FILSPARI® (sparsentan)

Sparsentan and the Treatment Landscape for IgA Nephropathy

Summary

Prescribing Information .

- FILSPARI is indicated to reduce proteinuria in adults with primary immunoglobulin A nephropathy (IgAN) at risk of rapid disease progression, generally a urine protein-to-creatinine ratio (UPCR) ≥1.5 g/g[1]

Background

- IgA nephropathy is a slow-progressing CKD and carries a high burden of illness, including a negative impact on physical and mental health and functionality[2-5]

Study Data

- Current SOC includes initial treatment with either an ACEi or an ARB and clinical practice guidelines recommend treatment with glucocorticoids for certain patients at high risk of progressive kidney disease. Patients must be risk stratified for steroid therapy[4]

The efficacy and safety data that follows is from the pre-specified primary analysis reported at the interim assessment, which includes proteinuria data from all 404 randomized and treated patients in the PROTECT clinical trial at the time of the analysis.

- In the PROTECT study, after 36 weeks of treatment, patients receiving sparsentan achieved a mean reduction in proteinuria from baseline of 49.8%, compared to a mean reduction from baseline of 15.1% for irbesartan-treated patients (P<0.0001)[7]
- Overall, the safety profile of sparsentan was consistent with the previously observed safety profile, with no new safety signals emerging in the sparsentan group[8,9]

The efficacy and safety data that follows is from a 2-year confirmatory analysis including data from all 404 randomized and treated patients in the PROTECT clinical trial at the time of the analysis

- Treatment with sparsentan resulted in a clinically meaningful difference compared to irbesartan in eGFR total slope (1.0 mL/min/1.73 m^2 per year; P=0.058) and eGFR chronic slope (1.1 mL/min/1.73 m^2 per year; P=0.037)[10]
- Over 2 years of treatment, patients treated with sparsentan exhibited one of the slowest annual rates of kidney function decline seen in a clinical trial in IgA nephropathy (-2.7 to -2.9 mL/min/1.73 m^2 per year)[10]
- Safety data from the 2-year confirmatory analysis showed sparsentan to be well-tolerated, with a consistent safety profile comparable to irbesartan and no new safety signals[10]

Prescribing Information

FILSPARI is indicated to reduce proteinuria in adults with primary immunoglobulin A nephropathy (IgAN) at risk of rapid disease progression, generally a urine protein-to-creatinine ratio (UPCR) ≥1.5 g/g.[1]

To learn more about FILSPARI, please refer to the attached PI.

Background

IgA Nephropathy Burden of Illness

IgA nephropathy is the most common primary glomerulonephritis worldwide.[5] Many types of CKD and KF impart a high burden of illness, negatively impacting patients' QoL, and physical and psychological well-being, including increased levels of depression.[2] Anxiety is also a frequent comorbidity of CKD and KF. Notably, some research has found greater prevalence of depression and anxiety in patients with CKD and KF compared to other chronic conditions.[3]

IgA Nephropathy Pathophysiology

The pathology of IgA nephropathy is generally believed to involve 4 factors[6]:

- Increased levels of gd-IgA1
- Production of antibodies against gd-IgA1
- Formation of IgA immune complexes
- Deposition of immune complexes in the mesangium

IgA nephropathy is triggered by an unknown factor of genetic, environmental, infectious, or other origin that initiates the production of gd-IgA1. Immune complexes form as autoantibodies attach to abnormal IgA.[6,11] Deposition of these immune complexes in the mesangium bring about increased levels of cytokines, ET-1, and Ang II. ET-1 and Ang II are mediators of inflammation, kidney damage, and disease progression, and play critical roles in the pathophysiology of IgA nephropathy, working in tandem via their receptors (ET_A and AT_1, respectively) to amplify a continuous inflammatory cytokine response, mesangial cell proliferation, and vascular dysfunction.[12] ET-1 increases production of Ang II, and Ang II stimulates ET-1 release, creating a positive feedback loop that causes damage to the glomerular filtration barrier. Ongoing injury to podocytes, basement membrane, endothelial cells, and glycocalyx results in increasing protein leakage across the barrier.[13-15] This persistent proteinuria ultimately leads to glomerulosclerosis and tubulointerstitial inflammation, fibrosis, and scarring, and further increases in ET-1 and Ang II.[16,17] Overall, ET-1 and Ang II facilitate damage to glomeruli, the tubulointerstitium, and vasculature, leading to proteinuria and driving progression to KF in IgA nephropathy.[12,14,17]

Treatment of IgA Nephropathy

Goals of therapy in IgA nephropathy include reduction of proteinuria, management of blood pressure, and slowing of disease progression. Treatment first includes ACEis or ARBs in patients with proteinuria >0.5 g/day.[18] Despite treatment, patients with proteinuria >1 g/day and eGFR <30 mL/min/1.73 m^2 remain at high risk for disease progression.[4,5,11,18-20] Glucocorticoids may be

utilized if the benefit–risk profile is acceptable; additionally, treatment with an SGLT2 inhibitor may be efficacious in high-risk patients.[4,18,21]

Dual Endothelin Angiotensin Receptor Antagonist (DEARA)

Sparsentan is a non-immunosuppressive, first-in-class, highly selective dual antagonist of both ET_A and AT_1 receptors, combining 2 mechanisms of action into a single molecule.[22,23] A single agent with dual antagonism capacity may have potential benefits above combinations of single-target molecules.[24] Each sparsentan molecule possesses 2 binding sites and can bind individually to ET_A or AT_1 receptors, though one molecule cannot bind to both receptors simultaneously.[22,24]

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.[25-27] Combined action of RAASi and ET_A receptor antagonists has demonstrated additive benefits in patients with CKD, including patients with IgA nephropathy.[28-31]

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.[28] 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.[32,33] 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.[7] 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.[7] Reduction in proteinuria and decline in rate of eGFR are largely accepted as surrogate markers of treatment effect in studies of KF.[7,34]

Study Data

Long-Term Outcomes in IgA Nephropathy

Both adult and pediatric patients with IgA nephropathy may experience detrimental disease progression and overall poor outcomes. The UK RaDaR study includes a large cohort of adult (n=2299) and pediatric (n=140) patients with biopsy-proven IgA nephropathy. In an assessment of disease burden, lifetime KF risk, and benefit of short-term proteinuria and eGFR slope assessments, the median kidney survival time was 10.8 years for adults and 21.6 years for patients diagnosed as children. Mean (SD) age at time of KF was 49 (14) years for adult patients

and 27 (10) years for those diagnosed in childhood. Most patients progressed to KF within 10-15 years.[35]

Effect of Sparsentan in Experimental Models of Kidney Disease

In multiple experimental models of kidney disease, including IgA nephropathy, sparsentan exhibited nephroprotective effects and preservation of kidney function. Dual antagonism of ET_A and AT_1 receptors demonstrated anti-inflammatory, antiproliferative, antiproteinuric, and antifibrotic actions. Mouse models of IgA nephropathy and FSGS showed less inflammation, glomerulosclerosis, and proteinuria with sparsentan treatment, all of which are associated with disease progression and KF.[26,27,36,37]

The gddY mouse model is an experimental model of spontaneous IgA nephropathy and displays damages characteristic of disease progression and loss of kidney function.[38] Compared with untreated controls, treatment with sparsentan resulted in several beneficial outcomes, including decreased proteinuria, less damage to podocytes and glycocalyx, more rapid reduction in albuminuria, and delayed progression of glomerulosclerosis.[26,27]

In the gddY model of IgA nephropathy, sparsentan was found to have a greater effect than a single-acting ARB.[27]

The PROTECT Study

The PROTECT study protocol provided for an unblinded interim analysis to evaluate the primary efficacy endpoint–the change in UPCR from baseline at Week 36–approximately 36 weeks following randomization of the first 280 patients.[9]

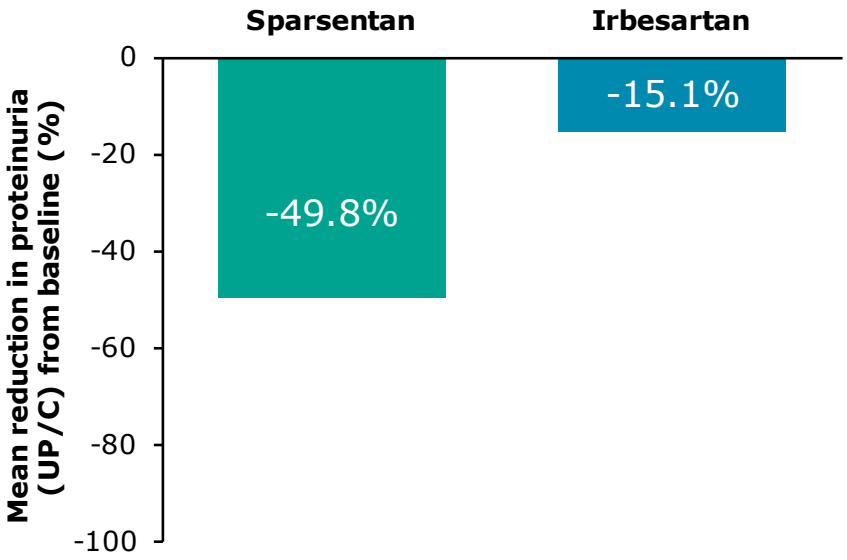
The efficacy and safety data that follows is from the pre-specified primary analysis reported at the interim assessment, which includes proteinuria data from all 404 randomized and treated patients in the PROTECT clinical trial at the time of the analysis

Interim Efficacy

Primary Efficacy Endpoint

After 36 weeks of treatment, patients receiving sparsentan achieved a mean reduction in proteinuria from baseline of 49.8%, compared to a mean reduction in proteinuria from baseline of 15.1% for irbesartan-treated patients ($P<0.0001$) (**Figure 1**). Reduction in proteinuria was greater with sparsentan compared to irbesartan at the first post-randomization visit (Week 4), continued to Week 36 of the interim analysis, and was consistent across patient subgroups of baseline demographic and clinical characteristics. The robust effect of sparsentan on reduction of proteinuria was found to be both statistically significant and clinically meaningful.[7]

Figure 1. Mean Reduction in Proteinuria (UPCR) From Baseline at Week 36 of the PROTECT Study



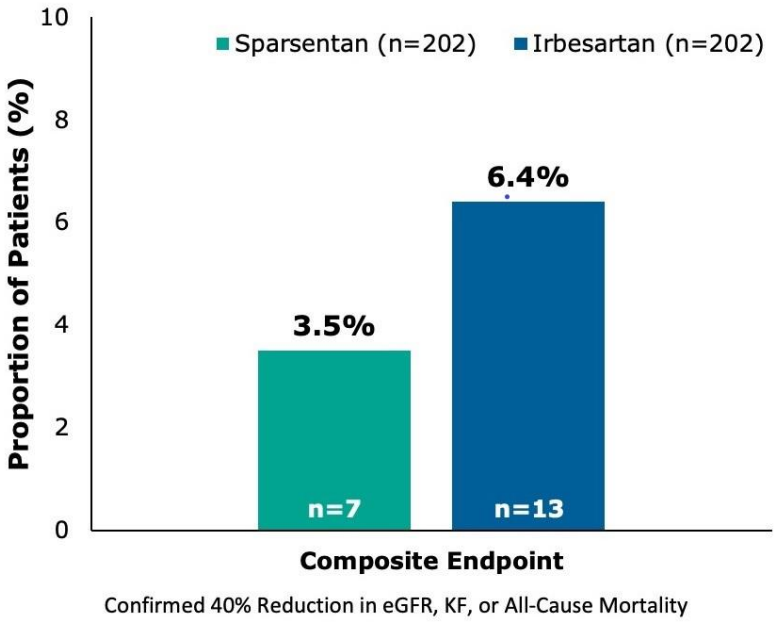
The proteinuria-lowering effect is unlikely to be attributed to the modest reduction in blood pressure. Treatment with sparsentan resulted in a large difference in proteinuria reduction compared to irbesartan, despite minimal differences in blood pressure changes between the groups.[7]

Secondary Efficacy Endpoints

36-Week Interim Analysis

An interim analysis of blinded data found that 20 patients reached the secondary composite endpoint of a confirmed 40% reduction in eGFR from baseline, KF, or all-cause mortality. Participants treated with sparsentan had a numerically lower incidence (n=7; 3.5%) compared with irbesartan (n=13; 6.4%) (**Figure 2**).[7,39]

Figure 2. Composite Endpoint Reached by 20 Participants at the Interim Analysis



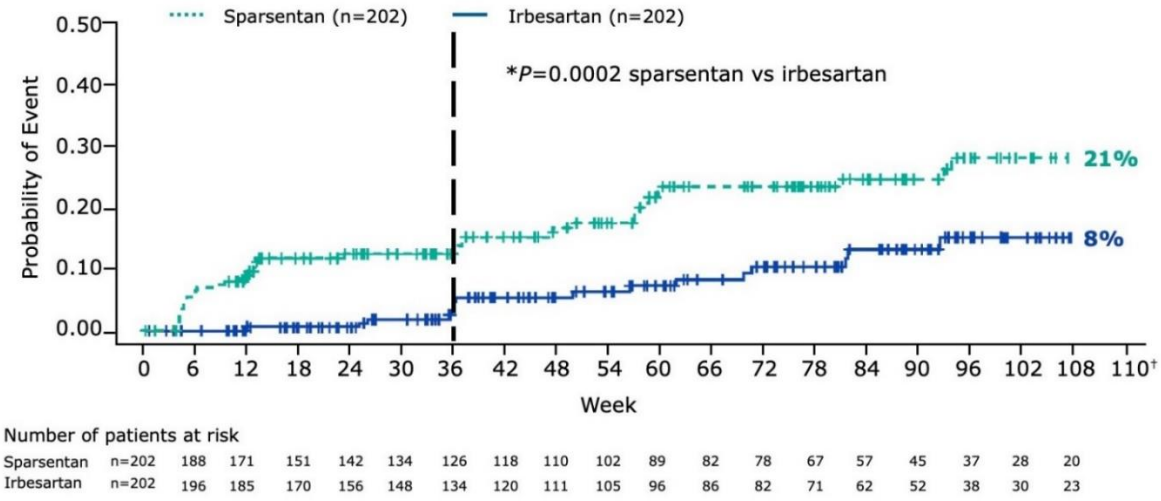
Primary Analysis Set. Interim descriptive analysis.

Consistent with the UPCR results, the geometric least squares mean percent change from baseline in UACR at week 36 was statistically significantly greater in the sparsentan group than the irbesartan group, resulting in a 45% reduction from baseline UACR in patients receiving sparsentan vs irbesartan (P<0.0001).[7]

Exploratory Efficacy Endpoints

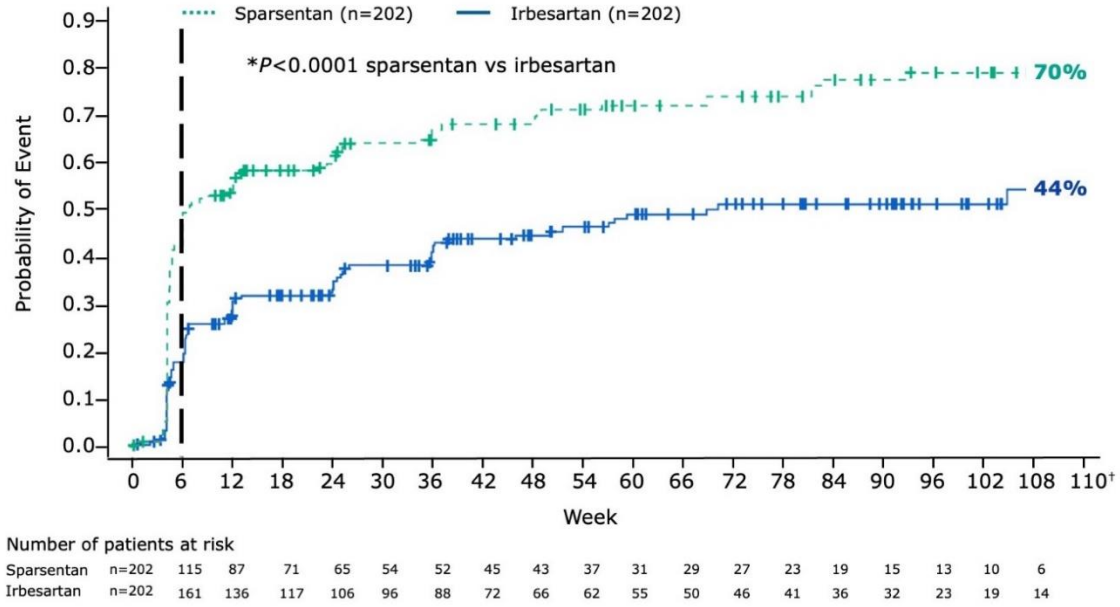
After 36 weeks of treatment, a significantly higher proportion of sparsentan-treated patients experienced complete proteinuria remission at least once (n=42; 21%) compared to the irbesartan group (n=16; 8%) (P=0.0002) (**Figure 3**). Partial proteinuria remission also occurred at a higher rate in the sparsentan group (n=142; 70%) vs the irbesartan group (n=89; 44%) (P<0.0001) (**Figure 4**). The observed higher rates of complete and partial remission in the sparsentan group occurred early after treatment initiation and were sustained throughout the trial.[7,39]

Figure 3. Time to First Complete Proteinuria Remission (<0.3 g/day) at the Interim Analysis



Complete proteinuria remission is urinary protein excretion <0.3 g/day. Kaplan-Meier plot; + censored. *P value from a stratified Cox proportional hazards model with treatment as covariate, stratified by randomization stratification factors. Primary analysis set. †Data collection extends to 110 weeks; data are presented in 6-week increments to Week 108.

Figure 4. Time to First Partial Proteinuria Remission (<1.0 g/day) at the Interim Analysis



Partial proteinuria remission is urinary protein excretion <1.0 g/day. Kaplan-Meier plot; + censored. *P value from a stratified Cox proportional hazards model with treatment as covariate, stratified by randomization stratification factors. Primary analysis set. †Data collection extends to 110 weeks; data are presented in 6-week increments to Week 108.

2-Year Confirmatory Endpoint Analysis

The PROTECT study included a confirmatory endpoint analysis following 2 years of sparsentan treatment. The confirmatory endpoint was the eGFR slope of progression to KF, measured by total slope in the US and by chronic slope in the EU.[10]

- The slope of eGFR following initiation of randomized treatment, from Day 1 to Week 110, defined the eGFR total slope
- The slope of eGFR following the initial acute effect of randomized treatment, from Week 6 to Week 110, defined the eGFR chronic slope

Topline efficacy endpoints assessing preservation of kidney function favored sparsentan over irbesartan following 2 years of treatment (**Table 1**). Patients taking sparsentan experienced an eGFR total slope 1.0 mL/min/1.73 m^2 per year favorable and clinically meaningful difference as compared to irbesartan. The observed difference in eGFR total slope narrowly missed statistical significance (*P*=0.058). For patients taking sparsentan, eGFR chronic slope showed a clinically meaningful and statistically significant difference of 1.1 mL/min/1.73 m^2 per year as compared to irbesartan (*P*=0.037).[10]

Table 1. Treatment With Sparsentan Demonstrated Long-Term Kidney Function Preservation

eGFR Slope	Sparsentan (n=202)	Irbesartan (n=202)	Difference (Sparsentan – Irbesartan) (95% CI)
eGFR total slope, mL/min/1.73 m^2 per year[a]	**-2.9**	**-3.9**	**1.0**, *P*=0.058 (-0.03, 1.94)
eGFR chronic slope, mL/min/1.73 m^2 per year[b]	**-2.7**	**-3.8**	**1.1**, *P*=0.037 (0.07, 2.12)

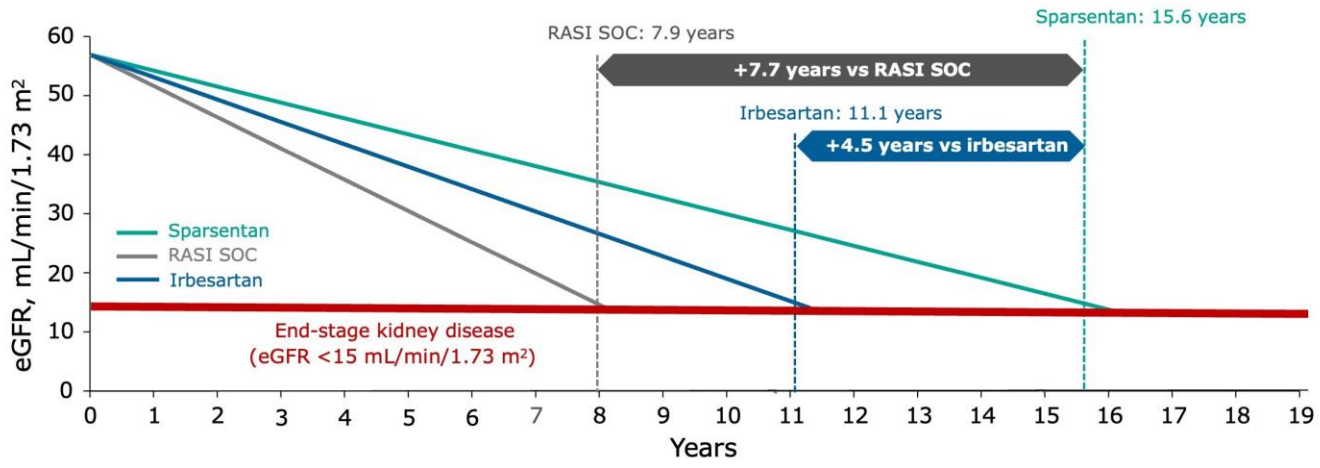
[a]LS mean and 95% CI from a random coefficient analysis including available on-treatment eGFR data from Week 6 through Week 110 with multiple imputation.
[b]LS mean and 95% CI from a random coefficient analysis including available on-treatment eGFR data through Week 110 with multiple imputation.

eGFR Slope

Treatment with sparsentan was associated with projected delay in time to KF, related to change in eGFR slope (**Figure 5**). Baseline eGFR was 57 mL/min/1.73 m^2, based on mean eGFR of the sparsentan group in the PROTECT study interim analysis. eGFR for SOC (maximized ACEi/ARB) equaled the mean of observed slopes reported in previous clinical trials. Observed eGFR chronic slope was -2.7 mL/min/1.73 m^2 per year for sparsentan, -3.8 mL/min/1.73 m^2 per year for irbesartan, and -5.3 mL/min/1.73 m^2 per year for SOC treatment. Corresponding time to KF was reported as 15.6 years, 11.1 years, and 7.9 years for sparsentan, irbesartan, and SOC, respectively.[10]

- Compared to patients utilizing SOC, patients taking sparsentan-treated experienced a mean 7.7 years longer delay to KF
- Compared to patients taking irbesartan, sparsentan-treated patients experienced a mean 4.5 years longer delay to KF

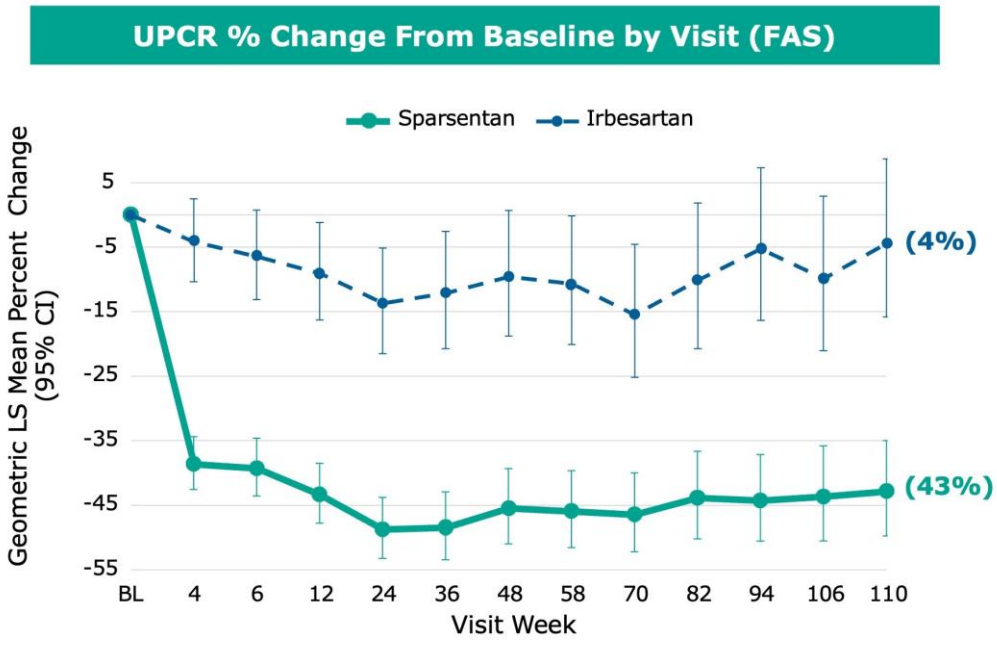
Figure 5. Treatment With Sparsentan Is Associated With Projected Delay in Time to Kidney Failure



Reduction in UPCR

Treatment with sparsentan resulted in a rapid and sustained antiproteinuric effect as demonstrated by proteinuria reduction. Following 2 years of treatment, patients taking sparsentan experienced a 43% proteinuria reduction from baseline compared to 4% for patients taking irbesartan (**Figure 6**).[10]

Figure 6. Sparsentan Provided Rapid and Sustained Antiproteinuric Effects After 2 Years of Treatment



Combined interim and confirmatory PROTECT study results demonstrated that sparsentan has a rapid and durable effect on proteinuria after 2 years of treatment.[10]

Safety

Interim Safety Results

Sparsentan was generally well-tolerated over 36 weeks of treatment. Overall, the safety profile of sparsentan was consistent with the previously observed safety profile, with no new safety signals emerging in the sparsentan group.[8,9] TEAEs were reported in 88% of patients in the sparsentan group and 78% in the irbesartan group. The most frequent TEAEs in patients receiving sparsentan were peripheral edema (14% vs 9% with irbesartan), hypotension (including orthostatic hypotension; 14% vs 6% with irbesartan), dizziness (13% vs 5% with irbesartan), and hyperkalemia (13% vs 10% with irbesartan). Most fluid retention AEs were mild in severity; importantly, none were severe and were well managed with diuretics. Diuretics were utilized at a similar rate among receiving sparsentan (18%) and irbesartan (19%), the most common being furosemide (8% of patients receiving sparsentan; 10% of patients receiving irbesartan). No fluid retention-associated TEAEs lead to treatment discontinuation. No fluid retention SAEs related to the study drug occurred, and no cases of heart failure were reported. Changes in body weight from baseline, as a proxy for fluid retention, were similar between the sparsentan and irbesartan groups.[7] Over a mean treatment duration of 86.9 weeks, discontinuations occurred in both groups, with 11% of patients taking sparsentan and 19% of patients taking irbesartan discontinuing study treatment.[39]

At 36 weeks, the adverse events of interest of ALT or AST increasing to >3× ULN occurred in 2% of each group (5 sparsentan patients vs 4 patients receiving irbesartan); all occurred without concurrent elevation in total bilirubin and were asymptomatic and reversible. There were no cases of hepatotoxicity and no deaths among participants receiving sparsentan. TEAEs that led to treatment discontinuation occurred in 15 (7%) participants receiving sparsentan and 10 (5%) receiving irbesartan. TEAEs that led to treatment discontinuation in ≥2 patients in sparsentan or irbesartan treated patients included acute kidney injury (3 vs 0), renal impairment (1 vs 2), chronic kidney disease (2 vs 0), and increased ALT (2 vs 0).[7]

2-Year Safety Results

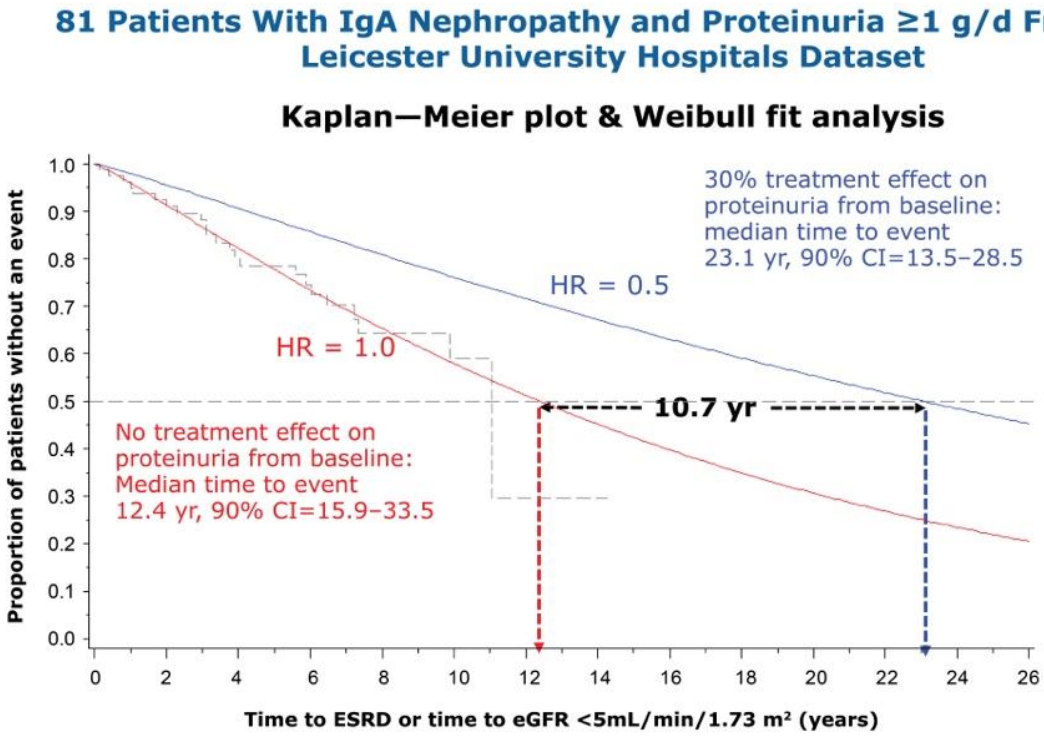
Additional safety data from the 2-year confirmatory analysis showed sparsentan to be well-tolerated, with a consistent safety profile comparable to irbesartan and no new safety signals. Among patients taking sparsentan, 187 (93%) reported TEAEs. Among patients taking irbesartan, 177 (88%) reported TEAEs. SAEs were reported by 75 (37%) patients taking sparsentan and 71 (35%) patients taking irbesartan. TEAEs leading to discontinuation occurred in 21 (10%) patients taking sparsentan and 18 (9%) patients taking irbesartan. There was 1 TEAE leading to death in the irbesartan group and none in the sparsentan group.[10]

Abnormal liver function tests were found in 5 (2%) patients taking sparsentan and 7 (3%) patients taking irbesartan. No new AEs of interest of 3× ULN AST or ALT, cases of Hy's law, or drug-induced liver injury occurred with sparsentan.[9]

Reduction of Proteinuria in Chronic Kidney Disease from Registry Cohort Studies

Research has found that reductions in proteinuria may be associated with slower progression of kidney damage and disease (**Figure 7**). One study demonstrated that a 30% decrease in proteinuria was associated with an increase in median time to KF of 10.7 years in patients at high risk for disease progression.[40] A large registry cohort study in one Canadian province examined the association between proteinuria and rate of change in eGFR. Data were included for 638,150 adult patients receiving routine care who had a recorded proteinuria level and 3 or more serum creatinine measurements over at least 1 year between May 2002 and March 2008. Data were stratified by baseline eGFR, marking original severity of kidney disease. Regardless of baseline eGFR, rate of change in kidney function varied with the presence and severity of proteinuria, with increasing severity of proteinuria associated with more rapid renal decline.[41]

Figure 7. Delay in Progression of Kidney Failure in Association With Reduced Proteinuria



Abbreviations

ACEi, angiotensin-converting enzyme inhibitor; AE, adverse event; ALT, alanine transaminase; Ang II, angiotensin II; AST, aspartate transaminase; AT_1, angiotensin II type 1; ARB, angiotensin receptor blocker; BL, baseline; CI, confidence interval; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; ET-1, endothelin-1; ET_A, endothelin-1 type A; FAS, full analysis set; FSGS, focal segmental glomerulosclerosis; gd-IgA1, galactose-deficient immunoglobulin A1; gddY, grouped ddY; HR, hazard ratio; IgA, immunoglobulin A; IgAN, immunoglobulin A nephropathy; KF, kidney failure; KRT, kidney replacement therapy; LS, least squares; QoL, quality of life; RAS, renin-angiotensin system; RAASi, renin-angiotensin-aldosterone system inhibitor; RaDaR, registry of rare kidney diseases; RASI, renin-angiotensin-system inhibitor; SAE, serious adverse event; SD, standard deviation; SGLT2, sodium-glucose cotransporter-2; SOC, standard of care; TEAE, treatment-emergent adverse event; UACR, urine albumin-to-creatinine ratio; ULN, upper limit of normal; UPCR, urine protein-to-creatinine ratio.

References

1. FILSPARI. Prescribing information. Travere Therapeutics Inc; February 2023.
2. Abdel-Kader K, Unruh ML, Weisbord SD. Symptom burden, depression, and quality of life in chronic and end-stage kidney disease. *Clin J Am Soc Nephrol*. 2009;4(6):1057-1064. doi:10.2215/CJN.00430109
3. Goh ZS, Griva K. Anxiety and depression in patients with end-stage renal disease: Impact and management challenges—a narrative review. *Int J Nephrol Renovasc Dis*. 2018;11:93-102. doi:10.2147/IJNRD.S126615
4. Kidney Disease: Improving Global Outcomes (KDIGO) Glomerular Diseases Work Group. KDIGO 2021 clinical practice guideline for the management of glomerular diseases. *Kidney Int*. 2021;100(4S):S1-S276. doi:10.1016/j.kint.2021.05.021
5. Le W, Liang S, Hu Y, et al. Long-term renal survival and related risk factors in patients with IgA nephropathy: Results from a cohort of 1155 cases in a chinese adult population. *Nephrol Dial Transplant*. 2012;27(4):1479-1485. doi:10.1093/ndt/gfr527
6. Chang S, Li XK. The role of immune modulation in pathogenesis of IgA nephropathy. *Front Med (Lausanne)*. 2020;7:92. doi:10.3389/fmed.2020.00092
7. 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
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. 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

10. Data on file. Travere Therapeutics Inc; 2023.
11. Wyatt RJ, Julian BA. IgA nephropathy. *N Engl J Med*. 2013;368(25):2402-2414. doi:10.1056/NEJMra1206793
12. Komers R, Plotkin H. Dual inhibition of renin-angiotensin-aldosterone system and endothelin-1 in treatment of chronic kidney disease. *Am J Physiol Regul Integr Comp Physiol*. 2016;310(10):R877-R884. doi:10.1152/ajpregu.00425.2015
13. Ebefors K, Wiener RJ, Yu L, et al. Endothelin receptor-A mediates degradation of the glomerular endothelial surface layer via pathologic crosstalk between activated podocytes and glomerular endothelial cells. *Kidney Int*. 2019;96(4):957-970. doi:10.1016/j.kint.2019.05.007
14. Kohan DE, Inscho EW, Wesson D, Pollock DM. Physiology of endothelin and the kidney. *Compr Physiol*. 2011;1(2):883-919. doi:10.1002/cphy.c100039
15. Raina R, Chauvin A, Chakraborty R, et al. The role of endothelin and endothelin antagonists in chronic kidney disease. *Kidney Dis (Basel)*. 2020;6(1):22-34. doi:10.1159/000504623
16. Abbate M, Zoja C, Remuzzi G. How does proteinuria cause progressive renal damage? *J Am Soc Nephrol*. 2006;17(11):2974-2984. doi:10.1681/ASN.2006040377
17. Sharma S, Smyth B. From proteinuria to fibrosis: An update on pathophysiology and treatment options. *Kidney Blood Press Res*. 2021;46(4):411-420. doi:10.1159/000516911
18. Floege J, Rauen T, Tang SC. Current treatment of IgA nephropathy. *Semin Immunopathol*. 2021;43:717-728. doi:10.1007/s00281-021-00888-3
19. Barratt J, Saleem M, Braddon FE, et al. Natural history of IgA nepropathy: Analysis of a UK national RaDaR IgA nephropathy cohort. *J Am Soc Nephrol*. 2021;32:PO1577.
20. Reich HN, Troyanov S, Scholey JW, Cattran DC, Toronto Glomerulonephritis Registry. Remission of proteinuria improves prognosis in IgA nephropathy. *J Am Soc Nephrol*. 2007;18(12):3177-3183. doi:10.1681/ASN.2007050526
21. Floege J, Barratt J, Coppo R, et al. International physicians delphi survey: Managing patients with IgA nephropathy. *Kidney Int Rep*. 2022;7(9):2076-2080. doi:10.1016/j.ekir.2022.05.022
22. Komers R. Development of sparsentan, a dual endothelin and angiotensin II receptor antagonist in rare kidney diseases. Poster presented at: APS/ASN Control of Renal Function in Health and Disease Conference; June 26-30, 2022; Charlottesville, VA.
23. 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
24. Kowala MC, Murugesan N, Tellew J, et al. Novel dual action AT_1 and ET_A receptor antagonists reduce blood pressure in experimental hypertension. *J Pharmacol Exp Ther*. 2004;309(1):275-284. doi:10.1124/jpet.103.055855
25. 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.
26. 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.

27. 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.
28. 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
29. Heerspink HJ, Parving HH, Andress DL, et al. Atrasentan and renal events in patients with type 2 diabetes and chronic kidney disease (SONAR): A double-blind, randomised, placebo-controlled trial. *Lancet*. 2019;393(10184):1937-1947. doi:10.1016/S0140-6736(19)30772-X
30. de Zeeuw D, Coll B, Andress DL, et al. The endothelin antagonist atrasentan lowers residual albuminuria in patients with type 2 diabetic nephropathy. *J Am Soc Nephrol*. 2014;25(5):1083-1093. doi:10.1681/ASN.2013080830
31. Dhaun N, MacIntyre IM, Kerr D, et al. Selective endothelin-A receptor antagonism reduces proteinuria, blood pressure, and arterial stiffness in chronic proteinuric kidney disease. *Hypertension*. 2011;57(4):772-779. doi:10.1161/HYPERTENSIONAHA.110.167486
32. 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). Mini oral presented at: ERA-EDTA Congress; May 19-22, 2022; Paris, France.
33. 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
34. 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
35. Pitcher D, Braddon FE, Hendry BM, et al. Long-term outcomes in IgA nephropathy. *Clin J Am Soc Nephrol*. 2023;18(6):727-738. doi:10.2215/CJN.0000000000000135
36. Gyarmati G, Shroff U, Izuhara A, Komers R, Bedard P, Peti-Peterdi J. Sparsentan improves glomerular blood flow and augments protective tissue remodeling in mouse models of focal segmental glomerulosclerosis (FSGS). Abstract presented at: ERA-EDTA Virtual Congress; June 5-8, 2021; Virtual Meeting.
37. Jenkinson C, Moldoveanu Z, Komers R, et al. Protective effects of sparsentan from proliferative glomerular inury induced by administration of human immune complexes in a murine model of experimental IgA nephropathy. Poster presented at: ISN World Congress of Nephrology; April 12-15, 2019; Melbourne, Australia.
38. Suzuki H, Suzuki Y, Novak J, Tomino Y. Development of animal models of human IgA nephropathy. *Drug Discov Today Dis Models*. 2014;11:5-11. doi:10.1016/j.ddmod.2014.07.002

39. Barratt J, Heerspink HJL, Wong MG, et al. Superior proteinuria reduction with sparsentan in immunoglobulin A nephropathy. Mini oral presented at: ERA Congress; June 15-18, 2023; Milan, Italy.

40. Carroll K, Conley L, Mercer A, Saleem M, Barratt J. Estimating delay in time to ESKD for treatment effects on proteinuria in IgA nephropathy and FSGS. Abstract presented at: ERA-EDTA Virtual Congress; June 5-8, 2021; Virtual Meeting.

41. Turin TC, James M, Ravani P, et al. Proteinuria and rate of change in kidney function in a community-based population. *J Am Soc Nephrol*. 2013;24(10):1661-1667. doi:10.1681/asn.2012111118