Sparsentan

Patient-Reported Outcomes in the Phase 3 DUPLEX Study

Summary

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

Prescribing Information

- FILSPARI (sparsentan) 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[3]

Background

- FSGS has been linked to multiple factors impacting QOL, including global health, depression, anxiety, and mobility[4]
- Patients with FSGS experience higher comorbidity and economic burdens compared to non-FSGS control groups, which have been significantly linked to degree of proteinuria[5]
- In the phase 3 DUPLEX study, PROs were assessed by the KDQOL-36 questionnaire throughout the course of treatment[6]

Study Data

- Adult patients experienced meaningful improvement in kidney disease burden from baseline and maintained HRQOL throughout 2 years of treatment[6]
- The DUPLEX study was not powered to assess differences between sparsentan and irbesartan in PROs. All presented analyses should be considered exploratory[6]

Prescribing Information

For more information, please refer to the Prescribing Information.

Background

Sparsentan is a novel, first-in-class, and the only single molecule antagonist of the ET_A and AT_1 receptors.[2,7,8] 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.[9-11]

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.[1,12] 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.[12] 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.[1,12]

Assessment of HRQOL Associated With Kidney Disease

FSGS is associated with a high burden of illness impacting multiple factors of patients' lives, including degree of comorbidities, healthcare utilization, mobility, healthcare costs, and QOL.[4,5]

The DUPLEX study included assessment of PROs utilizing the KDQOL-36 at baseline and every 12 weeks to Week 108 of the double-blind phase.[6] The KDQOL-36 is a 36-item short-form survey commonly used to assess HRQOL in patients with kidney disease and ESKD. The survey is comprised of ESKD-specific and general HRQOL subscales, namely Symptoms/Problems of Kidney Disease, Effects of Kidney Disease, Burden of Kidney Disease, Physical Component Summary, Mental Component Summary, and Bodily Pain scale. An overall Summary Score is also calculated.[6,13,14] Scores for each subscale range from 0 to 100, with lower scores reflecting worse self-reported QOL.[13] In the DUPLEX study, a 5-point change from baseline was considered clinically meaningful.[6]

Study Data

The DUPLEX Study

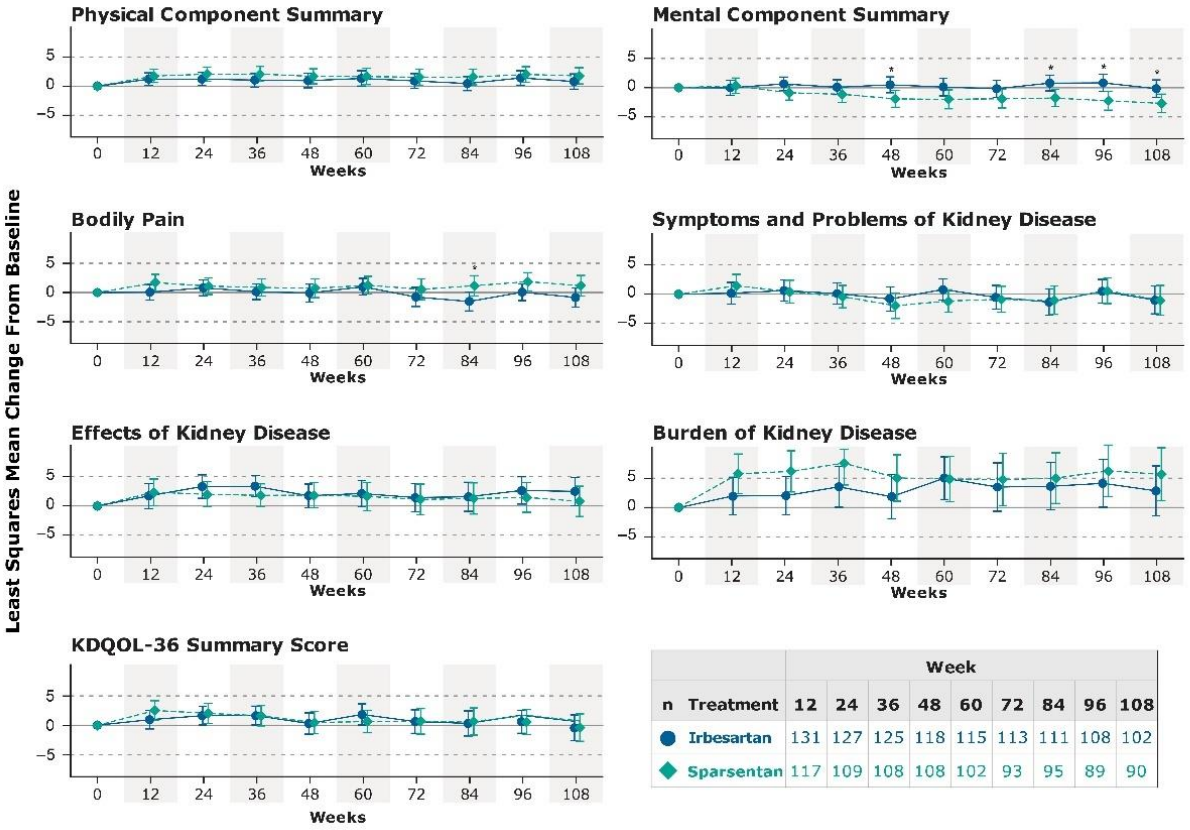
Among adult patients, 306 (91% of enrolled adults) completed the KDQOL-36. Demographics and baseline KDQOL-36 scores were comparable for sparsentan-treated and irbesartan-treated patients (**Table 1**).[6]

Table 1. Baseline Demographic and KDQOL-26 Scores of Patients in the DUPLEX Study

Characteristic	Sparsentan (N=148)	Irbesartan (N=158)
Age (years), mean (SD)	45.5 (14.6)	44.7 (15.2)
Male sex, no. (%)	85 (57.4)	87 (55.1)
Hispanic or Latino, no. (%)	23 (15.5)	36 (22.8)
Race, no. (%)		
Asian	23 (15.5)	25 (15.8)
Black	13 (8.8)	6 (3.8)
White	105 (71.0)	115 (72.8)
Other	7 (4.7)	12 (7.6)
KDQOL-36 Scores, mean (SD)		
Physical Component Summary	44.8 (10.38)	46.4 (10.09)
Mental Component Summary	49.8 (8.38)	48.5 (10.12)
Bodily Pain	47.9 (10.81)	49.3 (10.32)
Symptoms/Problems of Kidney Disease	82.8 (16.05)	82.9 (16.51)
Effects of Kidney Disease	80.1 (20.34)	82.3 (18.93)
Burden of Kidney Disease	61.5 (25.85)	64.3 (27.74)
KDQOL-36 Summary Score	78.5 (16.54)	79.7 (15.66)

In both sparsentan and irbesartan groups, a clinically meaningful change in least squares mean Burden of Kidney Disease scores was observed at Week 12 compared to baseline. Meaningful change was maintained for 7 of 9 assessment points through Week 108; at Week 60 the change was clinically meaningful only in irbesartan patients. No clinically meaningful differences were found between sparsentan and irbesartan groups; however, the nominal *P* value was less than 0.05 for a small number of time points (**Figure 1**).[6]

Figure 1. Least Squares Mean Change From Baseline for KDQOL-36 Scores by Treatment and Visit*

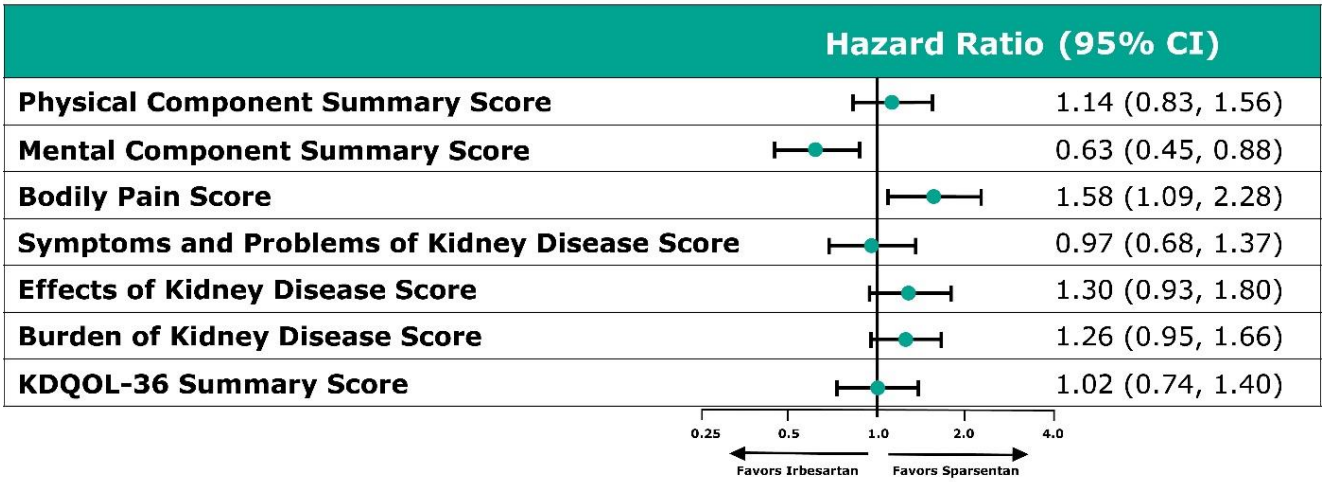


n	Treatment	Week 12	24	36	48	60	72	84	96	108
●	Irbesartan	131	127	125	118	115	113	111	108	102
◆	Sparsentan	117	109	108	108	102	93	95	89	90

**P*<0.05 for differences between sparsentan and irbesartan. Note: vertical bars indicate 95% CIs. Dotted lines indicate meaningful changes thresholds. A higher score indicates better HRQOL/functioning.

Hazard ratios were calculated for time to first clinically meaningful improvement. No differences were found between sparsentan and irbesartan groups, except for the Bodily Pain score (favoring sparsentan) and the Mental Component Summary score (favoring irbesartan) (**Figure 2**).[6]

Figure 2. Hazard Ratios for Time to First Meaningful Improvement in KDQOL-36 Scores in Sparsentan and Irbesartan Patients



Study Limitations

The DUPLEX study was not powered to assess differences between sparsentan and irbesartan in PROs. Additionally, the KDQOL-36 may not be sensitive enough to identify differences between the treatment arms in the clinical parameters in the DUPLEX study. Although a 5-point change from baseline in KDQOL-36 scores was defined as clinically meaningful for the purposes of this study, there is no standardization of meaningful change for patients with FSGS. Given these limitations, these analyses should be considered exploratory.[6]

Abbreviations

AT_1, angiotensin II type 1; BP, blood pressure; CI, confidence interval; eGFR, estimated glomerular filtration rate; ESKD, end-stage kidney disease; ET_A, endothelin-1 type A; FPRE, FSGS partial remission endpoint; FSGS, focal segmental glomerulosclerosis; HRQOL, health-related quality of life; IgAN, immunoglobulin A nephropathy; KDQOL-36, Kidney Disease Quality of Life-36; PRO, patient-reported outcome; QOL, quality of life; RAASi, renin–angiotensin–aldosterone system inhibitor; SD, standard deviation; UPCR, urine protein-to-creatinine ratio.

References

1. Komers R, Diva U, Inrig JK, Loewen A, Trachtman H, Rote WE. Study design of the phase 3 sparsentan versus irbesartan (DUPLEX) study in patients with focal segmental glomerulosclerosis. *Kidney Int Rep*. 2020;5(4):494-502. doi:10.1016/j.ekir.2019.12.017
2. Trachtman H, Nelson P, Adler S, et al. DUET: A phase 2 study evaluating the efficacy and safety of sparsentan in patients with FSGS. *J Am Soc Nephrol*. 2018;29(11):2745-2754. doi:10.1681/ASN.2018010091

3. FILSPARI. Prescribing information. Travere Therapeutics Inc; September 2024.
4. Troost JP, Waldo A, Carlozzi NE, et al. The longitudinal relationship between patient-reported outcomes and clinical characteristics among patiens with focal segmental glomerulosclerosis in the nephrotic syndrome study network. *Clin Kidney J*. 2020;13(4):597-606. doi:10.1093/ckj/sfz092
5. Kalantar-Zadeh K, Baker CL, Copley JB, et al. A retrospective study of clinical and economic burden of focal segmental glomeruolsclerosis (FSGS) in the United States. *Kidney Int Rep*. 2021;6(10):2679-2688. doi:10.1016/j.ekir.2021.07.030.
6. Ayoub I, Bensink M, Zhou X, et al. Health-related quality of life in adult patients with focal segmental glomerulosclerosis (FSGS): Sparsentan vs irbesartan. Poster presented at: ASN Kidney Week; October 23-27, 2024; San Diego, CA.
7. Komers R, Gipson DS, Nelson P, et al. Efficacy and safety of sparsentan compared with irbesartan in patients with primary focal segmental glomerulosclerosis: Randomized, controlled trial design (DUET). *Kidney Int Rep*. 2017;2(4):654-664. doi:10.1016/j.ekir.2017.02.019
8. Raczynska A, Pawlowicz-Szlarska E, Nowicki M. Sparsentan–a dual antagonist–literature review on endothelin and endothelin antagonists. *Nephrol Dial Pol*. 2021;25:77-82.
9. Nagasawa H, Suzuki H, Jenkinson C, et al. Sparsentan, the dual endothelin angiotensin receptor antagonist (DEARA), attenuates albuminuria and protects from the development of renal injury to a greater extent than losartan in the gddY mouse model of IgA nephropathy: A 16-week study. Mini oral presented at: ERA-EDTA Congress; May 19-22, 2022; Paris, France.
10. Nagasawa H, Suzuki H, Jenkinson C, et al. The dual endothelin type A receptor (ET_AR) and angiotensin II type 1 receptor (AT_1R) antagonist, sparsentan, protects against the development of albuminuria and glomerulosclerosis in the gddY mouse model of IgA nephropathy. Poster presented at: ERA-EDTA Virtual Congress; June 6-9, 2020; Virtual Meeting.
11. Bedard P, Jenkinson C, Komers R. Sparsentan protects the glomerular basement membrane and glycocalyx, and attenuates proteinuria in a rat model of focal segmental glomerulosclerosis (FSGS). Abstract presented at: ERA-EDTA Congress; May 19-22, 2022; Paris, France.
12. Rheault MN, Alpers CE, Barratt J, et al. Sparsentan versus irbesartan in focal segmental glomerulosclerosis. *N Engl J Med*. 2023;389(26):2436-2445. doi:10.1056/NEJMoa2308550
13. Hall RK, Luciano A, Pieper C, Colón-Emeric CS. Association of Kidney Disease Quality of Life (KDQOL-36) with mortality and hospitalization in older adults receiving hemodialysis. *BMC Nephrol*. 2018;19(11):1-9. doi:10.1186/s12882-017-0801-5
14. Peipert JD, Nair D, Klicko K, Schatell DR, Hays RD. Kidney Disease Quality of Life 36-item short form survey (KDQOL-36) normative values for the United States dialysis population and new single summary score. *J Am Soc Nephrol*. 2019;30(4):654-663. doi:10.1681/ASN.2018100994: 10.1681/ASN.2018100994