FILSPARI® (sparsentan)

In Combination With SGLT2 Inhibitors in IgA Nephropathy

Summary

Background

- Sparsentan is a novel, first-in-class, and the only single molecule antagonist of the ET_A and AT_1 receptors[1-3]
- Dual antagonism of both ET_A and AT_1 pathways in preclinical models of rare chronic kidney disease may have beneficial effects in reduction of proteinuria and preservation of kidney function[4]
- SGLT2 inhibitors are utilized as supportive care in patients with chronic kidney disease, including IgA nephropathy[5,6]
- Emerging data suggests that combining ET_A receptor antagonists and SGLT2 inhibitors may be a particularly beneficial treatment option, with potentially additive kidney protective efficacy and mild diuretic effect of SGLT2 inhibitors[7]
- The PROTECT OLE allowed use of SGLT2 inhibitors with sparsentan treatment[8]
- The SPARTACUS study is an exploratory phase 2 study to examine the safety and efficacy of sparsentan in patients with IgA nephropathy at risk for disease progression despite treatment with RAASi and SGLT2 inhibitors[9]

Study Data

- In the PROTECT OLE, at data cutoff, 39 patients received a stable dose of sparsentan and add-on SGLT2 inhibitors. The combined treatment appeared to be generally well-tolerated and demonstrated an additive benefit in reducing proteinuria[8]
- The effect of multiple sparsentan doses on single-dose PK of the SGLT2 inhibitor dapagliflozin was examined in an open-label crossover phase 1 study of healthy adults[10]
    - Steady-state sparsentan concentration did not affect a single dose of dapagliflozin PK
    - Sparsentan had a minimal effect on C_{max} and AUC values of the dapagliflozin metabolite dapagliflozin-3-O-glucuronide
    - Concomitant use of sparsentan and dapagliflozin was generally safe and well-tolerated

Background

Sparsentan is a novel, first-in-class, and the only single molecule antagonist of the ET_A and AT_1 receptors.[1-3] 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.[4,11,12]

SGLT2 Inhibitors

SGLT2, located in the proximal segment of the nephron, is responsible for ~90% of sodium-mediated glucose reabsorption in the tubular filtrate. Inhibition of SGLT2 function within the kidney reduces glucose reabsorption and increases urinary glucose excretion in an insulin-independent manner. Sodium is in turn delivered to the macula densa, which activates tubule glomerular feedback, reduces intraglomerular pressure, and limits podocyte damage.[13]

SGLT2 inhibitors are utilized as supportive care in patients with chronic kidney disease, including IgA nephropathy.[5,6] Studies of patients with CKD have found that treatment with SGLT2 inhibitors significantly reduces adverse kidney outcomes.[6]

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.[14] 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.[15] 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.[15,16] 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.[7] Reduction in proteinuria and decline in rate of eGFR are largely accepted as surrogate markers of treatment effect in studies of KF.[7,17]

Concomitant SGLT2 Inhibitor Treatment in the PROTECT OLE

Patients who completed the PROTECT double-blind period were eligible to enroll into the OLE. Patients continued on sparsentan with a target dose of 400 mg/day for up to 156 weeks. Patients could begin a concomitant SGLT2 inhibitor at any time during the OLE at the discretion of the investigator. The objective of this study was to investigate long-term efficacy, safety, and tolerability of combined sparsentan and SGLT2 inhibitor treatment.[8]

Assessments included body weight, SBP, DBP, and UPCR, taken at baseline and Weeks 12, 24, 36, and 48. Baseline was defined as the OLE visit closest to SGLT2 inhibitor initiation (before or <14 days after start of concomitant SGLT2 inhibitors).[8]

The SPARTACUS Study

The SPARTACUS study (NCT05856760) is a single-group, multicenter, open-label, exploratory phase 2 trial examining the safety and efficacy of sparsentan in adult patients with biopsy-proven IgA nephropathy at risk of disease progression despite ongoing treatment with RAASi and SGLT2 inhibitors.[9] Approximately 60 patients aged 18 years and older will be enrolled. Patients must be on stable doses of an ACEi/ARB and SGLT2 inhibitors for ≥12 weeks prior to enrollment and throughout the screening period. The primary outcome measure is change from baseline in UACR at Week 24. Secondary outcome measures include UACR <0.2 g/g at Week 24, 30% and 50% reduction from baseline in UACR at Week 24, and change from baseline in UACR, UPCR, eGFR, SBP, and DBP at each study visit. Safety assessments throughout the study include TEAEs, SAEs, AEs leading to treatment discontinuation, and AEs of interest.[9,18]

Drug Interaction Study in Healthy Volunteers

Interactions between multiple doses of sparsentan and single doses of the SGLT2 inhibitor dapagliflozin were assessed in an open-label, 1-sequence phase 1 crossover study in healthy adults. Subjects were given 10 mg dapagliflozin on study day 1, and subsequently dosed with 800 mg/day sparsentan on days 5-14. A single 10 mg dapagliflozin dose was coadministered on day 11. Dapagliflozin-3-O-glucuronide, an inactive metabolite, was measured as an indicator of uridine 5'-diphosphoglucuronosyltransferase 1A9, the primary metabolizing enzyme of dapagliflozin.[10]

Study Data

The PROTECT Study

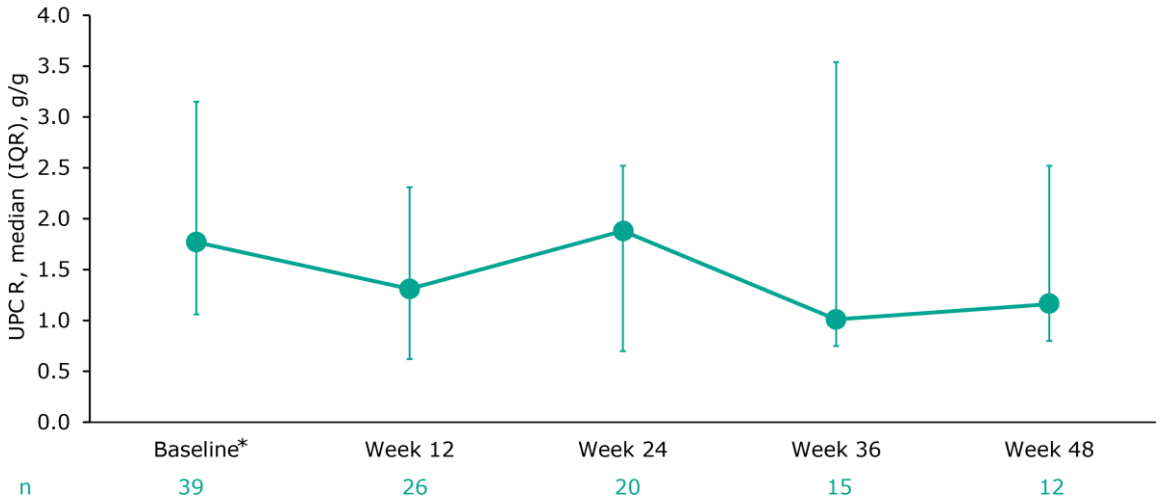
There are no data regarding the use of SGLT2 inhibitors from the double-blind PROTECT study as SGLT2 inhibitors were prohibited.[14] SGLT2 inhibitors are allowed during the open-label extension period of the PROTECT study at the discretion of the investigator with appropriate monitoring of blood pressure, serum creatinine, and eGFR.[8,19]

PROTECT OLE

Efficacy

At data cutoff, 39 patients (11 female; 28%) enrolled in the PROTECT OLE received combined SGLT2 inhibitors with stable doses of sparsentan. Median (IQR) time from OLE start to time of SGLT2 inhibitor initiation was 253 (92-358) days. Assessments of body weight, SBP, DBP, and UPCR were taken at baseline and at Weeks 12, 24, 36, and 48. Body weight, SBP, and DBP appeared to remain stable over time after initiation of concomitant SGLT2 inhibitors. Further reduction in UPCR was observed for up to 48 weeks from baseline (**Figure 1**), demonstrating an additive benefit on proteinuria reduction with concomitant sparsentan and SGLT2 inhibitor treatment.[8]

Figure 1. UPCR Over Time



*Baseline was defined as the OLE visit closest to the SGLT2 inhibitor start (ie, before or <14 days after start of SGLT2 inhibitor treatment). Data are shown at Weeks 12, 24, 36, and 48 after baseline.

Safety

TEAEs were reported by 26 (67%) patients. The most common were hyperkalemia in 5 (13%) patients, COVID-19 in 4 (10%) patients, and hypertension in 3 (8%) patients. Five patients discontinued the OLE; this included 2 patients who first discontinued SGLT2 inhibitors and then discontinued the OLE. Reasons for discontinuation included kidney replacement therapy (n=1), physician decision (n=1), and TEAEs (n=3; aggravation of IgA nephropathy [n=1] and elevated ALT [n=2]). Additional safety information is presented in **Table 1**.[8]

Table 1. TEAEs Reported in the PROTECT OLE

TEAEs*	Patients (N=39)
Patients with any TEAE, n (%)	26 (67)
TEAEs in >1 patient, n (%)	
Hyperkalemia	5 (13)
COVID-19	4 (10)
Hypertension	3 (8)
Acute kidney injury	2 (5)
Chronic kidney disease	2 (5)
Headache	2 (5)
Hypotension	2 (5)
Peripheral edema	2 (5)
Viral infection	2 (5)

*TEAEs were based on MedDRA preferred terms.

The SPARTACUS Study

The SPARTACUS study began enrollment in May 2023 and is currently recruiting. Approximately 30 study sites are planned in the US and Hong Kong. Safety and efficacy results are expected by late 2024.[18]

Drug Interaction Study in Healthy Volunteers

Interactions between multiple doses of sparsentan and single doses of the SGLT2 inhibitor dapagliflozin were assessed in healthy adults. Plasma PK parameters were comparable before and after single-dose dapagliflozin alone and coadministration of sparsentan, suggesting that steady-state sparsentan concentrations following multiple-dose administration did not affect single-dose dapagliflozin PK. Compared to single-dose dapagliflozin alone, C_{max} and AUC values for dapagliflozin-3-O-glucuronide were 10-12% lower following coadministration of sparsentan, indicating a minimal effect of sparsentan on dapagliflozin metabolism.[10]

Concomitant use of sparsentan and single doses of dapagliflozin was generally safe and well tolerated in healthy subjects, and no deaths or serious TEAEs occurred. Fewer TEAEs were reported with single dose dapagliflozin or multiple dose sparsentan alone compared to drug coadministration (ie, a single dose of dapaglifozin with multiple dose sparsentan).[10]

Abbreviations

ACEi, angiotensin-converting enzyme inhibitor; AE, adverse event; ALT, alanine aminotransferase; ARB, angiotensin receptor blocker; AT_1, angiotensin II type 1; AUC, area under the curve; CKD, chronic kidney disease; C_{max}, max serum concentration; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; ET_A, endothelin-1 type A; IgA, immunoglobulin A; IQR, interquartile range; KF, kidney failure; KRT, kidney replacement therapy; MedDRA, Medical Dictionary for Regulatory Activities; OLE, open-label extension; PK, pharmacokinetics; RAASi, renin-angiotensin-aldosterone system inhibitor; SAE, serious adverse event; SBP, systolic blood pressure; SD, standard deviation; SGLT2, sodium-glucose co-transporter 2; TEAE, treatment-emergent adverse event; UACR, urine albumin-to-creatinine ratio; UPCR, urine protein-to-creatinine ratio.

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19. Data on file. Travere Therapeutics Inc; 2023.

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