FILSPARI® (sparsentan)
Edema and Congestive Heart Failure

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, the most common adverse reactions (≥5%) are peripheral edema, hypotension (including orthostatic hypotension), dizziness, hyperkalemia, and anemia[1]
- In the PROTECT trial, peripheral edema occurred in 29 patients (14%) taking FILSPARI compared to 19 patients (9%) taking irbesartan[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 the phase 2 DUET study, higher incidence of peripheral edema was reported in patients taking sparsentan (12.3%) compared to those on irbesartan (2.8%) during the 8-week double-blind period[4]
- An analysis of DUET OLE data found that peripheral edema was the second most common TEAE reported across 240 weeks of sparsentan treatment (11.2 total study duration cases per 100 patient-years)[5]
- In the PROTECT study, change in edema from no edema at baseline to severe edema occurred in 2 (1%) irbesartan-treated patients and to moderate edema in 2 (1%) sparsentan-treated patients[6]
- In the DUPLEX study, no clinically meaningful concerns regarding edema were reported[7]
- No studies have been specifically conducted to evaluate any association between sparsentan and CHF. To date, no cases of CHF were observed in the DUET, DUPLEX, or PROTECT studies[8]

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In patients taking FILSPARI, monitor blood pressure, serum potassium, edema, and kidney function regularly when used concomitantly with moderate CYP3A inhibitors.[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.[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 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.[13,14] 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.[15] Reduction in proteinuria and decline in rate of eGFR are largely accepted as surrogate markers of treatment effect in studies of KF.[15,16]

The DUET Study

The DUET study (NCT01613118) is a phase 2, randomized, multicenter, double-blind, active- control trial examining the safety and efficacy of sparsentan compared to irbesartan in patients with biopsy-proven FSGS. Patients were randomized to 1 of 3 doses (200, 400, or 800 mg/day) of sparsentan or irbesartan (300 mg/day) and maintained through an 8-week double-blind phase. The primary endpoint was defined as reduction in UPCR after 8 weeks of treatment. The proportion of patients who achieved partial FSGS remission was evaluated as a secondary endpoint. Following the double-blind phase, patients had the option to continue into a 144-week OLE of treatment with sparsentan.[4]

The DUPLEX Study

The DUPLEX study (NCT03493685) is a global, randomized, multicenter, double-blind, active-controlled, phase 3 trial examining the safety and efficacy of sparsentan as compared to irbesartan in patients aged 8 to 75 years with biopsy-proven FSGS. Patients with UPCR ≥1.5 g/g at screening, eGFR ≥30 mL/min/1.73 m^2, and mean seated BP ≥100/60 mm Hg (patients ≥18 years) or above the 5th percentile for sex and height (<18 years) were eligible. After a 2-week washout period, 371 patients were randomized to receive either sparsentan or irbesartan, and subsequently dose titrated over 2 weeks to the maximum dose of either 800 mg/day sparsentan or 300 mg/day irbesartan, as

tolerated.[7,17] Patients remained on maintenance doses of sparsentan or irbesartan during a 108-week double blind phase. Standard-of-care treatment, including RAASi, was resumed in Weeks 108-112. The primary efficacy endpoint was eGFR slope over 108 weeks of treatment, defined as eGFR total slope from Day 1 to Week 108 of treatment and eGFR chronic slope from Week 6 to Week 108 (following the initial acute effect of randomized treatment). The key secondary endpoint was percent change in eGFR from baseline to 4 weeks post-cessation of randomized treatment at Week 112.[7] An additional interim endpoint was the proportion of patients achieving partial remission of proteinuria, defined as UPCR ≤1.5 g/g and a >40% reduction (FPRE) at Week 36. Proportion of patients achieving complete remission of proteinuria (UPCR <0.3 g/g) at any time in the double-blind period was also examined. Safety was assessed by double-blind monitoring of adverse events and safety endpoints.[7,17]

Study Data

The PROTECT Study

In the PROTECT study, protocol allowances were made for the management of patients with worsening edema. Patients received half the target dose for the first 2 weeks after randomization. Dose tolerance was evaluated in a blinded manner at the Week 2 visit and was defined as systolic blood pressure >100 mm Hg and diastolic blood pressure >60 mm Hg after 2 weeks, and no AEs (eg, worsening edema) or laboratory findings interfering with the patient's continuation on study medication. Patients who did not tolerate the initial dose for any reason could discontinue the study medication and could re-start or reduce the study medication at the investigator's discretion.[16] Potassium-sparing diuretics were not to be coadministered with sparsentan in the PROTECT study.[16]

2-Year Safety Analysis

Over 2 years of treatment, peripheral edema was reported in 31 (15%) sparsentan patients and 24 (12%) irbesartan patients; most cases were considered to be mild. Change from no edema at baseline to severe edema occurred in 0 sparsentan-treated patients and 2 irbesartan-treated patients. Change 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 frequent were thiazides, utilized by 35 (17%) and 42 (21%) sparsentan and irbesartan patients, respectively. No patients discontinued treatment due to edema and no serious AEs of fluid retention were reported. Dual antagonism of ET_A and AT_1 receptors may decrease the risk of fluid retention.[6,18]

The DUET Study

During the 8-week double-blind period, higher incidence of peripheral edema was reported in patients taking sparsentan compared to those on irbesartan. Across all 3 sparsentan dose cohorts, 12.3% (n=9) of patients experienced edema vs 2.8% (n=1) of patients taking irbesartan.[4]

There were no significant changes in severity of edema during the double-blind period and no meaningful between-group differences in use of diuretic treatment. However, loop diuretics were used more frequently in sparsentan-treated patients than in irbesartan-treated patients. The proportion of patients in the sparsentan group with mild to moderate edema remained stable, whereas the proportion with severe edema rose from 2% to 5%. This occurred in parallel with an increase in the use of loop diuretics. At baseline, patients displayed varying degrees of edema, and there were no significant changes in body weight or N-terminal pro–B-type natriuretic peptide levels from baseline in sparsentan-treated patients. There were no study withdrawals or severe TEAEs

related to edema.[4]

Analysis of long-term efficacy and safety data in the DUET study found that headache and peripheral edema were the 2 most common TEAEs across 240 weeks of sparsentan treatment, with incidence of 11.7 and 11.2 total study duration cases per 100 patient-years, respectively (**Table 1**).[5]

Table 1. Most Common TEAEs by Year and Cases Per 100 Patient-Years for Total Study Duration in the DUET OLE Study

	n (%) Within Each Year					Total Study Duration Cases Per 100 Patient-Years, Cases/100 Patient Years
	Year 0 to <1 n=108	Year 1 to <2 n=87	Year 2 to <3 n=72	Year 3 to <4 n=60	Year 4 to <5 n=54	
Headache	25 (23.1)	5 (5.7)	1 (1.4)	4 (6.7)	2 (3.7)	11.7
Edema peripheral	15 (13.9)	10 (11.5)	3 (4.2)	2 (3.3)	2 (3.7)	11.2
Upper respiratory tract infection	9 (8.3)	5 (5.7)	6 (8.3)	5 (8.3)	2 (3.7)	10.6
Hyperkalemia	7 (6.5)	9 (10.3)	3 (4.2)	6 (10.0)	6 (11.1)	10.4
Hypotension	17 (15.7)	6 (6.9)	3 (4.2)	2 (3.3)	1 (1.9)	9.3
Nausea	17 (15.7)	3 (3.4)	2 (2.8)	4 (6.7)	1 (1.9)	8.5
Hypertension	6 (5.6)	7 (8.0)	2 (2.8)	3 (5.0)	6 (11.1)	7.6
Vomiting	12 (11.1)	2 (2.3)	5 (6.9)	2 (3.3)	1 (1.9)	7.6
Diarrhea	14 (13.0)	3 (3.4)	3 (4.2)	1 (1.7)	4 (7.4)	7.1
Dizziness	14 (13.0)	3 (3.4)	1 (1.4)	2 (3.3)	0	6.3
Blood creatinine increased	11 (10.2)	1 (1.1)	4 (5.6)	0	1 (1.9)	5.5
Blood creatine phosphokinase increased	8 (7.4)	2 (2.3)	0	3 (5.0)	2 (3.7)	4.9
Anemia	11 (10.2)	1 (1.1)	0	2 (3.3)	1 (1.9)	4.1

The DUPLEX Study

At baseline, 9 (4.9%) sparsentan patients and 6 (3.2%) irbesartan patients presented with moderate or severe edema. Over 108 weeks of treatment, peripheral edema was the second most common TEAE in ≥10% of patients, occurring in 36 (19.6%) patients in the sparsentan group and 41 (21.9%) patients taking irbesartan. There were no clinically meaningful concerns regarding edema among patients taking sparsentan.[7]

Congestive Heart Failure

No studies have been specifically conducted to evaluate any association between sparsentan and CHF. To date, no cases of CHF have been observed in the DUET, DUPLEX, or PROTECT studies.[8]

Abbreviations

ACEi, angiotensin-converting enzyme inhibitor; AE, adverse event; ARB, angiotensin receptor blocker; AT_1, angiotensin II type 1; CHF, congestive heart failure; CYP, cytochrome P; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; ET_A, endothelin-1 type A; FPRE, FSGS partial remission endpoint; FSGS, focal segmental glomerulosclerosis; IgA, immunoglobulin A; KF, kidney failure; KRT, kidney replacement therapy; OLE, open-label extension; RAASi, renin-angiotensin-aldosterone system inhibitor; SBP, systolic blood pressure; TEAE, treatment-emergent adverse event; UACR, urine albumin-to-creatinine ration; UPCR, urine protein-to-creatinine ratio.

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