FILSPARI® (sparsentan)
Concomitant Medications Included 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 progression[1]
- In the PROTECT study, use of SGLT2 inhibitors, other RAS inhibitors, and aldosterone blockers were prohibited[1]
- Some medications should not be used concomitantly with FILSPARI, including ARBs, ERAs, aliskiren, strong CYP3A inhibitors or inducers, acid-reducing agents, and sensitive substrates of P-gp and BCRP[1]
- Use of other medications in conjunction with FILSPARI may require monitoring of blood pressure, serum potassium, edema, and kidney function, including moderate CYP3A inhibitors, NSAIDs, and COX-2 inhibitors[1]
- Administer FILSPARI 2 hours before or after administration of antacids. Antacids or acid reducing agents may decrease sparsentan exposure which may reduce FILSPARI efficacy[1]

Background

- 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[2]
- 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 phase 3, 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[4]
- The EPPIK study is a phase 2 open-label, single-arm, multicenter trial evaluating the safety, efficacy, and PK of liquid sparsentan in patients aged ≥1 to <18 years with FSGS or MCD and aged ≥2 to <18 years with IgAN, IgAV, or Alport syndrome[5]

Study Data

- In the PROTECT trial in IgA nephropathy and the DUET and DUPLEX studies in FSGS, patients were required to discontinue RAASi medications prior to initiation of study drug and certain concomitant medications were prohibited[6-8]
- Additional medications were permitted in clinical trials but were to be used with caution and with dosage adjustments as needed[6-8]

Prescribing Information

- During the PROTECT study, rescue immunosuppressive treatment could be initiated per investigator discretion, but use of SGLT2 inhibitors, other RAS inhibitors, and aldosterone blockers were prohibited[1]

Due to potential drug interactions and impact on efficacy, some medications should not be used concomitantly with FILSPARI.[1]

- Do not coadminister FILSPARI with ARBs, ERAs, or aliskiren. Combined use of these agents is associated with increased risks of hypotension, syncope, hyperkalemia, and changes in renal function (including acute renal failure)
- Avoid concomitant use of FILSPARI with strong CYP3A inhibitors (increases sparsentan C_{max} and AUC)
- Avoid concomitant use with strong CYP3A inducer (decreases sparsentan C_{max} and AUC)
- Avoid concomitant use of sensitive substrates of P-gp and BCRP with FILSPARI (sparsentan may increase exposure to these transporter substrates)
- Avoid concomitant use of acid reducing agents (histamine H2 receptor antagonist and PPI (proton pump inhibitor) with FILSPARI (may reduce FILSPARI exposure)

Other medications may be used with caution and monitoring in conjunction with FILSPARI.[1]

- Monitor blood pressure, serum potassium, edema, and kidney function regularly when used concomitantly with moderate CYP3A inhibitors
- Monitor for signs of worsening renal function with concomitant use with NSAIDs including selective COX-2 inhibitors
- Monitor for efficacy of concurrently administered CYP2B6, 2C9, and 2C19 substrates and consider dosage adjustment in accordance with the Prescribing Information
- Monitor serum potassium frequently in patients treated with FILSPARI and other agents that increase serum potassium
- Administer FILSPARI 2 hours before or after administration of antacids

For more information, please refer to the Prescribing Information, including Boxed Warning.

Background

Sparsentan is a novel, first-in-class, and the only single molecule antagonist of the ET_A and AT_1 receptors.[3,8,9] 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.[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 m^2, SBP ≤150 mm Hg, and DBP ≤100 mm Hg were eligible.[6] 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.[2,6] 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 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 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.[4] 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.[4,7]

The EPPIK Study

The EPPIK study (NCT05003986) is a phase 2, global, open-label, single-arm, multicenter cohort study to evaluate the safety, efficacy, and PK of a once-daily oral suspension of sparsentan in pediatric patients with selected proteinuric glomerular diseases. The primary objective of the EPPIK study is to examine long-term antiproteinuric and nephroprotective potential and safety in this

pediatric population.[16] Approximately 57 pediatric patients aged ≥1 to <18 years will be enrolled. EPPIK Population 1 will include ~30 patients aged 1 to <18 years with FSGS or treatment-resistant MCD. Population 2 will include ~27 patients aged 2 to <18 years with IgAN, IgAV, or Alport syndrome. Target exposure of sparsentan is equivalent to 800 mg in Population 1 and 400 mg in Population 2. Primary endpoints are the change from baseline in UPCR over a 108-week treatment period, incidence of TEAEs, SAEs, AEs leading to treatment discontinuation, and AEs of interest. Secondary endpoints include observed plasma PK concentration, steady-state PK parameters, change from baseline in UACR and eGFR over 108 weeks of treatment, and proportion of patients with FSGS or MCD histological patterns achieving partial remission (FPRE) in UPCR. Partial remission is defined as UPCR ≤1.5 g/g and >40% reduction in UPCR. Safety parameters are monitored throughout the duration of the study.[5,16,17]

Study Data

The PROTECT Study

At time of screening in the PROTECT study, potential patients could not receive or have a recent history of treatment with immunosuppressant agents. Once randomized and prior to titration with the study drug (sparsentan or irbesartan), patients discontinued prior ACEi and/or ARB treatment, as well as all other medications prohibited throughout the study. These included RAASis, ERAs, potassium-sparing diuretics, selected antidiabetic drugs, selected antiarrhythmic medications, amphetamines and amphetamine derivatives, St. John's wort or other hypericum-derived products, strong and moderate CYP3A inhibitors, and combined strong or moderate CYP3A and P-gp inhibitors (**Table 1**). Patients were further prohibited from eating or drinking anything containing grapefruit juice, starfruit, or Seville oranges.[6,14]

It was recommended that other antidiabetic drugs (eg, metformin or glyburide) be used in accordance with guidelines for patients with impaired kidney function. Other medications were to be used with caution, including CYP450-2B6 substrates, statins, nonsteroidal anti-inflammatory drugs used for >1 week, lithium, and warfarin. Dosages could be adjusted as needed. It was further recommended that patients avoid corticosteroid and immunosuppressive therapies throughout the duration of the study, but they could be used if warranted and at the investigator's discretion.[6]

SGLT2 inhibitors are allowed during the open-label extension period at the discretion of the investigator with appropriate monitoring of BP, serum creatinine, and eGFR.[4]

Table 1. Drugs Prohibited During the PROTECT Study

RAASis (eg, ACEi, ARB, aliskirin, and aldosterone blocker)	Amphetamines/amphetamine derivatives
Endothelin receptor antagonists	St. John's wort/hypericum-derived products
Potassium-sparing diuretics	Strong/moderate CYP3A inhibitors
Specific antidiabetic drugs* (thiazolidinediones, SGLT2 inhibitors)	Combined strong or moderate CYP3A and P-gp inhibitors
Specific antiarrhythmic medications (eg, digoxin, amiodarone)	

*Patients with diabetes may continue to use nonprohibited antidiabetic drugs (eg, metformin) in accordance with guidelines for use in patients with impaired kidney function.

The PROTECT OLE

The PROTECT OLE allowed use of SGLT2 inhibitors in addition to sparsentan treatment. At time of cutoff, 61 patients were receiving concomitant sparsentan and SGLT2 inhibitor therapy. Additional medications utilized by patients at time of SGLT2 inhibitor initiation included diuretics (n=21; 34%), β-blockers (n=15; 25%), α-blockers (n=7; 11%), calcium channel blockers (n=26; 43%), and other (n=2; 3%).[18]

The DUET Study

In the DUET study, patients taking RAASi medications (ACEi, ARB) underwent a 2-week washout period prior to randomization to sparsentan or irbesartan. In addition to RAASi, medications that were prohibited throughout the study included aldosterone blockers, potassium-sparing diuretics, interferon-β-1a, rituximab, cyclophosphamide, and long-term use of nonsteroidal anti-inflammatory treatments (**Table 2**). Immunosuppressive medications, with the exception of cyclophosphamide and rituximab, were permitted if dosing remained stable for at least 1 month prior to randomization. Doses remained stable during the 8-week, double-blind treatment period.[8]

Table 2. Drugs Prohibited During the DUET Study

RAASis (eg, ACEis, ARBs)	Interferon-b-1a
Cyclophosphamide	Rituximab
Long-term use of nonsteroidal anti-inflammatory drugs	Potassium-sparing diuretics

The DUPLEX Study

Patients taking RAASi medications underwent a 2-week washout period prior to randomization to sparsentan or irbesartan. Additional prohibited medications included ERAs, potassium-sparing diuretics, selected antidiabetic drugs, selected antiarrhythmics, amphetamines and amphetamine derivatives, St. John's wort or other hypericum-derived products, and strong CYP3A inhibitors (**Table 3**). Other medications were permitted but used with caution, including strong inhibitors of P-gp such as cyclosporine A, cytochrome P450 2B6 substrates, statins, nonsteroidal anti-inflammatory drugs used for >1 week, lithium, and warfarin, with dosage adjustments as needed.

For patients taking steroids, calcineurin inhibitors, mycophenolate mofetil, and azathioprine doses must be stable for at least 30 days before screening and during the screening period.[7]

Table 3. Drugs Prohibited During the DUPLEX Study

RAASis (eg, ACEis, ARBs)	Antiarrhythmics
Endothelin receptor antagonists	Amphetamines and amphetamine derivatives
Potassium-sparing diuretics	St. John's wort
Antidiabetic drugs	Strong CYP3A inhibitors

Other antidiabetic drugs (eg, metformin, glyburide) should be used in accordance with guidelines for use in patients with impaired kidney function.

The EPPIK Study

At data cutoff (February 15, 2024), 34 pediatric patients enrolled in the EPPIK study had received ≥1 dose of sparsentan oral suspension. Population 1 included 10 patients with MCD and 11 patients with FSGS; Population 2 included 4 patients with IgAN/IgAV and 9 patients with Alport syndrome.[5]

Prior to enrollment, patients taking RAASi underwent a 2-week washout period. Other antihypertensive medications, except endothelin inhibitors, were allowed for treatment of patients with hypertension.[16] At baseline, 11 patients in Population 1 were using immunosuppressant treatments (MCD, n=5, 50%; FSGS, n=6, 54.5%). Among patients in Population 2, 2 presented with immunosuppressant use at baseline (IgAN/IgAV, n=2, 50%; Alport syndrome, n=0).[5]

Abbreviations

ACEi, angiotensin-converting enzyme inhibitor; AE, adverse event; ARB, angiotensin receptor blocker; AT_1, angiotensin II type 1; AUC, area under plasma concentration curve; BCRP, breast cancer resistance protein; BP, blood pressure; CKD, chronic kidney disease; C_{max}, maximum serum concentration; COX-2, cyclooxygenase-2; CYP, cytochrome P; DBP, diastolic blood pressure; 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; IgAN, immunoglobulin A nephropathy; IgAV, immunoglobulin A-associated vasculitis; MCD, minimal change disease; NSAID, nonsteroidal anti-inflammatory agent; KF, kidney failure; KRT, kidney replacement therapy; OLE, open-label extension; P-gp, P-glycoprotein; PK, pharmacokinetics; PPI, proton pump inhibitor; RAASi, renin-angiotensin-aldosterone system inhibitor; RAS, renin-angiotensin system; SAE, serious adverse event; SBP, systolic blood pressure; SGLT2, sodium-glucose cotransporter-2; TEAE, treatment-emergent adverse event; UACR, urine albumin-creatinine ratio; UPCR, urinary protein-creatinine ratio; UPE, urinary protein excretion.

References

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