FILSPARI™ (sparsentan) Pharmacokinetic Profile

Summary

Prescribing Information

- 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

- 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 may have 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]

Study Data

- The mean C_{max} and AUCs increase with dose, but increases are less than dose-proportional[10]
- C_{max} and AUCs were higher in fed participants, but the effect of food was not statistically significant[10]

Prescribing Information

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 6.97 µg/mL and 83 µg · h/mL, respectively. Following daily doses of 400 mg sparsentan, the steady-state mean C_{max} and AUC are 6.47 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.

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.

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]

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.[5,11,12]

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.[10]

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.[4]

Study Data

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 1**). The mean C_{max} and AUCs increased with dose, but the increases were less than dose-proportional (**Figure 1**). While higher mean C_{max} (~50%) and AUCs (~20%) were observed in fed participants, the effect of food was not statistically significant (**Figure 2**, **Table 2**).[10]

Table 1. 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 1. C_{max} and AUC in Healthy Volunteers by Dose Level

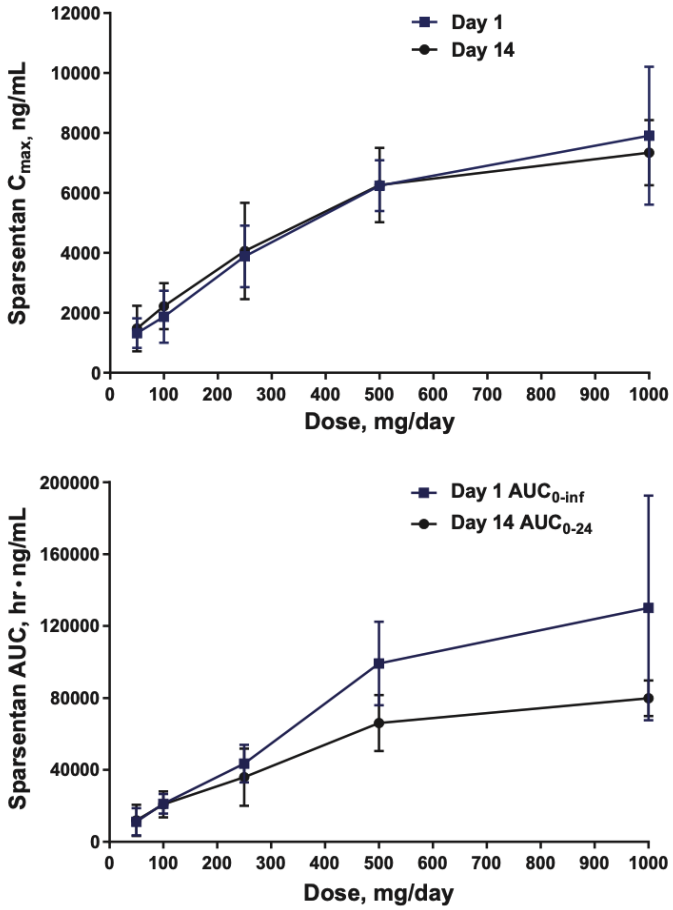


Figure 2. Sparsentan Plasma Concentration Time Profile by Food Treatment

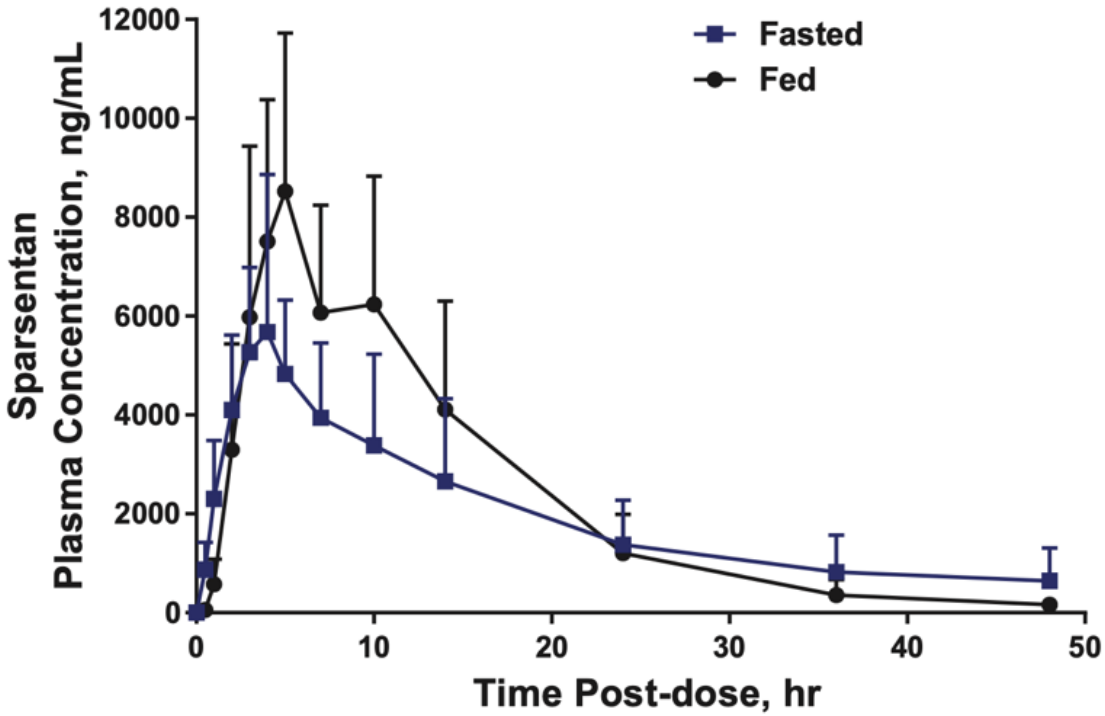


Table 2. Food Effect on Sparsentan Pharmacokinetics in Healthy Volunteers

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.[13]

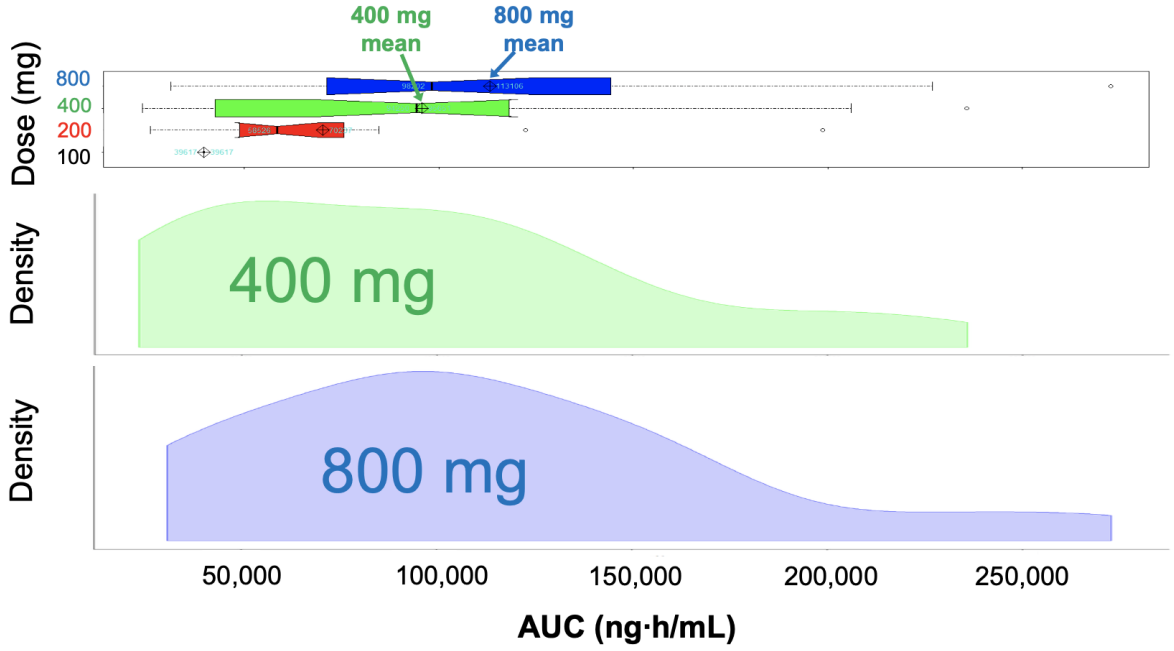
Combination Treatment in a Two-Sequence Study

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.[14]

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 3**).[15]

Figure 3. AUC Distributions by Sparsentan Dose Aligned With Box-Whisker Plot of AUC by Sparsentan Dose at Week 8



Abbreviations

AT_1, angiotensin II type 1; AUC, area under the curve; CI, confidence interval; CKD, chronic kidney disease; CL/F, clearance/drug availability; C_{max}, peak concentration; CsA, cyclosporine; E-R, exposure-response; eGFR, estimated glomerular filtration rate; ET_A, endothelin-1 type A; FSGS, focal segmental glomerulosclerosis; hERG, human ether-a-go-go related gene; IgA, immunoglobulin A; OLE, open-label extension; RAASi, renin-angiotensin-aldosterone system inhibitor; T_{max}, time to maximum concentration; UPCR, urine protein-creatinine ratio.

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