Sparsentan

Effect on Estimated Glomerular Filtration Rate (eGFR) in FSGS

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

- Sparsentan is a novel, first-in-class, and the only single molecule antagonist of the ET_A and AT_1 receptors[1,4,5]

Study Data

The DUET Study

- In the phase 3 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[6]

The DUPLEX Study

- In the phase 3 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[7]
- 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[8]

The EPPIK Study in Pediatric Patients

- In the phase 2 EPPIK study, eGFR remained fairly stable throughout the 12-week treatment period[9]

Prescribing Information

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.[1,4,5] 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 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.[2,8] 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]

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.[13] 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.[9,13,14]

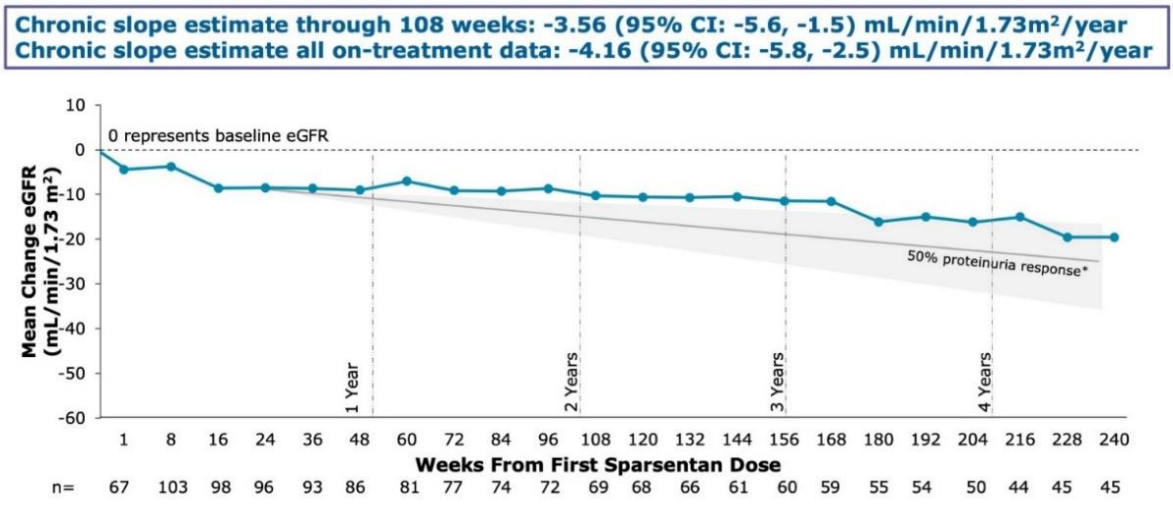
Study Data

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**).[6]

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.[15]

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.[6]

The DUPLEX Study

Efficacy

Primary Efficacy Endpoint

Sparsentan did not achieve the primary efficacy eGFR slope endpoint over 108 weeks of treatment.[8]

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**).[8]

Table 1. The eGFR Slope and Change in eGFR

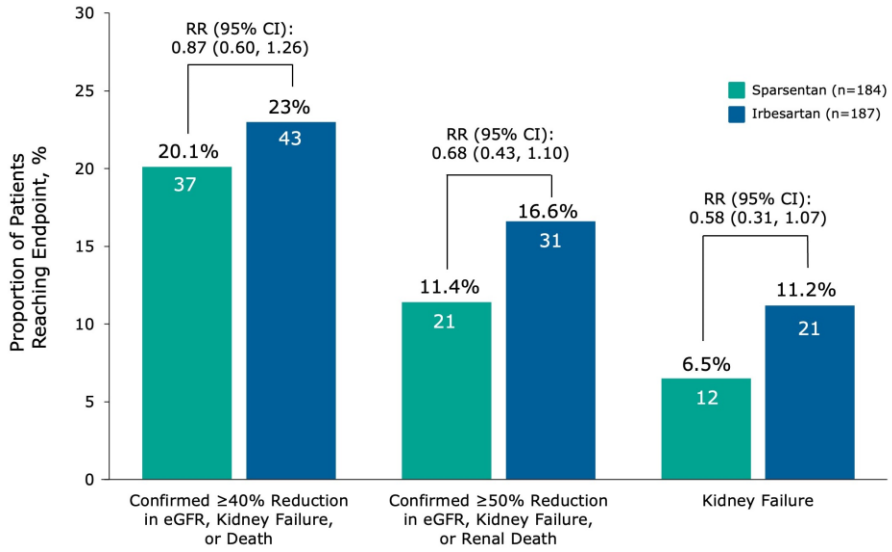
Variable	Sparsentan (n=184)	Irbesartan (n=187)	Difference
Least-squares mean eGFR slope (95% CI), mL/min/1.73 m^2 per year			
eGFR total slope*	**-5.4** (-6.9, -3.9)	**-5.7** (-7.2, -4.3)	**0.3,** *P*=0.75 (-1.7, 2.4)
eGFR chronic slope†	**-4.8** (-6.3, -3.3)	**-5.7** (-7.2, -4.2)	**0.9,** *P*=0.42 (-1.3, 3)
Least-squares mean change in eGFR from baseline to Week 112 (95% CI), mL/min/1.73 m^2‡	**-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**.[8]

Figure 2. Composite Renal Endpoints Trended Favorably for Sparsentan

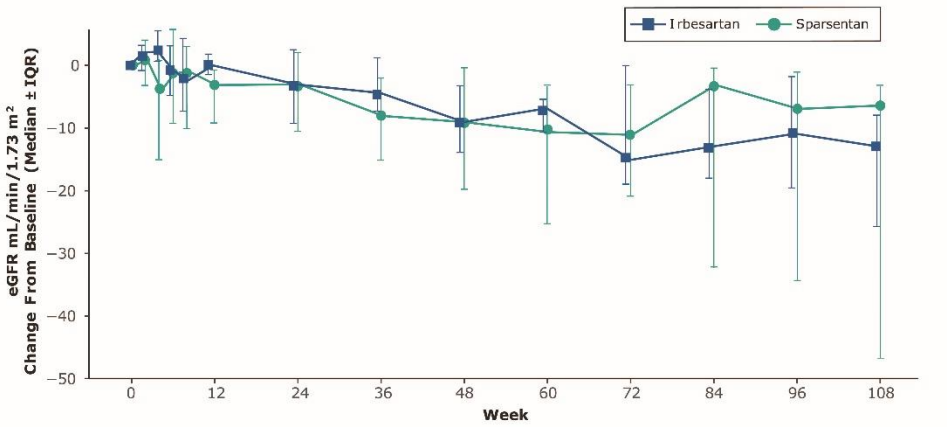


Patients With gFSGS

In a post hoc analysis of the DUPLEX study, 355 patients were genotyped by an FSGS panel; 31 (8.7%) were determined to have gFSGS. Clinical characteristics were comparable between sparsentan and irbesartan groups. Data were analyzed for all podocyte genes.[16]

eGFR trajectories after 6 weeks of treatment for sparsentan and irbesartan groups are presented in **Figure 3**.[16]

Figure 3. eGFR Trajectories in Sparsentan vs Irbesartan Groups



Safety

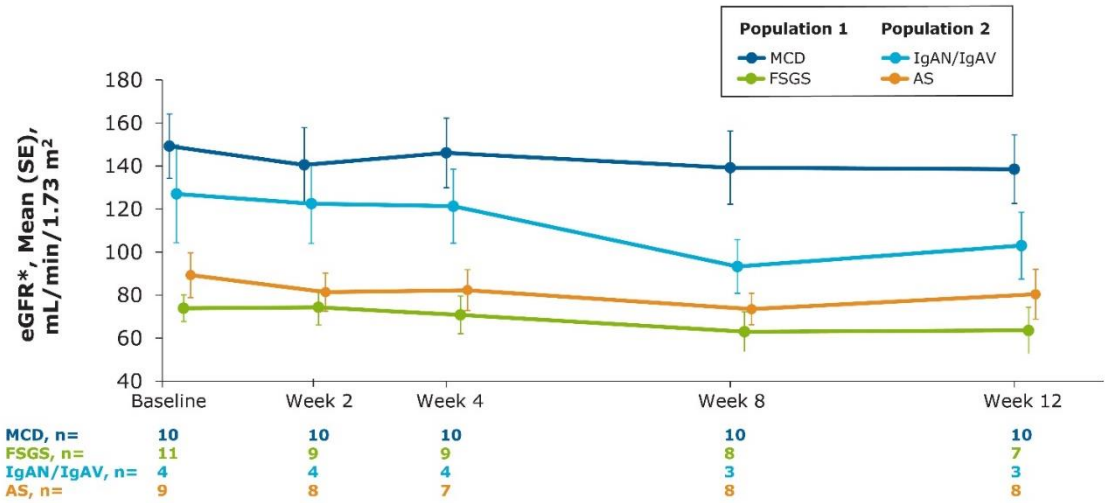
Over 108 weeks of treatment, TEAEs were reported with similar frequency in the sparsentan (n=172; 93.5%) and irbesartan (n=174; 93%) treatment groups. Serious TEAEs occurred in 68 (37%) sparsentan-treated patients and 82 (43.9%) irbesartan-treated patients.[8] Patients with gFSGS experienced a safety profile similar to the overall DUPLEX study population. Safety assessments were similar between treatment groups.[16]

The EPPIK Study

At data cutoff (February 15, 2024), 34 pediatric patients enrolled in the EPPIK study have received ≥1 dose of sparsentan oral suspension. Safety and efficacy were assessed over 12 weeks of treatment. 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.[9]

Over 12 weeks of treatment, eGFR remained fairly stable in all subgroups (**Figure 4**).[9]

Figure 4. eGFR During 12 Weeks of Sparsentan Treatment



*eGFR determined using the modified Schwartz formula.

Safety

Ten serious TEAEs were reported in 6 patients, and 1 patient discontinued study treatment due to worsening of nephrotic symptoms. The observed safety profile was consistent with that seen in adult FSGS and IgAN trials.[9,14]

Abbreviations

AE, adverse event; AS, Alport syndrome; 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; gFSGS, genetic focal segmental glomerulosclerosis; IgA, immunoglobulin A; IgAN, immunoglobulin A nephropathy; IgAV, immunoglobulin A-associated vasculitis; IQR, interquartile range; MCD, minimal change disease; OLE, open-label extension; PK, pharmacokinetics; RAASi, renin-angiotensin-aldosterone system inhibitor; RR, relative risk; SAE, serious adverse event; SE, standard error; TEAE, treatment-emergent adverse event; UACR, urine albumin-to-creatinine ratio; UPCR, urine protein-to-creatinine ratio; US, United States.

References

1. 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
2. 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
3. FILSPARI. Prescribing information. Travere Therapeutics Inc; September 2024.
4. 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
5. 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.
6. Srivastava T, Tesar V, Campbell KN, et al. Long-term efficacy and safety of sparsentan in FSGS: 240-week analysis of the DUET open-label extension (OLE). Abstract presented at: ASN Kidney Week; November 3-6 2022; Orlando, FL.
7. Rheault MN, Alpers CE, Barratt J, et al. Sparsentan versus irbesartan in focal segmental glomerulosclerosis, supplement. *N Engl J Med*. 2023;389(26):2436-2445. doi:10.1056/NEJMoa2308550
8. 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
9. Trachtman H, Coppo R, Ahmed NAM, et al. Sparsentan in pediatric patients with rare proteinuric kidney disease: Preliminary findings from the EPPIK study. Poster presented at: ASN Kidney Week; October 23-27, 2024; San Diego, CA.
10. 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. Abstract presented at: ERA-EDTA Congress; May 19-22, 2022; Paris, France.

11. 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.
12. 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.
13. Trachtman H, Saleem M, Coppo R, Rheault MN, He P, Komers R. Sparsentan for treatment of pediatric patients with selected proteinuric glomerular diseases: Design of the phase 2 EPPIK study. Poster presented at: American Society of Nephrology Kidney Week; November 4-7, 2021; San Diego, California.
14. Trachtman H, Coppo R, He P, et al. Preliminary findings from the phase 2 EPPIK study of sparsentan in pediatric patients with selected proteinuric glomerular diseases. Oral presentation presented at: ASN Kidney Week; November 2-5, 2023; Philadelphia, PA.
15. Troost JP, Trachtman H, Spino C, et al. Proteinuria reduction and kidney survival in focal segmental glomerulosclerosis. *Am J Kidney Dis*. 2021;77(2):216-225. doi:10.1053/j.ajkd.2020.04.014
16. Yee J, Gong W, Inrig JK, Rheault MN, Komers R, Trachtman H. Outcomes of the DUPLEX trial in patients with genetic focal segmental glomerulosclerosis (gFSGS). Poster presented at: ASN Kidney Week; October 23-27, 2024; San Diego, CA.