hg with mean daytime DBP ≤110 mm Hg were randomized to receive sparsentan 200 mg, 500 mg, or placebo once daily for 4 weeks. The primary efficacy endpoint was defined as mean change in 24-hour ambulatory SBP from baseline to Week 4.[5]

In study 2, patients aged 18 to 75 years with mean seated SBP ≥140 and ≤180 mm Hg and mean seated DBP ≥90 mm Hg and ≤109 mm Hg were randomized to sparsentan 200 mg, 400 mg, or 800 mg, irbesartan 300 mg, or placebo, once daily for 12 weeks. The primary efficacy endpoint was defined as mean change in mean seated SBP from baseline to Week 12.[5]

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.[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. 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.[12] 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.[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]

The SPARTAN Study

The SPARTAN study (NCT04663204) is a phase 2, open-label, single-arm trial investigating the safety, efficacy, and mechanism of action of sparsentan as first-line treatment for IgA nephropathy in newly diagnosed patients. Patients aged ≥18 years diagnosed with biopsy-proven IgA nephropathy within 6 months of enrollment are eligible. Additional eligibility criteria include eGFR ≥30 mL/min/1.73 m^2, proteinuria ≥0.5 g/day, and no exposure to ACEi or ARB treatment within 12 months of study screening. Sparsentan is initiated at a dose of 200 mg/day and titrated to 400 mg/day after 2 weeks. Treatment continues for 110 weeks, followed by a 4-week safety period. The primary efficacy endpoint is change in proteinuria (UPCR) from baseline at Week 36, based on a 24-hour urine sample. Secondary endpoints include complete remission of proteinuria defined as <0.3 g/day, rate of change in eGFR from Week 6 to Week 58, change in eGFR from Week 6 to Week 104, change in office and ambulatory BP, and change in UPCR and 24-hour protein excretion up to Week 114. Safety and tolerability assessments include abnormalities in clinical laboratory measures and vital signs, AEs, SAEs, AEs leading to discontinuation, and AEs leading to death.[7,16,17]

Study Data

Studies of Sparsentan in Hypertensive Patients

In a phase 2 study of sparsentan as treatment for hypertension (NCT00635232), 1 patient taking the 800 mg dose withdrew due to hypotension.[5]

The PROTECT Study

Interim Safety Analysis

The 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.

At baseline, mean SBP/DBP in the sparsentan and irbesartan groups were 128/82 and 130/83 mm Hg, respectively. Interim analysis at 36 weeks of treatment showed a mean (SD) change from baseline in SBP of −1.8 (14.0) mm Hg in the sparsentan group and −2.9 (12.9) mm Hg in the irbesartan group, and mean (SD) change from baseline in DBP of −2.5 (11.1) in the sparsentan group and −0.4 (10.4) in the irbesartan group.[14]

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.[14]

Hypotension (including orthostatic hypotension) was the second most frequent TEAE occurring in ≥5% of participants, occurring in 28 (14%) sparsentan-treated patients and 12 (6%) irbesartan-treated patients.[14]

2-Year Safety Analysis

The 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

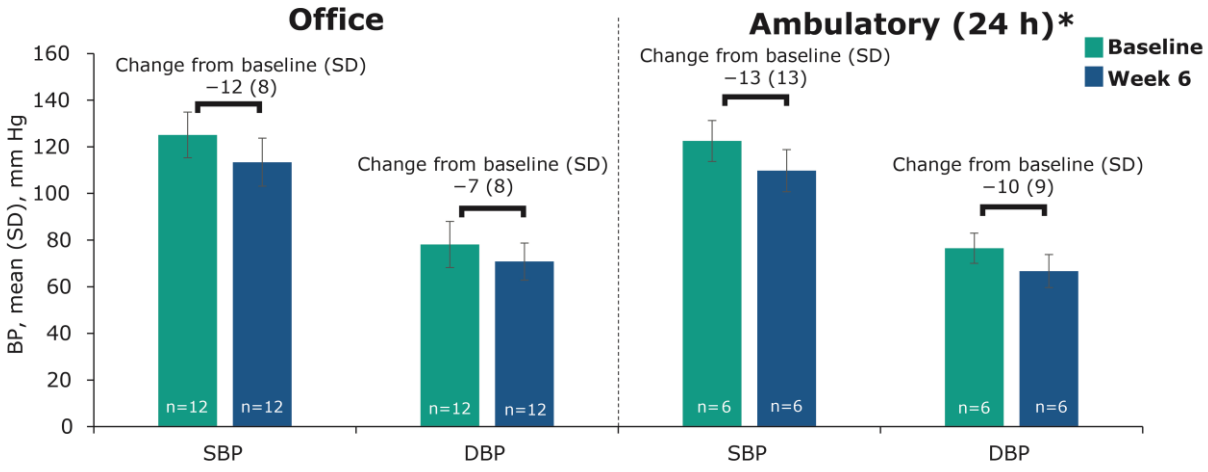
At baseline, mean (SD) SBP was 128 (14.4) mm Hg in the sparsentan treatment group and 129.9 (12.4) mm Hg in the irbesartan group. Mean (SD) DBP was 81.6 (10.6) and 83.2 (10.6) mm Hg for sparsentan and irbesartan patients, respectively. Least-squares mean (95% CI) change from baseline at Week 110 in SBP was −3.8 (−5.5 to −2.1) mm Hg in the sparsentan group and −2.5 (−4.3 to −0.8) mm Hg among irbesartan-treated patients. Least-squares mean (95% CI) DBP was 3.4 (−4.6 to −2.2) mm Hg and −1.2 (−2.5 to 0.0) mm Hg in sparsentan- and irbesartan-treated patients, respectively.[6]

Hypotension-associated TEAEs (hypotension, orthostatic hypotension, and SBP decreased) were reported in 33 (16%) patients in the sparsentan group and 13 (6%) patients in the irbesartan group. Hypotensive TEAEs led to treatment discontinuation in 3 (1%) patients in the sparsentan group; 2 (1%) had hypotension and 1 (<1%) reported orthostatic hypotension.[6]

The SPARTAN Study

Patients at baseline had a mean (SD) SBP/DBP of 125 (10)/78 (10) mm Hg. BP remained relatively stable with sparsentan treatment following an initial decrease. SBP and DBP exhibited similar measures at baseline and Week 6 for office and ambulatory BP. Ambulatory BP showed a slightly greater reduction in both SBP and DBP compared to measures of office BP (**Figure 1**).[7]

Figure 1. Mean Office and Ambulatory BP at Baseline and Week 6



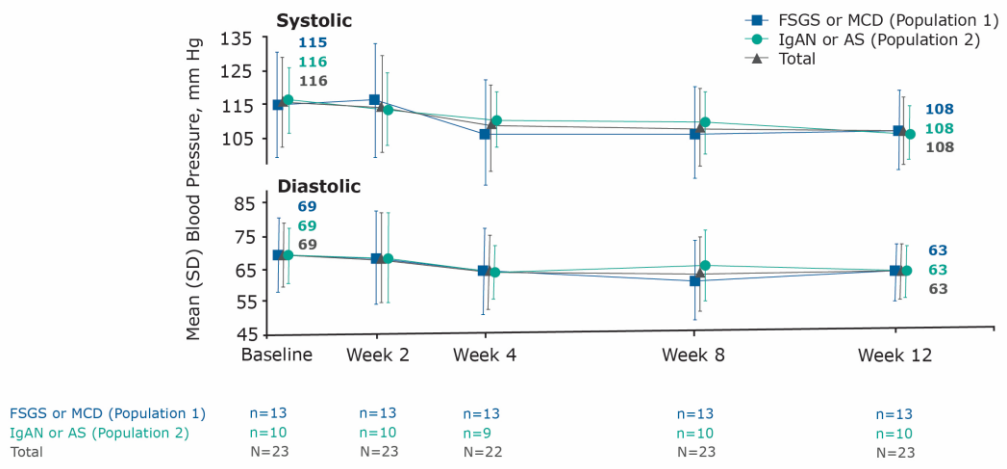
*Patients who had ambulatory BP data available at baseline and Week 6.

One patient discontinued treatment due to hypotension after 6 weeks.[7]

The EPPIK Study

The EPPIK study is an open-label, single-arm, multicenter trial evaluating the safety, efficacy, and PK of liquid sparsentan in patients aged ≥1 to <18 years with FSGS or MCD and aged ≥2 to <18 years with IgAN, IgAV, or Alport syndrome.[18,19] The effect of sparsentan on blood pressure is presented in **Figure 2**.[18]

Figure 2. Effect of Sparsentan on Blood Pressure During 12 Weeks of Treatment



Hypotension was reported in 1 (8%) patient in the FSGS or MCD group.[18]

Abbreviations

ACEi, angiotensin-converting enzyme inhibitor; AE, adverse event; ARB, angiotensin receptor blocker; AS, Alport syndrome; AT_1, angiotensin II type 1; BP, blood pressure; CI, confidence interval; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; ERA, endothelin receptor antagonist; ET_A, endothelin-1 type A; FSGS, focal segmental glomerulosclerosis; IgA, immunoglobulin A; IgAN, immunoglobulin A nephropathy; IgAV, immunoglobulin A-associated vasculitis; KF, kidney failure; KRT, kidney replacement therapy; MCD, minimal change disease; SAE, serious adverse event; SBP, systolic blood pressure; SD, standard deviation; TEAE, treatment-emergent adverse event; UACR, urine albumin-to-creatinine ratio; UPCR, urine protein-to-creatinine ratio.

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