FILSPARI™ (sparsentan)
Dual Receptor Antagonism in Renal Pathophysiology and Reduction of Proteinuria

Summary

Prescribing Information

- Sparsentan is a single molecule with antagonism of the endothelin type A receptor (ET_AR) and the angiotensin II type 1 receptor (AT_1R)[1]
- Sparsentan has high-affinity for both ET_AR (Ki=12.8 nM) and AT_1R (Ki=0.36 nM) and greater than 500-fold selectivity for these receptors over the endothelin type B and angiotensin II subtype 2 receptors[1]

Background

- Sparsentan is a novel, first-in-class, and the only single molecule antagonist of the ET_A and AT_1 receptors.[2-4] Dual antagonism of both ET_A and AT_1 pathways in preclinical models of rare chronic kidney disease has beneficial effects in reduction of proteinuria and preservation of kidney function[5]
- Combined action of RAASi and ET_A receptor antagonists has demonstrated additive benefits in patients with CKD, including patients with IgA nephropathy[6-9]
- Current SOC in IgA nephropathy includes initial treatment with either an ACEi or ARB, both of which solely target the Ang II pathway.[10] Blockade of the ET-1 pathway has demonstrated efficacy in chronic kidney disease, including IgA nephropathy and FSGS, indicating another possible target for treatment[11]
- In studies of IgA nephropathy, proteinuria reduction is largely accepted as a reasonable surrogate endpoint for treatment effect on progression to kidney failure[12,13]

Study Data

Preclinical Data

- Nephroprotective effects of dual ET_A and AT_1 receptor antagonism have been observed in experimental models of CKD[5,14,15]
- Dual antagonism of ET_A and AT_1 receptors is found to reduce proteinuria more than single-mechanism agents[16,17]
- Sparsentan was shown to prevent glomerulosclerosis and reduce proteinuria in vivo in the IgA nephropathy gddY mouse model and in a transgenic mouse model of FSGS[5,14,18]
- Across preclinical studies, sparsentan has been shown to preserve kidney function by ameliorating multiple factors associated with glomerular disease, including mesangial cell activation, glomerular injury, and podocyte and glycocalyx loss[5,14,18-20]

Prescribing Information

Sparsentan is a single molecule with antagonism of the endothelin type A receptor (ET_AR) and the angiotensin II type 1 receptor (AT_1R). Sparsentan has high-affinity for both the ET_AR (Ki=12.8 nM) and the AT_1R (Ki=0.36 nM), and greater than 500-fold selectivity for these receptors over the endothelin type B and angiotensin II subtype 2 receptors. Endothelin-1 and angiotensin II are thought to contribute to the pathogenesis of IgAN via the ET_AR and AT_1R, respectively.[1]

Background

Sparsentan is a novel, first-in-class, and the only single molecule antagonist of the ET_A and AT_1 receptors.[2-4] 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.[5,14,21]

The nephroprotective potential of sparsentan has been examined in rodent models of CKD, including IgA nephropathy and FSGS.[5,14,15]

ET-1 and Ang II in Renal Pathophysiology and CKD

ET-1 and Ang II are mediators of inflammation, kidney damage, and disease progression, and play critical roles in the pathophysiology of CKD, including IgA nephropathy, FSGS, diabetic nephropathy, and obesity-related kidney disease.[22-25] Abnormal activation of ET-1 is found to be increased in CKD, promoting disease progression. Ang II is involved in the development or tubulointerstitial fibrosis and recruitment of inflammatory cells into the kidney, ultimately bringing about multiple profibrotic elements.[26] Angiotensin can stimulate TGF-β, thus contributing to fibrosis, inducing oxidative stress, and impacting intracellular calcium and podocyte cytoskeleton.[23]

ET-1 and Ang II act in tandem via ET_A and AT_1 receptors to amplify a continuous inflammatory cytokine response, mesangial cell proliferation, and vascular dysfunction.[22] 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.[27-31] Ongoing injury to podocytes, basement membrane, endothelial cells, and glycocalyx results in increasing protein leakage across the barrier.[28-32] This persistent proteinuria ultimately leads to glomerulosclerosis and tubulointerstitial inflammation, fibrosis, and scarring, and further increases in ET-1 and Ang II.[33,34] Overall, ET-1 and Ang II facilitate damage to glomeruli, the tubulointerstitium, and vasculature, leading to proteinuria and driving progression to kidney failure in CKD.[22,28,34]

Evidence of the roles of ET-1 and Ang II in kidney damage and disease has been demonstrated in various rodent models of renal pathology, including IgA nephropathy, glomerulonephritis, FSGS, acute kidney injury induced by IRI, and diabetic nephropathy. In these models, antagonism of one or both pathways resulted in improved outcomes and decreased renal damage and injury.[5,14,15,25,35-37]

Study Data

In experimental models of various nephropathies, dual antagonism of ET_A and AT_1 receptors has resulted in slowing of disease progression and nephroprotective effects, including reduction in proteinuria, delayed progression of glomerulosclerosis, podocyte loss, glycocalyx damage, and reduced inflammation. The effects of dual antagonism were greater than those seen with AT_1 receptor antagonism alone.

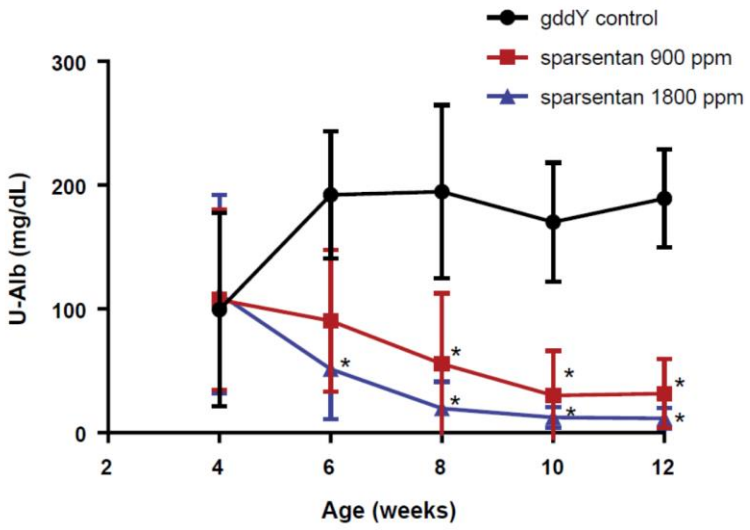
Preclinical Studies in IgA Nephropathy

gddY Mouse Model

The IgA nephropathy-prone mouse model (gddY) develops increased albuminuria and glomerular damage in the first 4-8 weeks of life. In one study, gddY mice were fed either control chow or chow containing 900 ppm (n=10) or 1800 ppm (n=10) sparsentan for 8 weeks. Albuminuria and plasma levels of sparsentan were assessed at multiple points throughout the study, with final assessments and kidney tissue samples collected at 12 weeks of age.[14]

Sparsentan doses of 900 and 1800 ppm were found to reduce albuminuria and prevent development of glomerulosclerosis, without effects on weight or serum total IgA or IgA galactose content (**Figure 1**).[14]

Figure 1. Sparsentan Attenuated Increases in Albuminuria

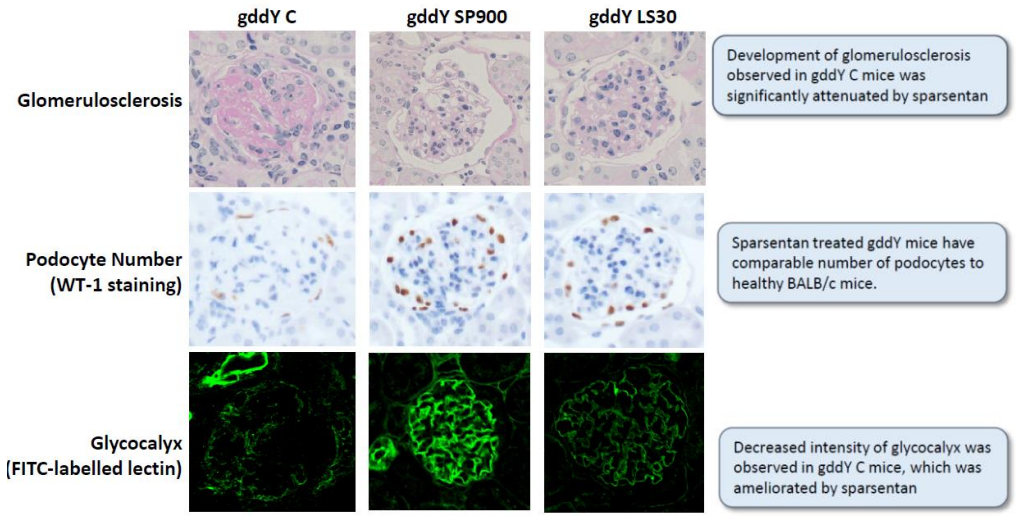


Data are presented as mean±SD. *P<0.05 vs gddY control.

A second study in gddY mice examined the effect of sparsentan and losartan on albuminuria and glomerulosclerosis compared to untreated mice. Mice were provided either sparsentan 900 ppm in their diet or losartan 30 mg/kg in drinking water up to 20 weeks of age, with albuminuria analysis every 2 weeks across 16 weeks of treatment. A subsample of mice was assessed for renal pathology at 12 weeks of age.[5]

Compared to the single-action ARB losartan, treatment with sparsentan resulted in greater and more rapid reduction in UACR. Sparsentan significantly attenuated development of glomerulosclerosis and glycocalyx damage to a greater extent than losartan after 16 weeks of treatment (**Figure 2**). Sparsentan-treated gddY mice also had a comparable number of podocytes to healthy mice. These differences were shown between sparsentan-treated and losartan-treated mice despite equivalent lowering of BP and prevention of inflammatory gene expression.[5]

Figure 2. Sparsentan Delayed Progression of Glomerulosclerosis, Podocyte Loss, and Glycocalyx Damage to a Significantly Greater Extent Than Losartan



C=control, LS30=losartan 30 mg/kg drinking water, SP900=sparsentan 900 ppm in diet.

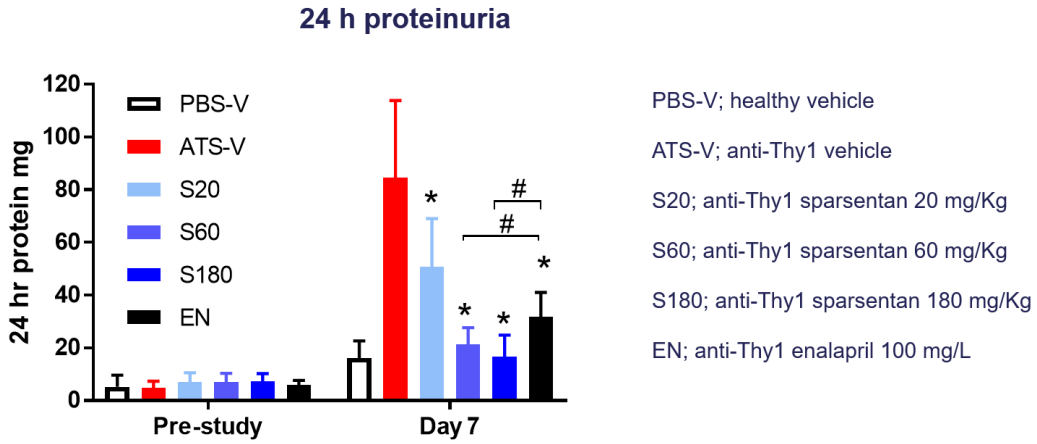
anti-Thy1 Rodent Model

The rat anti-Thy1 model serves as an experimental model of glomerulonephritis with characteristics similar to IgA nephropathy. Rodents received sparsentan 20, 60, and 180 mg/kg daily for 7 days; control groups received vehicle or enalapril drinking water 100 mg/day. Multiple factors associated with glomerulonephritis and mesangioproliferation were assessed, including IgG-mediated mesangiolysis, mesangial proliferation, inflammation, interstitial activation of profibrotic mediators, matrix accumulation, and proteinuria.[35]

In the anti-Thy1 model, sparsentan significantly reduced multiple IgA nephropathy-related features, in some cases to a greater extent than the active control enalapril. Sparsentan lowered proteinuria in a dose-dependent manner, with 60 and 180 mg/kg doses bringing about significantly greater efficacy than enalapril (**Figure 3**). Sparsentan dose-dependently decreased glomerular macrophage infiltration and mesangial cell proliferation, with significantly greater effect at 180

mg/kg compared to enalapril. In addition, sparsentan decreased the severity of mesangioproliferative pathology, and reduced mesangial cell and myofibroblast activation in glomeruli and interstitium.[35]

Figure 3. Sparsentan Dose-Dependently Lowered Proteinuria in Anti-Thy1 Rat



*P<0.05 vs ATS-V.
#P<0.05 vs EN.

EIC Mouse Model

In another murine model of IgA nephropathy, EICs injected intravenously induce glomerular injury similar to human IgA nephropathy.[38] Two studies utilized the EIC mouse model to assess the impact of sparsentan (60 mg/kg, 120 mg/kg daily) on nephropathology.[20,38] The first study examined effect of sparsentan vs vehicle (control) on EIC-induced proliferation of mesangial cells, increase in mesangial area, plasma creatinine, and proliferation of glomeruli.[20] Study 2 analyzed sparsentan vs vehicle effects on mesangial hypercellularity, expression of immune and inflammatory processes, and expression of genes associated with hypercellularity and glomerular pathology.[38]

After a 12-day treatment period, sparsentan at 60 or 120 mg/kg was found to attenuate EIC-induced increases in mesangial area, proliferation of glomeruli, and mesangial cellularity. Sparsentan 60 mg/kg also mitigated increases in plasma creatinine.[20] Additionally, sparsentan 60 and 120 mg/kg significantly reduced mesangial hypercellularity, comparable to healthy, non-EIC mice. Expression of immune and inflammatory processes was downregulated with sparsentan treatment, as determined by LFC analysis of genes associated with cytokine stimulation and immune and cellular activation.[38]

Preclinical Studies in FSGS

Living FSGS Mouse Model

In a genetically engineered mouse model of FSGS, impact of sparsentan vs losartan was examined using visualization of effects in the intact living mouse kidney. MPM imagery was utilized to capture hemodynamic changes, podocyte calcium, tissue regeneration, and metabolic and endothelial function in kidneys of living mice treated with sparsentan or losartan vs untreated control mice.[15]

In FSGS mice, MPM imaging of the kidney showed that treatment with sparsentan had multiple glomeruloprotective effects.[15]

These included[15]:

- Attenuation of mitochondrial stress in podocytes
- Restoration of glomerular endothelial surface layer
- Reduction in CD44+ immune cell homing
- Enhanced endogenous tissue repair

Overall, sparsentan improved glomerular hemodynamics, glomerular filtration barrier, and podocyte function, and was more effective than losartan at preserving kidney structure and function in the FSGS mouse model.[15]

Adriamycin Rat Model

A second study utilized a rodent model of Adriamycin-induced kidney injury representative of FSGS to compare efficacy of sparsentan vs sham animals (no Adriamycin) and vehicle (Adriamycin, no sparsentan treatment) in attenuating functional and structural nephropathology, including UPCR, podocyte loss, and glomerular macrophage infiltration.[21]

Dual ET_A and AT_1 receptor antagonism reduced the development of several structural and functional features of FSGS pathology. Sparsentan doses of 20, 60, and 180 mg/kg were shown to attenuate podocyte loss and increases in UPCR, maintain GBM width, protect the glycocalyx, and reduce glomerular macrophage infiltration. Notably, attenuation of proteinuria was found to correspond with reduction of disease pathology.[21]

Preclinical Studies in Other CKD

A mouse model of a hereditary kidney disease (Alport syndrome) has been utilized to assess the effect of sparsentan on multiple pathologies associated with this disorder, including hearing loss, UPCR, GFR, and glomerular damage.[16,19,39]

In Alport mice, treatment with sparsentan 60 or 200 mg/kg significantly lowered UPCR and percentage of sclerotic glomeruli compared to treatment with vehicle. Nephroprotective effects were observed in both glomerular and interstitial regions.[19] Additionally, sparsentan treatment at 120 mg/kg initiated at 4 weeks of age was found to delay declines in GFR and significantly attenuate glomerularsclerosis. Extended lifespan and delayed increase in UPCR were observed even in Alport mice that were not treated until 5-7 weeks of age, and functional auditory changes were decreased with initiation of sparsentan at age 5 weeks.[39]

Abbreviations

ACEi, angiotensin-converting enzyme inhibitor; Ang II, angiotensin II; AT_1, angiotensin II type 1; AT_1R, angiotensin II type 1 receptor; ARB, angiotensin receptor blocker; BP, blood pressure; CKD, chronic kidney disease; EIC, engineered immune complex; ET-1, endothelin-1; ET_A, endothelin-1 type A; ET_AR, endothelin-1 type A receptor; FITC, fluorescein isothiocyanate; FSGS, focal segmental glomerulosclerosis; GBM, glomerular basement membrane; gddY, grouped ddY; GFR, glomerular filtration rate; IgA, immunoglobulin A; IgAN, IgA nephropathy; IgG, immunoglobulin G; IRI, ischemia-reperfusion injury; Ki, inhibition constant; LFC, log fold change; MPM, multiphoton microscopy; RAASi, renin-angiotensin-aldosterone system inhibitor; SD, standard deviation; SOC,

standard of care; TGF-β, transforming growth factor beta; UACR, urine albumin-creatinine ratio; UPCR, urine protein-creatinine ratio; WT-1, Wilms' tumor gene 1.

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