Outcomes of the DUPLEX Trial in Patients With Genetic Focal Segmental Glomerulosclerosis (gFSGS)

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TH-PO1199

RESULTS

General Characteristics of Patients With gFSGS

- Overall, 8.7% (31 of 355) of patients were identified as having gFSGS (**Table 1**)
- Most patients with gFSGS were White and had nephrotic-range proteinuria
- Compared with the overall DUPLEX trial population,[3,4] patients with gFSGS were younger, which is consistent with the higher prevalence of gFSGS seen in pediatric patients
- Both treatment groups had similar baseline eGFR and UPCR

Table 1. Characteristics of Patients With gFSGS by Treatment Group

	Irbesartan n=18	Sparsentan n=13	Total n=31
Age at informed consent, y			
Mean (SD)	36.1 (15.43)	25.8 (13.37)	31.7 (15.26)
Age group, n (%)			
<18 years	2 (11.1)	6 (46.2)	8 (25.8)
≥18 years	16 (88.9)	7 (53.8)	23 (74.2)
Sex, n (%)			
Male	5 (28)	4 (31)	9 (29)
Female	13 (72)	9 (69)	22 (71)
Race, n (%)			
Asian	1 (6)	0 (0)	1 (3)
Black or African American	1 (6)	2 (15)	3 (10)
White	15 (83)	12 (92)	27 (87)
Other	1 (6)	0 (0)	1 (3)
BMI group, n (%)			
<27 kg/m^2	11 (61.1)	9 (69.2)	20 (64.5)
≥27 kg/m^2	7 (38.9)	4 (30.8)	11 (35.5)
eGFR, mL/min/1.73m^2*, mean (SD)	73.8 (46.78)	74.5 (42.62)	74.1 (44.35)
UPCR, g/g, mean (SD)	4.15 (2.331)	4.85 (2.400)	4.44 (2.347)

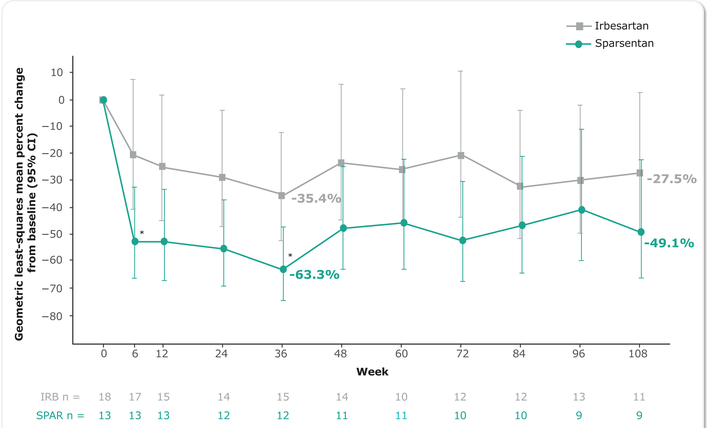
*eGFR is determined using the CKD-EPI equation for patients ≥16 years of age and the modified Schwartz formula for patients <16 years of age at screening.

Table 2. Podocytic Gene Mutations in DUPLEX by Treatment Group

Gene	Irbesartan n	Sparsentan n	Total n
NPHS2	6	9	15
CD2AP	1	0	1
INF2	3	1	4
LMX1B	3	1	4
NPHS1	0	1	1
TRPC6	2	0	2
WT1	3	1	4

Efficacy

Figure 1. UPCR Percentage Change From Baseline by Visit



Results from MMRM analysis.
*P<.05.

Figure 2. eGFR Change From Baseline by Visit

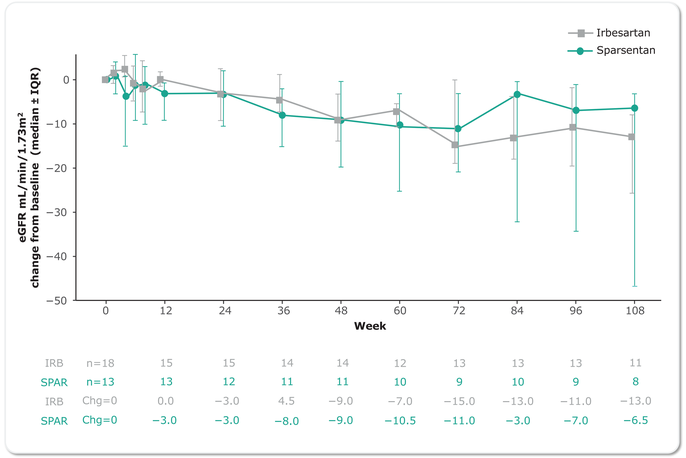


Table 3. Proportion of Patients Reaching Complete Remission and the Composite Kidney Failure Outcomes

	Irbesartan n=18	Sparsentan n=13
Complete remission, n (%)	0 (0)	1 (8)
Composite kidney failure outcomes (40% eGFR reduction, ESKD, death), n (%)	4 (22)	1 (8)

Safety

- Safety parameters were consistent with the overall DUPLEX trial population and comparable between irbesartan- and sparsentan-treated patients

CONCLUSIONS

- Consistent with the overall FSGS population in DUPLEX, patients with gFSGS displayed a more pronounced early and durable antiproteinuric response to sparsentan compared with irbesartan and favorable outcomes on complete remission and the composite kidney failure endpoint
- As the largest clinical trial to date in gFSGS, these results suggest that sparsentan could have a meaningful effect in historically treatment-resistant patients with genetic forms of FSGS
- Assessment of the effect of sparsentan in patients with collagen mutations and *APOL1* high-risk genotype is underway
- The findings support a recommendation for sparsentan administration to reduce proteinuria in patients with FSGS, including the subgroup with genetic mutations in podocyte proteins

ABBREVIATIONS

BMI, body mass index; **CKD-EPI,** Chronic Kidney Disease Epidemiology Collaboration; **Chg**, change; **eGFR,** estimated glomerular filtration rate; **ESKD,** end-stage kidney disease; **FSGS,** focal segmental glomerulosclerosis; **gFSGS,** genetic focal segmental glomerulosclerosis; **IRB,** irbesartan; **MMRM,** mixed model repeated measures; **SPAR,** sparsentan; **UPCR,** urine protein-to-creatinine ratio.

DISCLOSURES

JY has nothing to disclose. **WG**, **JI,** and **RK** are employees and stockholders of Travere Therapeutics, Inc. **MNR** has received research grants from Akebia Therapeutics Inc., Chinook Therapeutics, Genentech Inc., Kaneka Pharma America LLC, National Institute of Diabetes and Digestive and Kidney Diseases, Reata Pharmaceuticals, River 3 Renal, Sanofi, Travere Therapeutics, Inc., and the US Department of Defense and consulted for Enyo Pharma, Visterra, and Walden Biosciences. **HT** has an ownership interest in Aclipse and PhaseV. He has consulted for Aclipse, PhaseV, Otsuka, Bristol Meyers Squibb, ChemoCentryx, Goldfinch Bio, Travere Therapeutics, Inc., Natera (RenaSight), Angion, Akebia, Walden Biosciences, Boehringer Ingelheim, Maze Therapeutics, Alexion/AstraZeneca, Eloxx Pharmaceuticals, Dimerix, ProKidney, NephCure, Kidney International, Kaneka, Astellas and Complex. He has also received honoraria for attendance at glomerular disease panels organized by Reata Pharmaceuticals and Astellas and advisory boards for Otsuka and Travere Therapeutics, Inc.

ACKNOWLEDGMENTS

This study was funded by Travere Therapeutics, Inc. Medical editorial support was provided in accordance with Good Publications Practice 2022, and was funded by Travere Therapeutics, Inc., under the direction of the authors by Ruth Brown, PhD, working on behalf of Nucleus Global, an Inizio company.

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INTRODUCTION

BACKGROUND

- Genetic forms of FSGS (gFSGS), caused by mutations in podocyte genes, are generally refractory to most available treatments[1]
- In the overall DUPLEX FSGS trial population (NCT03493685), sparsentan leads to a greater reduction of proteinuria compared with irbesartan[2-4]
- Patients with gFSGS were included in DUPLEX

OBJECTIVE

- This post hoc analysis aims to assess the efficacy of sparsentan in the DUPLEX patients with gFSGS

METHODS

- 355 study patients were genotyped by the FSGS panel of Prevention Genetics (Marshfield, WI)
- Patients with pathogenic or likely pathogenic mutations in podocyte genes were classified to have gFSGS with Mendelian inheritance
- Data were analyzed for all podocyte genes
- We examined the following outcomes in the irbesartan vs sparsentan groups:
  - Reduction in UPCR (geometric least-squares mean percentage change from baseline)
  - Proportion of patients achieving complete remission of proteinuria (UPCR<0.3 g/g) at any time
  - eGFR trajectories for irbesartan- and sparsentan-treated patients
  - Proportion of patients reaching composite kidney failure outcomes, including 40% eGFR reduction, ESKD (eGFR <15 mL/min/1.73 m^2), dialysis or transplant, and death

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Presented at the American Society of Nephrology (ASN) Kidney Week 2024; October 23-27, 2024; San Diego, CA, USA

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