FILSPARI® (sparsentan)

Effect on Estimated Glomerular Filtration Rate (eGFR) in FSGS

Summary

Background

- Sparsentan is an investigational therapeutic candidate for the treatment of FSGS[1,2]
- Sparsentan is a novel, first-in-class, and the only single molecule antagonist of the ET_A and AT_1 receptors[1,3,4]

Study Data

The DUET Study

- Mean change in eGFR measured by chronic slope estimate through 108 weeks was −3.56 (95% CI, −5.6 to −1.5) mL/min/1.73 m^2 per year. Mean change in eGFR of on-treatment data, defined as within 1 day of last sparsentan dose, showed a chronic slope estimate of −4.16 (95% CI, −5.8 to −2.5) mL/min/1.73 m^2 per year[5]

The DUPLEX Study

- After 108 weeks of treatment, sparsentan showed a favorable (not statistically significant) difference on total eGFR slope of 0.3 mL/min/1.73 m^2 per year (95% CI, −1.7 to 2.4; P=0.75) and on eGFR chronic slope of 0.9 mL/min/1.73 m^2 per year (95% CI, −1.3 to 3.0; P=0.42) compared to irbesartan[6]
- At Week 112, mean change in eGFR from baseline was −10.4 mL/min/1.73 m^2 with sparsentan and −12.1 mL/min/1.73 m^2 with irbesartan[6]

Background

Sparsentan is an investigational therapeutic candidate for the treatment of FSGS[1,2]

Sparsentan is a novel, first-in-class, and the only single molecule antagonist of the ET_A and AT_1 receptors.[1,3,4] 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.[7-9]

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.[1]

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.[2,6] 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.[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.[2,6]

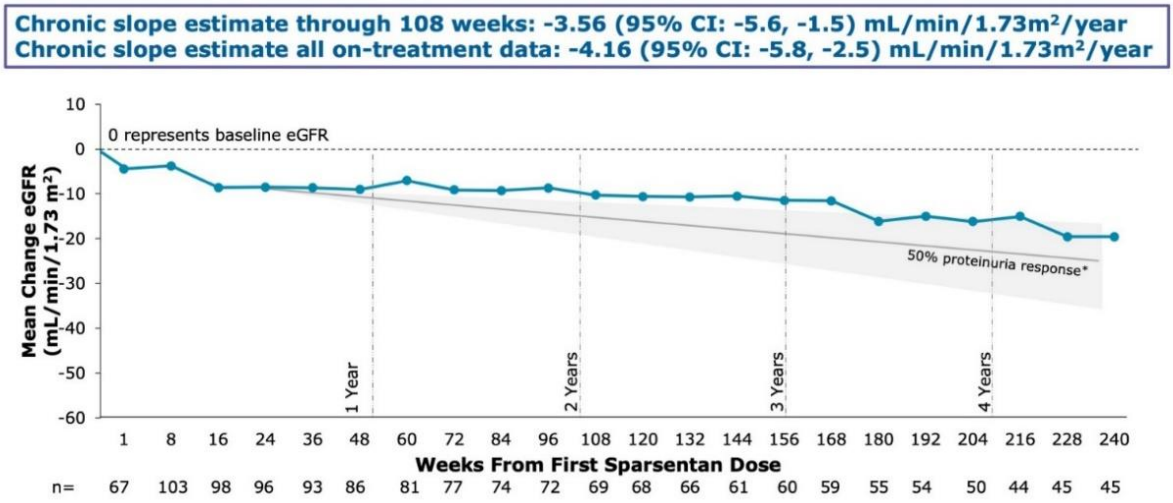
Study Data

The DUET Study

Efficacy

Mean change in eGFR measured by chronic slope estimate through 108 weeks was −3.56 (95% CI, −5.6 to −1.5) mL/min/1.73 m^2 per year. Mean change in eGFR of on-treatment data, defined as within 1 day of last sparsentan dose, showed a chronic slope estimate of −4.16 (95% CI, −5.8 to −2.5) mL/min/1.73 m^2 per year (**Figure 1**).[5]

Figure 1. DUET OLE: Mean Change From Baseline in eGFR by Visit



*Research in patients with steroid-resistant FSGS found that changes in proteinuria over 26 weeks were significantly related to eGFR slope. Patients who achieved 50% reduction in proteinuria at 26 weeks of treatment showed eGFR slope decline = 4.0 mL/min/1.73 m^2 per year, whereas patients with persistent proteinuria had significantly more decline, eGFR slope = 6.7 mL/min/1.73 m^2 per year.[10]

Only on-treatment observations (defined as occurring within 1 day of last sparsentan dose) are included.
Chronic slope was assessed starting at Day 42 of starting sparsentan treatment.

Safety

Safety assessments during the double-blind phase showed that compared with patients taking irbesartan, patients treated with sparsentan reported more frequent hypotension (16.4% vs 8.3%), dizziness (13.7% vs 11.1%), edema (12.3% vs 2.8%), and gastrointestinal (nausea, 12.3% vs 8.3%; diarrhea, 8.2% vs 2.8%; vomiting, 8.2% vs 2.8%) TEAEs. Overall, incidence of TEAEs, drug-related TEAEs, serious TEAEs, and the number of study withdrawals were similar between the two groups.[1] Analysis of OLE data found no new or unexpected safety signals.[5]

The DUPLEX Study

Efficacy

Primary Efficacy Endpoint

Sparsentan did not achieve the primary efficacy eGFR slope endpoint over 108 weeks of treatment.[6]

Primary efficacy endpoints were defined as eGFR total slope from Day 1 to Week 108 of treatment (US primary) and eGFR chronic slope from Week 6 to Week 108, following initial acute effect of randomized treatment (EU primary). A decrease from baseline in mean (95% CI) eGFR over the first 6 weeks of treatment was −4.1 (−5.8 to −2.4) mL/min/1.73 m^2 with sparsentan and −0.8 (−2.5 to 0.9) mL/min/1.73 m^2 with irbesartan (difference, −3.3 [−5.7 to −0.9] mL/min/1.73 m^2). After 108 weeks of treatment, sparsentan showed a favorable (not statistically significant) difference on total eGFR slope of 0.3 mL/min/1.73 m^2 per year (95% CI, −1.7 to 2.4; *P*=0.75) and on eGFR chronic slope of 0.9 mL/min/1.73 m^2 per year (95% CI, −1.3 to 3.0; *P*=0.42) compared to irbesartan (**Table 1**).[6]

Table 1. The eGFR Slope and Change in eGFR

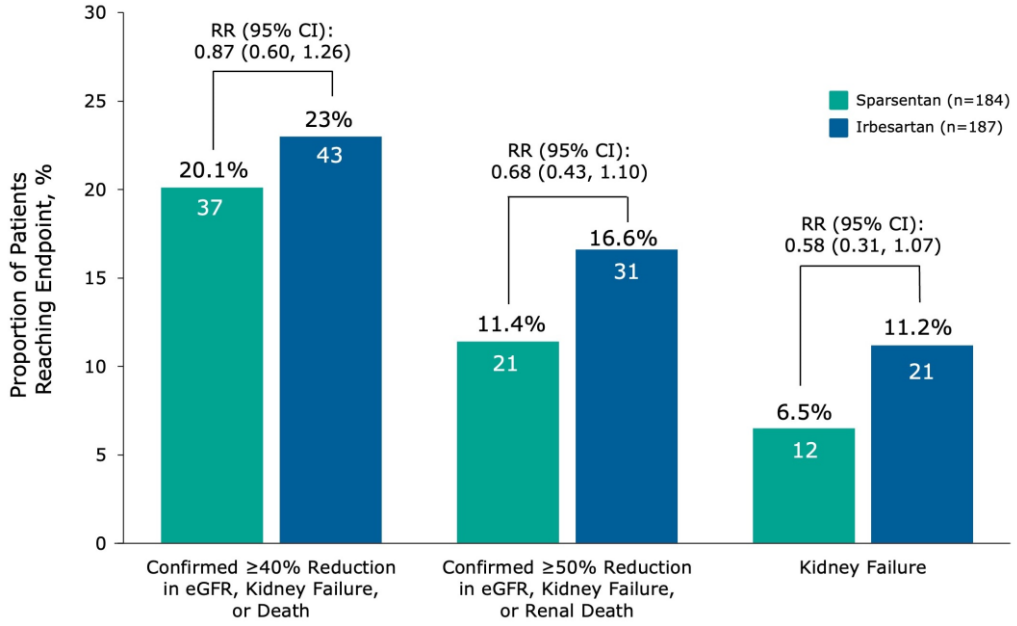
Variable	Sparsentan (n=184)	Irbesartan (n=187)	Difference
Least-squares mean eGFR slope (95% CI), mL/min/1.73 m² per year			
eGFR total slope*	**-5.4** (-6.9, -3.9)	**-5.7** (-7.2, -4.3)	**0.3,** *P*=0.75 (-1.7, 2.4)
eGFR chronic slope†	**-4.8** (-6.3, -3.3)	**-5.7** (-7.2, -4.2)	**0.9,** *P*=0.42 (-1.3, 3)
Least-squares mean change in eGFR from baseline to Week 112 (95% CI), mL/min/1.73 m²‡	**-10.4** (-12.6, 8.1)	**-12.1** (-14.4, -9.9)	**1.8** (-1.4, 4.9)

* The eGFR total slope was the slope from day 1 to week 108.
† The eGFR chronic slope was the slope from week 6 to week 108.
‡ Data are for patients who completed the double-blind treatment period (129 patients in the sparsentan group and 136 patients in the irbesartan group).

Composite Endpoints

Composite renal endpoints were also favorable for sparsentan. The number of events for the composite endpoints of a confirmed ≥40% reduction in eGFR, kidney failure, or death and of a confirmed ≥50% reduction in eGFR, kidney failure, or renal death are presented in **Figure 2**.[6]

Figure 2. Composite Renal Endpoints Trended Favorably for Sparsentan



Safety

Over 108 weeks of treatment, TEAEs were reported with similar frequency in the sparsentan (n=172; 93.5%) and irbesartan (n=174; 93%) treatment groups. Serious TEAEs occurred in 68

(37%) sparsentan-treated patients and 82 (43.9%) irbesartan-treated patients. ALT or AST elevations >3× ULN occurred in 5 (2.7%) patients taking sparsentan and 4 (2.2%) taking irbesartan; no cases were concurrent with elevated bilirubin levels ≥1.5× ULN. There were no drug-induced liver injuries with sparsentan; 1 was reported in the irbesartan group.[6]

Abbreviations

ALT, alanine aminotransferase; AST, aspartate aminotransferase; AT_1, angiotensin II type 1; BP, blood pressure; CI, confidence interval; eGFR, estimated glomerular filtration rate; ET_A, endothelin-1 type A; EU, European Union; FPRE, FSGS partial remission of proteinuria endpoint; FSGS, focal segmental glomerulosclerosis; OLE, open-label extension; RAASi, renin-angiotensin-aldosterone system inhibitor; RR, relative risk; TEAE, treatment-emergent adverse event; ULN, upper limit of normal; UPCR, urine protein-to-creatinine ratio; US, United States.

References

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