# FILSPARI® (sparsentan)

# Changes in Blood Pressure and Hypotensive Events in FSGS

## Summary


### Background

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

### Study Data

- In a phase 2 study of sparsentan as treatment for hypertension, 1 patient taking the 800 mg dose withdrew due to hypotension[5]
- Data from the DUET study demonstrated reduction in BP in patients with FSGS after 8 weeks of treatment and continuing to 84 weeks of treatment, with hypotension among the most frequent TEAEs after 8 weeks and 84 weeks of sparsentan treatment[3,6]
    - In pediatric patients in the DUET OLE, following an early decline in BP, mean SBP and DBP remained stable over ~4 years of sparsentan[7]
- In the DUPLEX study, early decreases in BP from baseline were observed in both sparsentan and irbesartan groups. SBP remained stable after 6 weeks and DBP remained stable after 4 weeks[8]


## Background

Sparsentan is an investigational therapeutic candidate for the treatment of FSGS.[3,4]

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

### Studies of Sparsentan 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.[5]

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.[5]

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.[5]

### 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 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 5$^{th}$ 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.[4,8] 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.[4,8]

## Study Data

### Studies of Sparsentan in Hypertensive Patients

In a phase 2 study of sparsentan as treatment for hypertension (NCT00635232), 1 patient taking the 800 mg dose withdrew due to hypotension.[5]

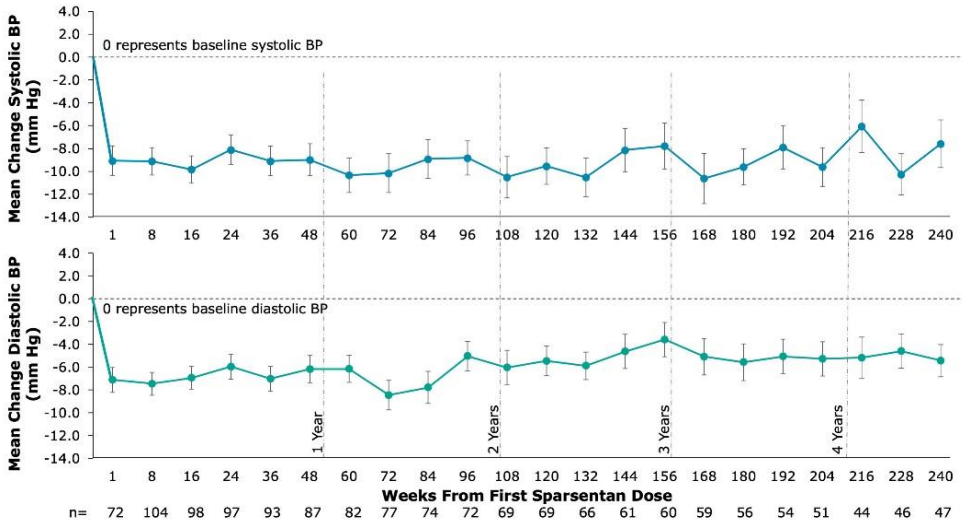
## The DUET Study

*OLE – 84 and 240 Week Data*

Changes in BP

In the DUET OLE, patients initially randomized to irbesartan were transitioned to sparsentan (IRB-SPAR). As measured up to 84 weeks, sparsentan treatment was associated with sustained decrease in BP in patients who received either sparsentan or irbesartan in the initial 8-week double blind period of the study.[6] The effect of sparsentan on BP after 240 weeks of treatment for patients in the DUET OLE is shown in **Figure 1**.[12]

### Figure 1. Mean Change From Baseline in Blood Pressure by Visit




Error bars show SE. Only on-treatment observations (defined as occurring within 1 day of last sparsentan dose) are included.

Hypotensive Events

In the DUET OLE, patients initially randomized to sparsentan remained in this treatment group (SPAR-SPAR); patients initially randomized to irbesartan were transitioned to sparsentan (IRB-SPAR). An interim data analysis with all patients taking sparsentan showed that after 84 weeks of treatment, 15 (22.4%) of the SPAR-SPAR group and 3 (8.6%) of the IRB-SPAR group reported hypotension as a TEAE.[6]

## The DUPLEX Study

Decreases in BP were observed in both groups early in the treatment period. Following this, SBP remained stable after Week 6 and DBP stabilized after Week 4. Mean BP at Week 108 was 124/78 mm Hg in the sparsentan group and 126/80 mm Hg in patients taking irbesartan.[8]

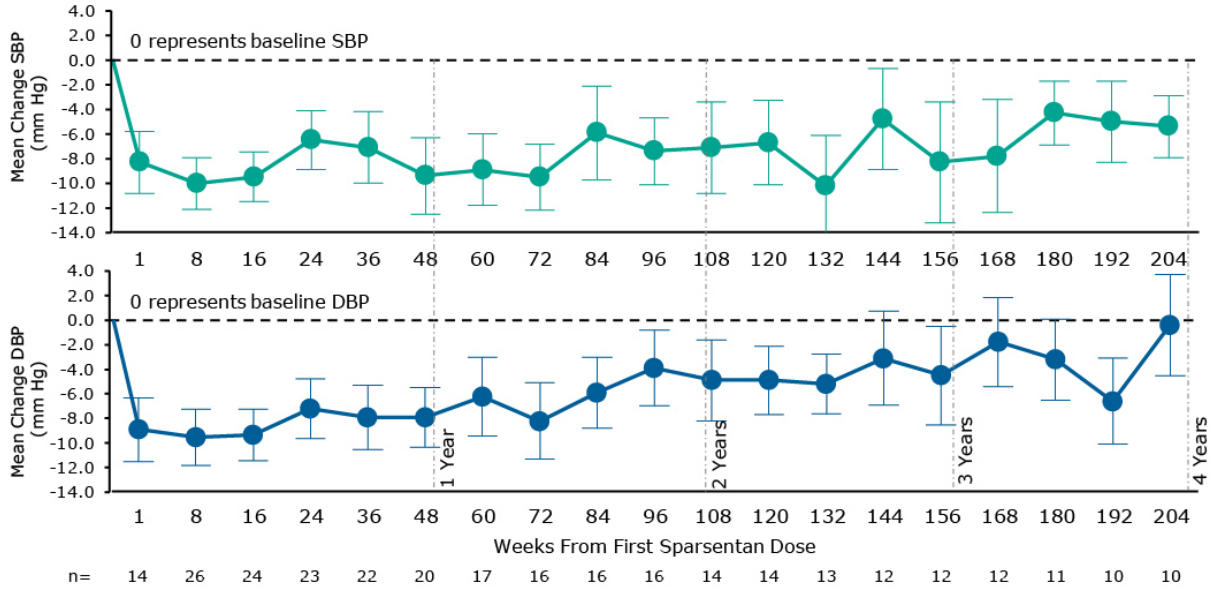
During the treatment period, hypotension was reported by 33 (17.9%) and 21 (11.2%) sparsentan and irbesartan patients, respectively.[8]

## Changes in BP and Hypotensive Events in Pediatric Patients

### *The DUET Study*

The DUET OLE included 26 patients aged <21 years who received at least one dose of sparsentan. An early decline in BP was observed, after which mean SBP and DBP remained stable over ~4 years of sparsentan treatment (**Figure 2**).[7]

### Figure 2. Mean Change From Baseline in BP by Visit in Patients Age ≤21 Years



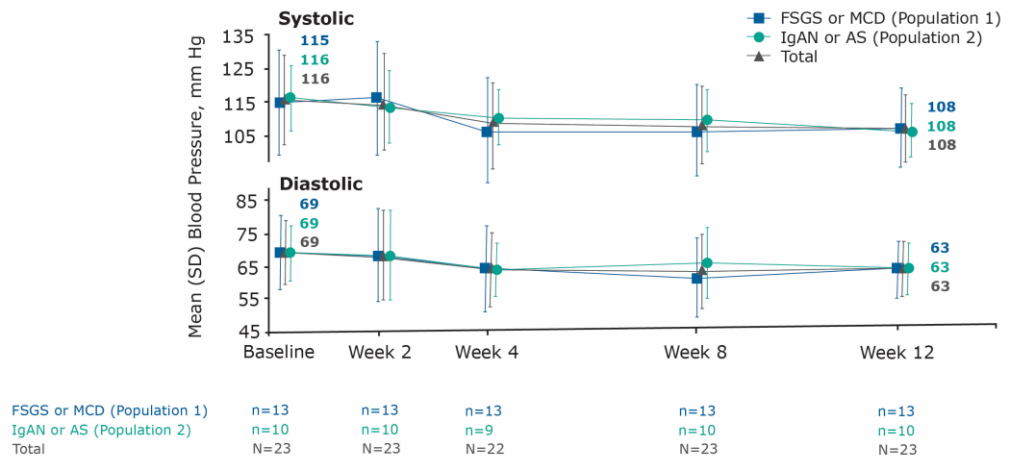

Error bars show SE. Only on-treatment observations (defined as occurring within 1 day of last sparsentan dose) are included. Blood pressure measurements are from patients randomized to sparsentan (n=15 at Week 8, including 11 with RAASi use before washout) and patients who transitioned from irbesartan to sparsentan (n=11 at Week 8). Patients who transitioned from irbesartan to sparsentan did not have a 1-week visit after starting sparsentan.

Hypotension was reported in 1 (4%) patient in Year 1 of the OLE and 1 (8%) patient in Year 4.[7]

### *The EPPIK Study*

The EPPIK study is an open-label, single-arm, multicenter trial evaluating the safety, efficacy, and PK of liquid sparsentan in patients aged ≥1 to <18 years with FSGS or MCD and aged ≥2 to <18 years with IgAN, IgAV, or Alport syndrome.[13,14] The effect of sparsentan on blood pressure is presented in **Figure 3**.[13]

**Figure 3. Effect of Sparsentan on Blood Pressure During 12 Weeks of Treatment**




Hypotension was reported in 1 (8%) patient in the FSGS or MCD group.[13]

# Abbreviations

AS, Alport syndrome; $AT_1$, angiotensin II type 1; 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; IgAN, immunoglobulin A nephropathy; IgAV, immunoglobulin A-associated vasculitis; IRB, irbesartan; MCD, minimal change disease; OLE, open-label extension; PK, pharmacokinetics; RAASi, renin-angiotensin-aldosterone system inhibitor; SBP, systolic blood pressure; SD, standard deviation; SE, standard error; SPAR, sparsentan; TEAE, treatment-emergent adverse event; UPCR, urine protein-to-creatinine ratio.

# References

1. 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
2. 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.
3. 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
4. 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

5. Komers R, Shih A, Belder R. Anti-hypertensive effects of sparsentan, a dual angiotensin II and endothelin type A receptor antagonist. Poster presented at: ASN Kidney Week; November 15-20 2016; Chicago, IL.
6. Hogan J, Derebail V, Murphy E, et al. Long-term effects of sparsentan, a dual angiotensin and endothelin receptor antagonist in primary focal segmental glomerulosclerosis (FSGS): Interim 84 week analysis of the DUET trial. Presentation presented at: ASN Kidney Week; October 23-28 2018; San Diego, CA.
7. Lieberman K, Paredes A, Srivastava T, Komers R, Murphy E, Trachtman H. Long-term efficacy and safety of sparsentan in young patients with FSGS: 240-week analysis of the DUET open-label extension (OLE). Poster presented at: World Congress of Nephrology; March 30-April 2, 2023; Bangkok, Thailand.
8. Rheault MN, Alpers CE, Barratt J, et al. Sparsentan versus irbesartan in focal segmental glomerulosclerosis. *N Engl J Med*. Published online November 3, 2023;doi:10.1056/NEJMoa2308550
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. 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.
13. 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.
14. 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.