Sparsentan

Changes in Blood Pressure and Hypotensive Events 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[2,4,5]

Study Data

- In a phase 2 study of sparsentan as treatment for hypertension, 1 patient taking the 800 mg dose withdrew due to hypotension[6]
- Data from the phase 2 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[2,7]
    - In pediatric patients in the DUET OLE, following an early decline in BP, mean SBP and DBP remained stable over ~4 years of sparsentan[8]
- In the phase 3 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[9]
- In the phase 2 EPPIK study, BP remained relatively stable over 12 weeks of sparsentan treatment[10]

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.[2,4,5] 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.[11-13]

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.[6]

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.[6]

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.[6]

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.[2]

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.[1,9] 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.[9] 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.[1,9]

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.[14] 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.[10,14,15]

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.[6]

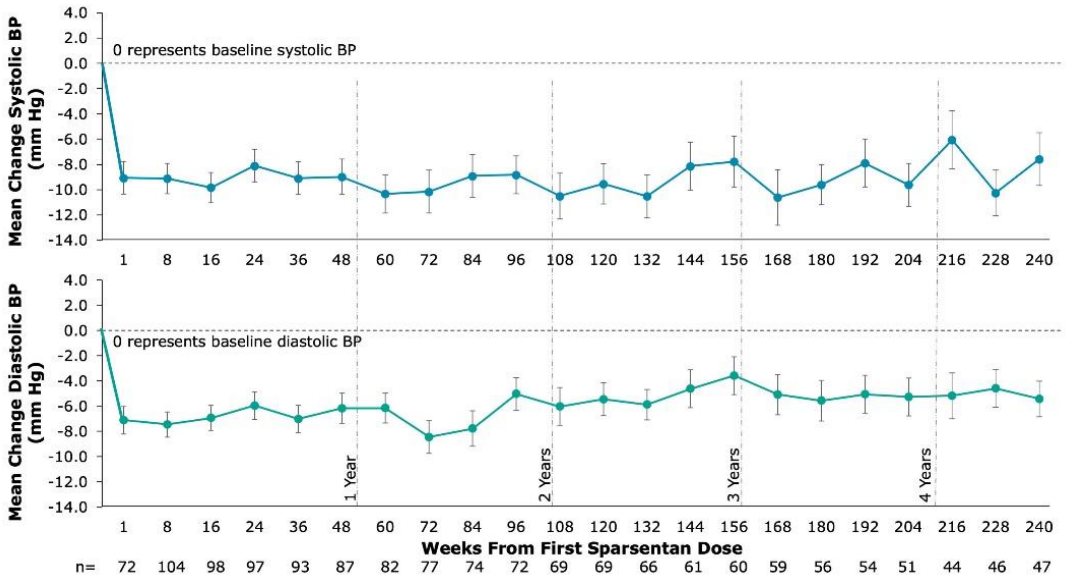
The DUET Study

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.[7] The effect of sparsentan on BP after 240 weeks of treatment for patients in the DUET OLE is shown in **Figure 1**.[16]

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.

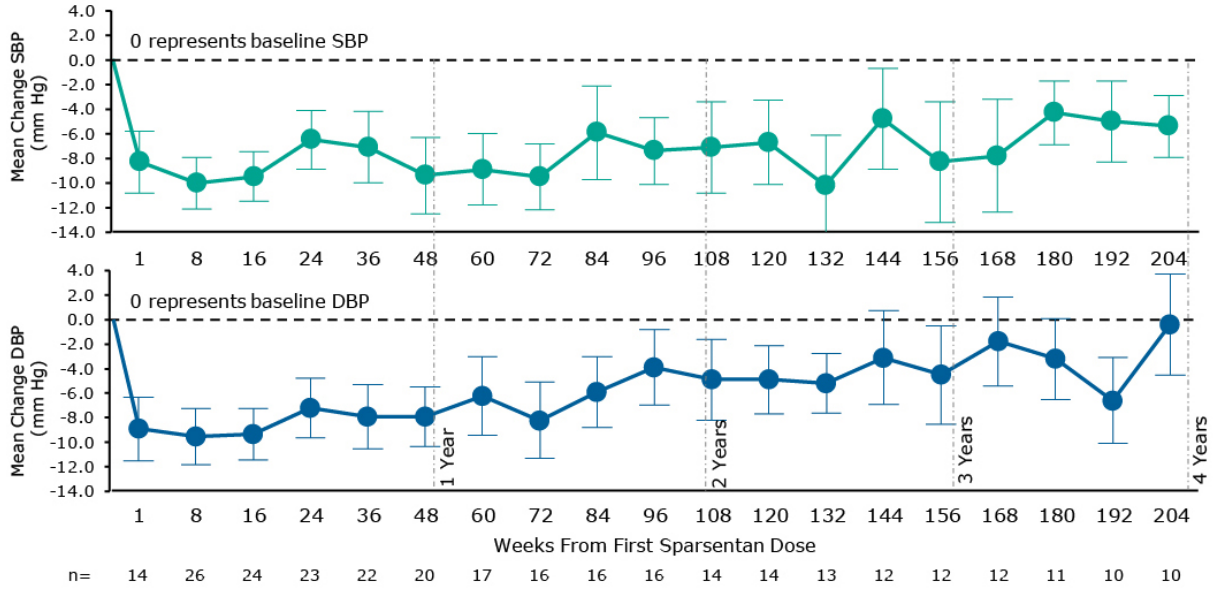
Hypotensive Events

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.[7]

Changes in BP and Hypotensive Events in Pediatric Patients

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**).[8]

Figure 2. Mean Change From Baseline in Blood Pressure 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.[8]

The DUPLEX Study

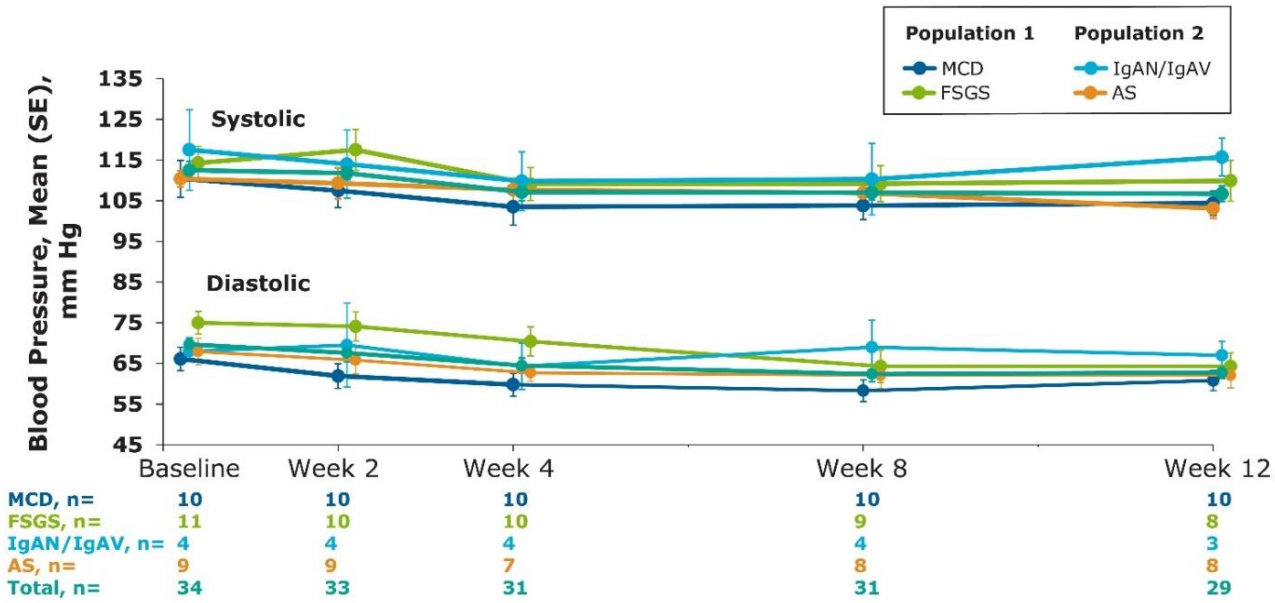
Decreases in BP were observed in both groups early in the treatment period. Following this, SBP remained stable after Week 6 and DBP stabilized after Week 4. Mean BP at Week 108 was 124/78 mm Hg in the sparsentan group and 126/80 mm Hg in patients taking irbesartan.[9]

During the treatment period, hypotension was reported by 33 (17.9%) and 21 (11.2%) sparsentan and irbesartan patients, respectively.[9]

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. BP remained fairly stable throughout the 12-week treatment period (**Figure 3**).[10]

Figure 3. Mean Blood Pressure Change From Baseline



Abbreviations

AE, adverse event; 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; SAE, serious adverse event; SE, standard error; SBP, systolic blood pressure; SD, standard deviation; SE, standard error; SPAR, sparsentan; TEAE, treatment-emergent adverse event; UACR, urine albumin-to-creatinine ratio; UPCR, urine protein-to-creatinine ratio.

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