

FILSPARI[®] (sparsentan)

Transitioning from ACEi/ARB Treatment to Sparsentan in Clinical Trials

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 progression¹
- Prior to initiating treatment with FILSPARI, discontinue use of renin-angiotensin-aldosterone system (RAAS) inhibitors and endothelin receptor antagonists (ERAs)¹
- Do not coadminister FILSPARI with ARBs, ERAs, or aliskiren¹

Study Data

The PROTECT Study

- On Day 1 following randomization, current ACEi and/or ARB therapies were discontinued for the duration of the study²
- Initial doses were sparsentan 200 mg/day or irbesartan 150 mg/day, and target doses were 400 mg/day sparsentan and 300 mg/day irbesartan²

The DUET Study

- Prior to randomization, patients discontinued prescribed ARB and ACEi therapies³
- Patients were randomized 3:1 to receive sparsentan 200 mg/day, 400 mg/day (two cohorts), or 800 mg/day (two cohorts) or irbesartan 300 mg/day³

The DUPLEX Study

- Prior to randomization, patients discontinued prescribed ARB and ACEi therapies⁴
- Patients were randomized 1:1 to receive 800 mg/day sparsentan or 300 mg/day irbesartan⁴

Additional Studies

- In additional clinical studies, ACEi/ARB therapy was discontinued prior to initiation of sparsentan treatment⁵⁻⁷

Prescribing Information

General Consideration

Prior to initiating treatment with FILSPARI, discontinue use of renin-angiotensin-aldosterone system (RAAS) inhibitors and endothelin receptor antagonists (ERAs).¹

Monitoring

Initiate treatment with FILSPARI only after measuring aminotransferase levels and total bilirubin. Avoid initiation in patients with elevated aminotransferases greater than 3 times ULN. Continue required monitoring monthly for the first 12 months after initiation or restarting following an interruption due to elevated transaminases, then every 3 months during treatment with FILSPARI.¹

Recommended Dosage

Initiate treatment with FILSPARI at 200 mg orally once daily. After 14 days, increase to the recommended dose of 400 mg once daily, as tolerated. When resuming treatment with FILSPARI after an interruption, consider titration of FILSPARI, starting at 200 mg once daily. After 14 days, increase to the recommended dose of 400 mg once daily.¹

Renin-Angiotensin System (RAS) Inhibitors and ERAs

Do not coadminister FILSPARI with ARBs, ERAs, or aliskiren.¹

Combined use of these agents is associated with increased risks of hypotension, syncope, hyperkalemia, and changes in renal function (including acute renal failure).¹

Background

Sparsentan is a novel, first-in-class, and the only single molecule antagonist of the ET_A and AT₁ receptors.^{3,8,9} Preclinical studies in rodent models of chronic kidney disease have shown that blockade of both ET_A and AT₁ pathways reduces proteinuria, protects podocytes, and prevents glomerulosclerosis and mesangial cell proliferation.¹⁰⁻¹²

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 m², 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 m².¹⁶ 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 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 with biopsy-proven FSGS. 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.¹⁸ Patients remained on maintenance doses of sparsentan or irbesartan during a 108-week double blind phase. 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). An additional interim endpoint was the proportion of patients achieving a UPCR ≤1.5 g/g and a >40% reduction (FPRE) at Week 36. Safety was assessed by double-blind monitoring of adverse events and safety endpoints.^{4,18}

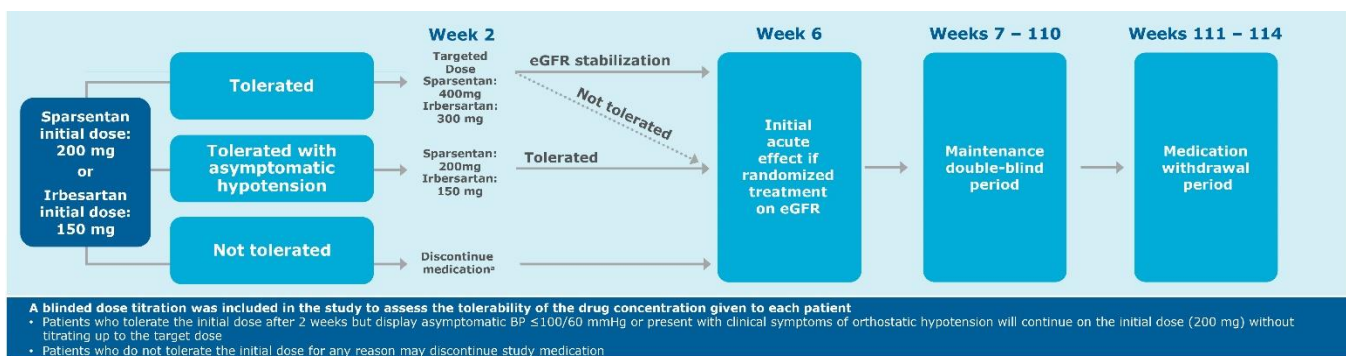
Study Data

The PROTECT Study

On Day 1 following randomization, current ACEi and/or ARB therapies were discontinued for the duration of the study. Patients began initial doses of either study drug (sparsentan once-daily 200 mg) or active control (irbesartan once-daily 150 mg). Target doses were 400 mg/day sparsentan and 300 mg/day irbesartan; patients received half of target dose for the first 2 weeks after randomization, with a goal to titrate to the target doses at Week 2 (**Figure 1**). 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 (eg, serum potassium >5.5 mEq/L) interfering with the patient's continuation on study medication.¹⁴

Patients who tolerated initial doses were titrated up to target doses. Patients who tolerated the initial dose but experienced asymptomatic blood pressure values $\leq 100/60$ mm Hg or presented with clinical symptoms of orthostatic hypotension continued initial dose without titration to target dose. 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. Decreases in target dose and titrations to target dose were permitted at any time throughout the study.¹⁴

Figure 1. Blinded Dose Titration in the PROTECT Study



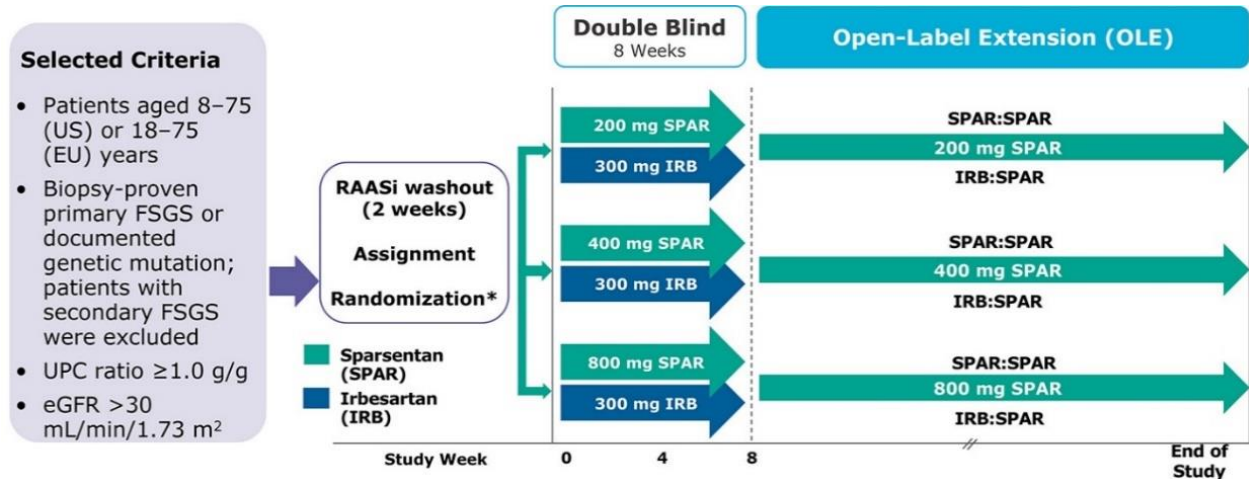
^aPatients who do not tolerate the initial dose will be encouraged to restart study medication throughout the study. Patients who do not tolerate study medication should continue in the study even if they permanently discontinue study medication.

In an interim analysis of PROTECT data after 36 weeks of treatment, the safety profile of sparsentan was consistent with that previously observed and showed no new safety signals.^{9,19}

The DUET Study

Prior to randomization, patients discontinued prescribed ARB and ACEi therapies. Patients were then randomized 3:1 through an interactive web response system within sequential dose-escalating, 20-patient cohorts to receive sparsentan 200 mg/day, 400 mg/day (two cohorts), or 800 mg/day (two cohorts) or irbesartan 300 mg/day (**Figure 2**). Incremental safety reviews were performed by an independent DMC. Only patients aged 18 years and older were initially enrolled in cohort 1 at the 200 mg/day dose. After 8 patients completed 4 weeks of treatment, a safety review was conducted and enrollment was opened to patients aged 8-17 years. Cohort 2 was also opened for randomization of patients to receive sparsentan 400 mg or irbesartan 300 mg. This process was repeated after 8 patients completed 4 weeks of treatment at 400 mg, and again after 8 patients completed 4 weeks at 800 mg. DMC reviews continued every 6 months. Patients randomized to irbesartan received 150 mg/day for the first week before escalating to 300 mg/d for the remaining 7 weeks. Patients with body weight ≤ 50 kg received 50% of the assigned study drug doses.³

Figure 2. DUET Study Schematic

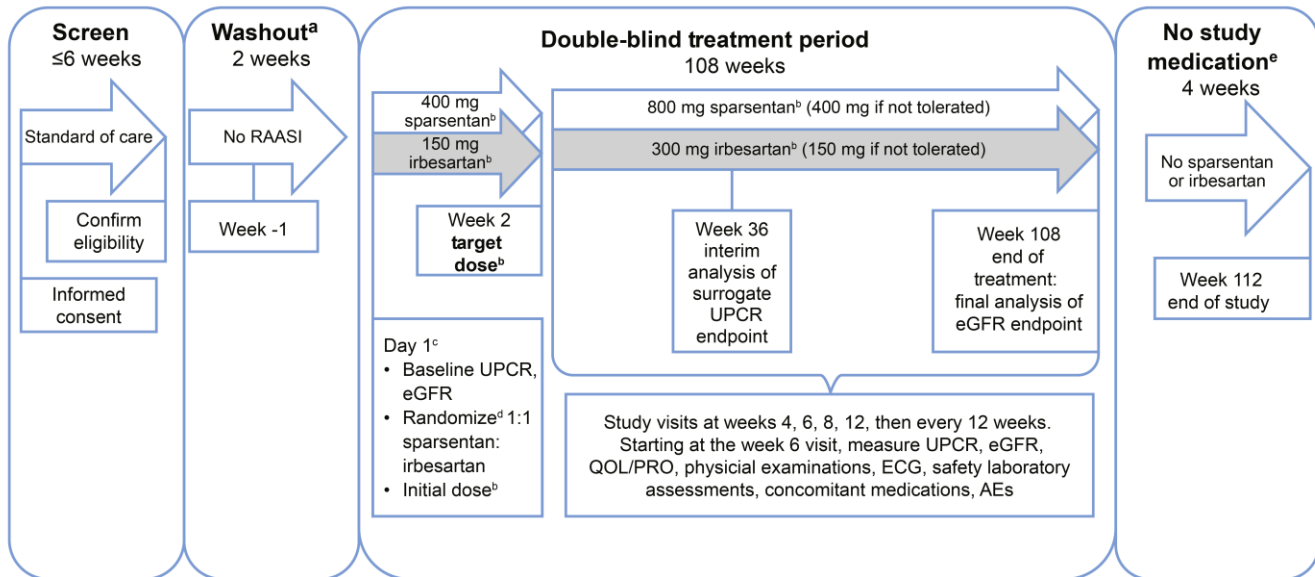


*Patients were assigned to dose cohort, then randomized to sparsentan or irbesartan within the dose cohort. The study drug was administered orally, once daily. Patients who weighed ≤ 50 kg received half of the daily dose of sparsentan or irbesartan according to the assigned dose cohort. Randomization after 2 weeks of RAASi washout. IRB:SPAR = patients randomized to irbesartan who then transitioned to sparsentan in the OLE; SPAR:SPAR = patients randomized to sparsentan who also received sparsentan in the OLE.

In a post-hoc assessment through 240 weeks of the DUET OLE, no new or unexpected safety signals emerged.²⁰

The DUPLEX Study

Prior to randomization, patients discontinued prescribed ARB and ACEi therapies (**Figure 3**). Patients were then randomized 1:1 through an interactive web response system to 800 mg/day sparsentan or 300 mg/day irbesartan. Patients who weighed ≤ 50 kg at screening received half the otherwise specified doses of sparsentan or irbesartan. Randomization was stratified by eGFR (≥ 30 to < 60 mL/min per 1.73 m² and ≥ 60 mL/min per 1.73 m² for all patients) and UPCR (≤ 3.5 g/g and > 3.5 g/g [patients ≥ 18 years old] or ≤ 2 g/g and > 2 g/g [patients < 18 years old]) at screening. After 108 weeks, study treatment was discontinued and the investigator resumed standard-of-care treatment, including treatment with RAASi (with the exception of irbesartan) provided there are no contraindications for their use.⁴

Figure 3. DUPLEX Study Schematic


^aFor patients who are undergoing washout from RAASI. ^bPatients whose body weight is ≤50 kg at screening will receive half the otherwise specified doses of sparsentan or irbesartan (active control). Weight will be measured at each visit and the dose increased at the investigator's discretion if the patient's weight reaches >50 kg. ^cDay 1 events shown will occur in the order in which they are listed. ^dRandomization will be stratified by eGFR value (≥30 to <60 mL/min per 1.73 m² and ≥60 mL/min per 1.73 m² for all patients) and UPCR (≤3.5 g/g and >3.5 g/g [patients ≥18 years old] or ≤2 g/g and >2 g/g [patients <18 years old]) at screening. ^eFollowing the 108-week blinded treatment period, treatment with study medication will be discontinued. At this time, the investigator should resume standard-of-care treatment, including treatment with RAASI (with the exception of irbesartan) provided there are no contraindications for their use. The investigator may make additional adjustments in antihypertensive medications as clinically indicated to adequately control the patient's BP.

Over 108 weeks of treatment, TEAEs were reported with similar frequency in the sparsentan (n=172, 93%) and irbesartan (n=174, 93%) treatment groups. Serious TEAEs occurred in 44 (24%) sparsentan-treated patients and 41 (22%) irbesartan-treated patients. There was a total of 12 (3%) events of abnormal liver function tests in the study, with 7 (4%) events in the sparsentan arm and 5 (3%) events in the irbesartan arm. There were no reports of Hy's law or drug-induced liver injury with sparsentan and no SAEs due to CHF. SAEs due to peripheral edema occurred in 3% of patients treated with irbesartan and none in the sparsentan group. No new safety signals emerged.¹⁸

Additional Studies and Clinical Trials

In the EPPIK study of pediatric patients with rare proteinuric kidney diseases, patients underwent a 2-week washout of RAASI prior to initiating sparsentan treatment.⁵ In the SPARTACUS study of combination SGLT2 inhibitor and sparsentan therapy, patients discontinued ACEi/ARB treatment by Day 1 of combined treatment.⁶ All patients (N=5) in a case series of sparsentan with prior or concurrent immunosuppressive therapy had a history of ACEi or ARB therapy, all of which was discontinued prior to sparsentan treatment.⁷

Abbreviations

ACEi, angiotensin-converting enzyme inhibitor; AE, adverse event; ARB, angiotensin receptor blocker; AT₁, angiotensin II type 1; BP, blood pressure; CHF, congestive heart failure; DBP, diastolic blood pressure; DMC, data monitoring committee; ECG, electrocardiogram; eGFR, estimated glomerular filtration rate; ERA, endothelin receptor antagonist; ET_A, endothelin-1 type A; FPRE, FSGS partial remission endpoint; FSGS, focal segmental glomerulosclerosis; IgA, immunoglobulin A; INR, international normalized ratio; IRB, irbesartan; KF, kidney failure; KRT, kidney replacement therapy; OLE, open-label extension; PRO, patient-reported outcome; QOL, quality of life; RAASi, renin-angiotensin-aldosterone system inhibitor; SAE, serious adverse event; SBP, systolic blood pressure; SGLT2, sodium-glucose co-transporter 2; SPAR, sparsentan; TEAE, treatment-emergent adverse event; ULN, upper limit of normal; UACR, urine albumin-creatinine ratio; UPE, urinary protein excretion; UPCR, urine protein-creatinine ratio.

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