FILSPARI® (sparsentan)

Changes in Blood Pressure and Hypotensive Events in IgA Nephropathy

Summary

Prescribing Information

- FILSPARI is an endothelin and angiotensin II receptor antagonist indicated to slow kidney function decline in adults with primary immunoglobulin A nephropathy (IgAN) who are at risk for disease progression[1]
- In the PROTECT trial, hypotensive events (including orthostatic hypotension) occurred in 33 (16%) patients taking FILSPARI compared to 13 (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 phase 3 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 phase 2 SPARTAN study, after an initial slight decrease, BP remained stable in all patients (N=12) during 24 weeks of follow-up[7]
- Among 34 pediatric patients in the phase 2 EPPIK study, including 4 patients diagnosed with IgAN/IgAV BP remained fairly stable throughout the first 12 weeks of sparsentan treatment[8]
- In the phase 2 SPARTACUS study, patients (N=20) experienced a slight decrease following initiation of sparsentan treatment to SGLT2 inhibitor therapy over 24 weeks of treatment. Hypotension was reported as a TEAE in 2 (10%) patients[9]

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 33 (16%) patients taking FILSPARI compared to 13 (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 Prescribing Information, including Boxed Warning.

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.[10-12]

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.[13] 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.[14] 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.[14,15] 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 (UPE <0.3 g/day) and partial (UPE <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.[16] Reduction in proteinuria and decline in rate of eGFR are largely accepted as surrogate markers of treatment effect in studies of KF.[16,17]

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, being conducted at 5 participating sites in the UK.[7] 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.[18-20]

The EPPIK Study

The EPPIK study (NCT05003986) is a phase 2, global, open-label, single-arm, multicenter cohort study to evaluate the safety, efficacy, and PK of a once-daily oral suspension of sparsentan in pediatric patients with selected proteinuric glomerular diseases. The primary objective of the EPPIK study is to examine long-term antiproteinuric and nephroprotective potential and safety in this pediatric population.[21] Approximately 57 pediatric patients aged ≥1 to <18 years will be enrolled. EPPIK Population 1 will include ~30 patients aged 1 to <18 years with FSGS or treatment-resistant MCD. Population 2 will include ~27 patients aged 2 to <18 years with IgAN, IgAV, or Alport syndrome. Target exposure of sparsentan is equivalent to 800 mg in Population 1 and 400 mg in Population 2. Primary endpoints are the change from baseline in UPCR over a 108-week treatment

period, incidence of TEAEs, SAEs, AEs leading to treatment discontinuation, and AEs of interest. Secondary endpoints include observed plasma PK concentration, steady-state PK parameters, change from baseline in UACR and eGFR over 108 weeks of treatment, and proportion of patients with FSGS or MCD histological patterns achieving partial remission (FPRE) in UPCR. Partial remission is defined as UPCR ≤1.5 g/g and >40% reduction in UPCR. Safety parameters are monitored throughout the duration of the study.[8,21,22]

The SPARTACUS Study

The SPARTACUS study (NCT05856760) is a single-group, multicenter, open-label, exploratory phase 2 trial examining the safety and efficacy of sparsentan in adult patients with biopsy-proven IgA nephropathy at risk of disease progression despite ongoing treatment with RAASi and SGLT2 inhibitors.[23] Approximately 60 patients aged 18 years and older who are on stable doses of an ACEi/ARB and SGLT2 inhibitors will be enrolled. The primary outcome measure is change from baseline in UACR at Week 24. Secondary efficacy outcome measures include UACR <0.2 g/g at Week 24, ≥30% and ≥50% reduction from baseline in UACR at Week 24, and change from baseline in UACR, UPCR, eGFR, and BP at each study visit. Safety assessments throughout the study include TEAEs, SAEs, AEs leading to treatment discontinuation, and AEs of interest.[9,23,24]

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

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.[1,6]

PROTECT OLE

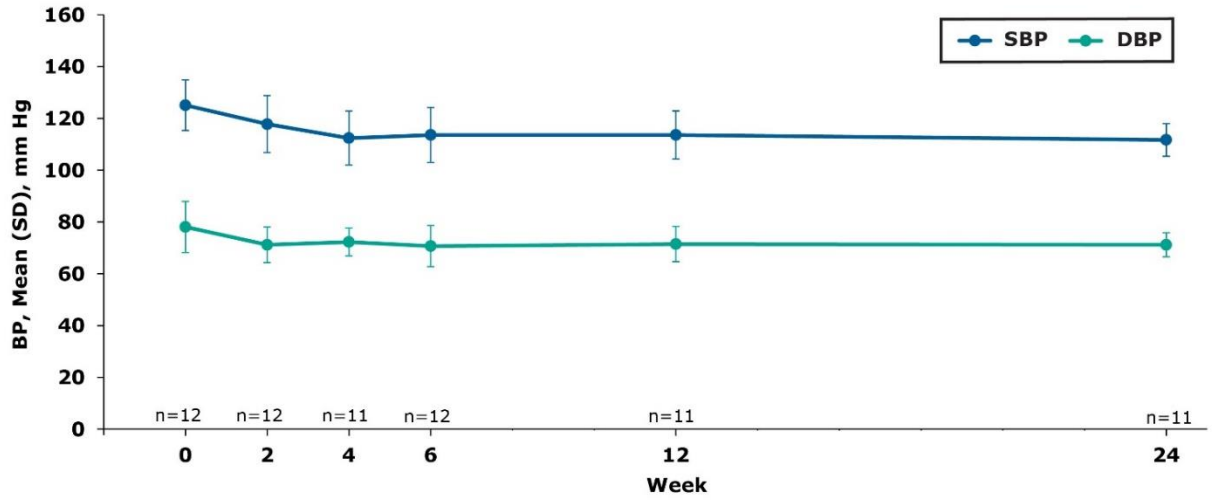
Patients who completed the PROTECT double-blind period were eligible to enroll into the OLE. Patients continued on sparsentan with a target dose of 400 mg/day for up to 156 weeks and could begin a concomitant SGLT2 inhibitor at any time during the OLE at the discretion of the

investigator. Among 61 patients taking combined sparsentan and SGLT2 inhibitor therapy, 4 (7%) reported hypotension as a TEAE. BP remained relatively stable throughout treatment.[25]

The SPARTAN Study

At baseline, patients (N=12) had a mean (SD) SBP/DBP of 125 (10)/78 (10) mm Hg. BP, as measured by office BP and ambulatory BP, remained relatively stable with sparsentan treatment following an initial slight decrease (**Figure 1**). After 6 weeks of treatment, 1 patient discontinued the study due to hypotension.[7]

Figure 1. Mean Office BP Over 24 Weeks of Sparsentan Treatment

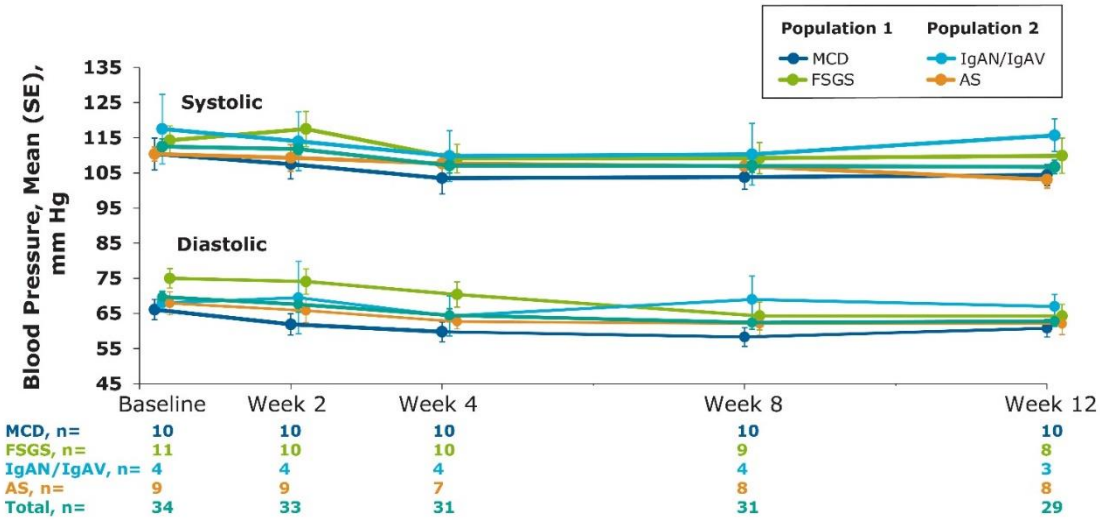


*Patients who had ambulatory BP data available at baseline and Week 6.

The EPPIK Study

At data cutoff (February 15, 2024), 34 pediatric patients enrolled in the EPPIK study had received ≥1 dose of sparsentan oral suspension. Safety and efficacy were assessed over 12 weeks of treatment. Population 1 included 10 patients with MCD and 11 patients with FSGS; Population 2 included 4 patients with IgAN/IgAV and 9 patients with Alport syndrome.[8] Throughout the first 12 weeks of treatment, BP remained fairly stable across all diagnostic groups (**Figure 2**).[8]

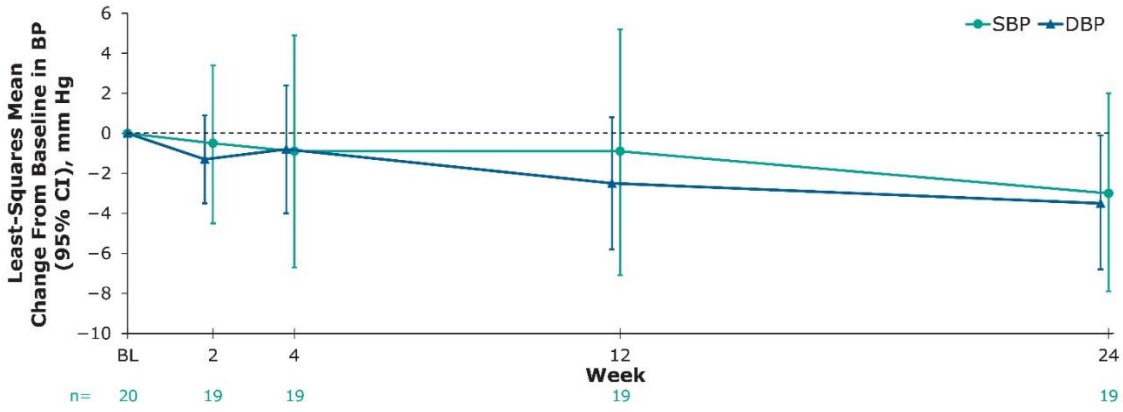
Figure 2. Mean Blood Pressure Change From Baseline



The SPARTACUS Study

In an interim analysis, patients (N=20) experienced a slight decrease in BP following the addition of sparsentan to stable SGLT2 inhibitor therapy after switching from a RAASi (**Figure 3**). Hypotension was reported as a TEAE in 2 (10%) patients.[9]

Figure 3. Change in Blood Pressure From Baseline per Study Visit



Abbreviations

ACEi, angiotensin-converting enzyme inhibitor; AE, adverse event; ARB, angiotensin receptor blocker; AS, Alport syndrome; AT_1, angiotensin II type 1; BL, baseline; 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; FPRE, FSGS partial remission of proteinuria; 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; PK, pharmacokinetics; RAASi, renin-angiotensin-aldosterone system inhibitor; SAE, serious adverse event; SBP, systolic blood pressure; SD, standard deviation; SE, standard error; SGLT2, sodium-glucose cotransporter-2; TEAE, treatment-emergent adverse event; UACR, urine albumin-to-creatinine ratio; UPCR, urine protein-to-creatinine ratio; UPE, urinary protein excretion.

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