FILSPARI™ (sparsentan)

Transitioning from ACEi/ARB Treatment to Sparsentan in Clinical Trials

Summary

Prescribing Information

- Prior to initiating treatment with FILSPARI, discontinue use of renin-angiotensin-aldosterone system (RAAS) inhibitors, endothelin receptor antagonists (ERAs), and aliskiren[1]
- Do not coadminister FILSPARI with ARBs, ERAs, or aliskiren[1]

Background

- The PROTECT study is a phase 3, global, randomized, multicenter, double-blind, parallel-arm, active-control study of the efficacy and safety of sparsentan compared to irbesartan for the treatment of IgA nephropathy[2]
- The DUET study is a phase 2, randomized, multicenter, double-blind, active-control trial examining the safety and efficacy of sparsentan compared to irbesartan in patients with FSGS[3]
- The DUPLEX study is a global, randomized, multicenter, double-blind, active-controlled, phase 3 trial assessing the efficacy and safety of sparsentan as compared to irbesartan in 371 patients, ages 8 to 75 years, with primary and genetic FSGS[4]

Study Data

The PROTECT Study

- On Day 1 following randomization, current ACEi and/or ARB therapies were discontinued for the duration of the study[5]
- Initial doses were sparsentan 200 mg/day or irbesartan 150 mg/day, and target doses were 400 mg/day sparsentan and 300 mg/day irbesartan[5]

The DUET Study

- Prior to randomization, patients discontinued prescribed ARB and ACEi therapies[3]
- Patients were randomized 3:1 to receive sparsentan 200 mg/day, 400 mg/day (two cohorts), or 800 mg/day (two cohorts) or irbesartan 300 mg/day[3]

The DUPLEX Study

- Prior to randomization, patients discontinued prescribed ARB and ACEi therapies[6]
- Patients were randomized 1:1 to receive 800 mg/day sparsentan or 300 mg/day irbesartan[6]

Prescribing Information

General Consideration

Prior to initiating treatment with FILSPARI, discontinue use of renin-angiotensin-aldosterone system (RAAS) inhibitors, endothelin receptor antagonists (ERAs), and aliskiren.[1]

Monitoring

Initiate treatment with FILSPARI only after measuring aminotransferase levels and total bilirubin. Avoid initiation in patients with elevated aminotransferases (>3x ULN). Continue required monitoring monthly for the first 12 months after initiation or restarting following an interruption due to elevated transaminases, then every 3 months during treatment with FILSPARI.[1]

Recommended Dosage

Initiate treatment with FILSPARI at 200 mg orally once daily. After 14 days, increase to the recommended dose of 400 mg once daily, as tolerated. When resuming treatment with FILSPARI after an interruption, consider titration of FILSPARI, starting at 200 mg once daily. After 14 days, increase to the recommended dose of 400 mg once daily.[1]

Dosage Adjustment for Aminotransferase Elevations

If aminotransferase levels increase, adjust monitoring and treatment plan according to **Table 1**.

Do not resume treatment in patients who have experienced clinical symptoms of hepatotoxicity or in patients whose hepatic enzyme levels and bilirubin have not returned to pretreatment levels.[1]

Table 1. Dosage Adjustment and Monitoring in Patients Developing Aminotransferase Elevations >3x ULN

ALT/AST levels	Treatment and monitoring recommendations
>3x and ≤8x ULN	Confirm elevation with a repeat measure. If confirmed, interrupt treatment, and monitor aminotransferase levels and bilirubin at least weekly, and INR as needed, until the levels return to pretreatment values and the patient is asymptomatic. Do not resume treatment if any of the following occurs without other cause found: • ALT or AST >3x ULN and total bilirubin >2x ULN or INR >1.5 • ALT or AST >3x ULN, with symptoms of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5% eosinophils) • ALT or AST >5x ULN for more than 2 weeks If treatment is resumed, initiate FILSPARI at 200 mg once daily, with reassessment of hepatic enzyme levels and bilirubin within 3 days. Close monitoring is required in these patients.
>8x ULN	Stop treatment permanently if no other cause found.

Renin-Angiotensin System (RAS) Inhibitors and ERAs

Do not coadminister FILSPARI with ARBs, ERAs, or aliskiren.

Combined use of these agents is associated with increased risks of hypotension, syncope, hyperkalemia, and changes in renal function (including acute renal failure).[1]

Background

Sparsentan is a novel, first-in-class, and the only single molecule antagonist of the ET_A and AT_1 receptors.[3,7,8] 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 PROTECT Study

The PROTECT study (NCT03762850) is a phase 3, global, randomized, multicenter, double-blind, parallel-arm, active-controlled clinical trial evaluating long-term antiproteinuric and nephroprotective efficacy and safety of 400 mg of sparsentan compared to 300 mg of irbesartan.[12] The study includes 404 patients ages 18 years and older with biopsy proven IgA nephropathy who experience persistent proteinuria despite available ACEi or ARB therapy. The PROTECT study protocol provides for an unblinded interim analysis of at least 280 patients to be performed after 36 weeks of treatment to evaluate the primary efficacy endpoint, defined as change in proteinuria (UPCR) at Week 36 from baseline. Secondary efficacy endpoints include the rate of change in eGFR following the initiation of randomized treatment over 58-week and 110-week periods, as well as rate of change in eGFR over 52-week and 104-week periods following the first 6 weeks of randomized treatment.[2,13] The PROTECT study also examines change from baseline in UACR based on a 24-hour urine sample at Week 36, and prespecified exploratory endpoints of complete (urinary protein excretion <0.3 g/day) and partial (urinary protein excretion <1.0 g/day) proteinuria remission at least once at any time during the double-blind period. In addition, this study evaluates the proportion of patients in each group reaching a confirmed 40% reduction in eGFR from baseline, KF, or all-cause mortality. KF is defined as initiation of KRT or sustained eGFR value of <15 mL/min/1.73 m^2.[14] Reduction in proteinuria and decline in rate of eGFR are largely accepted as surrogate markers of treatment effect in studies of KF.[14,15]

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 with biopsy-proven FSGS. 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] Patients remained on maintenance doses of sparsentan or irbesartan during a 108-week double blind phase. 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). An additional interim endpoint was the proportion of patients achieving a UPCR ≤1.5 g/g and a >40% reduction (FPRE) at Week 36. Safety was assessed by double-blind monitoring of adverse events and safety endpoints.[4,6]

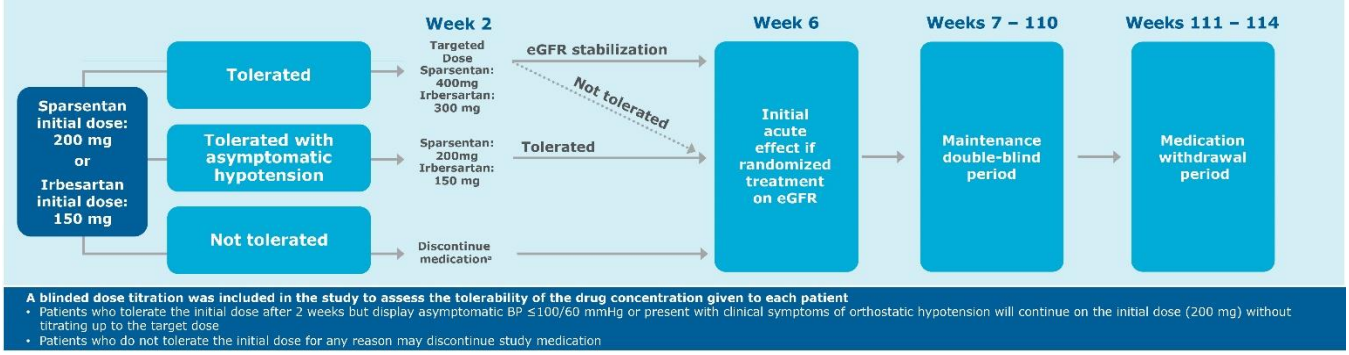
Study Data

The PROTECT Study

On Day 1 following randomization, current ACEi and/or ARB therapies were discontinued for the duration of the study. Patients began initial doses of either study drug (sparsentan once-daily 200 mg) or active control (irbesartan once-daily 150 mg). Target doses were 400 mg/day sparsentan and 300 mg/day irbesartan; patients received half of target dose for the first 2 weeks after randomization, with a goal to titrate to the target doses at Week 2 (**Figure 1**). Dose tolerance was evaluated in a blinded manner at the Week 2 visit and was defined as systolic blood pressure >100 mm Hg and diastolic blood pressure >60 mm Hg after 2 weeks, and no AEs (eg, worsening edema) or laboratory findings (eg, serum potassium >5.5 mEq/L) interfering with the patient's continuation on study medication.[13]

Patients who tolerated initial doses were titrated up to target doses. Patients who tolerated the initial dose but experienced asymptomatic blood pressure values ≤100/60 mm Hg or presented with clinical symptoms of orthostatic hypotension continued initial dose without titration to target dose. Patients who did not tolerate the initial dose for any reason could discontinue the study medication and could re-start or reduce the study medication at the investigator's discretion. Decreases in target dose and titrations to target dose were permitted at any time throughout the study.[13]

Figure 1. Blinded Dose Titration in the PROTECT Study



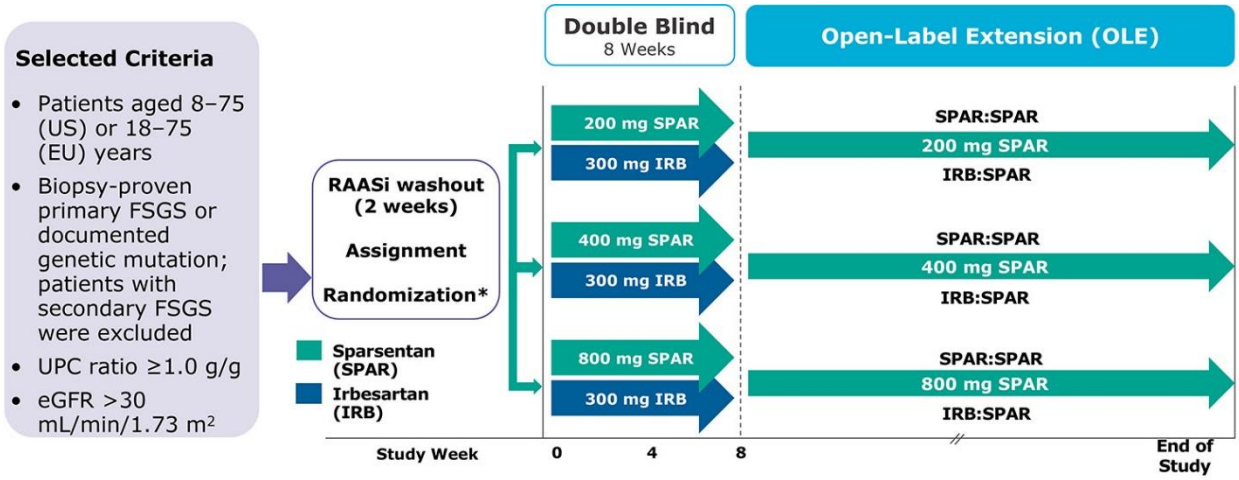
[a]Patients who do not tolerate the initial dose will be encouraged to restart study medication throughout the study. Patients who do not tolerate study medication should continue in the study even if they permanently discontinue study medication.

In an interim analysis of PROTECT data after 36 weeks of treatment, the safety profile of sparsentan was consistent with that previously observed and showed no new safety signals.[8,16]

The DUET Study

Prior to randomization, patients discontinued prescribed ARB and ACEi therapies. Patients were then randomized 3:1 through an interactive web response system within sequential dose-escalating, 20-patient cohorts to receive sparsentan 200 mg/day, 400 mg/day (two cohorts), or 800 mg/day (two cohorts) or irbesartan 300 mg/day (**Figure 2**). Incremental safety reviews were performed by an independent DMC. Only patients aged 18 years and older were initially enrolled in cohort 1 at the 200 mg/day dose. After 8 patients completed 4 weeks of treatment, a safety review was conducted and enrollment was opened to patients aged 8-17 years. Cohort 2 was also opened for randomization of patients to receive sparsentan 400 mg or irbesartan 300 mg. This process was repeated after 8 patients completed 4 weeks of treatment at 400 mg, and again after 8 patients completed 4 weeks at 800 mg. DMC reviews continued every 6 months. Patients randomized to irbesartan received 150 mg/day for the first week before escalating to 300 mg/d for the remaining 7 weeks. Patients with body weight ≤50 kg received 50% of the assigned study drug doses.[3]

Figure 2. DUET Study Schematic



*Patients were assigned to dose cohort, then randomized to sparsentan or irbesartan within the dose cohort. The study drug was administered orally, once daily. Patients who weighed ≤50 kg received half of the daily dose of sparsentan or irbesartan according to the assigned dose cohort. Randomization after 2 weeks of RAASi washout. IRB:SPAR = patients randomized to irbesartan who then transitioned to sparsentan in the OLE; SPAR:SPAR = patients randomized to sparsentan who also received sparsentan in the OLE.

In a post-hoc assessment through 240 weeks of the DUET OLE, no new or unexpected safety signals emerged.[17]

The DUPLEX Study

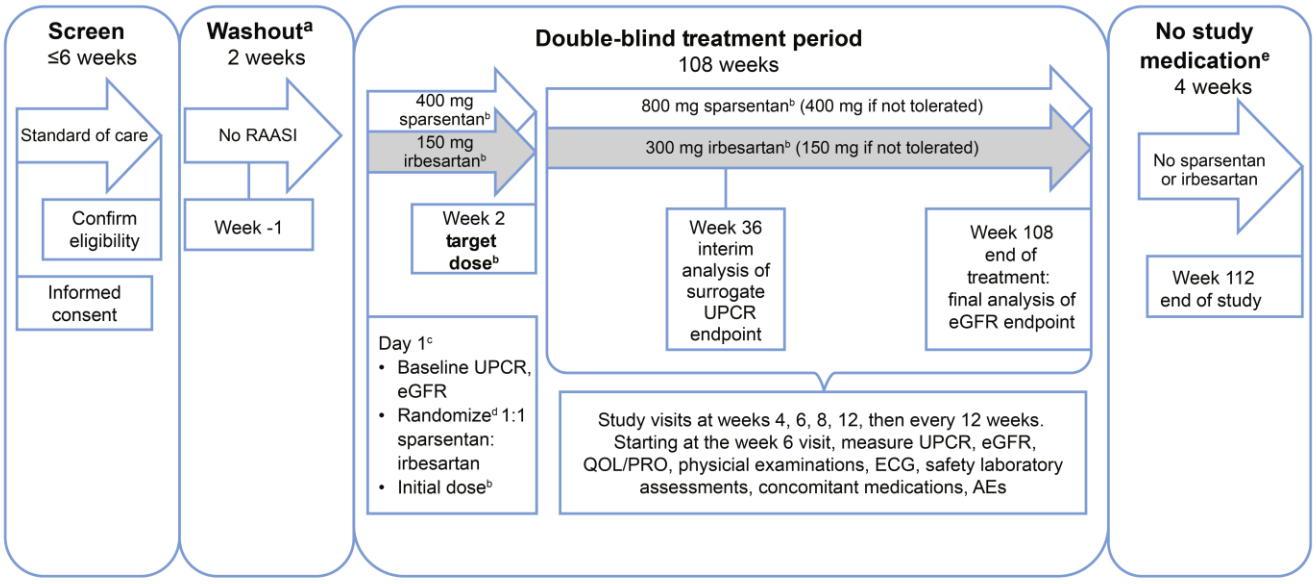
Prior to randomization, patients discontinued prescribed ARB and ACEi therapies (**Figure 3**). Patients were then randomized 1:1 through an interactive web response system to 800 mg/day sparsentan or 300 mg/day irbesartan. Patients who weighed ≤50 kg at screening received half the otherwise specified doses of sparsentan or irbesartan. Randomization was stratified by eGFR (≥30 to <60 mL/min per 1.73 m^2 and ≥60 mL/min per 1.73 m^2 for all patients) and UPCR (≤3.5 g/g and

>3.5 g/g [patients ≥18 years old] or ≤2 g/g and >2 g/g [patients <18 years old]) at screening. After 108 weeks, study treatment was discontinued and the investigator resumed standard-of-care treatment, including treatment with RAASi (with the exception of irbesartan) provided there are no contraindications for their use.[6]

Interim data after 36 weeks of treatment from the ongoing DUPLEX study indicate that sparsentan has been generally well-tolerated and no new safety signals have emerged. Overall tolerability has been comparable to the active control irbesartan.[18]

Over 108 weeks of treatment, TEAEs were reported with similar frequency in the sparsentan (n=172, 93%) and irbesartan (n=174, 93%) treatment groups. Serious TEAEs occurred in 44 (24%) sparsentan-treated patients and 41 (22%) irbesartan-treated patients. There was a total of 12 (3%) events of abnormal liver function tests in the study, with 7 (4%) events in the sparsentan arm and 5 (3%) events in the irbesartan arm. There were no reports of Hy's law or drug-induced liver injury with sparsentan and no SAEs due to CHF. SAEs due to peripheral edema occurred in 3% of patients treated with irbesartan and none in the sparsentan group. No new safety signals emerged.[4]

Figure 3. DUPLEX Study Schematic



[a]For patients who are undergoing washout from RAASi. [b]Patients whose body weight is ≤50 kg at screening will receive half the otherwise specified doses of sparsentan or irbesartan (active control). Weight will be measured at each visit and the dose increased at the investigator's discretion if the patient's weight reaches >50 kg. [c]Day 1 events shown will occur in the order in which they are listed. [d]Randomization will be stratified by eGFR value (≥30 to <60 mL/min per 1.73 m^2 and ≥60 mL/min per 1.73 m^2 for all patients) and UPCR (≤3.5 g/g and >3.5 g/g [patients ≥18 years old] or ≤2 g/g and >2 g/g [patients <18 years old]) at screening. [e]Following the 108-week blinded treatment period, treatment with study medication will be discontinued. At this time, the investigator should resume standard-of-care treatment, including treatment with RAASi (with the exception of irbesartan) provided there are no contraindications for their use. The investigator may make additional adjustments in antihypertensive medications as clinically indicated to adequately control the patient's BP.

Abbreviations

ACEi, angiotensin-converting enzyme inhibitor; AE, adverse event; ALT, alanine aminotransferase; ARB, angiotensin receptor blocker; AST, aspartate aminotransferase; AT_1, angiotensin II type 1; BP, blood pressure; CHF, congestive heart failure; DMC, data monitoring committee; ECG, electrocardiogram; eGFR, estimated glomerular filtration rate; ERA, endothelin receptor antagonist; ET_A, endothelin-1 type A; FPRE, FSGS partial remission endpoint; FSGS, focal segmental glomerulosclerosis; IgA, immunoglobulin A; INR, international normalized ratio; IRB, irbesartan; KF, kidney failure; KRT, kidney replacement therapy; OLE, open-label extension; PRO, patient-reported outcome; QOL, quality of life; RAASi, renin-angiotensin-aldosterone system inhibitor; SAE, serious adverse event; SPAR, sparsentan; TEAE, treatment-emergent adverse event; ULN, upper limit of normal; UACR, urine albumin-creatinine ratio; UPCR, urine protein-creatinine ratio.

References

1. FILSPARI. Prescribing information. Travere Therapeutics Inc; February 2023.
2. Wong M, Barratt J, Komers R, Mercer A, Rosenberg N. Baseline characteristics of adults enrolled in the ongoing phase 3 randomized, double-blind, active-control trial of sparsentan for the treatment of immunoglobulin A nephropathy (PROTECT). Abstract presented at: ERA-EDTA Congress; May 19-22, 2022; Paris, France.
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. Data on file. Travere Therapeutics Inc; 2023.
5. Barratt J, Rovin B, Diva U, Mercer A, Komers R, PROTECT Study Design Group. Implementing the kidney health initiative surrogate efficacy endpoint in patients with IgA nephropathy (the PROTECT trial). *Kidney Int Rep*. 2019;4(11):1633-1637. doi:10.1016/j.ekir.2019.08.007
6. 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
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. Abstract 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. Barratt J, Rovin B, Wong MG, et al. IgA nephropathy patient baseline characteristics in the sparsentan PROTECT study. *Kidney Int Rep*. 2023:1-14. doi:10.1016/j.ekir.2023.02.1086
13. Barratt J, Rovin B, Diva U, Mercer A, Komers R, PROTECT Study Design Group. Supplementary material: Implementing the kidney health initiative surrogate efficacy endpoint in patients with IgA nephropathy (the PROTECT trial). *Kidney Int Rep*. 2019;4(11):1633-1637. doi:10.1016/j.ekir.2019.08.007
14. Heerspink HJ, Radhakrishnan J, Alpers CE, et al. Sparsentan in patients with IgA nephropathy: A prespecified interim analysis from a randomised double-blind active-controlled clinical trial. *Lancet*. Published online April 1, 2023;doi:10.1016/S0140-6736(23)00569-X
15. Thompson A, Carroll K, Inker LA, et al. Proteinuria reduction as a surrogate end point in trials of IgA nephropathy. *Clin J Am Soc Nephrol*. 2019;14(3):469-481. doi:10.2215/CJN.08600718
16. Travere Therapeutics announces positive topline interim results from the ongoing phase 3 PROTECT study of sparsentan in IgA nephropathy. Press release. August 16, 2021. Accessed February 17, 2023. https://ir.travere.com/news-releases/news-release-details/travere-therapeutics-announces-positive-topline-interim-results
17. 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.
18. Travere Therapeutics announces achievement of interim proteinuria endpoint in the ongoing phase 3 DUPLEX study of sparsentan in focal segmental glomerulosclerosis. Press release. February 2, 2021. Accessed February 17, 2023. https://ir.travere.com/news-releases/news-release-details/travere-therapeutics-announces-achievement-interim-proteinuria