DUPLEX *Post Hoc* Analyses: Achieving Low Proteinuria Earlier and More Often With Sparsentan vs Irbesartan

Data as presented at the National Kidney Foundation Spring Clinical Meetings 2025 and European Renal Association Congress 2025

- Focal segmental glomerulosclerosis (FSGS) is a rare, progressive kidney condition; 40% to 60% of patients progress to end-stage kidney disease (ESKD) within 10 to 20 years of diagnosis[1-5]
- There are no FDA-approved therapies for FSGS, highlighting an unmet need for safe and effective treatments[1,6]
- PARASOL identified proteinuria as a biologically plausible and clinically meaningful endpoint, with lower proteinuria associated with reduced kidney failure risk[1,7]
- Sparsentan is a novel, non-immunosuppressive, Dual Endothelin Angiotensin Receptor Antagonist (DEARA) currently being studied in patients with FSGS[*1,8-10]
- In the Phase 3 DUPLEX study, compared to irbesartan, sparsentan demonstrated[10]:
  - Rapid and sustained reductions in proteinuria
  - A similar safety profile

Aim

This *post hoc* analysis evaluated the impact of sparsentan 800 mg/day vs irbesartan 300 mg/day on achieving the FSGS partial remission endpoint (UPCR of ≤1.5 g/g and >40% reduction from baseline) or complete remission of proteinuria (UPCR of <0.3 g/g).[1] A separate pooled analysis of both treatment groups assessed the effect of achieving complete remission of proteinuria on progression to kidney failure in patients with FSGS[1]

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Focal segmental glomerulosclerosis

An overview

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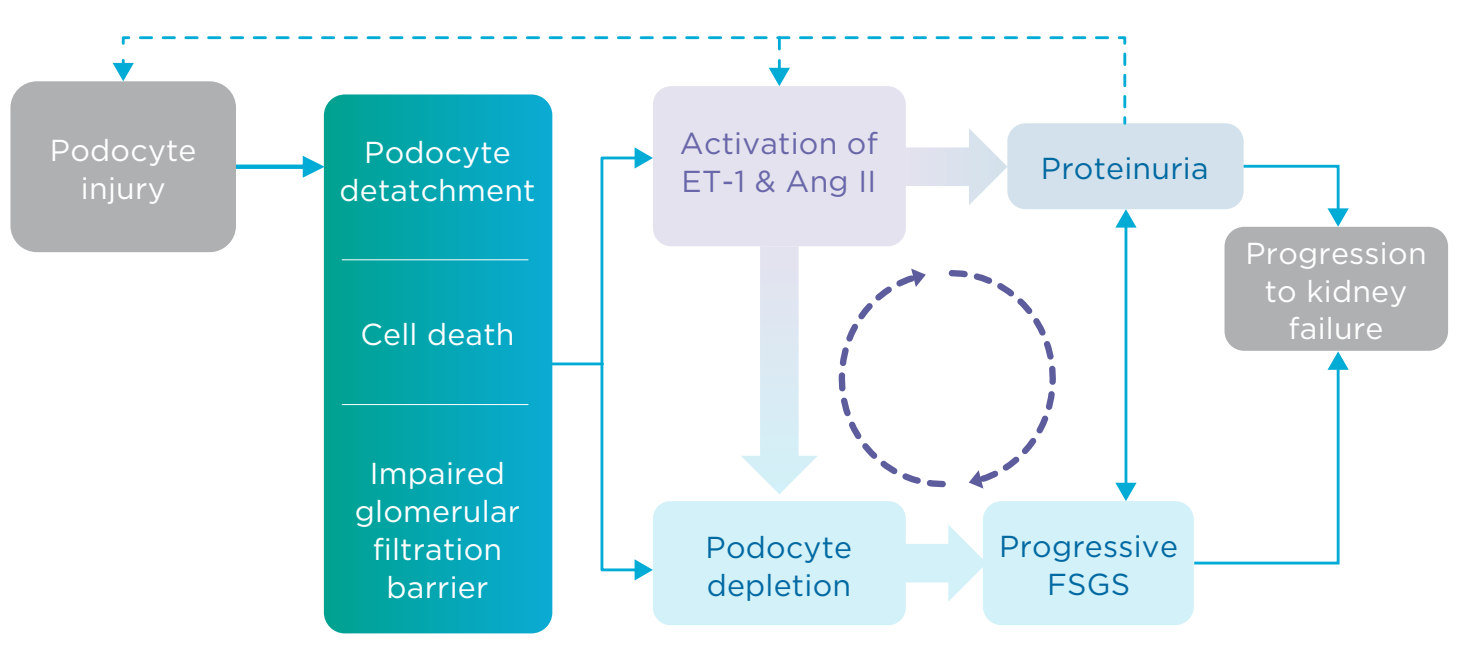
- FSGS is a rare, progressive kidney condition defined by a histological pattern of glomerular and podocyte injury[1-3]
- It is associated with a high symptom, patient, and financial burden, including a substantial risk of progression to kidney failure[1,4,11-13]
- There is a need for safe and effective treatments that lower proteinuria and reduce the risk of kidney failure[1,6,14]
- Initial drivers of podocyte injury in FSGS include serum factors, genetic causes, viral infections, and drug-induced processes[1,15,16]
- Endothelin 1 (ET-1) and angiotensin II (Ang II) are key mediators of podocyte damage in FSGS[1,15,17]



Sparsentan

An investigational therapy

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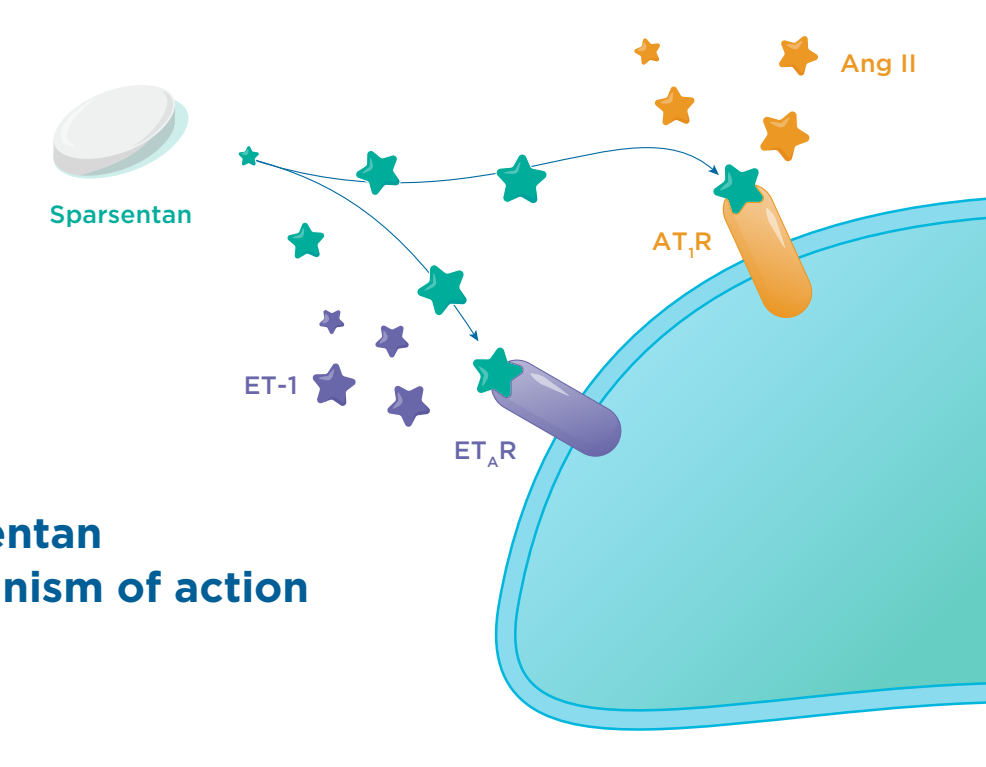
Sparsentan is a non-immunosuppressive, single-molecule, DEARA[8,9]

Sparsentan is an investigational therapeutic candidate for the treatment of FSGS[1]



Sparsentan mechanism of action

DUPLEX

Study design

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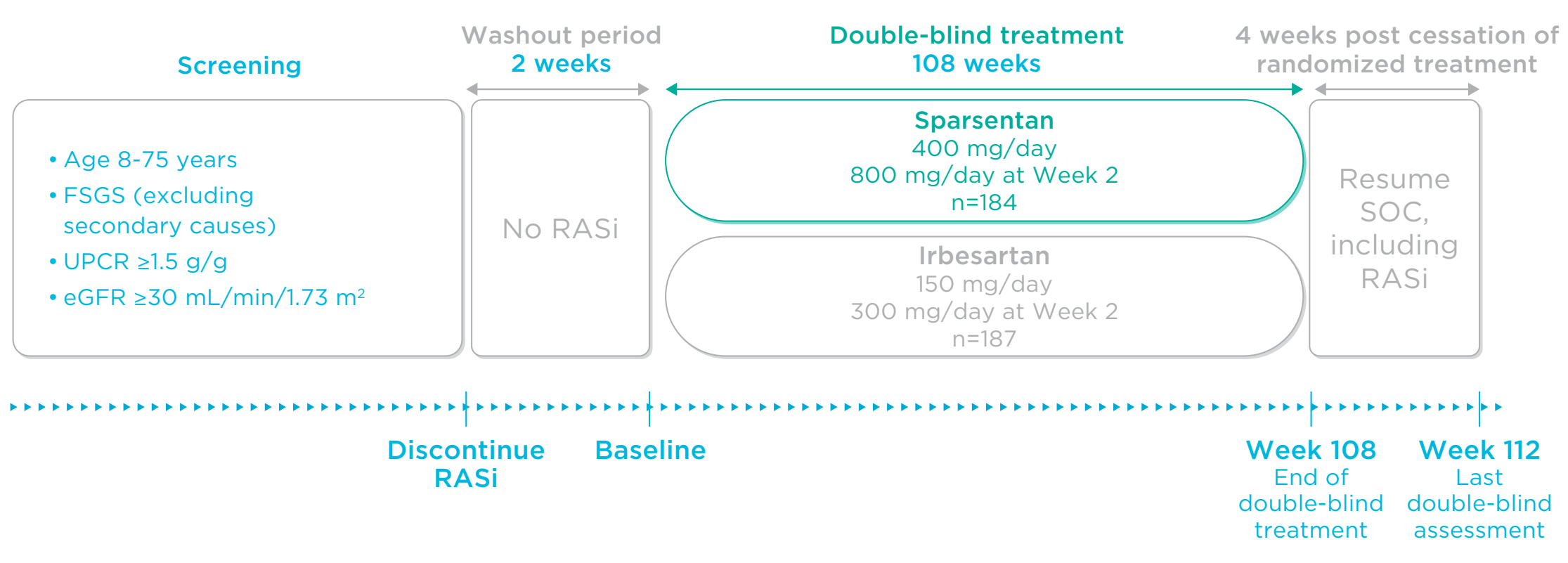
DUPLEX is a Phase 3, randomized, double-blind trial investigating the safety and efficacy of sparsentan vs active control, maximum labeled dose irbesartan in adults and children (aged ≥8 years) with FSGS[10]

DUPLEX study design



Study endpoints[10]

Primary endpoint

Total eGFR slope

Secondary

- Chronic eGFR slope
- Change in eGFR from Week 6 to Week 108 and from baseline to Week 112

Exploratory

- Surrogate endpoint: FSGS partial remission endpoint (UPCR ≤1.5 g/g and >40% reduction from baseline)
- Complete remission of proteinuria (UPCR <0.3 g/g)
- Reductions in proteinuria
- Kidney failure (eGFR <15 mL/min/1.73m² or kidney replacement therapy)
- Composite kidney failure endpoints (≥40% or ≥50% reduction in eGFR, ESKD, or death)
- Safety outcomes

Post hoc analyses have assessed:

- Achievement of FSGS partial remission endpoint (UPCR ≤1.5 g/g and >40% reduction from baseline) or complete proteinuria remission and the effect on kidney failure
- Achievement of proteinuria thresholds including the FSGS partial remission endpoint (UPCR ≤1.5 g/g and >40% reduction from baseline)

Efficacy outcomes

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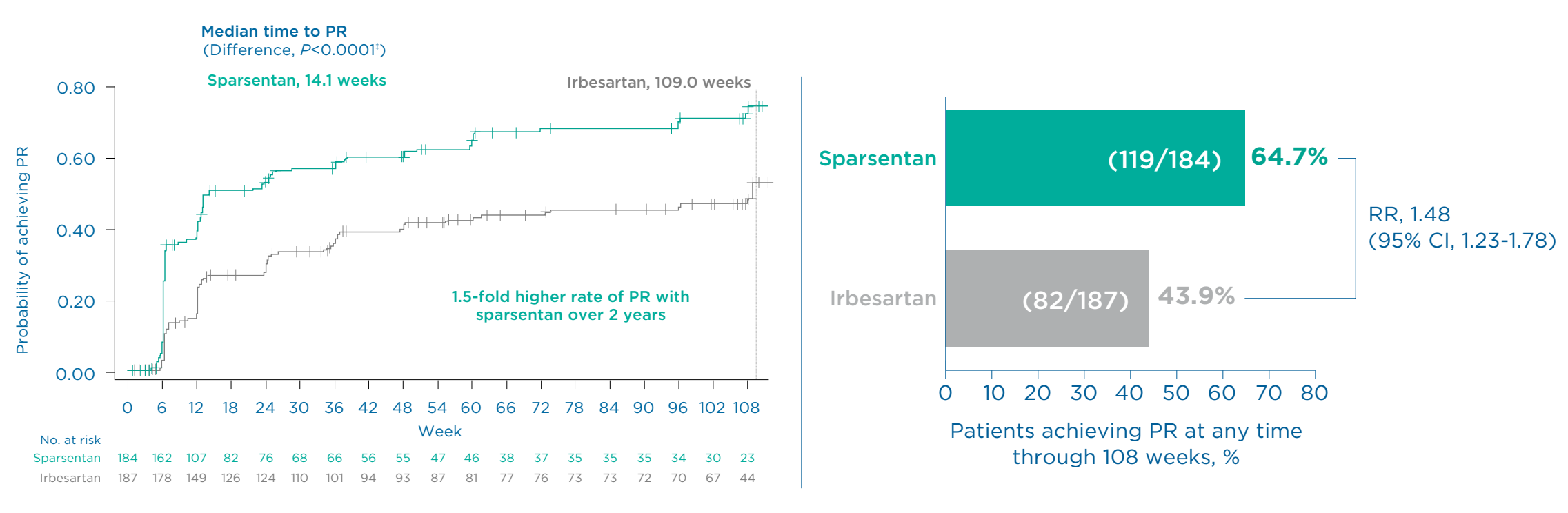
FSGS partial remission endpoint (UPCR ≤1.5 g/g and >40% reduction from baseline)

- Patients achieved the FSGS partial remission endpoint earlier and more often with sparsentan vs irbesartan[1]
- Patients on sparsentan achieved the FSGS partial remission endpoint at a 1.5-fold higher rate compared to irbesartan

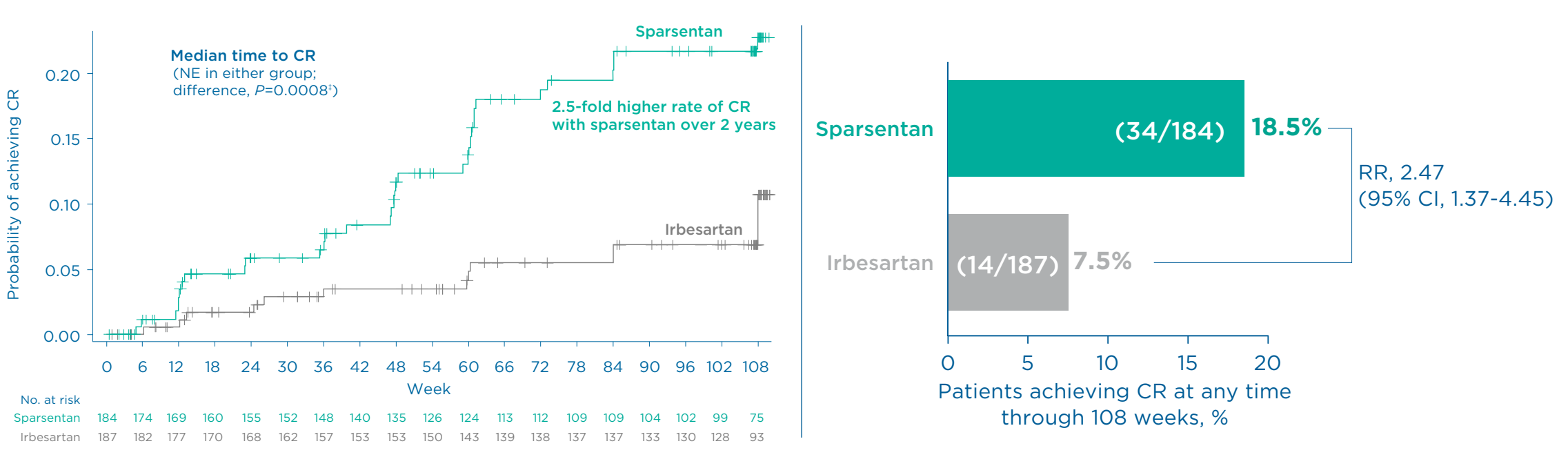
Probability of achieving the FSGS partial remission endpoint[†] of proteinuria through 108 weeks



Complete remission of proteinuria (UPCR of <0.3 g/g)

- Patients achieved complete remission of proteinuria earlier and more often with sparsentan vs irbesartan[1]
- Patients on sparsentan achieved complete remission of proteinuria at a 2.5-fold higher rate compared to irbesartan

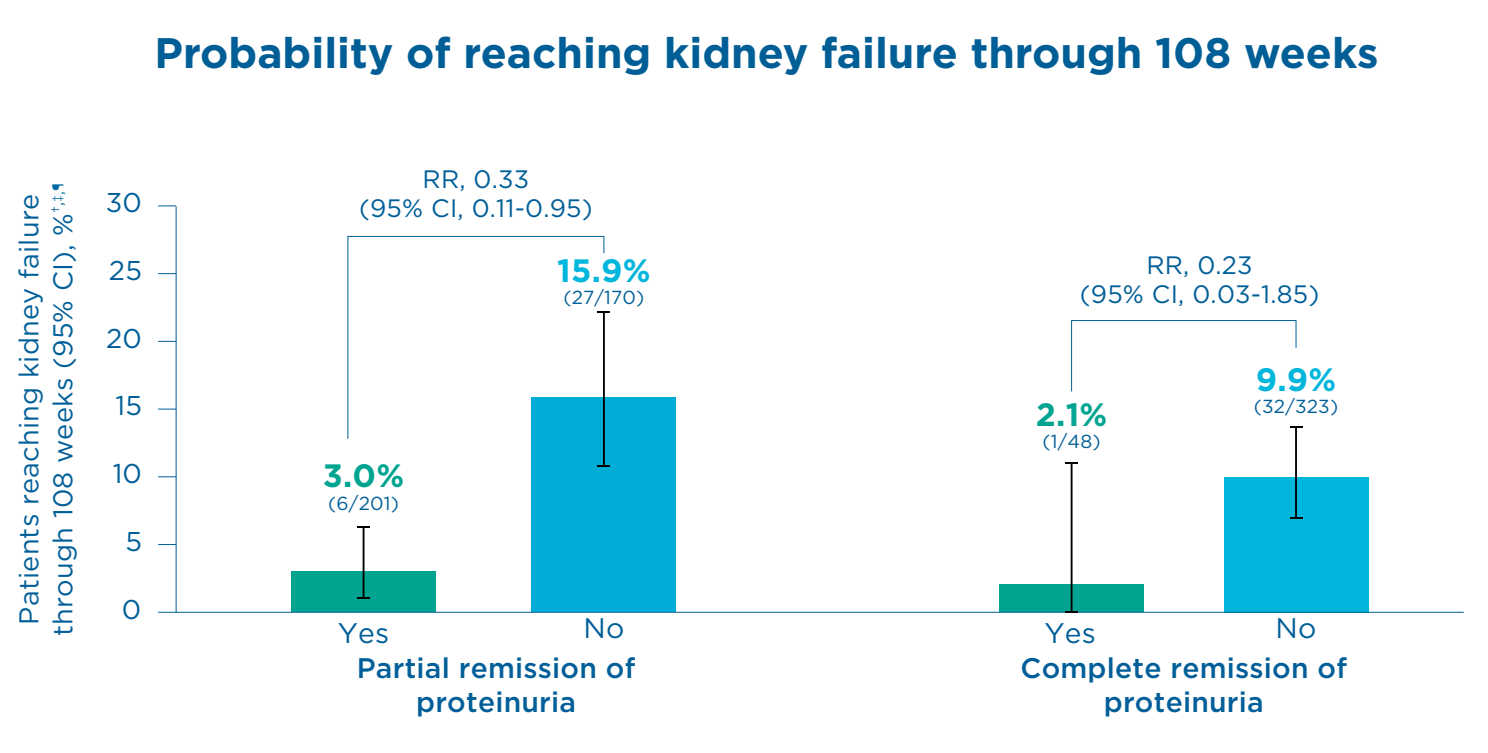
Probability of achieving complete remission[§] of proteinuria through 108 weeks



Proteinuria remission and kidney failure risk

Regardless of treatment group, patients who achieved the FSGS partial remission endpoint (UPCR ≤1.5 g/g and >40% reduction from baseline) or complete remission of proteinuria (UPCR of <0.3 g/g) were less likely to develop kidney failure vs those who did not[1,11]

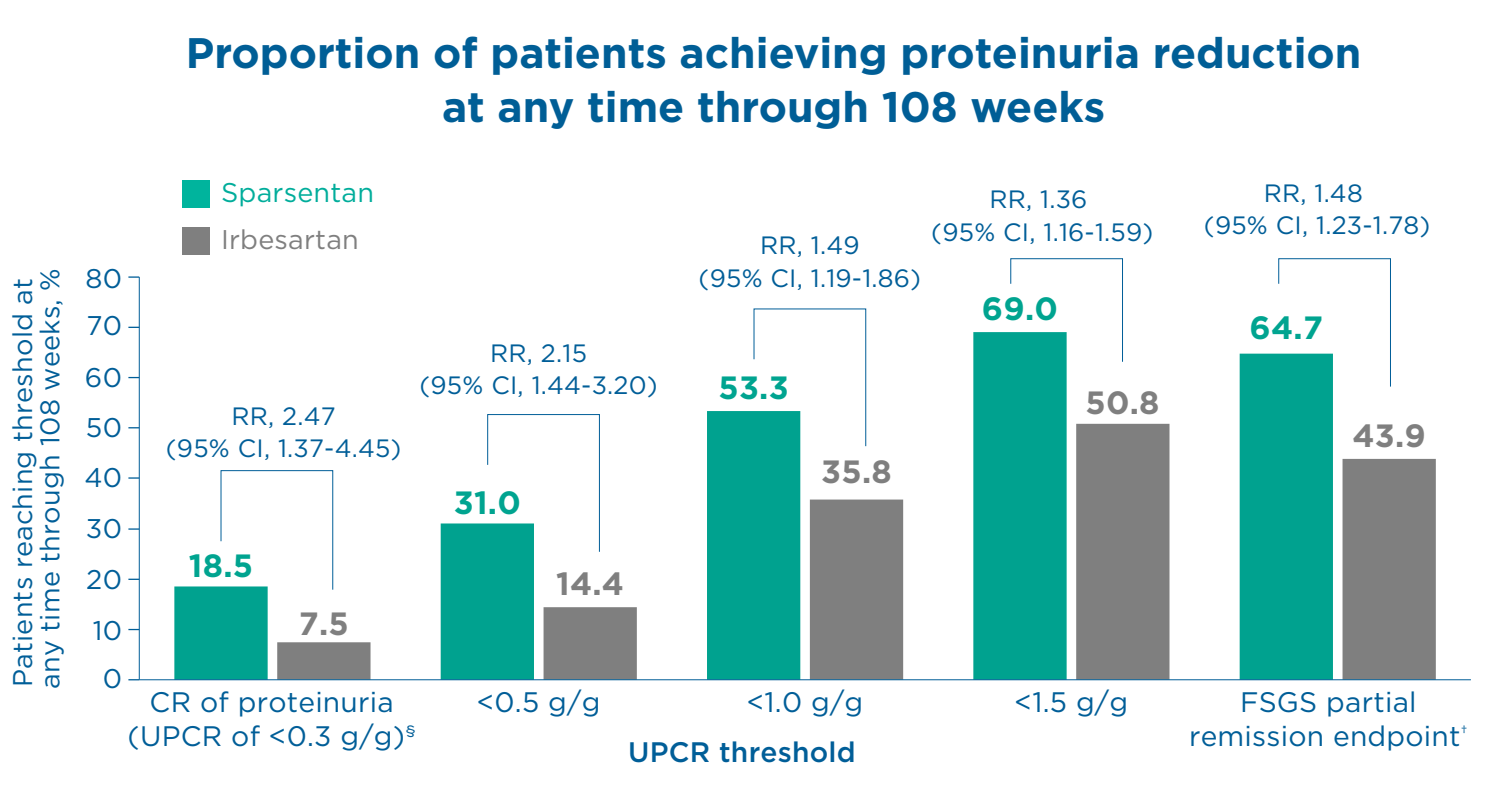
Probability of reaching kidney failure through 108 weeks



Reductions in proteinuria

Over 108 weeks, more patients receiving sparsentan achieved proteinuria reductions across UPCR thresholds vs maximum labeled dose irbesartan[11]

Proportion of patients achieving proteinuria reduction at any time through 108 weeks



Safety outcomes

TEAEs

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Sparsentan 800 mg/day was generally well tolerated, with a safety profile comparable to that of irbesartan.[1] The most common TEAEs (≥15% in either group) included COVID-19,[**] hyperkalemia, peripheral edema, and hypotension.[1] No cases of heart failure were reported in either group[1]

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

Key takeaways

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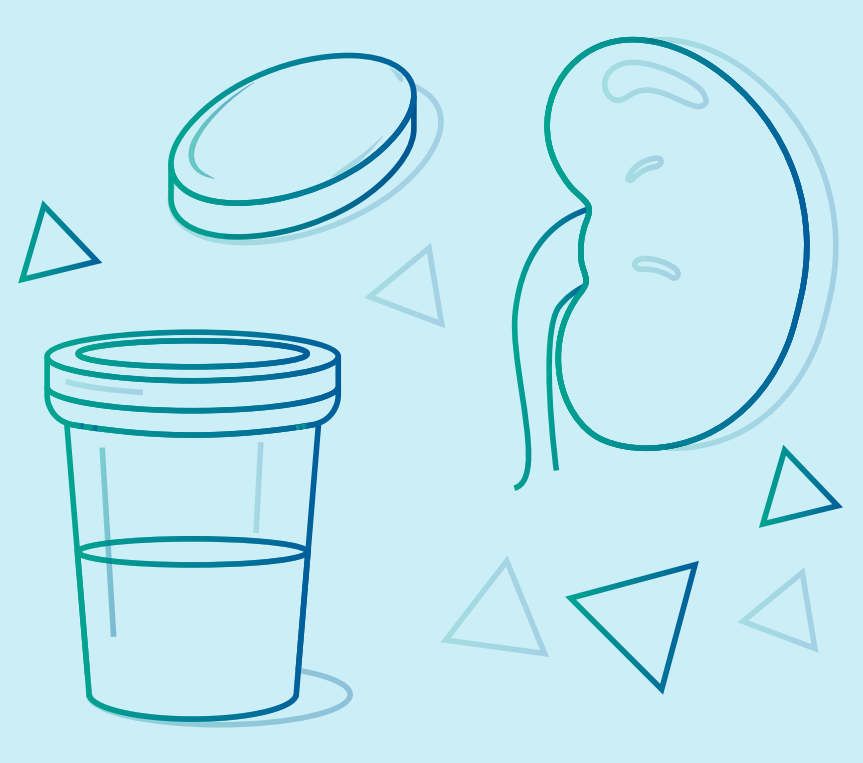
- In the DUPLEX study, patients with FSGS who were randomized to sparsentan experienced rapid and sustained reduction in proteinuria compared to maximum label irbesartan[1]
- In *post hoc* analyses, patients achieved the FSGS partial remission endpoint (UPCR ≤1.5 g/g and >40% reduction from baseline) or complete remission of proteinuria (UPCR of <0.3 g/g) earlier and more often with sparsentan compared to maximum labeled dose irbesartan[1]
- Regardless of the treatment group, those who reached the FSGS partial remission endpoint (UPCR ≤1.5 g/g and >40% reduction from baseline) or complete remission of proteinuria (UPCR of <0.3 g/g) also had a lower risk of kidney failure[1]
- Sparsentan 800 mg/day was generally well tolerated over 108 weeks, with a safety profile comparable to irbesartan[1]



*Sparsentan is not FDA-approved for the treatment of FSGS.

†Partial remission of proteinuria was defined as UPCR of ≤1.5 g/g and >40% reduction from baseline (FSGS partial remission endpoint).

‡*P* value generated from a stratified Cox proportional hazards model with treatment and baseline log (UPCR) as covariates, stratified by randomization stratification factors.

§Complete remission was defined as UPCR of <0.3 g/g

¶Kidney failure was defined as confirmed eGFR of <15 mL/min/1.73 m2 or initiation of kidney replacement therapy

**Study was conducted during the COVID-19 pandemic.

Ang II, angiotensin II; CI, confidence interval; COVID-19, coronavirus disease of 2019; DEARA, Dual Endothelin Angiotensin Receptor Antagonist; eGFR, estimated glomerular filtration rate; ESKD, end-stage kidney disease; ET-1, endothelin-1; FDA, Food and Drug Administration; FSGS, focal segmental glomerulosclerosis; NE, not estimable; RASi, renin angiotensin system inhibitor; RR, relative risk; SOC, standard of care; TEAE, treatment-emergent adverse event; UPCR, urine protein-creatinine ratio.

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