FILSPARI® (sparsentan)
Decreases in Hemoglobin

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]

The safety data that follows is from the pre-specified primary analysis reported at the interim assessment, which includes proteinuria data from all 404 randomized and treated patients in the PROTECT clinical trial at the time of the analysis.

- In the PROTECT study in IgA nephropathy, the incidence of a hemoglobin decrease >2 g/dL compared to baseline and below the lower limit of normal was greater for the FILSPARI arm (11%) compared to the irbesartan arm (5%)[1]
- This decrease is thought to be in part due to hemodilution. There were no treatment discontinuations due to anemia or hemoglobin decrease in the PROTECT study[1]

Background

- Sparsentan is an investigational therapeutic candidate for the treatment of FSGS[2,3]

Study Data

- Over 2 years of sparsentan treatment in the PROTECT study, anemia was reported as a TEAE in 16 (8%) patients taking sparsentan and 9 (4%) patients taking irbesartan[4]
- In the DUET study, 16 patients (10 initially randomized to sparsentan) who entered the OLE reported TEAEs of anemia (including anemia, iron-deficiency anemia, and decreased blood hemoglobin).[5] An analysis of the OLE at 240 weeks showed 4.1 cases of anemia per 100 patient years[6]
    - In a sub-sample of pediatric patients in the DUET study, anemia was reported as a TEAE in 3.9 patients per 100 patient-years over 4 years of sparsentan treatment[7]
- In the DUPLEX study, 24 (13%) patients taking sparsentan and 10 (5.3%) patients taking irbesartan experienced anemia as an AE over 108 weeks of treatment[8]
- Studies in hypertensive patients: In one study of sparsentan in hypertensive patients, mean hemoglobin and hematocrit levels decreased from baseline to week 4 and appeared to be dose related. In a second study of sparsentan in hypertensive patients, modest decreases in hemoglobin and hematocrit were observed with sparsentan 400 mg and 800 mg[9]

- DDI study: In a safety study of DDI, 4 (1.4%) patients reported decreased hemoglobin, which was ongoing at the end of the study[10]

Prescribing Information

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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.[3,11,12] 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.[13-15]

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.[16] 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.[17] 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.[17,18] 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.[19] Reduction in proteinuria and decline in rate of eGFR are largely accepted as surrogate markers of treatment effect in studies of KF.[19,20]

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 DUET OLE included 26 patients aged <21 years who received at least one dose of sparsentan. Of these, 23% had nephrotic syndrome in their medical history or at baseline and 73% had nephrotic range proteinuria at baseline, defined as UPCR ≥2.0 g/g in patients age <18 years and ≥3.5 g/g in patients aged 18-21 years.[7]

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.[2,8] 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.[8] 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.[2,8]

Studies in Hypertensive Patients

Two phase 2, double-blind, placebo-controlled studies examined antihypertensive effects of sparsentan in patients with stage 1 or stage 2 hypertension.[9]

In study 1, patients aged 30 to 80 years with mean seated SBP ≥150 and ≤179 mm Hg and mean seated DBP ≤110 mm Hg, and mean daytime SBP ≥140 and ≤179 mm Hg with mean daytime DBP ≤110 mm Hg were randomized to receive sparsentan 200 mg, 500 mg, or placebo once daily for 4 weeks. The primary efficacy endpoint was defined as mean change in 24-hour ambulatory SBP from baseline to week 4. Secondary endpoints included mean change in 24-hour ambulatory DBP from baseline to week 4, and assessments of sparsentan safety and tolerability.[9]

In study 2, patients aged 18 to 75 years with mean seated SBP ≥140 and ≤180 mm Hg and mean seated DBP ≥90 mm Hg and ≤109 mm Hg were randomized to sparsentan 200 mg, 400 mg, or

800 mg, irbesartan 300 mg, or placebo, once daily for 12 weeks. The primary efficacy endpoint was defined as mean change in mean seated SBP from baseline to week 12. Secondary endpoints included mean change in seated DBP from baseline to week 12, and assessments of sparsentan safety and tolerability.[9]

DDI Study

A phase 1 clinical study evaluated the potential for DDI with sparsentan. Study 021HVOL16008 examined the effect of multiple-dose administration of 800 mg sparsentan on the PK of midazolam and buproprion. This study included a sample of 28 healthy male volunteers.[10]

Study Data

The PROTECT Study

Over 2 years of treatment, anemia was reported as a TEAE in 16 (8%) and 9 (4%) of sparsentan and irbesartan patients, respectively.[4]

The DUET Study

Interim analyses of the DUET OLE study at 84 weeks found that 16 patients reported anemia as a TEAE. These cases included anemia, iron-deficiency anemia, and decreased blood hemoglobin. Of the 16 cases, 10 were patients who had initially been randomized to sparsentan and continued sparsentan in the OLE. Six were patients who had initially been randomized to irbesartan and switched to sparsentan upon entering the OLE.[5]

Further analysis of long-term safety and efficacy of sparsentan found that 15 cases of anemia were reported as a TEAE over 240 weeks of treatment (4.1 cases per 100 patient years).[6]

In pediatric (≤21 years) patients in the DUET OLE, anemia was reported as a TEAE by year and cases per 100 patient-years throughout the study duration. Anemia occurred in 2 of 26 patients (8%) in Year 0 to <1, 0 of 20 patients in Year 1 to <2, 0 of 16 patients in Year 2 to <3, and 1 (8%) of 12 patients in Year 3 to <4. Over the total study duration, 3.9 cases of anemia per 100 patient-years were reported. Anemia lead to discontinuation in 1 patient in Year 0 to <1.[7]

The DUPLEX Study

Anemia was reported in 24 (13%) patients in the sparsentan group and 10 (5.3%) patients in the irbesartan group.[8]

Studies in Hypertensive Patients

Study 1 of patients with stage 1 and stage 2 hypertension, mean hemoglobin and hematocrit levels decreased from baseline to week 4 of sparsentan treatment in a dose-related manner (**Table 1**). Study 2 reported modest decreases in mean hemoglobin and hematocrit after 12 weeks of 400 mg and 800 mg doses (**Table 2**).[9]

Table 1. Laboratory Parameters at Baseline and Week 4 in Study 1

Parameter	Mean Value (min, max)					
	Sparsentan 200 mg (n = 39)		Sparsentan 500 mg (n = 38)		Placebo (n = 36)	
	Baseline	Week 4	Baseline	Week 4	Baseline	Week 4
Hemoglobin, g/dL	14.4 (11.5, 17.5)	13.9 (10.6, 17.1)	14.8 (12.0, 17.0)	14.1 (11.9, 16.3)	14.3 (12.2, 16.6)	14.5 (12.6, 16.3)
Hematocrit, %	44.0 (36.9, 51.6)	42.3 (32.8, 50.3)	44.9 (36.3, 52.0)	42.7 (37.7, 52.1)	43.7 (38.9, 49.6)	44.5 (38.2, 51.0)

Table 2. Laboratory Parameters at Baseline and Week 12 in Study 2

Parameter	Mean Value (min, max)									
	Sparsentan 200 mg (n = 58)		Sparsentan 400 mg (n = 58)		Sparsentan 800 mg (n = 28)		Irbesartan (n = 58)		Placebo (n = 59)	
	Baseline	Week 12	Baseline	Week 12	Baseline	Week 12	Baseline	Week 12	Baseline	Week 12
Hemoglobin, g/dL	13.9 (10.7, 16.9)	13.6 (10.2, 17.0)	14.3 (11.0, 17.2)	13.8 (11.4, 16.7)	14.2 (12.1, 16.7)	13.5 (10.3, 15.6)	14.0 (12.1, 16.4)	13.9 (11.9, 16.6)	14.1 (11.0, 16.6)	14.2 (11.3, 16.7)
Hematocrit, %	42.7 (34, 50)	41.8 (34, 52)	43.8 (35, 53)	41.8 (35, 49)	42.8 (36, 50)	40.5 (32, 46)	43.0 (37, 49)	42.6 (36, 50)	43.1 (37, 53)	43.5 (36, 53)

DDI Study

Four subjects in study 021HVOL16008 reported decreased hemoglobin as a TEAE. Hemoglobin levels first decreased following administration of midazolam (n=1) or buproprion (n=3) and continued to decrease with administration of sparsentan. Decreased hemoglobin levels were ongoing at the end of the study, and were considered by the investigator to be related to midazolam or buproprion plus sparsentan.[10]

Abbreviations

ACEi, angiotensin-converting enzyme inhibitor; AE, adverse event; ARB, angiotensin receptor blocker; AT_1, angiotensin II type 1; BP, blood pressure; DBP, diastolic blood pressure; DDI, drug-drug interaction; 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; OLE, open-label extension; PK, pharmacokinetics; RAASi, renin-angiotensin-aldosterone system inhibitor; SBP, systolic blood pressure; TEAE, treatment-emergent adverse event; UACR, urine albumin-to-creatinine ratio; UPCR, urine protein-to-creatinine ratio.

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