FILSPARI® (sparsentan)

SPARTAN (Phase 2 Study): Sparsentan as First-Line Therapy in the Treatment of IgA Nephropathy

Summary

Prescribing Information

- The effect of FILSPARI on proteinuria was assessed in a randomized, double-blind, active-controlled, multicenter, global study (PROTECT, NCT03762850) in adults with biopsy-proven IgAN, eGFR ≥30 mL/min/1.73 m^2, and total urine protein ≥1.0 g/day on a maximized stable dose of RAS inhibitor treatment that was at least 50% of maximum labeled dose.[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]
- SPARTAN 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[5]

Study Data

- Reduction in proteinuria (~60% from baseline) was observed at 4 weeks of treatment and sustained over 36 weeks of the study[6]
- Eight (67%) patients achieved complete remission of proteinuria (<0.3 g/day) at any point in the study[6]
- Sparsentan was generally well-tolerated during the study period[6]

Prescribing Information

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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.[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.[7-9]

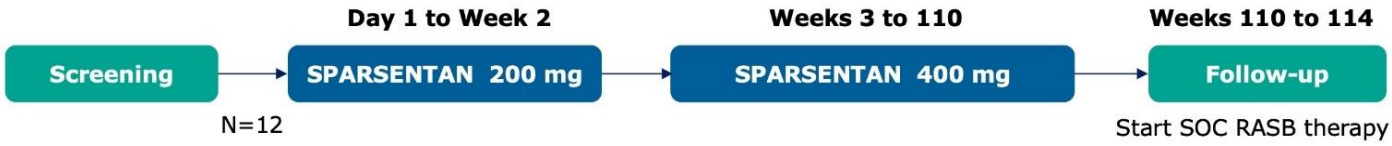
The SPARTAN Study

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 110, change in office and ambulatory BP from baseline, 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.[5,6,10]

Study Design

Following enrollment, patients receive a sparsentan starting dose of 200 mg/day, maintained from Day 1 to Week 2. Sparsentan is then increased to 400 mg/day and continued to Week 110. Patients who are unable to tolerate 400 mg/day may have their dose reduced. Study Weeks 110 to 114 constitute a safety period, during which patients begin SOC RASB therapy and are off sparsentan treatment (**Figure 1**).[5]

Figure 1. SPARTAN Study Design



Baseline assessments of all outcome parameters are made at time of screening. Proteinuria (24-hour collection) and eGFR are measured at each clinical office visit from Day 1 to Week 114, with the exception of Week 2, which does not include a proteinuria assessment. mGFR is evaluated at Weeks 6 and 24. Additional assessments include ambulatory BP at Week 6, TBW (bioimpedance) at

Weeks 6, 12, 24, and 110, and kidney biopsy at Week 24. Renal and cardiac MRI are performed at Weeks 24, 48, and 106.[5]

Study Data

Preliminary Study Results

At data cutoff (September 26, 2023), 12 patients had received sparsentan for ≥6 weeks. Preliminary clinical findings are reported for the first 36 weeks of sparsentan treatment.[6]

Baseline Characteristics

Baseline characteristics of the 12 SPARTAN patients are presented in **Table 1**.[5]

Table 1. SPARTAN Study Patient Baseline Characteristics

Patients With IgAN (N = 12)	
Age at informed consent, mean (SD), years	35.8 (12.2)
Male sex, n (%)	7 (58.3)
White race, n (%)	10 (83.3)
BMI, mean (SD), kg/m²	27.5 (7.2)
Weight, mean (SD), kg	83.1 (24.7)
BP (systolic/diastolic), mean (SD), mm Hg*	125 (10)/78 (10)
eGFR, mean (SD), mL/min/1.73 m²	70.2 (25.0)
UPE, median (IQR), g/day	1.4 (0.6-3.2)
UPCR, median (IQR), g/g	1.3 (0.4-1.7)
Total body water, mean (SD), L	47.1 (7.4)

Efficacy

Reduction in Proteinuria

Baseline median (IQR) UPCR was 1.3 (0.4-1.7) g/g. Reduction in proteinuria was observed as early as Week 4. Mean reduction from baseline was approximately 60% and was maintained through 36

weeks of treatment (**Figure 2**). All patients experienced reduction in proteinuria. Four patients had a baseline protein excretion of >2 g/day; 3 of these patients demonstrated UPCR reduction ≥75% at any point during treatment. Complete remission of proteinuria (<0.3 g/day) was achieved by 8 (67%) patients at any time during the 36 week treatment period (**Figure 3**).[6]

Figure 2. Proteinuria Change (UPCR) from Baseline

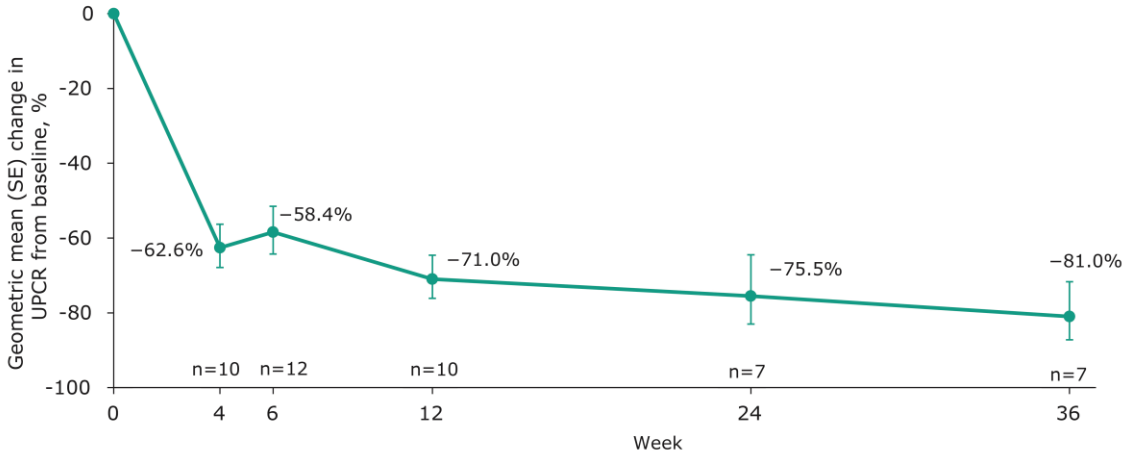
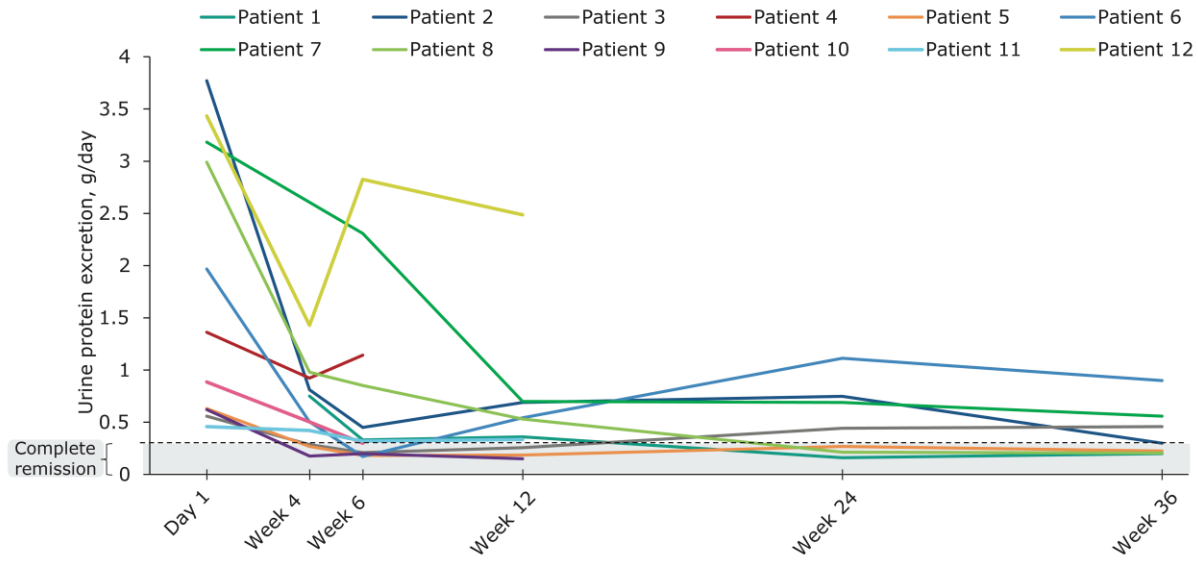


Figure 3. Proteinuria per Individual Patient in the SPARTAN Study



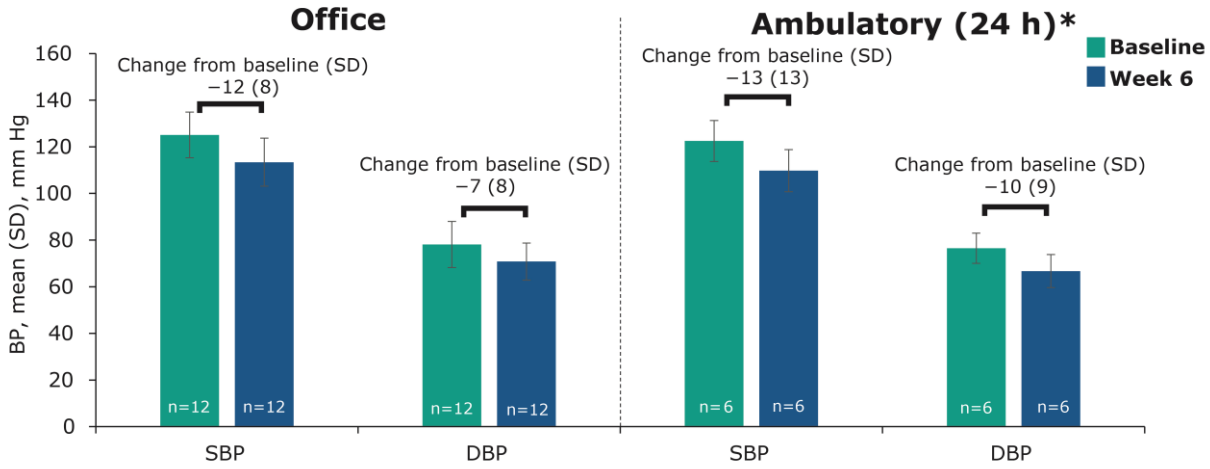
Changes in eGFR

Mean (SD) eGFR of patients at baseline was 70.2 (25.0) mL/min/1.73 m^2. Over 36 weeks of treatment, changes in eGFR remained relatively stable.[6]

Changes in BP

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 4**).[6]

Figure 4. Mean Office and Ambulatory BP at Baseline and Week 6



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

Changes in Body Weight and Total Body Water

Mean (SD) body weight at baseline was 83.1 (24.7) kg. Over 36 weeks of treatment, body weight showed minor fluctuations. Baseline mean (SD) total body water equaled 47.1 (7.4) L and demonstrated modest reductions through study follow-up.[6]

Safety

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.[6]

Abbreviations

ACEi, angiotensin-converting enzyme inhibitor; AE, adverse event; ARB, angiotensin receptor blocker; AT_1, angiotensin II type 1; BMI, body mass index; BP, blood pressure; eGFR, estimated glomerular filtration rate; DBP, diastolic blood pressure; ET_A, endothelin-1 type A; IgA, immunoglobulin A; IgAN, immunoglobulin A nephropathy; IQR, interquartile range; mGFR, measured glomerular filtration rate; MRI, magnetic resonance imaging; RASB, renin-angiotensin system blocker; SAE, serious adverse event; SBP, systolic blood pressure; SD, standard deviation; SE, standard error; SOC, standard of care; TBW, total body water; UPCR, urine protein-to-creatinine ratio; UPE, urine protein excretion.

References

1. FILSPARI. Prescribing information. Travere Therapeutics Inc; February 2023.
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6. Cheung CK, Moody S, Dhaun N, et al. Sparsentan as first-line treatment of incident patients with IgA nephropathy: Preliminary findings from the SPARTAN trial. Poster presented at: ASN Kidney Week; November 2-5, 2023; Philadelphia, PA.
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8. Nagasawa H, Suzuki H, Jenkinson C, et al. The dual endothelin type A receptor (ET_AR) and angiotensin II type 1 receptor (AT_1R) antagonist, sparsentan, protects against the development of albuminuria and glomerulosclerosis in the gddY mouse model of IgA nephropathy. Poster presented at: ERA-EDTA Virtual Congress; June 6-9, 2020; Virtual Meeting.
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