FILSPARI® (sparsentan)
Mechanism of Action and Pharmacology

Summary

Prescribing Information

- FILSPARI 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[1]
- Steady-state plasma levels are reached within 7 days with no accumulation of exposure at the approved recommended dosage[1]
- No clinically significant differences in sparsentan pharmacokinetics were observed following administration of a single 200 mg dose with a high fat, high calorie meal[1]
- The half-life of sparsentan is estimated to be 9.6 hours at steady state[1]
- CYP4503A is the major isozyme responsible for the metabolism of sparsentan[1]
- No clinically significant difference in the pharmacokinetics of sparsentan were observed based on age (18-73 years), sex, race, mild to moderate renal impairment (eGFR 30 to 89 mL/min/1.73 m^2), or mild to moderate hepatic impairment (Child-Pugh class A or B)[1]

Background

- Dual antagonism of both ET_A and AT_1 pathways in preclinical models of rare chronic kidney disease may have beneficial effects in reduction of proteinuria and preservation of kidney function.[2] Combined action of RAASi and ET_A receptor antagonists has demonstrated additive benefits in patients with CKD, including patients with IgA nephropathy[3-6]
- The pharmacokinetic profile of sparsentan was evaluated in healthy volunteers in a double-blind, randomized, placebo-controlled, multiple-ascending dose study. Volunteers were assigned to a single oral 50, 100, 250, 500, or 1000 mg dose of sparsentan and received the study treatment daily for 2 consecutive weeks[7]

Study Data

- The mean C_{max} and AUCs increase with dose, but increases are less than dose-proportional[7]
- C_{max} and AUCs were higher in fed participants, but the effect of food was not statistically significant[7]
- Sparsentan receptor occupancy (RO; as measured by Ki) demonstrated a stable relationship in relative RO of ET_AR to AT_1R in which AT_1R RO always exceeds ET_AR[8]
- In clinical studies, dual antagonism with sparsentan resulted in sustained proteinuria reduction with a safety profile comparable to that of irbesartan[9]

Prescribing Information

Mechanism of Action

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 if IgAN via the ET_AR and AT_1R, respectively.[1]

Pharmacodynamics

Dose-response information is not available. At the recommended dose regimen, no statistically significant exposure-response (E-R) relationship was identified between sparsentan exposure and the percentage reduction from baseline in UPCR at Week 36 over the observed sparsentan exposure range. No clinically meaningful E-R relationships were observed for hypotension of any grade and peripheral edema worst grade. A statistically significant relationship was observed between sparsentan exposures and the incidence of hyperkalemia of any grade.[1]

Cardiac electrophysiology

In a randomized, positive-, and placebo-controlled study in healthy subjects, sparsentan caused QTcF prolongation with maximal mean effect of 8.8 msec (90% CI: 5.9, 11.8) at 800 mg and 8.1 msec (90% CI: 5.2, 11.0) at 1600 mg. The underlying mechanism behind the observed QTc prolongation is unknown but is unlikely to be mediated via direct inhibition of hERG channels. At the recommended dose, no clinically relevant QTc prolongation (ie, >20 msec) is expected.[1]

Pharmacokinetics

The pharmacokinetics of sparsentan are presented as geometric mean (% coefficient of variation) unless otherwise specified. The C_{max} and AUC of sparsentan increase less than proportionally following administration of single doses of 200 mg to 1600 mg. Sparsentan showed time-dependent pharmacokinetics which may be related to the drug inducing its own metabolism over time. Steady-state plasma levels are reached within 7 days with no accumulation of exposure at the approved recommended dosage. Following a single oral dose of 400 mg sparsentan, the mean C_{max} and AUC are 7.0 µg/mL and 83.0 µg×h/mL, respectively. Following daily doses of 400 mg sparsentan, the steady-state mean C_{max} and AUC are 6.5 µg/mL and 63.6 µg×h/mL, respectively.[1]

Absorption

Following a single oral dose of 400 mg sparsentan, the median (minimum to maximum) time to peak plasma concentration is approximately 3 hours (2 to 8 hours).[1]

Effect of Food

Sparsentan AUC and C_{max} increased by 22% and 108%, respectively, following administration of a single oral 800 mg dose with a high fat, high calorie meal (1000 kcal, 50% fat). No clinically significant differences in sparsentan pharmacokinetics were observed following administration of a single 200 mg dose with a high fat, high calorie meal.[1]

Distribution

The apparent volume of distribution at steady state is 61.4 L at the approved recommended dosage.[1]

Sparsentan is >99% bound to human plasma proteins.[1]

Elimination

The clearance of sparsentan is time-dependent which may be related to the drug inducing its own metabolism over time. The apparent clearance (CL/F) of sparsentan is 3.88 L/h following the initial 400 mg dose then increases to 5.11 L/h at steady state.[1]

The half-life of sparsentan is estimated to be 9.6 hours at steady state.[1]

Metabolism

Cytochrome P450 3A is the major isozyme responsible for the metabolism of sparsentan.[1]

Excretion

After a single dose of radiolabeled sparsentan 400 mg to healthy subjects, approximately 80% of the dose was recovered in feces (9% unchanged) and 2% in urine (negligible amount unchanged). 82% of the dosed radioactivity was recovered within a 10-day collection period.[1]

Specific Populations

No clinically significant difference in the pharmacokinetics of sparsentan were observed based on age (18-73 years), sex, race, mild to moderate renal impairment (eGFR 30 to 89 mL/min/1.73 m^2), or mild to moderate hepatic impairment (Child-Pugh class A or B). Patients with severe hepatic impairment (Child-Pugh class C) and eGFR <30 mL/min/1.73 m^2 have not been studied.[1]

For more information, please refer to the attached Prescribing Information.

Background

Sparsentan is a novel, first-in-class, and the only single molecule antagonist of the ET_A and AT_1 receptors.[10-12] 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.[2,13,14]

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 in patients with IgA nephropathy compared to 300 mg of irbesartan.[3] 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. Patients with urine protein ≥1 g/day at screening, eGFR ≥30 mL/min/1.73 m^2, SBP ≤150 mm Hg, and DBP ≤100 mm Hg were eligible.[15] 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.[15,16] 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.[17] Reduction in proteinuria and decline in rate of eGFR are largely accepted as surrogate markers of treatment effect in studies of KF.[17,18]

Multiple-Ascending Dose Study

The pharmacokinetic profile of sparsentan was evaluated in healthy volunteers in a double-blind, randomized, placebo-controlled, multiple-ascending dose study. Volunteers were assigned to 1 of 5 dose levels (50, 100, 250, 500, or 1000 mg sparsentan); each patient received the study treatment in a single oral dose daily for 2 consecutive weeks. To evaluate the effect of food, 12 healthy volunteers in the fasted state received a 500 mg dose of sparsentan and outcomes were compared to when the same group of volunteers received the same treatment under fed conditions.[7]

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.[12]

Study Data

Mechanism of Action

Sparsentan is a non-immunosuppressive, first-in-class, highly selective dual antagonist of both ET_A and AT_1 receptors, combining two mechanisms of action into a single molecule (**Figure 1**; **Figure 2**).[12,19] As a dual endothelin angiotensin receptor antagonist (DEARA), sparsentan blocks activity of the potent vasoconstrictors angiotensin II and endothelin 1 by acting as a highly selective (10,000-fold) antagonist of ET_A and AT_1 receptors.[11] ET_A and AT_1 are both associated with potent vasoconstrictive, mitogenic, proliferative, proinflammatory, and profibrotic effects.[2,20-23]

Figure 1. Dual Mechanism of Action of Sparsentan

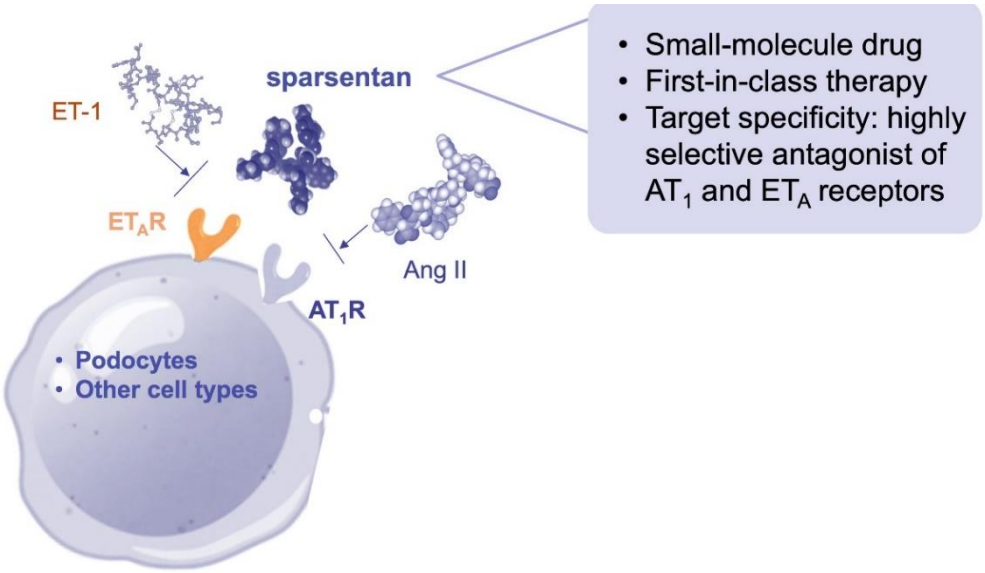
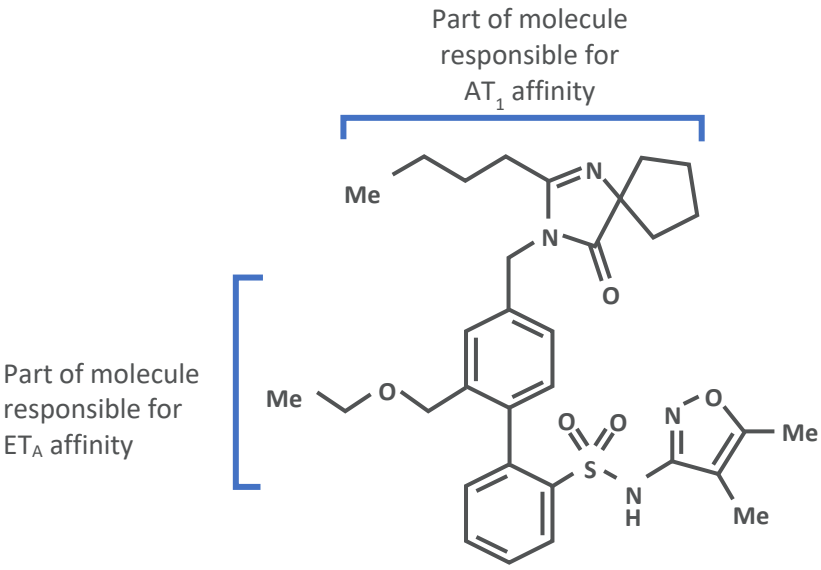


Figure 2. Molecular Structure of Sparsentan, $C_{32}H_{40}N_4O_5S$



The PROTECT Study

Sparsentan has previously demonstrated high affinity for human ET_A receptors. Binding is highly selective, as sparsentan was shown to be relatively inactive against ET_B and AT_2 receptors.[24] Radioligand binding assays were used to determine receptor affinities (Ki) for sparsentan at ET_AR, ET_BR, AT_1R, and AT_2R (**Table 1**).[8]

Table 1. Sparsentan Receptor Affinities and Steady-State PK Estimates From the PROTECT Study

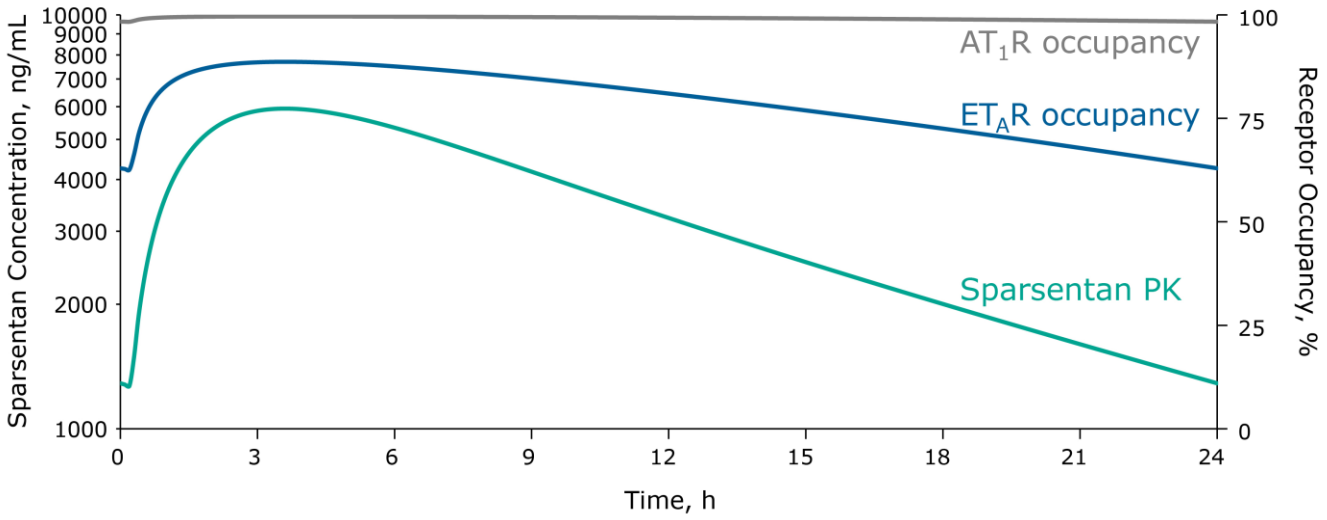
Receptor Target	Value
Ki for AT_1R, nM	0.36
Ki for AT_2R, nM	190
Ki for ET_AR, nM	12.8
Ki for ET_BR, nM	6582
Protein binding, %	99
Steady-State Parameter*	**Value**
C_{max}, ng/mL	5936
C_{min}, ng/mL	1266
$t_{1/2}$, hours	9.6
AUC, ng×h/mL	80,000

*PK data based on population PK model prediction for a patient with IgAN.

Population PK modeling of sparsentan was used to determine 24-hour PK and RO profile in PROTECT patients. Using PK data estimated for 400 mg/day of sparsentan, a 24-hour plot showed that sparsentan AT_1R occupancy (>95%) consistently surpassed ET_AR occupancy (>60% and

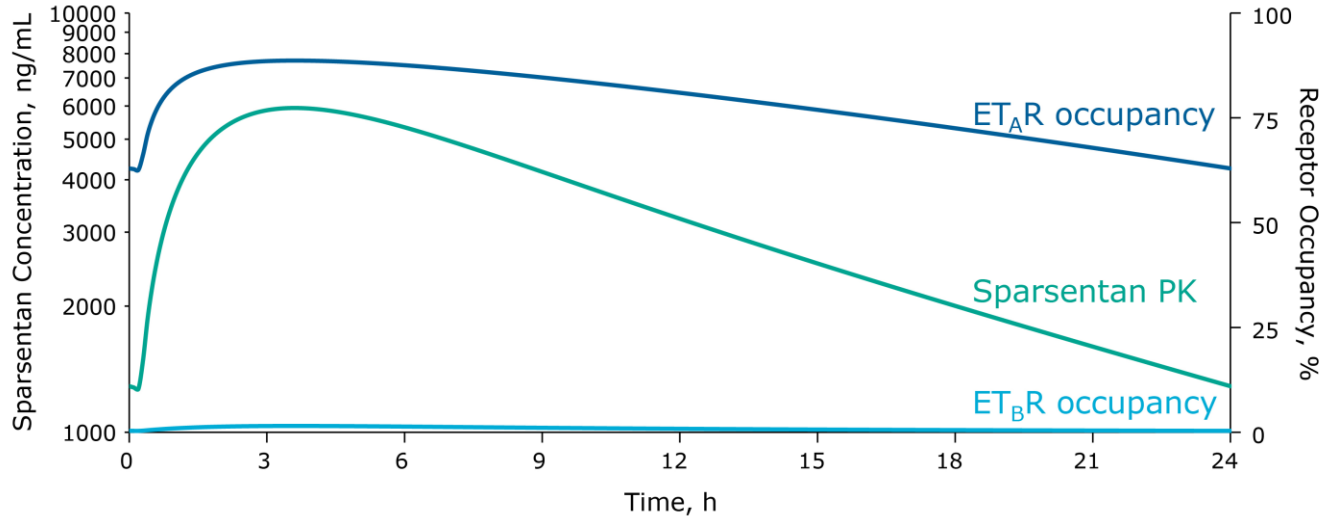
<90%) (**Figure 3**), and sparsentan ET_AR occupancy (>60% and <90%) exceeded ET_BR occupancy (<2%) (**Figure 4**).[8]

Figure 3. Sparsentan AT_1R and ET_AR Occupancies and Steady-State Concentration*



*Over 24 hours for a single daily 400-mg oral dose in PROTECT. PK data are based on population PK model prediction for a patient with IgAN.

Figure 4. Sparsentan ET_AR and ET_BR Occupancies and Steady-State Concentration*



*Over 24 hours for a single daily 400-mg oral dose in PROTECT. PK data are based on population PK model prediction for a patient with IgAN.

Sparsentan demonstrated a stable and substantial 24-hour relationship in relative RO of ET_AR to AT_1R. AT_1R RO was shown to always exceed ET_AR RO. ET_BR occupancy was negligible. These findings are in contrast to drugs targeting ET_AR only, in conjunction with AT_1R blocking. In this

circumstance, relatively unaccompanied ET_AR antagonism may occur, increasing the risk for fluid retention. The binding specificity of sparsentan may in part explain the minimal changes in fluid retention with sparsentan treatment.[8]

Pharmacology

The potential of sparsentan to inhibit activities of multiple CYP enzymes was assessed in pooled HLMs. Based on this assay, the calculated Ki for CYP3A4 equaled 26.9 µM. The IC_{50} of CYP2C8 was 99.2 µM. Across additional tested CYP enzymes, no inhibition was observed (**Table 2**).[7]

Table 2. CYP Inhibition Potential of Sparsentan

CYP Enzymes	1A2	2A6	2B6	2D6	2C8	2C9	2C19	2E1	3A4
Sparsentan (IC_{50} µM)	>100	>100	>100	>100	99.2	>100	>100	>100	53.8

Healthy Volunteers

In a study of healthy volunteers, the mean terminal half-life of sparsentan was 11 to 17 hours, and there was no detectable accumulation (**Table 3**). The mean C_{max} and AUCs increased with dose, but the increases were less than dose-proportional (**Figure 5**). While higher mean C_{max} (~50%) and AUCs (~20%) were observed in fed participants, the effect of food was not statistically significant (**Figure 6**; **Table 4**).[7]

Table 3. Pharmacokinetics of Sparsentan in Healthy Volunteers by Dose Level

Daily dose (mg)	Study day	C_{max} (µg/mL)	T_{max} (hr) [min, max]	AUC_{0-24} (µg*hr/mL)	Half-life (hr)	Accumulation ratio (AUC)
50	1	1.3 ± 0.5	2 [2,4]	9.9 ± 6.1	6.3 ± 1.8	
	14	1.5 ± 0.8	2 [1,4]	11.9 ± 8.7	13.6 ± 5.5	1.13 ± 0.11
100	1	1.9 ± 0.9	2 [1,4]	15.1 ± 5.0	15.2 ± 3.8	
	14	2.2 ± 0.8	4 [2,4]	20.8 ± 7.3	11.1 ± 4.2	1.33 ± 0.22
250	1	3.9 ± 1.0	2 [2,4]	35.7 ± 13.4	11.9 ± 1.8	
	14	4.1 ± 1.6	2 [1,4]	35.9 ± 15.9	13.7 ± 5.8	1.00 ± 0.22
500	1	6.2 ± 0.9	3 [2,4]	60.0 ± 11.6	17.1 ± 2.9	
	14	6.3 ± 1.2	2 [1,4]	66.0 ± 15.6	12.9 ± 4.9	1.12 ± 0.25
1000	1	7.9 ± 2.3	2 [1,4]	76.3 ± 27.6	13.7 ± 5.3	
	14	7.3 ± 1.1	2 [1,6]	79.8 ± 9.9	14.6 ± 6.3	1.15 ± 0.37

Figure 5. C_{max} and AUC in Healthy Volunteers by Dose Level

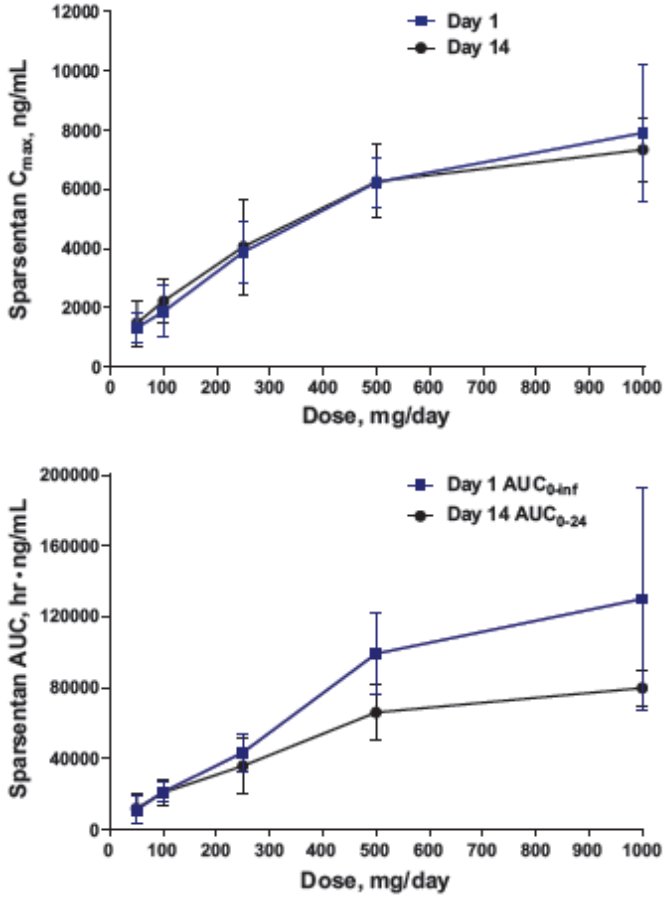


Figure 6. Sparsentan Plasma Concentration Time Profile by Food Treatment

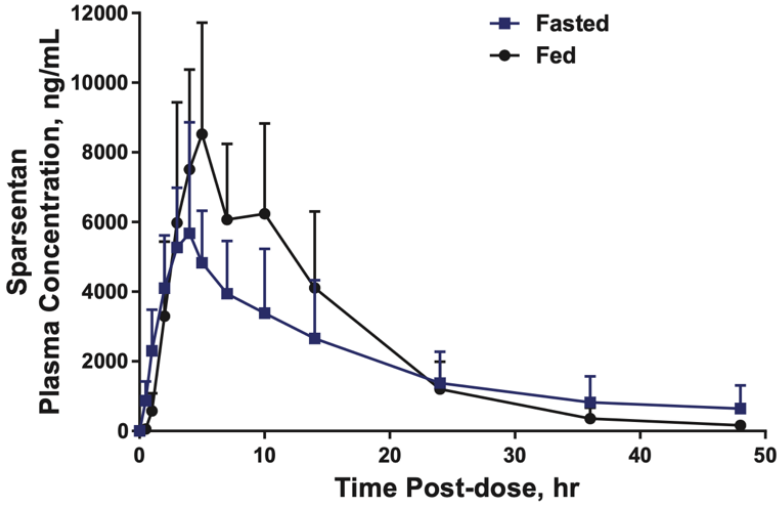


Table 4. Food Effect on Sparsentan Pharmacokinetics in Healthy Volunteers

Parameter[a]	Fed:Fasted Ratio[b]	*P* Value	90% CI
AUC_{0-t} (ng*hr/mL)	1.202	0.1140	0.991, 1.458
AUC_{0-inf} (ng*hr/mL)	1.148	0.3436	0.890, 1.481
C_{max} (ng/mL)	1.493	0.0119	1.178, 1.891

[a]Data reported as natural logarithm; [b]Ratio calculated as fed mean parameter divided by the fasted mean parameter.

Pooled Analysis of 9 Clinical Studies

In a pooled population analysis of 9 clinical studies including 446 healthy volunteers and patients with FSGS, the pharmacokinetics were best described by a 2-compartment model with first-order absorption and absorption lag time, dose-dependent bioavailability, and first order elimination from the central compartment.[25]

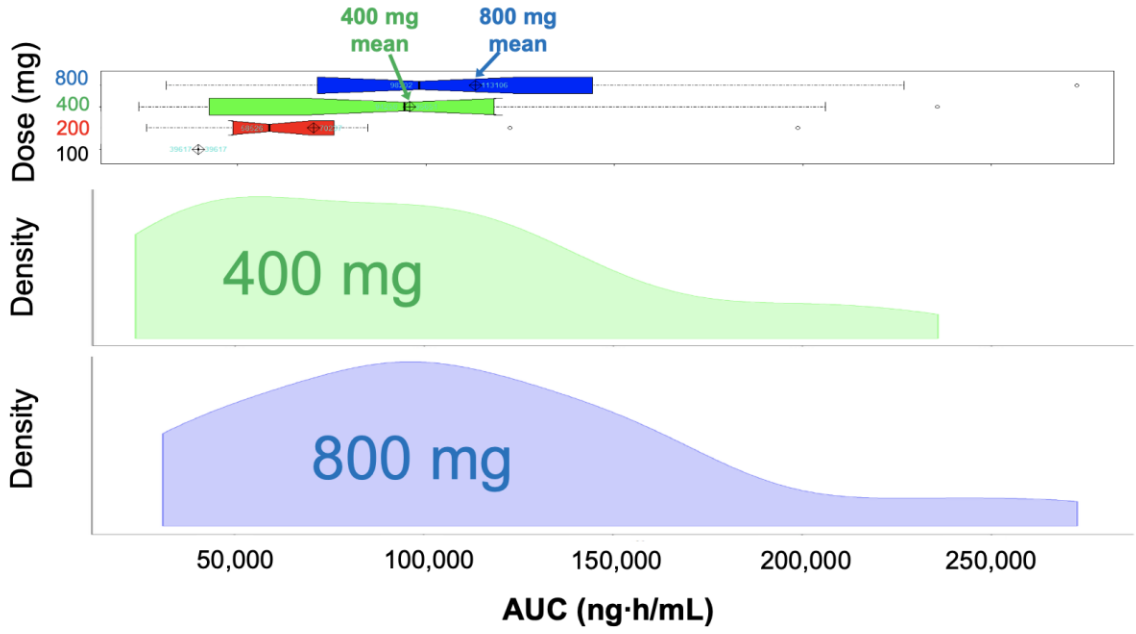
Combination Treatment in a Two-Sequence Study

Healthy volunteers were administered 200 mg sparsentan with or without concomitant CsA (single dose, 600 mg) or itraconazole (multi-dose, 200 mg). In the sparsentan-only group (n=32), T_{max} was 3 hours and half-life was 9.9 hours. CsA increased AUC and T_{max} but did not affect half-life; itraconazole increased AUC, C_{max}, and half-life.[26]

The DUET Study

In the DUET study, median and mean AUC values were not different between the 400 mg and 800 mg doses of sparsentan. AUC distribution curves shifted higher with the higher sparsentan dose (**Figure 7**).[27]

Figure 7. AUC Distributions by Sparsentan Dose Aligned With Box-Whisker Plot of AUC by Sparsentan Dose at Week 8



Preclinical and Clinical Evidence

Dual antagonism of ET_AR and AT_1R has been shown to exhibit nephroprotective and antiproteinuric effects in both preclinical and clinical studies of proteinuric CKD.[9]

In rodent models of IgA nephropathy, FSGS, and Alport Syndrome, sparsentan has exerted numerous protective effects[9]:

- Preservation of glycocalyx integrity
- Reduced oxidative stress, preservation of glomerular basement membrane, and inhibition of Ca^{2+} flux in podocytes
- Inhibition of profibrotic cytokine and ECM protein production, therefore decreasing glomerular lesions
- Alleviation of fibrosis in the tubulointerstitial compartment, along with normalization of proinflammatory cytokine mRNA, profibrotic mediators, ECM proteins, and complement components
- Mitigation of Ang II- and ET-1-mediated efferent arteriolar constriction in renal vasculature

Clinical evidence further supports the effect of sparsentan in CKD[9]:

- In the PROTECT study, treatment with sparsentan over 2 years in patients with IgA nephropathy showed sustained proteinuria reduction and delayed decline of kidney function compared to patients treated with irbesartan, with a tolerable safety profile
- In Phase 2 (DUET) and Phase 3 (DUPLEX) trials in FSGS, patients treated with sparsentan experienced significantly greater declines in proteinuria vs patients treated with irbesartan, with a tolerable safety profile
- In clinical studies, patients treated with sparsentan did not experience clinically significant edema at any treatment dose
- Anti-proteinuric effects occurred without exacerbation of hyperkalemia, significant impact on BP, changes in DBP greater than SBP, or additional acute reductions of eGFR

Abbreviations

ACEi, angiotensin-converting enzyme inhibitor; Ang II, angiotensin II; ARB, angiotensin receptor blocker; AT_1, angiotensin II type 1; AT_1R, angiotensin II type 1 receptor; AT_2, angiotensin II type 2; AT_2R, angiotensin II type 2 receptor; AUC, area under the curve; BP, blood pressure; CI, confidence interval; CKD, chronic kidney disease; CL/F, apparent clearance; C_{max}, peak concentration; C_{min}, minimum concentration; CsA, cyclosporine; DBP, diastolic blood pressure; ECM, extracellular matrix; eGFR, estimated glomerular filtration rate; ET-1, endothelin-1; ET_A, endothelin-1 type A; ET_AR, endothelin-1 type A receptor; ET_B, endothelin-1 type B; ET_BR, endothelin-1 type B receptor; FSGS, focal segmental glomerulosclerosis; h, hours; hERG, human ether-a-go-go related gene; HLM, human liver microsomes; IC_{50}, half-maximal inhibitory concentration; IgA, immunoglobulin A; IgAN, immunoglobulin A nephropathy; KF, kidney failure; Ki, inhibitor constant; KRT, kidney replacement therapy; mRNA, messenger RNA; OLE, open-label extension; PK, pharmacokinetics; RAASi, renin-angiotensin-aldosterone system inhibitor; RO, receptor occupancy; SBP, systolic blood pressure; $t_{1/2}$, half-life; T_{max}, time to maximum concentration; UACR, urine albumin-to-creatinine ratio; UPCR, urine protein-to-creatinine ratio.

References

1. FILSPARI. Prescribing information. Travere Therapeutics Inc; September 2024.
2. 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.
3. 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
4. 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
5. 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
6. 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
7. Pan-Zhou X, Leach K, Beconi M. Pharmacokinetics of sparsentan in healthy subjects: In vitro metabolism and effects of food, gender, age, and multiple-dose escalation. Abstract presented at: ASN Kidney Week; November 19, 2016; Chicago, IL.
8. Hendry BM, Kohan DE, Geletka R, Jenkinson C, Chen SC, Bedard P. Sparsentan receptor occupancy modeling, clinical actions, and safety. Poster presented at: ASN Kidney Week; November 2-5, 2023; Philadelphia, PA.
9. Kohan DE, Bedard PW, Jenkinson C, Hendry B, Komers R. Mechanism of protective actions of sparsentan in the kidney: Lessons from studies in models of chronic kidney disease. *Clin Sci (Lond)*. 2024;138(11):645-662. doi:10.1042/CS20240249
10. 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
11. 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.
12. 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
13. 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.

14. 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.
15. 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
16. 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.
17. 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*. 2023;401(10388):1584-1594. doi:10.1016/S0140-6736(23)00569-X
18. 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
19. 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.
20. Benigni A, Corna D, Maffi R, Benedetti G, Zoja C, Remuzzi G. Renoprotective effect of contemporary blocking of angiotensin II and endothelin-1 in rats with membranous nephropathy. *Kidney Int*. 1998;54(2):353-359. doi:10.1046/j.1523-1755.1998.00011.x
21. Gagliardini E, Corna D, Zoja C, et al. Unlike each drug alone, lisinopril if combined with avosentan promotes regression of renal lesions in experimental diabetes. *Am J Physiol Renal Physiol*. 2009;297(5):F1448-F1456. doi:10.1152/ajprenal.00340.2009
22. Gomez-Garre D, Ruiz-Ortega M, Ortego M, et al. Effects and interactions of endothelin-1 and angiotensin II on matrix protein expression and synthesis and mesangial cell growth. *Hypertension*. 1996;27(4):885-892. doi:10.1161/01.hyp.27.4.885
23. 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.
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. Wada R, Kleijn H, Zhang L, Chen S. Population pharmacokinetic analysis of sparsentan in healthy volunteers and subjects with focal segmental glomerulosclerosis (FSGS). Poster presented at: American Society for Clinical Pharmacology and Therapeutics (ASCPT) Online Annual Meeting; March 16-18, 2022; Virtual Meeting.
26. Karol M, Pan-Zhou X, Leach K, Martinez A, Komers R. Effects of CYP3A4 and p-glycoprotein inhibition by itraconazole and cyclosporine, individually, on the pharmacokinetics of sparsentan (RE-021), a first-in-class, potent, orally-active, dual-acting angiotensin II (type 1) receptor

blocker and endothelin type A receptor antagonist. Poster presented at: ACCP Annual Meeting; September 13-17, 2017; San Diego, CA.

27. Karol M, Pan-Zhou X, Tuller S, Komers R. Sparsentan pharmacokinetics and pharmacodynamics as the basis of dose selection for primary focal segmental glomerular sclerosis (FSGS). Poster presented at: ASN Kidney Week; November 4, 2017; New Orleans, LA.