Sparsentan vs Irbesartan in Patients With Focal Segmental Glomerulosclerosis (FSGS): Results From the Phase 3 DUPLEX Trial

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RESULTS

Patient Population

- Patients with FSGS were randomized 1:1 to received sparsentan (n=184) or irbesartan (n=187) (see **Supplementary Figure 1** via the QR code)
- Patient demographics and characteristics at baseline are reported in **Table 1**

Table 1. Baseline Demographics and Clinical Characteristics

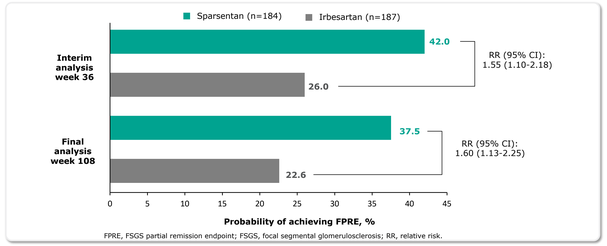
	Sparsentan n=184	Irbesartan n=187
Age, mean (SD), years	41.7 (16.5)	41.5 (17.3)
<18 years, n (%)	16 (8.7)	19 (10.2)
Male sex, n (%)	101 (55)	99 (53)
eGFR, mean (SD), mL/min/1.73 m²	63.3 (28.6)	64.1 (31.7)
UPCR, g/g		
Median (interquartile range)	3.1 (2.27-4.47)	3.0 (2.10-4.66)
Mean (SD)	3.74 (2.32)	3.70 (2.70)
Blood pressure, mean (SD) systolic/diastolic, mm Hg	133.1 (14.8)/85.5 (10.6)	130.9 (14.6)/82.4 (10.1)
FSGS-associated genetic variants, n (%)		
Monogenic variants in podocyte structure/ function proteins	15 (9)	18 (10)
COL4A3-5 variants	12 (7)	15 (8)
High-risk *APOL1* variants	9 (5)	5 (3)
Prior RASi use (stopped before washout), n (%)	152 (83)	143 (76)
Baseline use of immunosuppressive agents, n (%)	50 (27)	46 (25)
Baseline use of diuretics, n (%)	68 (37)	73 (39)

eGFR, estimated glomerular filtration rate; FSGS, focal segmental glomerulosclerosis; RASi, renin-angiotensin system inhibitor; UPCR, urine protein-to-creatinine ratio.

Efficacy

- Sparsentan resulted in a significantly higher rate of FSGS partial remission endpoint (FPRE)[10] vs irbesartan after 36 weeks (difference [95% CI], 16.0 [4.0-28.0]; nominal *P*<.01) (**Figure 3**)
- This effect was maintained at the 108-week final analysis (difference [95% CI], 14.9 [4.10-25.61]; nominal *P*<.01) (**Figure 3**)

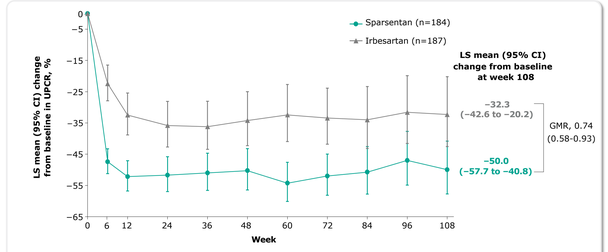
Figure 3. FSGS Partial Remission With Sparsentan vs Irbesartan at Week 36 and Week 108



FPRE, FSGS partial remission endpoint; FSGS, focal segmental glomerulosclerosis; RR, relative risk.

- Sparsentan resulted in a rapid decline in urine protein-to-creatinine ratio (UPCR) that was sustained through 108 weeks (**Figure 4**)

Figure 4. Mean Change in UPCR From Baseline to Week 108

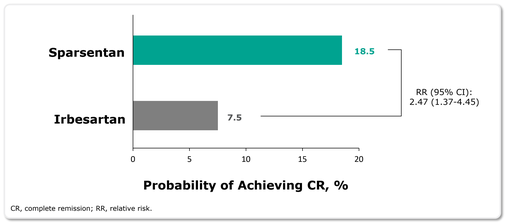


Sparsentan, n=184 168 163 157 158 146 139 135 135 128 119
Irbesartan, n=187 178 169 156 155 150 141 138 144 132 128

GMR, geometric mean ratio; LS, least squares; UPCR, urine protein-to-creatinine ratio.

- Complete remission (CR) of proteinuria (UPCR <0.3 g/g) was achieved more frequently with sparsentan vs irbesartan (**Figures 5**)

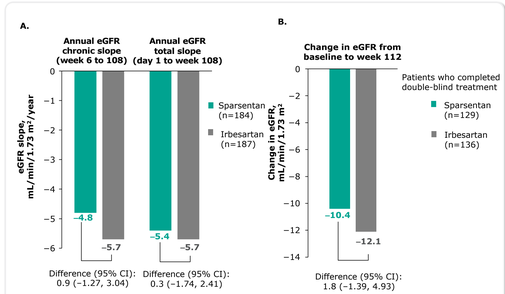
Figure 5. Patients Achieving CR at Any Time During the Double-Blind Period



CR, complete remission; RR, relative risk.

- Estimated glomerular filtration rate (eGFR) chronic and total slope and change in eGFR are presented in **Figure 6**

Figure 6. eGFR Endpoints Over the Double-Blind Period

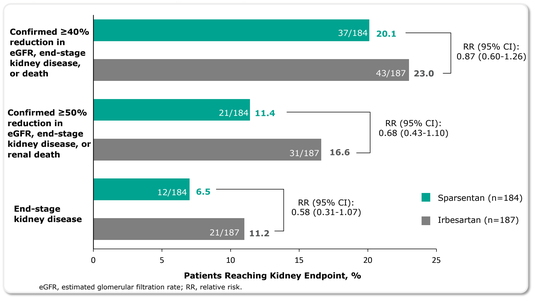


eGFR, estimated glomerular filtration rate.

- eGFR chronic slope was lower with sparsentan vs irbesartan when measurements after initiation or intensification of immunosuppressive treatments were excluded
- Other sensitivity analyses were consistent with the main analysis (See **Supplementary Figure 2** via the QR code)

- Fewer patients reached composite kidney endpoints or end-stage kidney disease with sparsentan vs irbesartan (**Figure 7**)

Figure 7. Proportion of Patients Reaching Composite Kidney Endpoints and End-Stage Kidney Disease



eGFR, estimated glomerular filtration rate; RR, relative risk.

Safety

- Sparsentan was well tolerated with a safety profile comparable to that of irbesartan (**Table 2**)
- The most common treatment-emergent adverse events (TEAEs) (≥15% in either group) included COVID-19, hyperkalemia, peripheral edema, and hypotension

Table 2. Summary of TEAEs

Patients with TEAEs, n (%)	Sparsentan n=184	Irbesartan n=187
Any TEAEs	172 (93)	174 (93)
Serious TEAEs	68 (37)	82 (44)
TEAEs of interest		
Fluid retention-associated TEAEs	47 (26)	56 (30)
Hyperkalemia-associated TEAEs	37 (20)	21 (11)
Hypotension	33 (18)	21 (11)
Anemia-associated TEAEs	30 (16)	15 (8)
Dizziness	23 (13)	21 (11)
Acute kidney injury	8 (4)	13 (7)
ALT or AST >3 × ULN	5 (3)	4 (2)
Heart failure	0 (0)	0 (0)

ALT, alanine aminotransferase; AST, aspartate aminotransferase; TEAE, treatment-emergent adverse event; ULN, upper limit of normal.

- After an initial decrease, blood pressure remained stable after 4-6 weeks (See **Supplementary Figure 3** via the QR code)

CONCLUSIONS

- Sparsentan achieved a sustained reduction in proteinuria, with higher rates of FPRE and CR vs irbesartan
- While not statistically significant, the difference in eGFR chronic slope of nearly 1 mL/min/1.73 m²/year with sparsentan vs irbesartan could delay the need for kidney replacement therapy within a patient's lifetime
- Fewer patients reached the composite kidney endpoints or end-stage kidney disease with sparsentan vs irbesartan
- The safety profiles of sparsentan and irbesartan were comparable; heart failure, liver injury, and fluid retention/ edema were not identified as safety concerns
- Overall, results indicate a clinical benefit of sparsentan for proteinuria reduction in patients with FSGS

DISCLOSURES

MNR has served as a site PI for clinical trials funded by Akebia, Chinook, Reata, River 3 Renal, Sanofi, and Travere Therapeutics, Inc.; and as a consultant for ENYO Pharma, Walden Biosciences, and Visterra. **HT** has received consulting fees from Aclipse, Boehringer Ingelheim, Maze Therapeutics, Natera, Otsuka, PhaseV, Travere Therapeutics, Inc., and Walden; received speaking honoraria from National Kidney Foundation; and participated on data safety monitoring or advisory boards for ChemoCentryx, Otsuka, and Travere Therapeutics, Inc. **EM, RK,** and **AP** are employees of Travere Therapeutics, Inc., and may have an equity or other financial interest in Travere Therapeutics, Inc.

These data were previously presented at the American Society of Nephrology (ASN) Kidney Week 2023; November 1-5, 2023; Philadelphia, PA, USA.

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REFERENCES

1. Trachtman H. *Expert Opin Emerg Drugs*. 2020;25(3):367-375. **2.** Gipson DS, et al. *JAMA Netw Open*. 2022;5(8):e2228701. **3.** Hodson EM, et al. *Cochrane Database Syst Rev*. 2022;2(2):CD003233. **4.** Nagasawa H, et al. *Nephrol Dial Transplant*. 2022;37:183. **5.** Kowala MC, et al. *J Pharmacol Exp Ther*. 2004;309(1):275-284. **6.** Trachtman H, et al. *J Am Soc Nephrol*. 2018; 29(11):2745-2754. **7.** Gómez-Garre D, et al. *Hypertension*. 1996;27:885-892. **8.** Benigni A, et al. *Kidney Int*. 1998;54:353-359. **9.** Gagliardini E, et al. *Am J Physiol Renal Physiol*. 2009;297:F1448-F1456. **10.** Troost JP, et al. *Clin J Am Soc Nephrol*. 2018;13(3):414-421.

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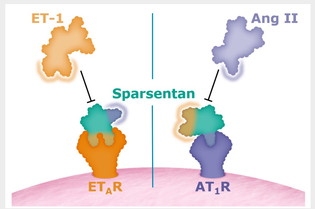
INTRODUCTION

- There are no approved therapies for FSGS, highlighting an unmet need for safe and effective treatments that lower proteinuria and reduce the risk of kidney failure[1-3]
- Sparsentan is an orally active dual endothelin angiotensin receptor antagonist (DEARA; **Figure 1**)[1,4,5] that reduced proteinuria in patients with FSGS in a phase 2 trial[6]
- Dual endothelin-A and angiotensin II type 1 receptor antagonism has anti-inflammatory, antiproliferative, and antifibrotic actions of therapeutic potential in addition to hemodynamic benefits[1,4,7-9]

Objective

- Evaluate the efficacy and safety of sparsentan vs the active control irbesartan in patients with FSGS

Figure 1. Sparsentan Is a Dual ET_AR and AT_1R Antagonist



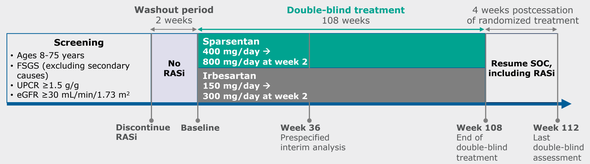
Ang II, angiotensin II; AT_1R; angiotensin II type 1 receptor; ET-1, endothelin-1; ET_AR, endothelin type A receptor.

METHODS

Phase 3 DUPLEX Study

- **Trial Design:** Phase 3, double-blind, active-controlled global trial (NCT03493685) in patients with biopsy-proven FSGS or genetic FSGS (**Figure 2**)

Figure 2. Trial Design



Surrogate Efficacy Endpoint
(36-Week Interim Analysis)
- Proportion of patients achieving FPRE at week 36 (UPCR ≤1.5 g/g and ≥40% reduction from baseline)

Primary Endpoints
- eGFR chronic slope (weeks 6 to 108)
- eGFR total slope (day 1 to week 108)

eGFR, estimated glomerular filtration rate; FPRE, FSGS partial remission endpoint; FSGS, focal segmental glomerulosclerosis; RASi, renin-angiotensin system inhibitor; SOC, standard of care; UPCR, urine protein-to-creatinine ratio.

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