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Patients (Pts) With Focal Segmental Glomerulosclerosis (FSGS) Achieved Low Proteinuria Targets Earlier and More Often With Sparsentan (SPAR) vs Irbesartan (IRB) in DUPLEX

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CONCLUSIONS

- Dual endothelin angiotensin receptor blockade with SPAR led to clinically meaningful low proteinuria thresholds, including CR of proteinuria or the FSGS partial remission endpoint, being achieved earlier and more often in patients with FSGS than did angiotensin receptor blockade alone with IRB
- Consistent with recently reported results from PARASOL,[4] patients who reached CR of proteinuria or the FSGS partial remission endpoint showed markedly reduced risk of progression to kidney failure
- SPAR was generally well tolerated over 108 weeks of treatment, with a safety profile comparable to that of IRB

KEY TAKEAWAY

Patients with FSGS achieved proteinuria reductions, including CR of proteinuria or the FSGS partial remission endpoint, earlier and more often with SPAR vs IRB, and those who reached these targets had a lower risk of kidney failure, supporting the nephroprotective benefit of SPAR in FSGS

INTRODUCTION

- FSGS is associated with a substantial risk of kidney failure, with 40% to 60% of patients progressing to kidney failure or death within 10 to 20 years of diagnosis[1,2]
- There are no approved therapies for FSGS, highlighting an unmet need for safe and effective treatments[3]
- In large-scale analyses of observational data, proteinuria was identified as a biologically plausible and clinically meaningful endpoint, with lower proteinuria strongly associated with reduced kidney failure risk[4]
- Sparsentan is a non-immunosuppressive dual endothelin angiotensin receptor antagonist (DEARA)[5,6] that led to rapid and sustained proteinuria reductions in patients with FSGS in the phase 3 DUPLEX trial[7]

OBJECTIVE

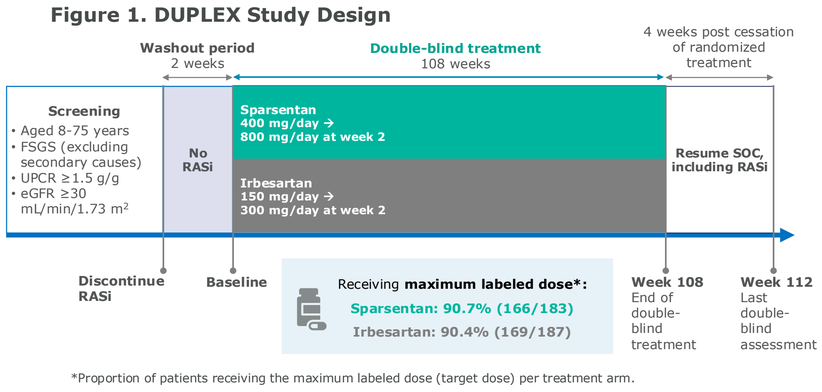
- Expanding on earlier findings from this trial, we investigated the impact of sparsentan vs irbesartan on low proteinuria targets and the effect of achieving CR of proteinuria or the FSGS partial remission endpoint on progression to kidney failure in DUPLEX

METHODS

DUPLEX Study Design

- DUPLEX (NCT03493685) is a phase 3, randomized, double-blind trial investigating the safety and efficacy of sparsentan vs active control, maximum labeled dose irbesartan, in adults and children (aged ≥8 years) with FSGS

Figure 1. DUPLEX Study Design



*Proportion of patients receiving the maximum labeled dose (target dose) per treatment arm.

- Analyses investigated the impact of sparsentan vs irbesartan on the proportion of patients achieving CR of proteinuria, the FSGS partial remission endpoint, and UPCR of <0.5 g/g, <1.0 g/g, and <1.5 g/g at any time during the 108-week double-blind treatment period
- Pooled analyses using data from both treatment arms evaluated rates of progression to kidney failure in patients who achieved vs did not achieve CR of proteinuria or the FSGS partial remission endpoint

RESULTS

Patient Population

- A total of 371 patients were randomized to receive sparsentan or irbesartan in DUPLEX

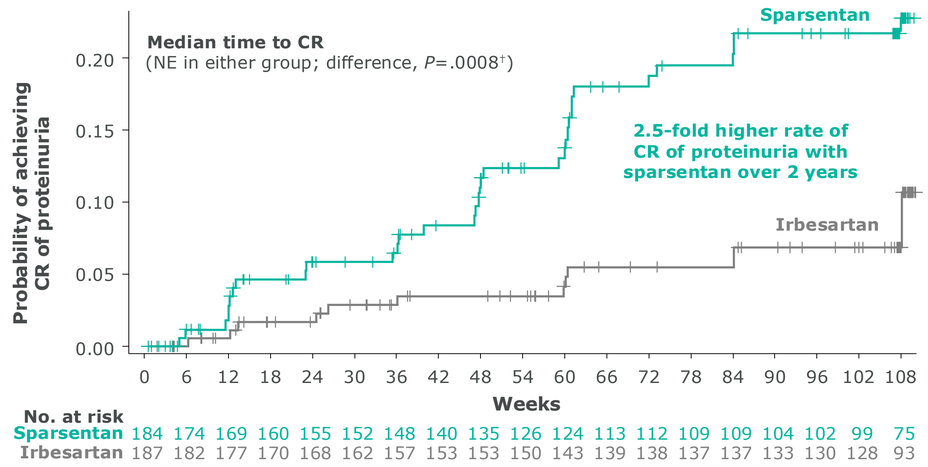
Table 1. Patient Demographics and Baseline Characteristics

	Sparsentan n=184	Irbesartan n=187	All patients N=371
Age, mean (SD), years	41.7 (16.5)	41.5 (17.3)	41.6 (16.9)
<18 years, n (%)	16 (8.7)	19 (10.2)	35 (9.4)
Male sex, n (%)	101 (55)	99 (53)	200 (54)
eGFR, mean (SD), mL/min/1.73 m²	63.3 (28.6)	64.1 (31.7)	63.7 (30.1)
UPCR, g/g			
Median (interquartile range)	3.1 (2.3-4.5)	3.0 (2.1-4.7)	3.0 (2.2-4.6)
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 (%)			
Variants in podocyte structure/function proteins	13 (7)	18 (10)	31 (8)
COL4A3-5 variants	11 (6)	14 (7)	25 (7)
High-risk *APOL1* variants	9 (5)	5 (3)	14 (4)
Prior RASi use (stopped before washout), n (%)	152 (83)	143 (76)	295 (80)
Baseline use of immunosuppressive agents, n (%)	50 (27)	46 (25)	96 (26)
Baseline use of diuretics, n (%)	68 (37)	73 (39)	141 (38)

Proteinuria

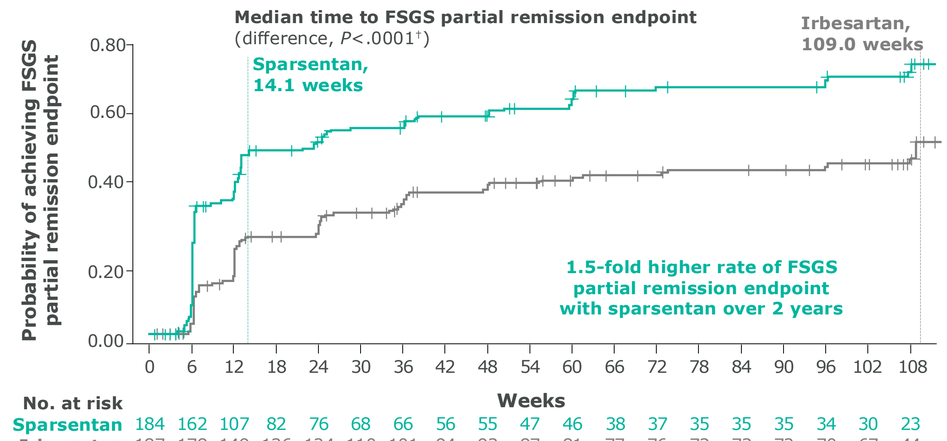
- Sparsentan demonstrated superior and consistent proteinuria reduction across low proteinuria thresholds vs maximum labeled dose irbesartan
  - Patients reached CR of proteinuria and the FSGS partial remission endpoint earlier with sparsentan vs maximum labeled dose irbesartan
    - Similar results were observed for UPCR of <0.5 g/g, <1.0 g/g, and <1.5 g/g, with patients reaching all thresholds earlier with sparsentan vs irbesartan (P≤.0001 for difference)

Figure 2. Probability of Achieving CR of Proteinuria Through 108 Weeks*



*CR of proteinuria was defined as UPCR of <0.3 g/g. †P value is generated from a stratified Cox proportional hazards model with treatment and baseline log (UPCR) as covariates, stratified by randomization stratification factors.

Figure 3. Probability of Achieving the FSGS Partial Remission Endpoint Through 108 Weeks*

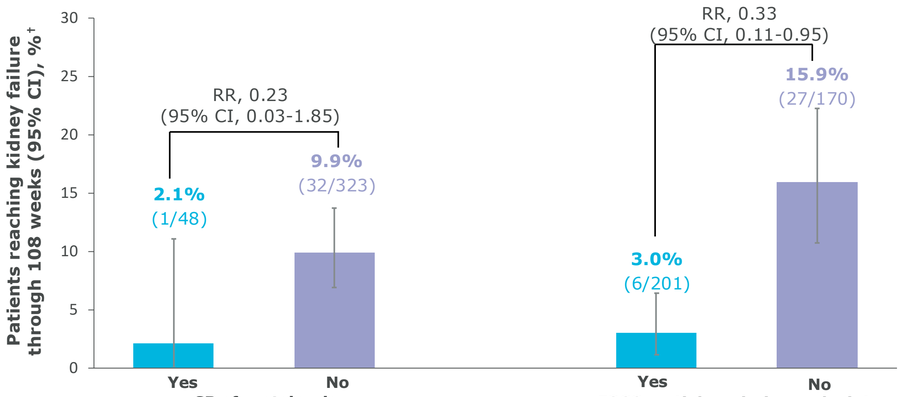


*The FSGS partial remission endpoint was defined as UPCR of ≤1.5 g/g and >40% reduction from baseline. †P value is generated from a stratified Cox proportional hazards model with treatment and baseline log (UPCR) as covariates, stratified by randomization stratification factors.

Kidney Failure Risk

- Irrespective of treatment arm, patients who achieved CR of proteinuria or the FSGS partial remission endpoint were less likely to reach kidney failure vs those who did not

Figure 4. Probability of Reaching Kidney Failure Through 108 Weeks*



*Results from post hoc analyses using pooled data irrespective of treatment arm. CR of proteinuria was defined as UPCR of <0.3 g/g. The FSGS partial remission endpoint was defined as UPCR of ≤1.5 g/g and >40% reduction from baseline. †Kidney failure was defined as confirmed eGFR of <15 mL/min/1.73 m² or kidney replacement therapy.

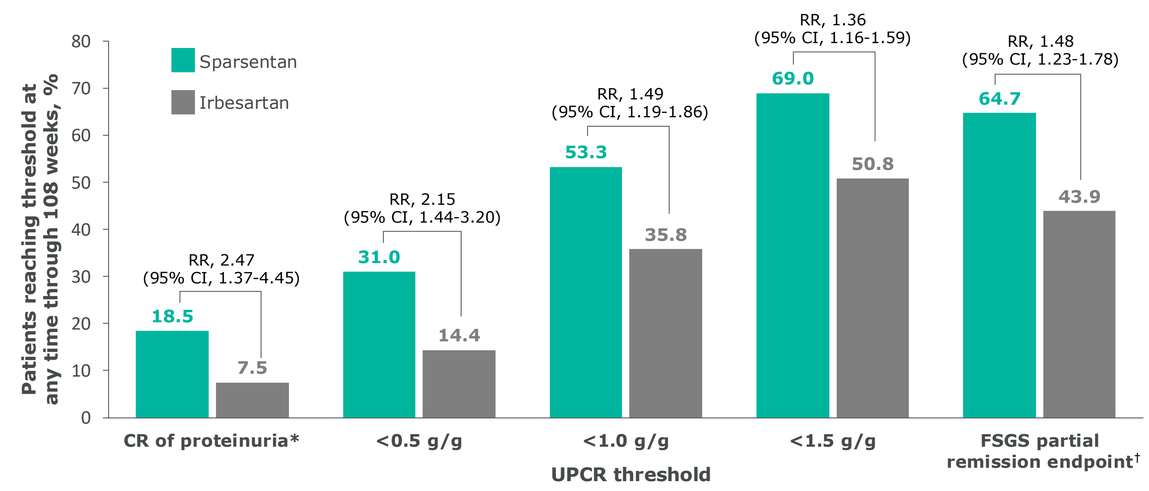
Safety

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

Table 2. Adverse Events

Patients with TEAEs, n (%)	Sparsentan n=184	Irbesartan n=187	All patients N=371
Any TEAEs	172 (93)	174 (93)	346 (93)
Serious TEAEs	68 (37)	82 (44)	150 (40)
TEAEs of interest			
Fluid retention-associated TEAEs	47 (26)	56 (30)	103 (28)
Hyperkalemia-associated TEAEs	37 (20)	21 (11)	58 (16)
Hypotension	33 (18)	21 (11)	54 (15)
Anemia	24 (13)	10 (5)	34 (9)
Dizziness	23 (13)	21 (11)	44 (12)
Acute kidney injury	8 (4)	13 (7)	21 (6)
ALT or AST >3 × ULN	5 (3)	4 (2)	9 (2)
Heart failure	0	0	0

Figure 1. Patients Achieved Low Proteinuria Thresholds More Often With Sparsentan vs Irbesartan



*CR of proteinuria was defined as UPCR <0.3 g/g. †The FSGS partial remission endpoint was defined as UPCR ≤1.5 g/g and >40% reduction from baseline.

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ABBREVIATIONS

ALT, alanine aminotransferase; **AST**, aspartate aminotransferase; **CI**, confidence interval; **CR**, complete remission; **eGFR**, estimated glomerular filtration rate; **FSGS**, focal segmental glomerulosclerosis; **NE**, not estimable; **RASi**, renin-angiotensin system inhibitor; **RR**, relative risk; **SD**, standard deviation; **SOC**, standard of care; **TEAE**, treatment-emergent adverse event; **ULN**, upper limit of normal; **UPCR**, urine protein-to-creatinine ratio.

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