FILSPARI® (sparsentan)

Elevated Liver Transaminases and Hepatic Safety Results

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]
- Elevations in ALT or AST of at least 3-fold ULN have been observed in up to 3.5% of FILSPARI-treated patients, including cases confirmed with rechallenge[1]
- While no concurrent elevations in bilirubin >2-times ULN or cases of liver failure were observed in FILSPARI-treated patients in clinical trials, some endothelin receptor antagonists have caused elevations of aminotransferases, hepatotoxicity, and liver failure[1]
- Due to risks of hepatotoxicity and embryo-fetal toxicity, FILSPARI is available only through the FILSPARI REMS[1]

Study Data

- The impact of sparsentan on the liver has been assessed in single- and repeated-dose nonclinical toxicology studies[2]
- Dose-dependent increases in liver weight and hepatocellular hypertrophy were observed, which reversed after a recovery period[2]
- Some compounds that antagonize the endothelin receptor are associated with liver damage; capacity for damage appears to be compound specific[3]
- After 110 weeks in the PROTECT study, elevations in ALT or AST >3× ULN occurred in 7 (3.5%) patients taking sparsentan and 8 (4%) patients taking irbesartan.[1] No cases of drug-induced liver injury occurred in either group[4,5]
- After 108 weeks in the DUPLEX study, elevations in ALT or AST >3× ULN occurred in 5 (2.7%) patients taking sparsentan and 4 (2.2%) patients taking irbesartan. No events of drug-induced liver injury occurred with sparsentan and 1 occurred with irbesartan[6]
- In clinical trials, more than 1200 patients have taken sparsentan, including patients who have been on therapy for nearly 7 years. Regular quarterly liver function tests were required throughout studies[7,8]

Prescribing Information

Elevations in ALT or AST of at least 3-fold ULN have been observed in up to 3.5% of FILSPARI-treated patients, including cases confirmed with rechallenge. While no concurrent elevations in bilirubin >2-times ULN or cases of liver failure were observed in FILSPARI-treated patients in clinical trials, some endothelin receptor antagonists have caused elevations of aminotransferases, hepatotoxicity, and liver failure. To reduce the risk of potential serious hepatotoxicity, measure serum aminotransferase levels and total bilirubin prior to initiation of treatment and monthly for the first 12 months, then every 3 months during treatment.[1]

Advise patients with symptoms suggesting hepatotoxicity (nausea, vomiting, right upper quadrant pain, fatigue, anorexia, jaundice, dark urine, fever, or itching) to immediately stop treatment with FILSPARI and seek medical attention. If aminotransferase levels are abnormal at any time during treatment, interrupt FILSPARI and monitor as recommended.[1]

Consider re-initiation of FILSPARI only when hepatic enzyme levels and bilirubin return to pretreatment values and only in patients who have not experienced clinical symptoms of hepatotoxicity.[1]

Avoid initiation of FILSPARI in patients with elevated aminotransferases (>3× ULN) prior to drug initiation because monitoring hepatotoxicity in these patients may be more difficult and these patients may be at increased risk for serious hepatotoxicity.[1]

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

Risk Evaluation and Mitigation Strategy

The REMS for sparsentan is implemented to mitigate potential risks.

For all patients, FILSPARI is available only through a restricted program under a REMS called the FILSPARI REMS because of the risk of hepatoxicity and embryo-fetal toxicity.[1]

Important requirements of the FILSPARI REMS include[1]:

- Prescribers must be certified with the FILSPARI REMS by enrolling and completing training.
- All patients must enroll in the FILSPARI REMS prior to initiating treatment and comply with monitoring requirements.
- Pharmacies that dispense FILSPARI must be certified with the FILSPARI REMS and must dispense only to patients who are authorized to receive FILSPARI.

Further information is available at www.filsparirems.com or 1-833-513-1325.

Background

Sparsentan is a novel, first-in-class, and the only single molecule antagonist of the ET_A and AT_1 receptors.[9-11] 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.[12-14]

Nonclinical Toxicology Studies

The toxicologic profile of sparsentan was assessed in a comprehensive series of in vitro and in vivo studies in mice, rats, and monkeys. Single-dose studies evaluated sparsentan doses up to 2000 mg/kg in mice and rats. Repeated-dose toxicity studies assessed doses up to 750 mg/kg/day in mice for 3 months, 320 mg/kg/day in rats for 6 months, and 200 mg/kg/day in monkeys for 9 months. Evaluations included the effect of sparsentan on clinical signs and associated pathology, renal and hepatic pathology and function, and hematologic outcomes.[2]

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.[15] 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.[16] 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.[16,17] 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.[18] Reduction in proteinuria and decline in rate of eGFR are largely accepted as surrogate markers of treatment effect in studies of KF.[18,19]

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.[11]

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.[6,20] 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.[6] 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.[6] 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.[6,20]

Study Data

Nonclinical Toxicology Studies

In single-dose studies, sparsentan did not pose an acute toxicity hazard up to the maximal oral dose of 2000 mg/kg in rats or up to 1000 mg/kg in mice. In a 3-month, repeated dose study of mice, sparsentan-related increases in ALT were observed in males at doses of 50, 200, and 750 mg/kg/day, and at 750 mg/kg/day in females. Increases in liver weight were observed in males and females at 200 and 750 mg/kg/day, with correlating hepatocellular hypertrophy. Single cell necrosis of hepatocytes was observed with doses of 750 mg/kg/day.[2]

A 6-month repeated dose study in rats found sparsentan-related increases in mean liver weights and hepatocellular hypertrophy in males at doses of 15, 80, and 320 mg/kg/day, and in females at 80 and 320 mg/kg/day. Dose dependent increases in mean liver weights and hepatocellular hypertrophy were reversed after an 8-week recovery period. Such increases in liver weight and corresponding hepatocellular hypertrophy are commonly observed in rodent repeat-dose toxicity studies and are most often an adaptive response to chemical stress, which is typically related to increased functional capacity.[21,22] Increases in ALT and single cell necrosis of hepatocytes were not observed at any dosage.[8]

No liver findings were recorded in any repeat-dose toxicity study in the monkey up to the dose of 250 mg/kg/day, 6 and 4 times the human exposure (AUC) at the MRHD of 400 mg/day for males and females, respectively.[15]

The PROTECT Study

The safety of sparsentan was evaluated in PROTECT (NCT03762850), a randomized, double-blind, active-controlled clinical study in adults with IgAN.[1]

Interim Safety Results

At 36 weeks, the adverse events of interest of ALT or AST increasing to >3× ULN occurred in 2% of each group (5 sparsentan patients vs 4 patients receiving irbesartan); all occurred without concurrent elevation in total bilirubin and were asymptomatic and reversible. There were no cases of hepatotoxicity and no deaths among participants receiving sparsentan. TEAEs that led to treatment discontinuation occurred in 15 (7%) participants receiving sparsentan and 10 (5%)

receiving irbesartan. TEAEs that led to treatment discontinuation in ≥2 patients in sparsentan- or irbesartan-treated patients included acute kidney injury (3 vs 0), renal impairment (1 vs 2), chronic kidney disease (2 vs 0), and increased ALT (2 vs 0).[18]

2-Year Safety Results

After 110 weeks of treatment, elevations in liver transaminases were reported in 7 (3.5%) patients taking sparsentan and 8 (4%) patients treated with irbesartan.[1] Serious hepatic TEAEs were reported in 0 sparsentan-treated patients and 2 (1%) irbesartan-treated patients. No new cases of Hy's law or drug-induced liver injury occurred with sparsentan.[4,5]

PROTECT OLE

Among patients in the PROTECT OLE (N=61) taking combined sparsentan and SGLT2 inhibitor therapy, there were no reported cases of Hy's Law (ALT or AST >3× ULN with total bilirubin >2× ULN).[23]

The DUET Study

Among 108 patients in the DUET study, incidence of hepatic AEs and/or LFTs >3× ULN are low and have shown no trend in terms of duration of treatment. Four cases of ALT/AST elevations >3× ULN have been reported (**Figure 1**, **Figure 2**, **Figure 3**, **Figure 4**).[5]

- In 2 patients, treatment was discontinued. One case was considered to be serious, and one case was considered to be non-serious. In both patients, ALT/AST elevations resolved when sparsentan was withdrawn
- In 2 patients, ALT/AST elevations resolved without treatment discontinuation and both cases were considered non-serious

There have been no cases of Hy's Law for drug-induced liver injury, defined as ALT/AST elevations >3× ULN in association with bilirubin elevations >2× ULN, and no other reason can be found to explain elevations.[5]

Figure 1. DUET Liver Biochemistry Studies (Ratio to ULN) for Subject 1: SAE, subject discontinued

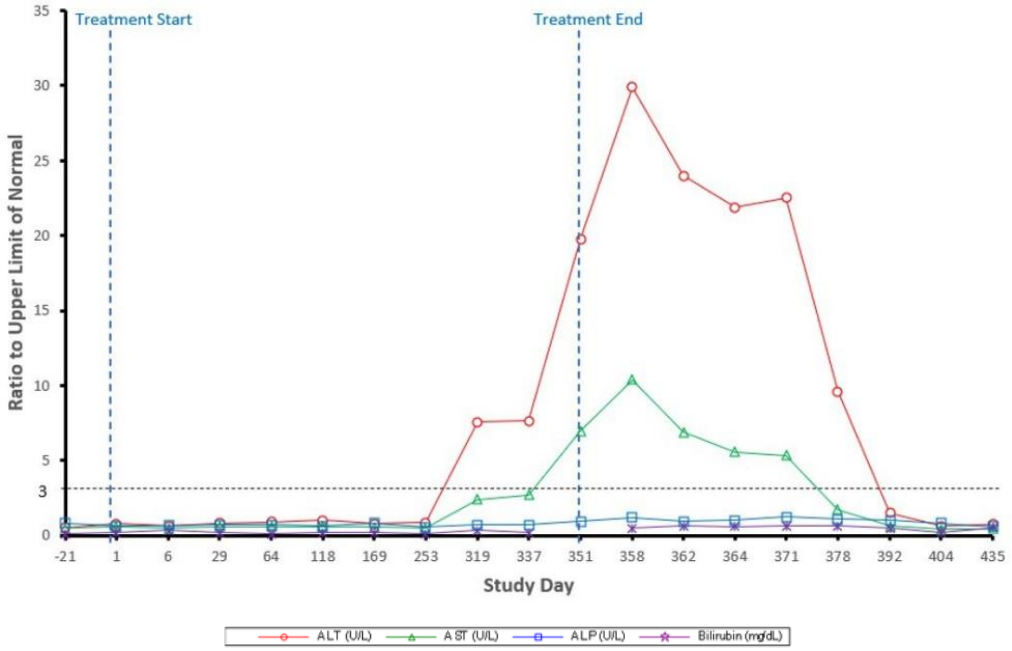


Figure 2. DUET Liver Biochemistry Studies (Ratio to ULN) for Subject 2: Non-serious, subject discontinued

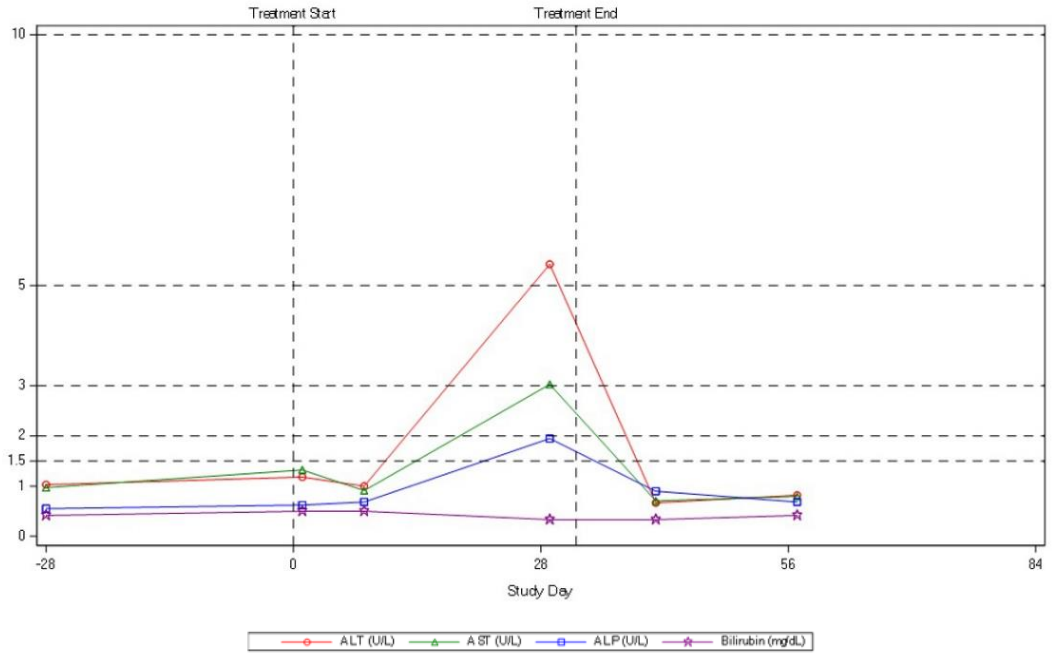


Figure 3. DUET Liver Biochemistry Studies (Ratio to ULN) for Subject 3: Non-serious, no action taken with study medication

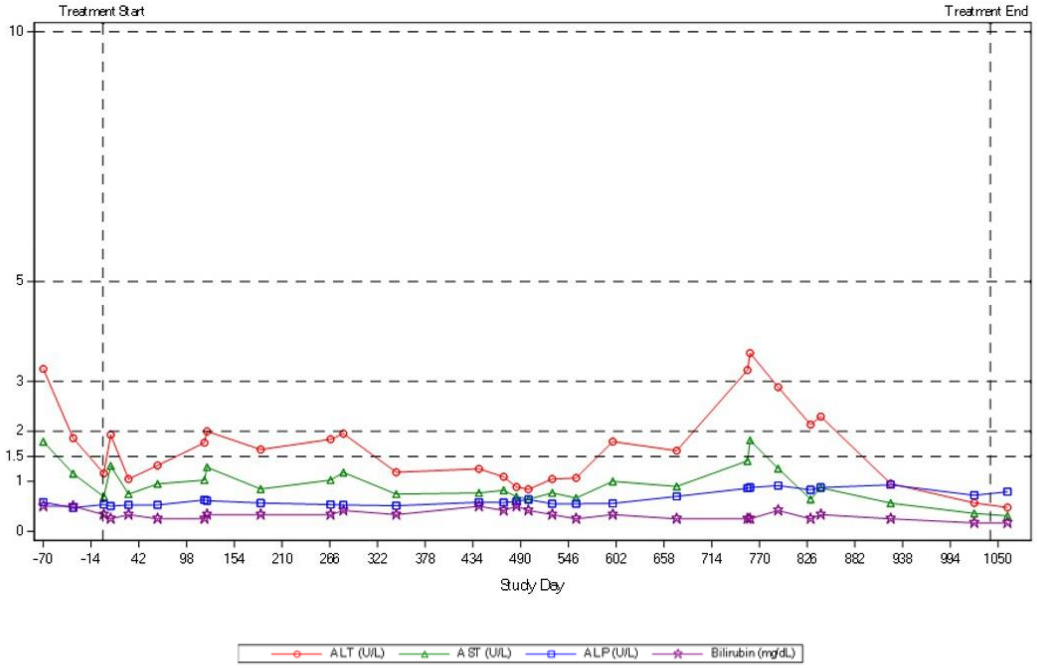
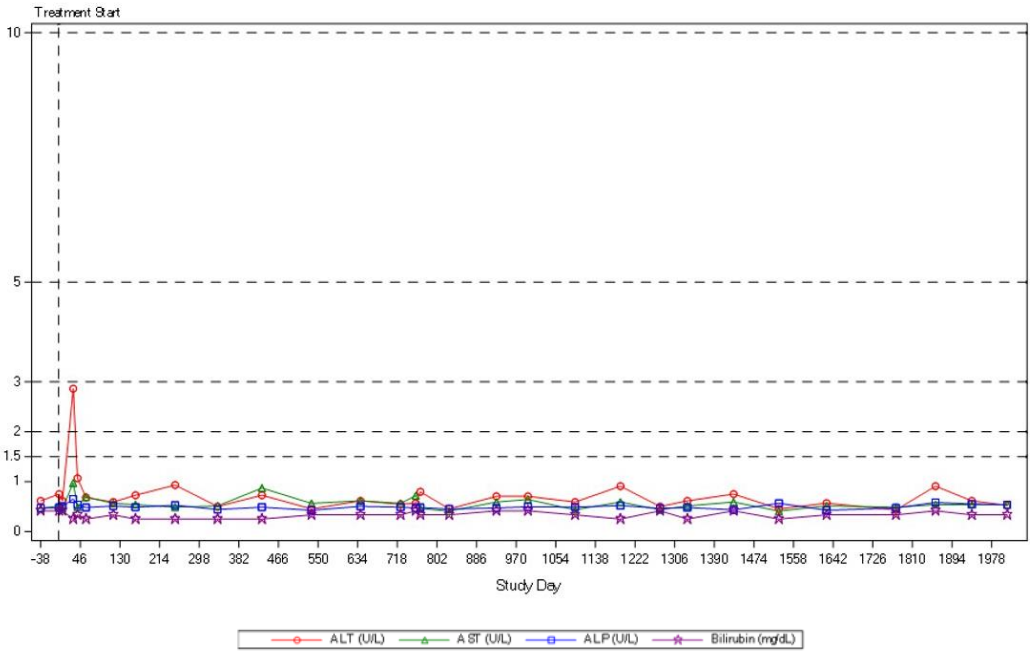


Figure 4. DUET Liver Biochemistry Studies (Ratio to ULN) for Subject 4, Non-serious, no action taken with study medication



The DUPLEX Study

Safety analysis in the DUPLEX study included liver-related AEOIs, defined as liver function tests meeting the following criteria[5]:

- New elevation in ALT or AST >3× ULN with or without elevation of total serum bilirubin >2× ULN
- 2-fold increase in ALT or AST above the baseline value in patients who had elevated values prior to starting study medication

After 108 weeks of treatment, elevations in ALT or AST to >3× ULN occurred in 5 (2.7%) sparsentan-treated patients and 4 (2.2%) irbesartan-treated patients; none were concurrent with elevated total bilirubin levels ≥1.5× ULN. No events of drug-induced liver injury occurred with sparsentan and 1 occurred with irbesartan. Liver injury was not identified as a safety concern in the DUPLEX study.[6]

Additional Clinical Trials

SPARTACUS is a phase 2 clinical trial of combined sparsentan and SGLT2 inhibitor treatment. Abnormal liver function was defined as a new elevation in ALT or AST >3× ULN with or without elevation of total serum bilirubin >2× ULN, and 2-fold increase in ALT or AST above baseline values among patients who experienced elevated values prior to initiation of combined treatment. In patients at time of interim analysis (N=12), no abnormal liver function tests had been observed through Week 24 of treatment.[24]

Hepatic Safety Results of Sparsentan Compared to Placebo in Clinical Studies

There are more than 1200 patients in clinical trials of sparsentan, including patients who have been on therapy for nearly 7 years. As part of these clinical studies, regular quarterly liver function tests were required.[5,7,8,23]

To date there have been:

- No diagnoses of clinical liver injury or abnormal liver function
- No cases of Hy's Law
- No elevations in bilirubin

Abbreviations

ACEi, angiotensin-converting enzyme inhibitor; AE, adverse event; AEOI, adverse event of interest; ALP, alkaline phosphatase; ALT, alanine transaminase; ARB, angiotensin receptor blocker; AST, aspartate aminotransferase; AT_1, angiotensin II type 1; AUC, area under the curve; 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; KF, kidney failure; KRT, kidney replacement therapy; IgA, immunoglobulin A; IgAN, immunoglobulin A nephropathy; LFT, liver function test; MRHD, maximum recommended human dose; OLE, open-label extension; RAASi, renin-angiotensin-aldosterone system inhibitor; REMS, risk evaluation and mitigation strategy; SAE, serious adverse event; SBP, systolic blood pressure; SGLT2, sodium-glucose cotransporter 2; TEAE, treatment-emergent adverse event;

UACR, urine albumin-to-creatinine ratio; ULN, upper limit of normal; UPCR, urine protein-to-creatinine ratio.

References

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