FILSPARI® (sparsentan)
In Combination With Immunosuppressant Therapy

Summary

Prescribing Information

- 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]
- Patients who had been recently treated with systemic immunosuppressive medications were excluded from the PROTECT study[1]
- During the PROTECT study, rescue immunosuppressive treatment could be initiated per investigator discretion[1]

Background

- Sparsentan is an investigational therapeutic candidate for the treatment of FSGS[4,5]
- 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[6]
- The DUPLEX study 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[5]

Study Data

- Clinical guidelines recommend that patients at high risk of progressive chronic kidney disease despite maximal supportive care be considered for treatment with immunosuppressive drugs[7]
- In the PROTECT study, patients at screening could not receive or have a recent history of immunosuppressive treatment[8]
- It was recommended in the PROTECT study that systemic corticosteroids and/or immunosuppressive therapy be avoided for the duration of the study. If deemed necessary by the study investigator, systemic corticosteroid and/or immunosuppressive treatment was allowed in addition to study medication[8]
- In the DUPLEX study, exploratory endpoints included proportion of patients requiring initiation, increase or decrease of immunosuppressive medication[5]

Prescribing Information

- Patients who had been recently treated with systemic immunosuppressive medications were excluded from the PROTECT study[1]
- During the PROTECT study, rescue immunosuppressive treatment could be initiated per investigator discretion[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.[8] 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.[6,8] 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.[13] Reduction in proteinuria and decline in rate of eGFR are largely accepted as surrogate markers of treatment effect in studies of KF.[13,14]

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.[5,15] 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.[15] 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.[5,15]

Study Data

Use of Immunosuppressive Therapy in IgA Nephropathy

The clinical benefit of glucocorticoids as treatment in IgA nephropathy has not been fully established. In vivo studies have shown that glucocorticoids impact some pathological characteristics of IgA nephropathy, such as reducing serum levels of galactose-deficient IgA. In vitro studies in models of IgA nephropathy suggest that treatment with glucocorticoids may reduce glomerular and interstitial inflammation. Clinical studies found that treatment with glucocorticoids in patients with IgA nephropathy reduced risk of kidney failure, and an increased number of patients achieving full remission of proteinuria.[16]

Current care guidelines indicate that patients who are at high risk of progressive kidney disease despite treatment with maximal supportive care to stabilize blood pressure and minimize proteinuria may be considered for a 6-month course of immunosuppressive (glucocorticoid) therapy. It is recommended that treatment be used with caution or avoided in patients with eGFR <30 mL/min/1.73 m^2, diabetes, BMI >30 kg/m^2, latent infections, secondary disease (eg, cirrhosis), active peptic ulceration, uncontrolled psychiatric illness, or severe osteoporosis. Patients should be risk stratified in making treatment decisions.[7]

The PROTECT Study

A total of 404 patients were enrolled in the study; 202 patients were randomized to each treatment group. Over 2 years of treatment, rescue immunosuppressive therapy was initiated sooner and more frequently among patients taking irbesartan (n=16; 8%) than sparsentan-treated patients (n=6; 3%). Treatments were mostly corticosteroid medications.[17]

The DUPLEX Study

A total of 371 patients were enrolled in the study; 184 patients were randomized to sparsentan and 187 patients were randomized to irbesartan. Use of immunosuppressants was similar between the sparsentan (n=30; 16.3%) and irbesartan (n=30; 16%) groups.[15]

Abbreviations

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; AT_1, angiotensin II type 1; BMI, body mass index; BP, blood pressure; 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; RAASi, renin-angiotensin-aldosterone system inhibitor; SBP, systolic blood pressure; UACR, urine albumin-to-creatinine ratio; UPCR, urine protein-to-creatinine ratio.

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