FILSPARI® (sparsentan)
Safety in Clinical Trials

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.

- FILSPARI is indicated to reduce proteinuria in adults with primary immunoglobulin A nephropathy (IgAN) at risk of rapid disease progression, generally a urine protein-to-creatinine ratio (UPCR) ≥1.5 g/g[1]
- In the PROTECT study, the most common adverse reactions (≥5%) are edema peripheral, hypotension (including orthostatic hypotension), dizziness, hyperkalemia, and anemia[1]
- Because of the risks of hepatotoxicity and birth defects, FILSPARI is available only through a restricted program called the FILSPARI REMS[1]

Background

- Sparsentan is an investigational therapeutic candidate for the treatment of FSGS[2,3]
- 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[4]
- The DUET study is a phase 2, randomized, multicenter, double-blind, active-control trial examining the safety and efficacy of sparsentan compared to irbesartan in patients with FSGS[3]
- The DUPLEX study is a global, randomized, multicenter, double-blind, active-controlled, phase 3 trial assessing the efficacy and safety of sparsentan as compared to irbesartan in 371 patients, ages 8 to 75 years, with primary and genetic FSGS[2,5]

Study Data

- Sparsentan has been generally well-tolerated in clinical trials, with a safety profile comparable to the active control (irbesartan)
    - Phase 3 data in IgA nephropathy have shown a sparsentan safety profile comparable to irbesartan[6]
    - Phase 3 data in FSGS indicate that sparsentan had a comparable safety profile to irbesartan, and heart failure and liver injury were not identified as safety concerns[5]

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.

- Adverse reactions reported in ≥2% in subjects treated with FILSPARI were peripheral edema (14%), hypotension (including orthostatic hypotension) (14%), dizziness (13%), hyperkalemia (13%), anemia (5%), acute kidney injury (4%), and transaminase elevations (2.5%)[1]
- Based on data from animal reproductive toxicity studies, FILSPARI can cause fetal harm, including birth defects and fetal death, when administered to a pregnant patient and is contraindicated during pregnancy[1]
- In clinical studies, elevations in aminotransferases (ALT or AST) of at least 3-times the ULN have been observed in up to 2.5% of FILSPARI-treated patients, including cases confirmed with rechallenge[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.[3,7,8] 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 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.[4,13] 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 DUET Study

The DUET study (NCT01613118) is a phase 2, randomized, multicenter, double-blind, active-control trial 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.[3]

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.[2,5] 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.[5] 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.[2,5]

Study Data

Safety of Sparsentan in IgA Nephropathy

The PROTECT Study

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.[6]

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

Additional safety data is reported in **Table 1**.

Table 1. TEAEs Over 2 Years of Sparsentan Treatment

	Sparsentan (n=202)	Irbesartan (n=202)
Any TEAE, n (%)	187 (93)	177 (88)
TEAEs in ≥5% of patients in ≥1 group		
COVID-19	53 (26)	46 (23)
Hyperkalemia	32 (16)	26 (13)
Peripheral edema	31 (15)	24 (12)
Dizziness	30 (15)	13 (6)
Headache	27 (13)	26 (13)
Hypotension	26 (13)	8 (4)
Hypertension	22 (11)	28 (14)
Upper respiratory tract infection	18 (9)	18 (9)
Fatigue	17 (8)	11 (5)
Anemia	16 (8)	9 (4)
Nasopharyngitis	15 (7)	16 (8)
Blood creatinine phosphokinase increased	15 (7)	10 (5)
Cough	15 (7)	7 (3)
Muscle spasms	14 (7)	17 (8)
Arthralgia	14 (7)	13 (6)
Proteinuria	13 (6)	15 (7)
Backpain	12 (6)	16 (8)
Lipase increased	12 (6)	9 (4)
Acute kidney injury	12 (6)	5 (2)
Gout	11 (5)	10 (5)
Pruritus	11 (5)	8 (4)
Diarrhea	10 (5)	19 (9)
Blood creatinine increased	10 (5)	14 (7)
ALT increased	10 (5)	8 (4)
Gastroesophageal reflux disease	10 (5)	8 (4)
Nausea	10 (5)	5 (2)
Myalgia	10 (5)	4 (2)
Renal impairment	7 (3)	12 (6)
Urinary tract infection	7 (3)	12 (6)
Hyperuricemia	7 (3)	11 (5)
Pain in extremity	6 (3)	12 (6)
Transaminase elevations,* n (%)	5 (2)	7 (3)
Serious TEAEs, n (%)	75 (37)	71 (35)
Serious TEAEs in ≥2 patients in ≥1 group, n (%)		
COVID-19	42 (21)	38 (19)
Chronic kidney disease	6 (3)	6 (3)
Acute kidney injury	4 (2)	1 (<1)
Dizziness	2 (1)	1 (<1)
Proteinuria	2 (1)	1 (<1)
Malaise	2 (1)	0 (0)
Appendicitis	1 (<1)	2 (1)
Cellulitis	1 (<1)	2 (1)
COVID-19 pneumonia	1 (<1)	2 (1)
IgAN	1 (<1)	2 (1)
Meniscus injury	1 (<1)	2 (1)
TEAEs leading to treatment discontinuation in ≥2 patients in ≥1 group, n (%)	21 (10)	18 (9)
Chronic kidney disease	3 (1)	3 (1)
Acute kidney injury	3 (1)	0 (0)
ALT increased	3 (1)	0 (0)
Hypotension	2 (1)	0 (0)
Lipase increased	2 (1)	0 (0)
Renal impairment	1 (<1)	4 (2)
TEAEs leading to death, n (%)	0 (0)	1 (<1)†

* Abnormal liver function test results that met the following criteria: (1) new elevation in ALT or AST of >3× ULN with or without elevation of total serum bilirubin of >2× ULN and (2) twofold increase in ALT or AST above the baseline value in patients who had elevated values before taking study medication.

† One patient in the irbesartan group died due to a severe AE of cardiorespiratory arrest that was considered not related to study drug.

Safety of Sparsentan in FSGS

The DUET Study

In a post-hoc assessment through 240 weeks of the DUET OLE, no new or unexpected safety signals emerged. The most frequent TEAEs were headache, peripheral edema, upper respiratory tract infection, and hyperkalemia (**Table 2**). The most common TEAEs leading to discontinuation were glomerular filtration rate decreased, blood creatinine increased, pregnancy, acute kidney injury, and hepatic enzyme increased.[16]

Table 2. Most Common TEAEs by Year and Cases Per 100 Patient-Years for Total Study Duration

	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

Among pediatric participants in the DUET OLE (n=26, mean age=15±4 years), no new or unexpected TEAEs occurred.[17]

The DUPLEX Study

Over 108 weeks of treatment, TEAEs were reported with similar frequency in the sparsentan (n=172; 93.5%) and irbesartan (n=174; 93%) treatment groups. Serious TEAEs occurred in 68 (37%) sparsentan-treated patients and 82 (43.9%) irbesartan-treated patients. ALT or AST elevations >3× ULN occurred in 5 (2.7%) patients taking sparsentan and 4 (2.2%) taking irbesartan; no cases were concurrent with elevated bilirubin levels ≥1.5× ULN. There were no drug-induced liver injuries with sparsentan; 1 was reported in the irbesartan group. Additional safety data is presented in **Table 3**.[5]

Table 3. Summary of TEAEs in the DUPLEX Study

Variable	Sparsentan (n=184)	Irbesartan (n=187)
	n (%)	
Any AE	172 (93.5)	174 (93)
TEAE*	88 (47.8)	88 (47.1)
SAE	68 (37)	82 (43.9)
AE leading to treatment discontinuation	26 (14.1)	22 (11.8)
AE leading to death†	4 (2.2)	3 (1.6)
AEs reported in ≥10% of patients‡		
COVID-19	41 (22.3)	50 (26.7)
Diarrhea	25 (13.6)	27 (14.4)
Nausea	10 (5.4)	18 (9.6)
Hyperkalemia	31 (16.8)	20 (10.7)
Peripheral edema	36 (19.6)	41 (21.9)
Blood creatine kinase increased	19 (10.3)	8 (4.3)
Muscle spasms	25 (13.6)	15 (8)
Back pain	15 (8.2)	20 (10.7)
Hypotension	33 (17.9)	21 (11.2)
Hypertension	20 (10.9)	24 (12.8)
Chronic kidney disease	13 (7.1)	22 (11.8)
Dizziness	23 (12.5)	21 (11.2)
Headache	20 (10.9)	23 (12.3)
Anemia	24 (13)	10 (5.3)

* Treatment-related adverse events were defined as events that were considered to be "related" or "possibly related" to the trial drug by the investigator. Events with missing relationship information were counted as treatment-related events.
† Adverse events that led to death included neuroendocrine carcinoma, subdural hematoma, coronavirus disease 2019 (COVID-19), and suicide (in 1 patient each) in the sparsentan group; and COVID-19 pneumonia, COVID-19, and respiratory distress (in 1 patient each) in the irbesartan group.
‡ If a patient had more than one event with a given preferred term, the patient was counted only once for that term.

Additional Studies in IgA Nephropathy and FSGS

SPARTAN (NCT04663204) is a phase 2 study of sparsentan as first-line treatment for IgA nephropathy in newly diagnosed patients.[18] Sparsentan appeared to be generally well-tolerated over 36 weeks of treatment. SAEs were reported in 3 patients; none were believed to be related to study treatment. One patient discontinued treatment after 6 weeks due to hypotension.[19]

In an interim analysis of the phase 2 EPPIK study (NCT05003986) of sparsentan treatment for pediatric patients with FSGS, sparsentan appeared to be safe and well-tolerated. The observed safety profile was consistent with those in other studies of FSGS. One patient discontinued study treatment due to worsening of nephrotic symptoms.[20,21]

Abbreviations

ACEi, angiotensin-converting enzyme inhibitor; AE, adverse event; ALT, alanine transaminase; ARB, angiotensin receptor blocker; AST, aspartate aminotransferase; AT_1, angiotensin II type 1; 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; IgAN, immunoglobulin A nephropathy; KF, kidney failure; KRT, kidney replacement therapy; OLE, open-label extension; RAASi, renin-angiotensin-aldosterone system inhibitor; REMS, risk evaluation and mitigation strategy; SAE, serious adverse event; SBP, systolic blood pressure; TEAE, treatment-emergent adverse event; UACR, urine albumin-to-creatinine ratio; ULN, upper limit of normal; UPCR, urine protein-to-creatinine ratio.

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