FR-OR108

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

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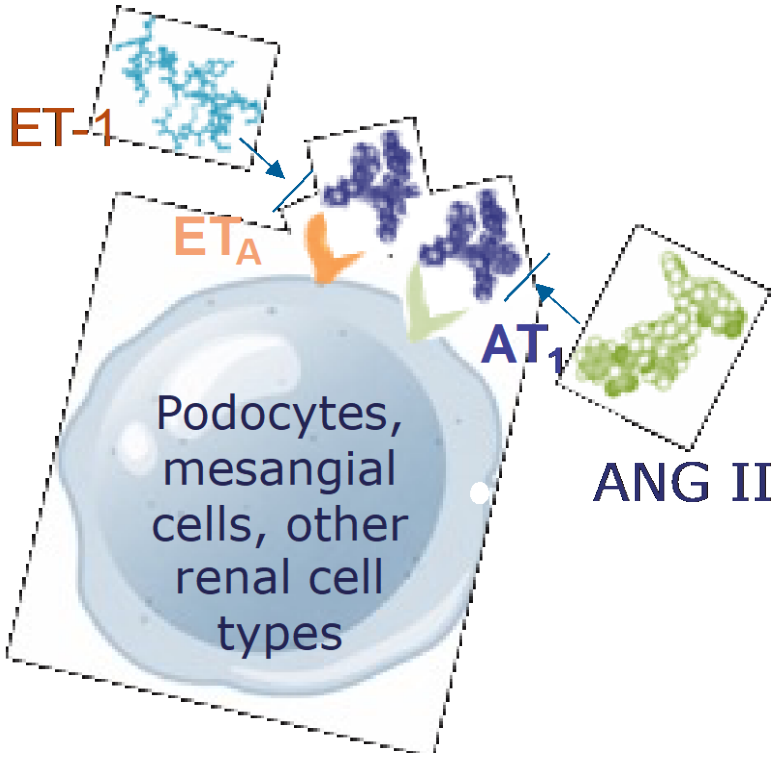
DISCLOSURES

- **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; participated on data safety monitoring or advisory boards for ChemoCentryx, Otsuka, and Travere Therapeutics, Inc.
- **UD** and **RK** are employees of Travere Therapeutics, Inc. and may have an equity or other financial interest in Travere Therapeutics, Inc.

Background

- 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)[1,4-5] that reduced proteinuria in patients with FSGS in a phase 2 trial[6]



Dual ET_A and AT_1 receptor antagonism has anti-inflammatory, antiproliferative, and antifibrotic actions of therapeutic potential in addition to hemodynamic benefits[1,4,7-9]

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Phase 3 DUPLEX Study

- **Objective:** Evaluate the efficacy and safety of sparsentan vs the active control irbesartan in patients with FSGS
- **Trial Design:** Phase 3, double-blind, active-controlled global trial (NCT03493685) in patients with biopsy-proven FSGS or genetic FSGS

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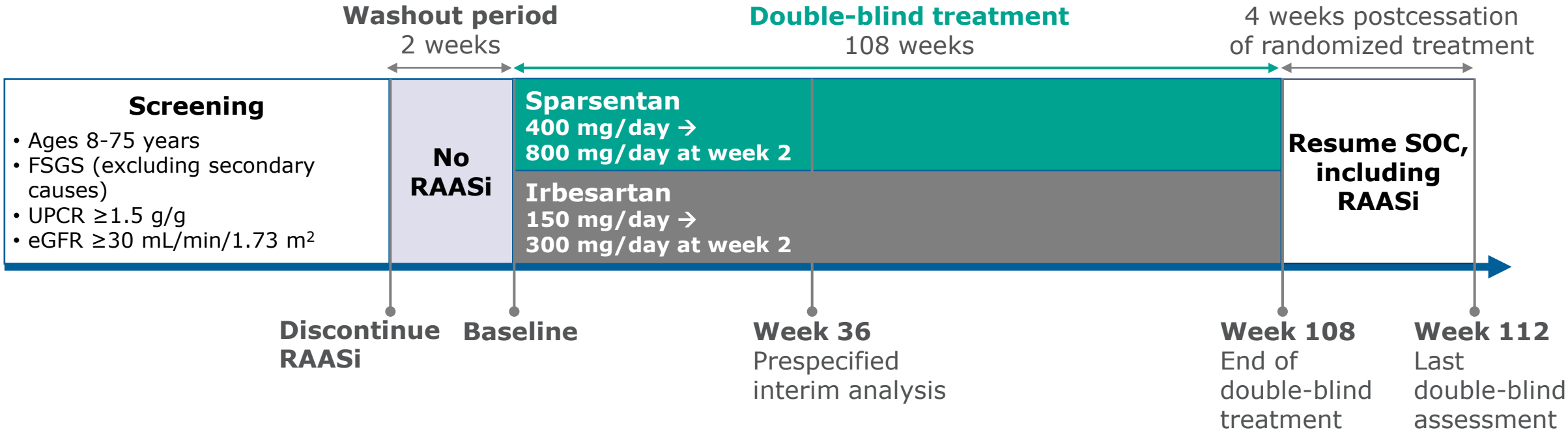

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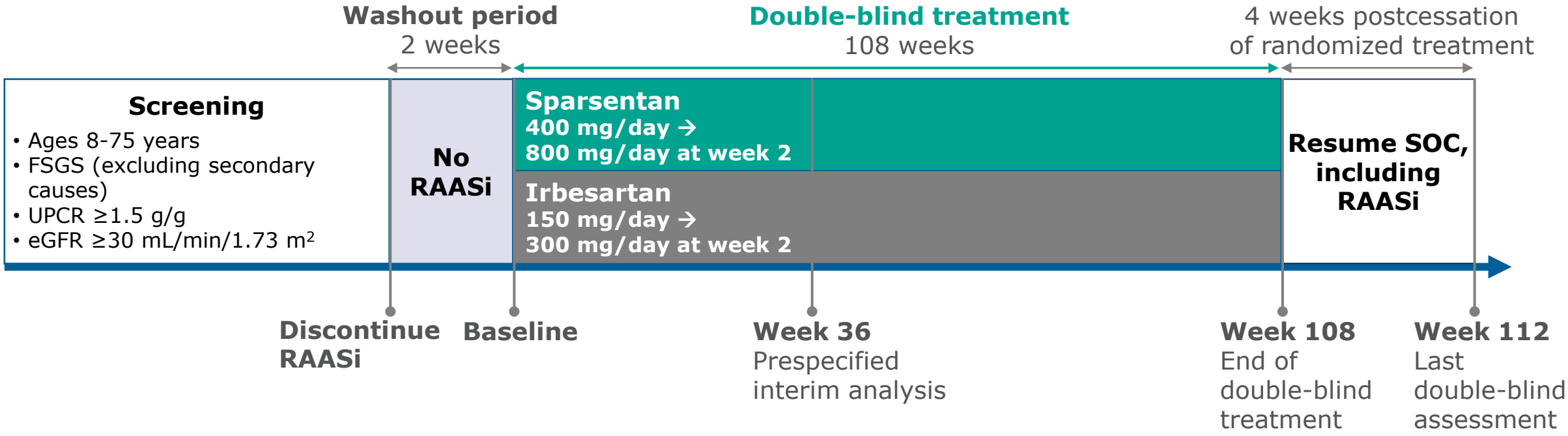


Surrogate Efficacy Endpoint
(36-Week Interim Analysis)

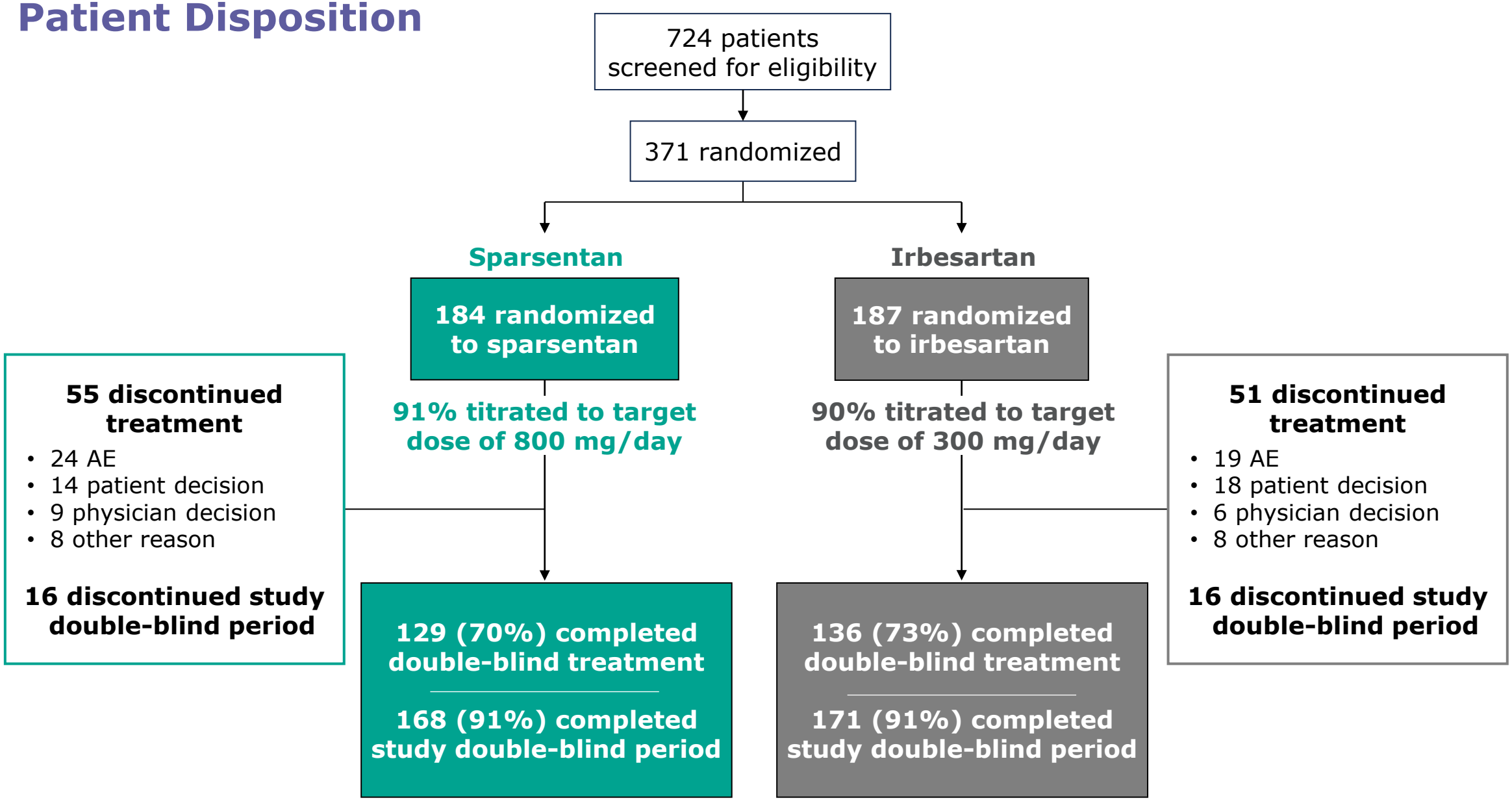
- Proportion of patients achieving FPRE at week 36 (UPCR ≤1.5 g/g and ≥40% reduction from baseline)

Primary Endpoint

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

FPRE, FSGS partial remission endpoint.

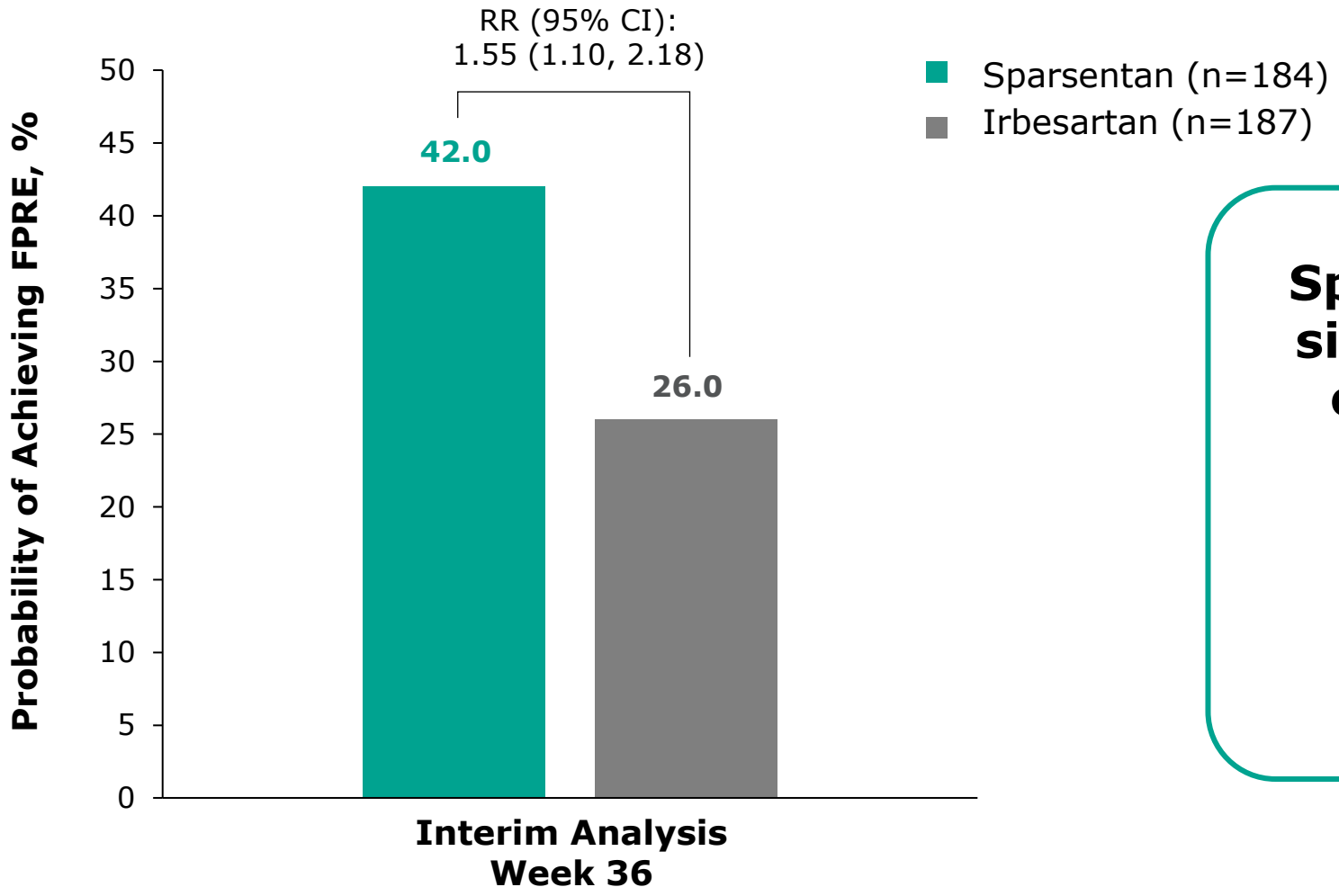
Patient Disposition



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 RAASi 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)

More Patients Achieved the FSGS Partial Remission Endpoint[1] (FPRE; UPCR ≤1.5 g/g and >40% Reduction From Baseline) With Sparsentan vs Irbesartan



Sparsentan resulted in a significantly higher rate of FPRE vs irbesartan after 36 weeks

Difference (95% CI):
16.0 (4.0, 28.0)
P<0.01

1. Troost JP, et al. *Clin J Am Soc Nephrol.* 2018;13(3):414-21.

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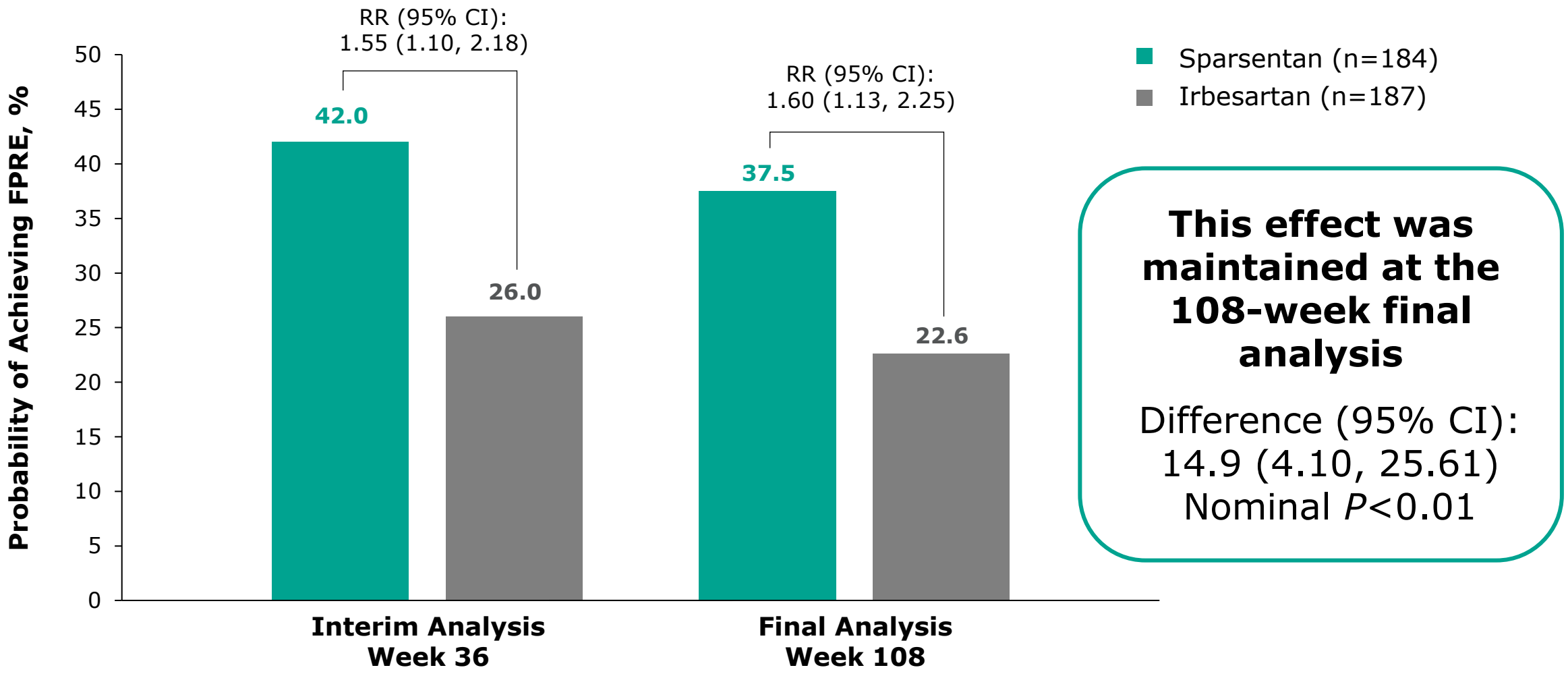
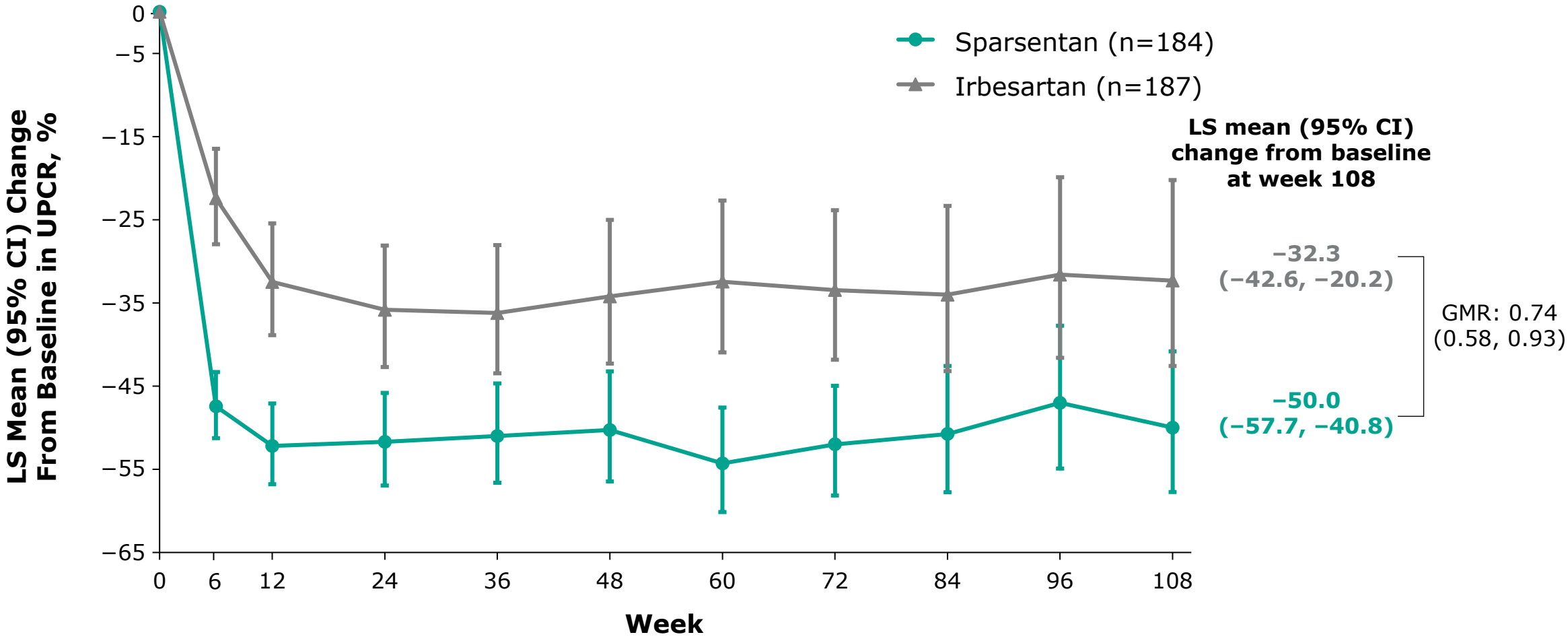


This effect was maintained at the 108-week final analysis

Difference (95% CI): 14.9 (4.10, 25.61)
Nominal *P*<0.01

FPRE, FSGS partial remission endpoint; RR, relative risk.

Sparsentan Resulted in a Rapid Decline in UPCR That Was Sustained Through 108 Weeks

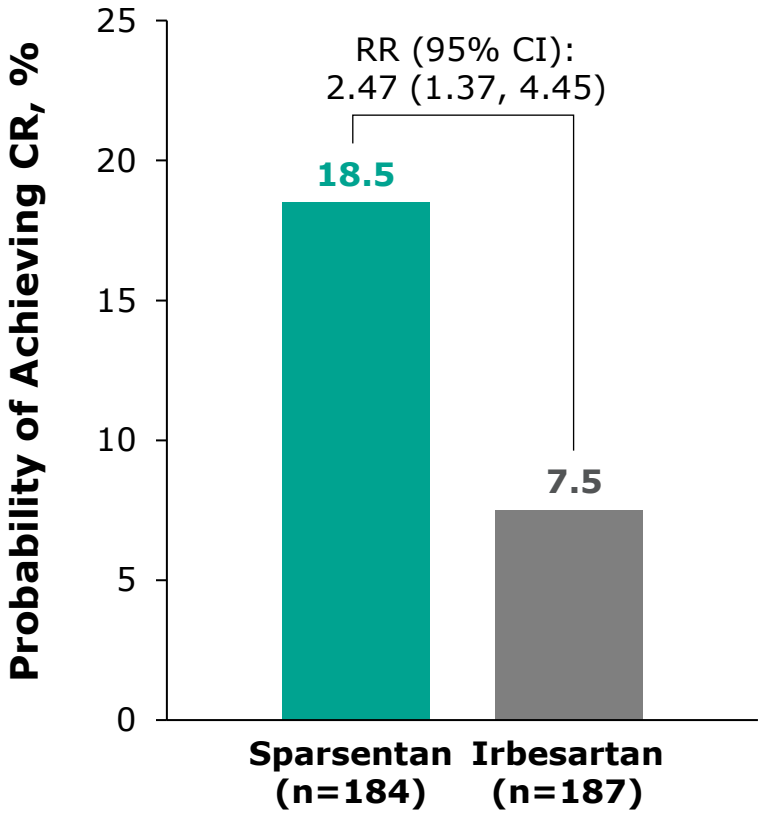


Sparsentan, n=	184	168	163	157	158	146	139	135	135	128	119
Irbesartan, n=	187	178	169	156	155	150	141	138	144	132	128

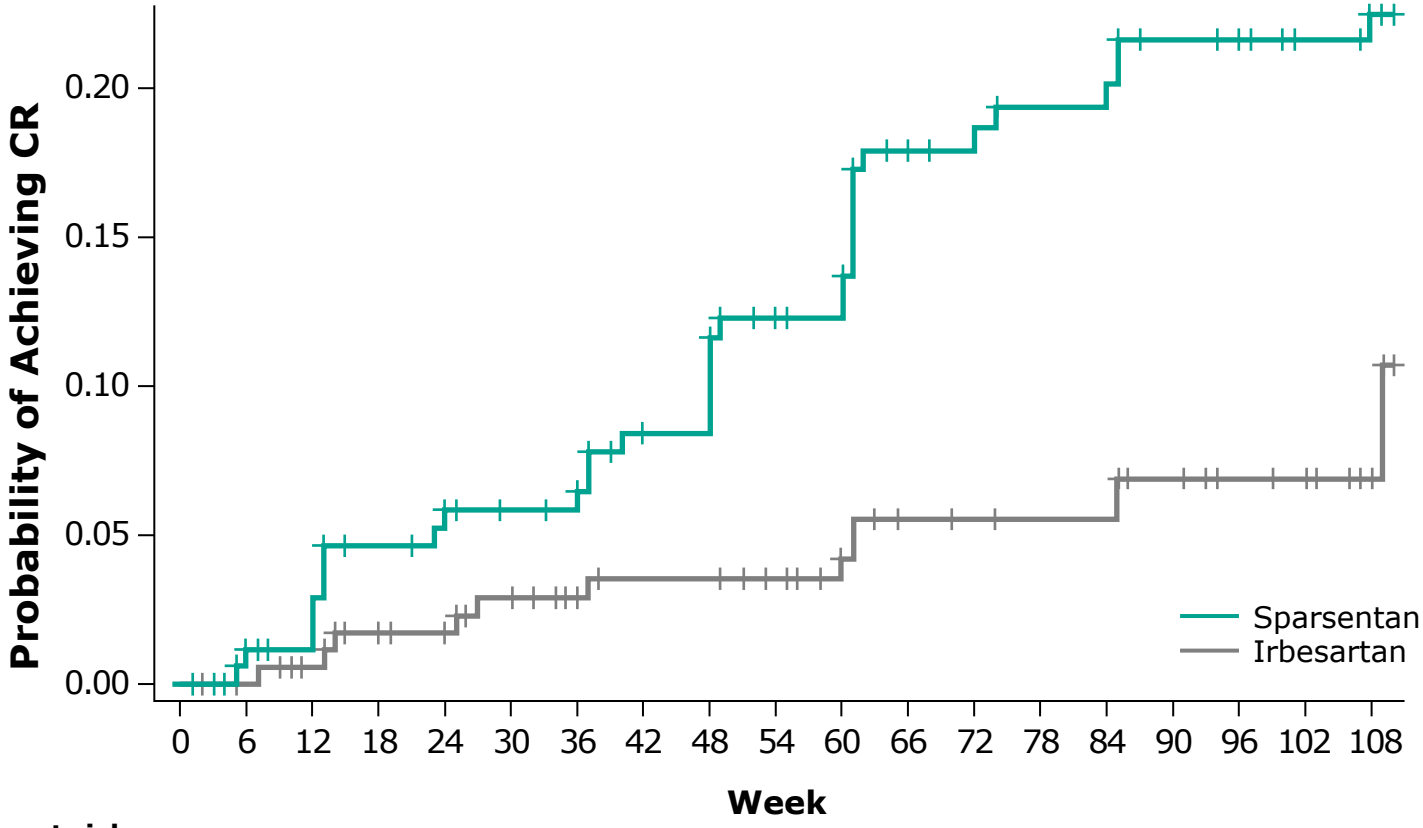
BL, baseline; GMR, geometric mean ratio.

Complete Remission of Proteinuria (CR; UPCR <0.3 g/g) was Achieved Earlier and More Frequently With Sparsentan vs Irbesartan

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



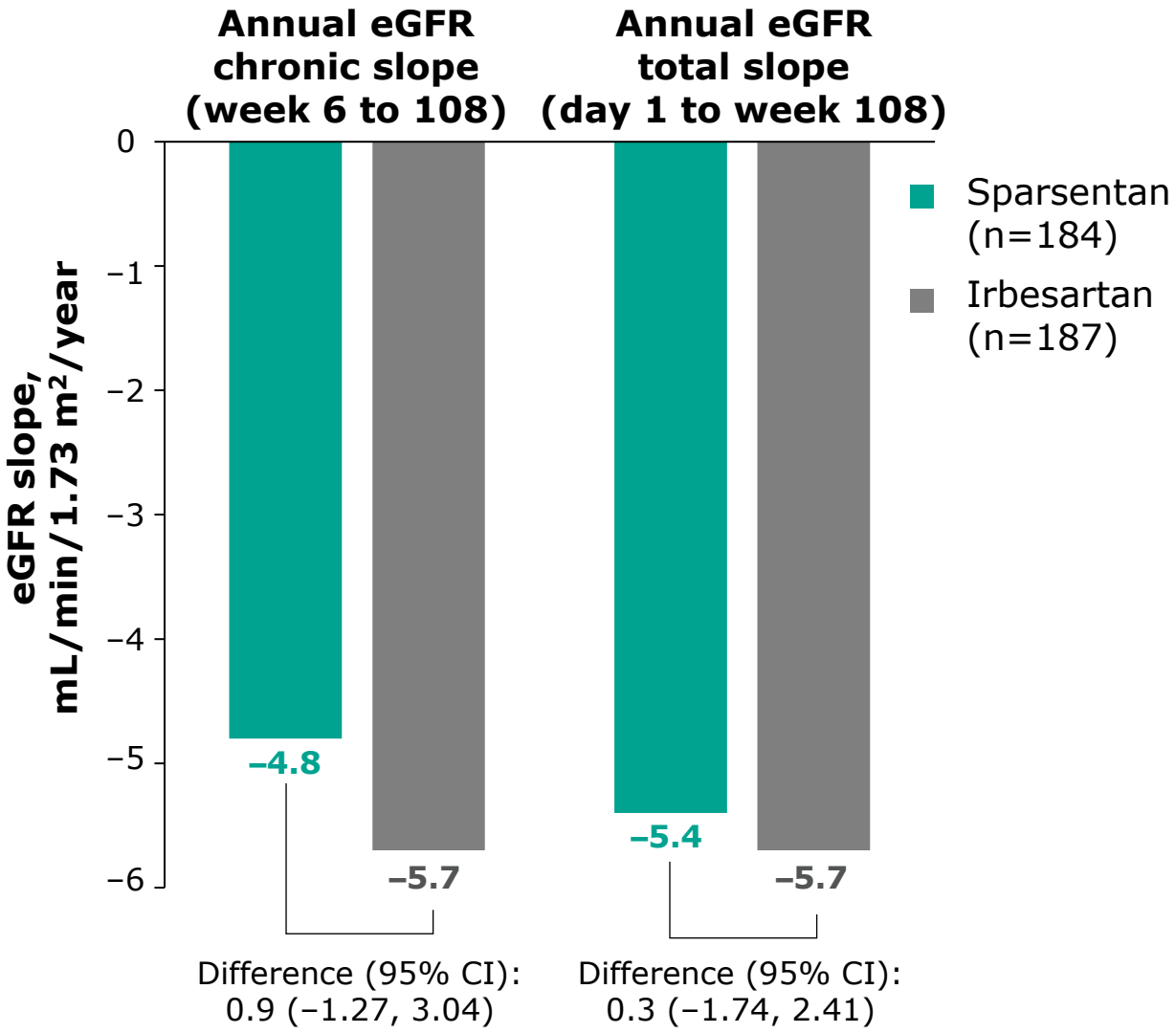
Time to First CR



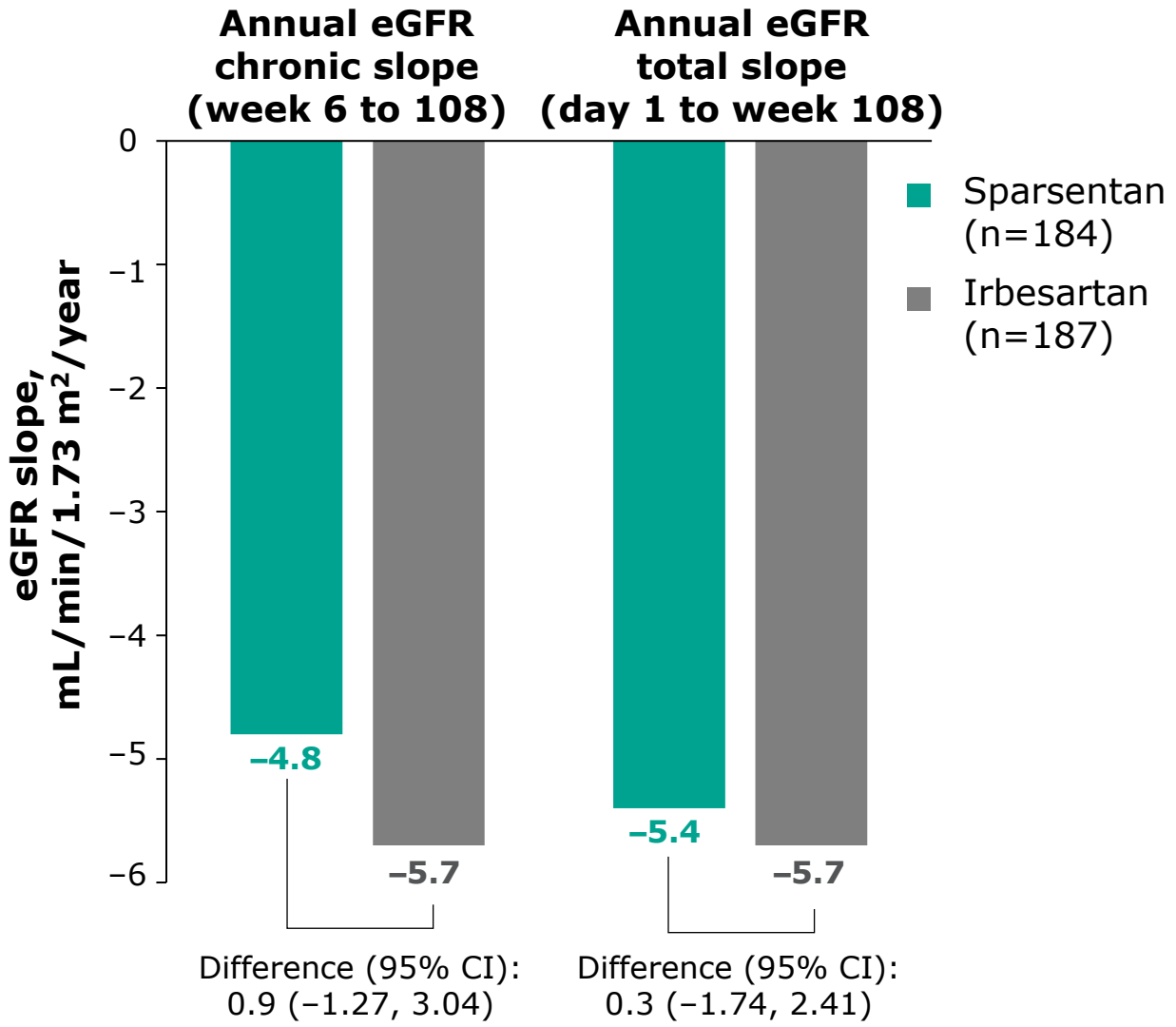
No. at risk																			
Sparsentan	184	174	169	160	155	152	148	140	135	126	124	113	112	109	109	104	102	99	75
Irbesartan	187	182	177	170	168	162	157	153	153	150	143	139	138	137	137	133	130	128	93

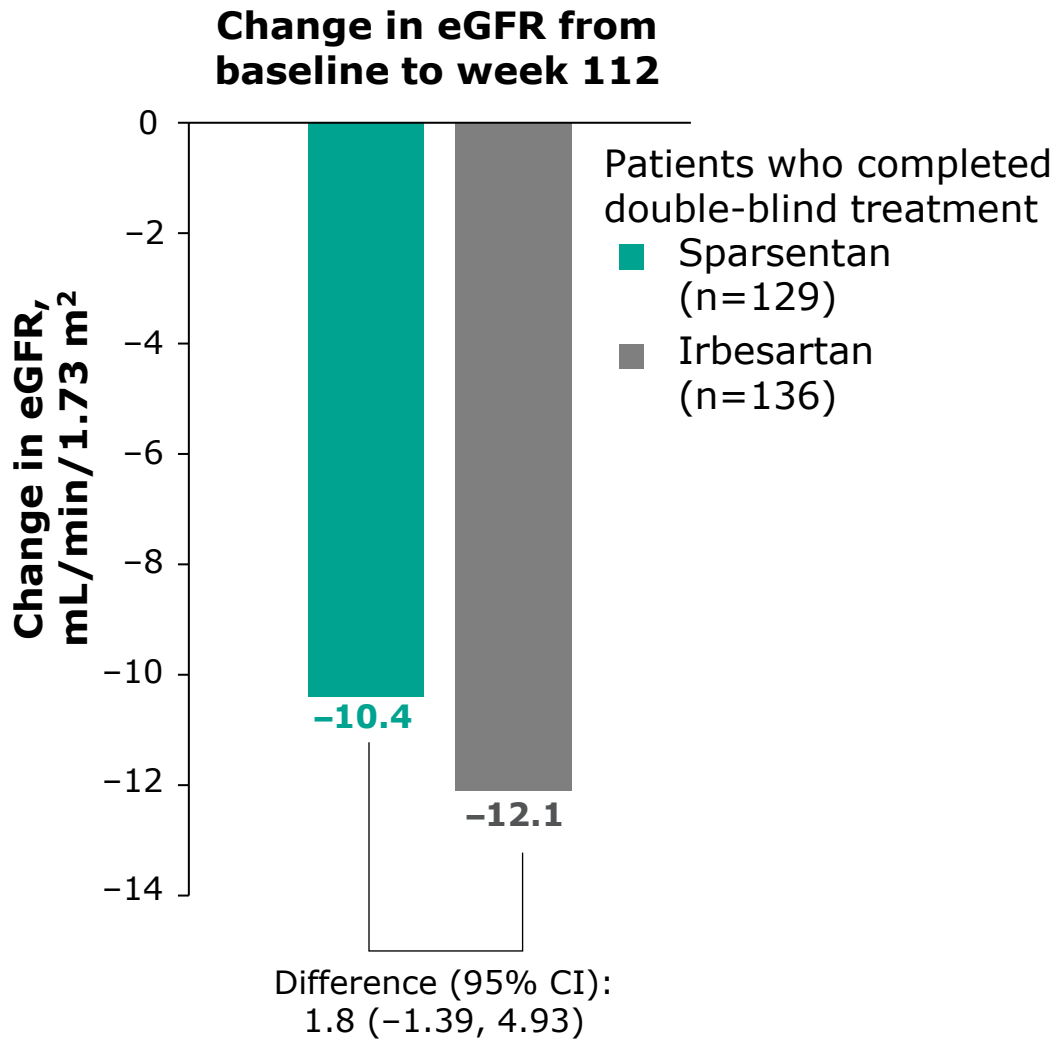
RR, relative risk.

eGFR Endpoints Over the Double-Blind Period: Primary Endpoint



eGFR Endpoints Over the Double-Blind Period

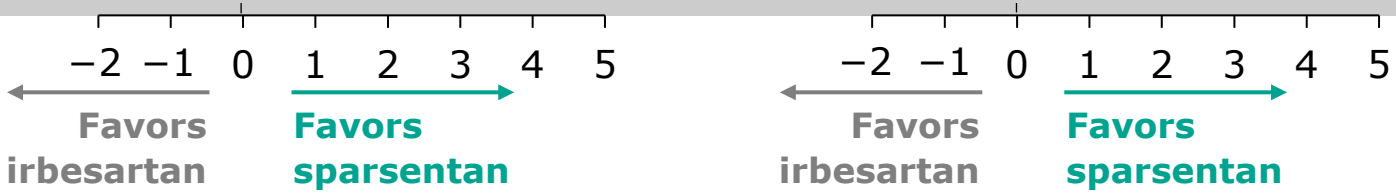




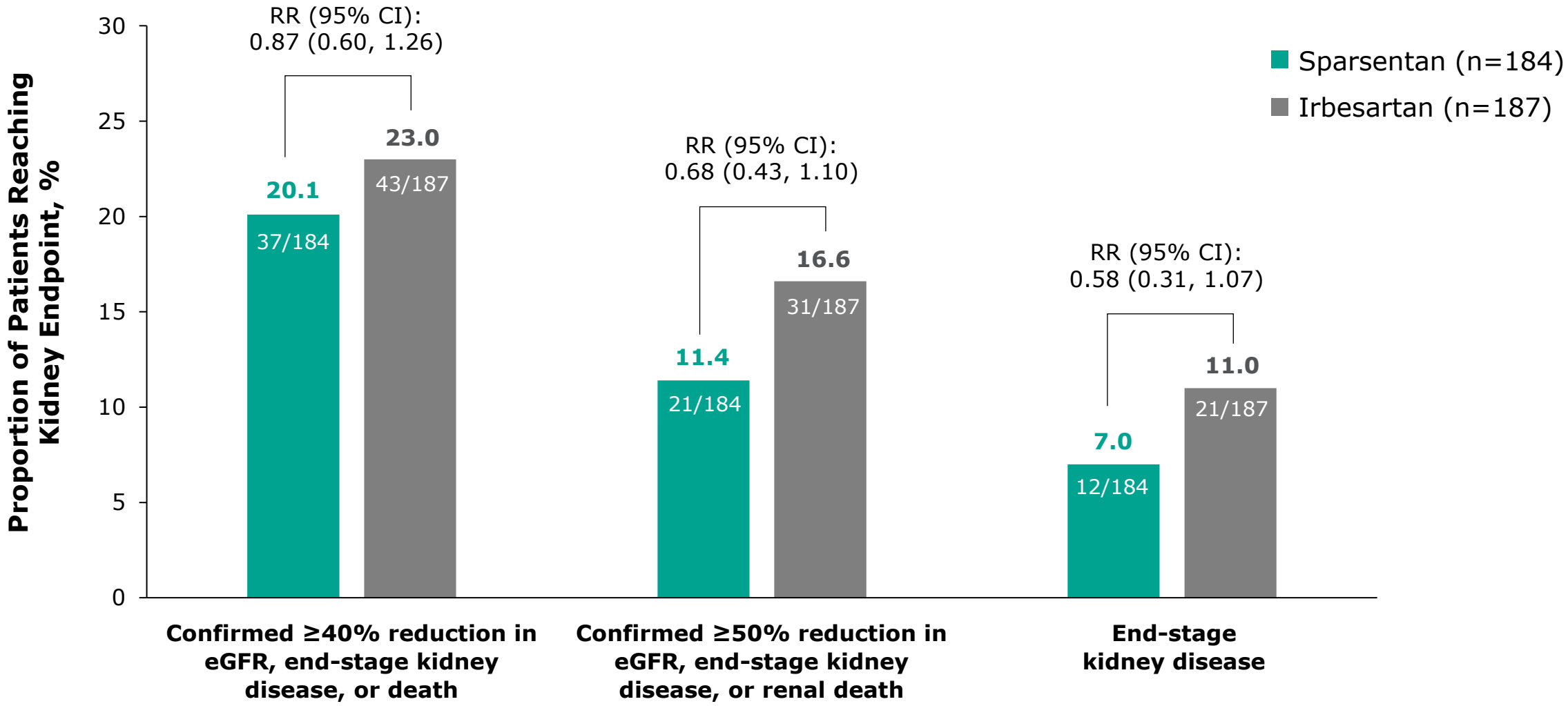
Treatment Effect on eGFR Slope Sensitivity Analyses

- eGFR chronic slope was lower with sparsentan vs irbesartan when measurements after initiation or intensification of immunosuppressive treatments were excluded
  - 16.3% of patients in the sparsentan group and 16.0% in the irbesartan group required initiation or intensification of immunosuppressive treatments
- Other sensitivity analyses were consistent with the main analysis

	Sparsentan, n	Irbesartan, n	Annual eGFR chronic slope Difference (95% CI) for sparsentan vs irbesartan, mL/min/1.73 m^2	Annual eGFR total slope Difference (95% CI) for sparsentan vs irbesartan mL/min/1.73 m^2
With multiple imputation	184	187	1.1 (−0.88, 2.99)	0.6 (−1.25, 2.53)
Excluding data after initiation or intensification of immunosuppressive treatment	184	187	2.1 (0.5, 4.10)	1.5 (−0.40, 3.44)
Excluding patients who had major protocol deviations that might affect efficacy measurements	164	170	1.5 (−0.74, 3.66)	0.9 (−1.22, 2.99)



Fewer Patients Reached Composite Kidney Endpoints or End-Stage Kidney Disease With Sparsentan vs Irbesartan



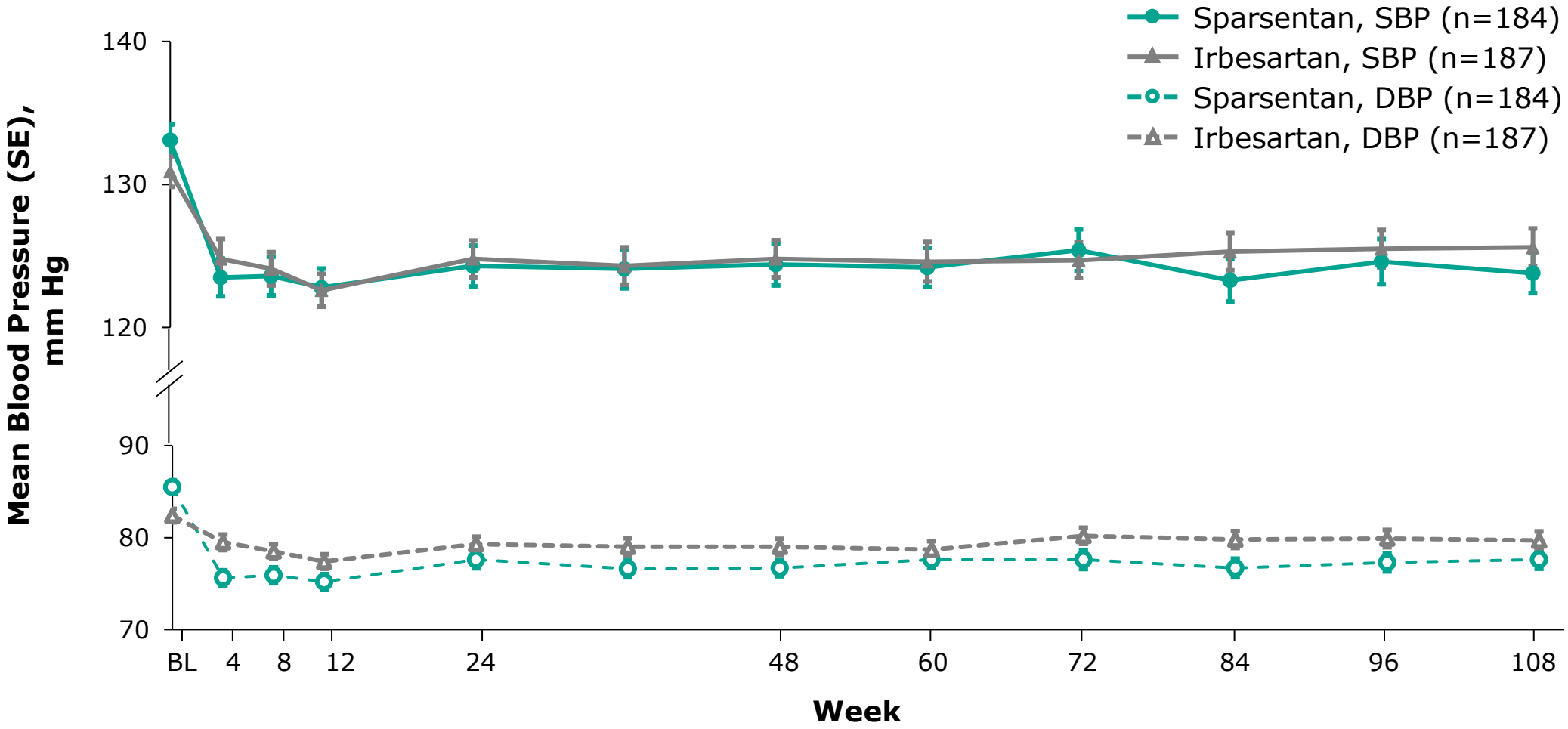
RR, relative risk.

Sparsentan Was Well Tolerated With a Safety Profile Comparable to That of Irbesartan

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)

- The most common TEAEs (≥15% in either group) included COVID-19, hyperkalemia, peripheral edema, and hypotension

After an Initial Decrease, Blood Pressure Remained Stable After 4-6 Weeks



DBP, diastolic blood pressure; SBP, systolic blood pressure.

- In the largest randomized trial of FSGS to date, sparsentan achieved a sustained reduction in proteinuria, with higher rates of FPRE and CR vs irbesartan
- Although differences in eGFR slopes for the sparsentan and irbesartan groups were not statistically significant, the magnitude of the difference in eGFR chronic slope is clinically meaningful as a decrease of nearly 1 mL/min/1.73 m^2/year could delay the need for renal replacement therapy
- Fewer patients reached the composite kidney endpoints or end-stage renal disease with sparsentan than irbesartan
- The safety profile of sparsentan was comparable to that of irbesartan. There were no TEAEs of heart failure or liver injury and no clinically meaningful fluid retention/edema concerns were identified
- Overall, results indicate a clinical benefit of sparsentan for proteinuria reduction in patients with FSGS

CR, complete remission of proteinuria; FPRE, FSGS partial remission endpoint.

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ORIGINAL ARTICLE

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Questions?

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