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SPARSENTAN VS IRBESARTAN IN PATIENTS WITH IMMUNOGLOBULIN A NEPHROPATHY (IgAN): SUBGROUP ANALYSES OF 2-YEAR RESULTS FROM THE PIVOTAL PHASE 3 PROTECT TRIAL

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on behalf of the DUPRO Steering Committee and PROTECT investigators

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DISCLOSURES

- JB reports a research grant and consulting fees from Travere Therapeutics, Inc.
- BR reports consulting fees from Alexion Pharmaceuticals, Alpine Pharma, BioCryst Pharmaceuticals, Calliditas Therapeutics, Novartis, Q32 Bio, Omeros, Otsuka Pharmaceuticals, Travere Therapeutics, Inc., and Vera Therapeutics and has a leadership role at NephroNet, Lupus ABC/LRA, and Lupus Foundation of America.
- EM and RK are employees and stockholders of Travere Therapeutics, Inc.
- HT reports grants from AstraZeneca, Bayer, BioCryst Pharmaceuticals, Calliditas Therapeutics, Chinook Therapeutics, Dimerix, George Clinical, Novartis, Omeros, Otsuka Pharmaceuticals, and Vera Therapeutics; reports consulting fees from AstraZeneca, BioCryst Pharmaceuticals, Calliditas Therapeutics, Chinook Therapeutics, Dimerix, George Clinical, Novartis, Omeros, Travere Therapeutics, Inc., and Vera Therapeutics; reports honoraria from AstraZeneca, BioCryst Pharmaceuticals, Calliditas Therapeutics, Chinook Therapeutics, George Clinical, Novartis, and Travere Therapeutics, Inc.; reports travel support from BioCryst Pharmaceuticals, Calliditas Therapeutics, and Chinook Therapeutics; and serves as a member of a data safety monitoring or advisory board for AstraZeneca, BioCryst Pharmaceuticals, Calliditas Therapeutics, Chinook Therapeutics, Novartis, and Travere Therapeutics, Inc.
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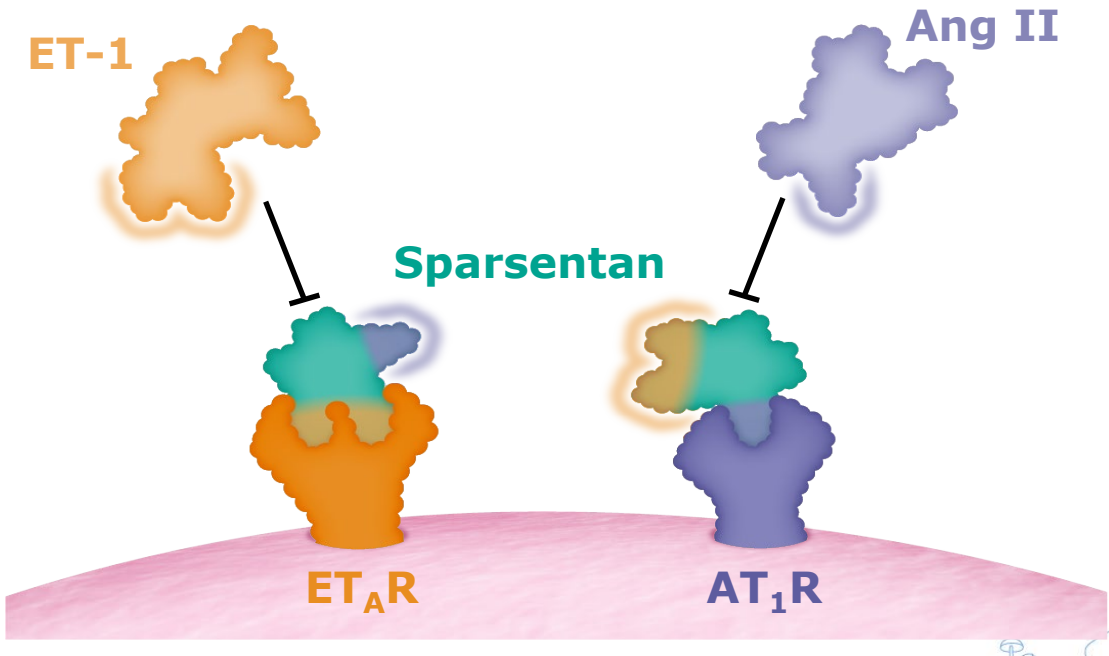
BACKGROUND: SPARSENTAN MODE OF ACTION

- Sparsentan is an orally active dual endothelin angiotensin receptor antagonist (DEARA) that reduces proteinuria and preserves eGFR in patients with IgAN[1,2]
- Sparsentan molecules bind individually to either ET_A or AT_1 receptors and inhibit intracellular signaling[3]
- In IgAN, the endothelin system is activated along with the RAAS
- Both systems mediate kidney injury through multiple mechanisms, including inflammation and fibrosis



- Sparsentan has received accelerated approval in the US for treatment of patients with IgAN who are at risk of rapid disease progression[4]

1. Heerspink HJL, et al. *Lancet*. 2023;401(10388):1584-1594. 2. Rovin BH, et al. *Lancet*. 2023;402(10417):2077-2090. 3. Trachtman H, et al. *Expert Rev Clin Immunol*. Published online February 26, 2024. 4. Filspari (sparsentan). Prescribing information. Travere Therapeutics, Inc.; 2023.

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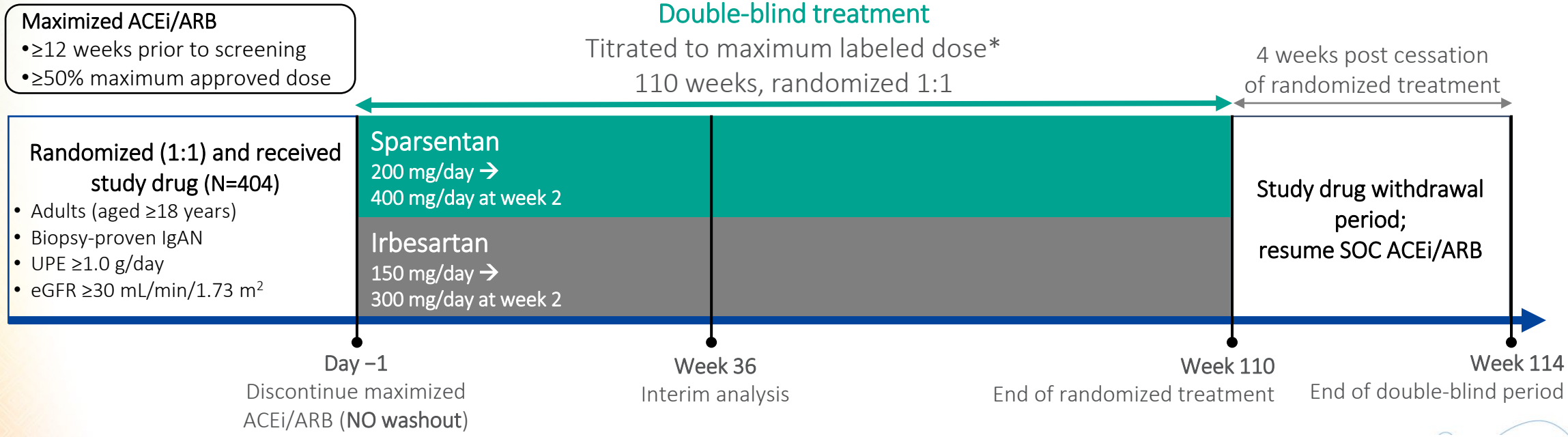
TRIAL OBJECTIVE AND DESIGN

Objective: Test the efficacy and safety of sparsentan vs active control (irbesartan) in patients with IgAN, including across different levels of baseline proteinuria



Primary Efficacy Endpoint
Change in UPCR from baseline to week 36

Key Secondary Efficacy Endpoint
eGFR slope: **chronic** (weeks 6-110) and **total** (day 1-week 110)

*95% and 97% of patients titrated to maximum labeled dose of sparsentan and irbesartan, respectively.

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PATIENT DISPOSITION

669 Patients screened for eligibility

406 Enrolled and randomized

2 Received no study drug

Sparsentan	Irbesartan
202 Assigned to and received sparsentan	202 Assigned to and received irbesartan
28 Discontinued treatment	**48 Discontinued treatment**
AE 19	AE 18
Patient decision 5	Patient decision 21
Physician decision 0	Physician decision 7
4 Discontinued study double-blind period	12 Discontinued study double-blind period
174 of 202 (86.1%) Completed treatment	154 of 202 (76.2%) Completed treatment
199 of 203 (98.0%) Completed study double-blind period	191 of 203 (94.1%) Completed study double-blind period

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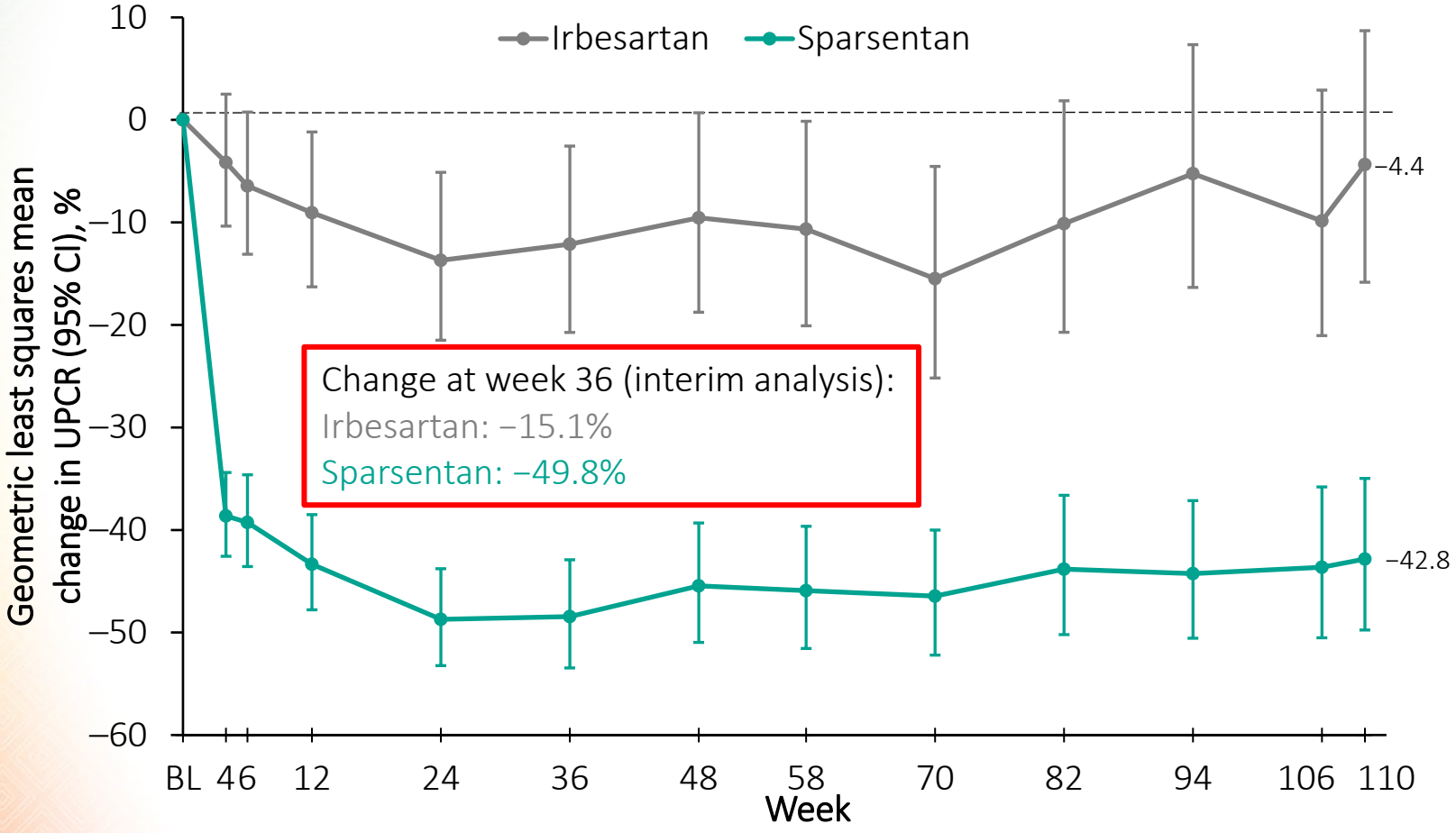
BASELINE DEMOGRAPHICS AND CLINICAL CHARACTERISTICS

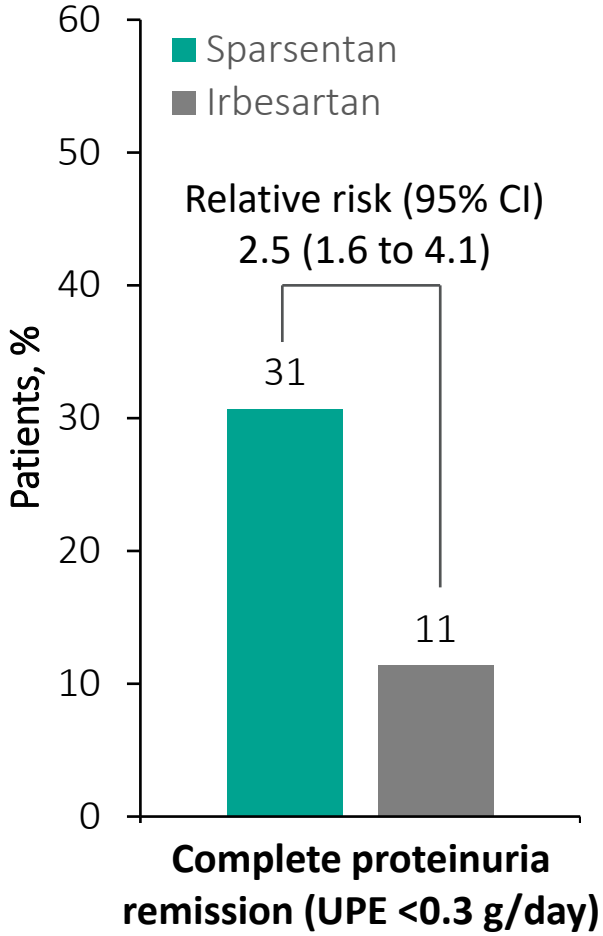
	Sparsentan (n=202)	Irbesartan (n=202)
Age at IgAN diagnosis, mean (SD), years	40.2 (13.4)	39.0 (12.4)
Time from initial kidney biopsy to informed consent, median (IQR), years	4.0 (1.0-10.0)	4.0 (1.0-10.0)
Male sex, n (%)	139 (69)	143 (71)
Blood pressure, mean (SD), mm Hg		
Systolic	128.0 (14.4)	129.9 (12.4)
Diastolic	81.6 (10.6)	83.2 (10.6)
Maximum labeled ACEi or ARB dose at screening, n (%)	130 (64)	125 (62)
eGFR, mean (SD), mL/min/1.73 m^2	56.8 (24.3)	57.1 (23.6)
Subgroups: baseline proteinuria quartiles		
UPCR <0.80 g/g	57.3 (24.0)	61.9 (27.3)
UPCR ≥0.80 to <1.25 g/g	60.6 (25.0)	59.3 (25.2)
UPCR ≥1.25 to <1.80 g/g	55.9 (24.0)	55.1 (21.9)
UPCR ≥1.80 g/g	53.6 (24.5)	52.1 (18.8)
Urine protein excretion, median (IQR), g/day	1.8 (1.2-2.9)	1.8 (1.3-2.6)
Urine protein-to-creatinine ratio, median (IQR), g/g	1.3 (0.8-1.8)	1.2 (0.9-1.7)
Hematuria, n (%)	111 (55)	114 (56)

Study drug dose	Sparsentan (n=202)	Irbesartan (n=202)
Titrated to maximum labeled dose, n (%)	192 (95)	196 (97)

SUSTAINED REDUCTION OF PROTEINURIA BY SPARSENTAN

Primary endpoint was met at the 36-week interim analysis, with a 41% relative reduction in proteinuria (*P*<.0001)





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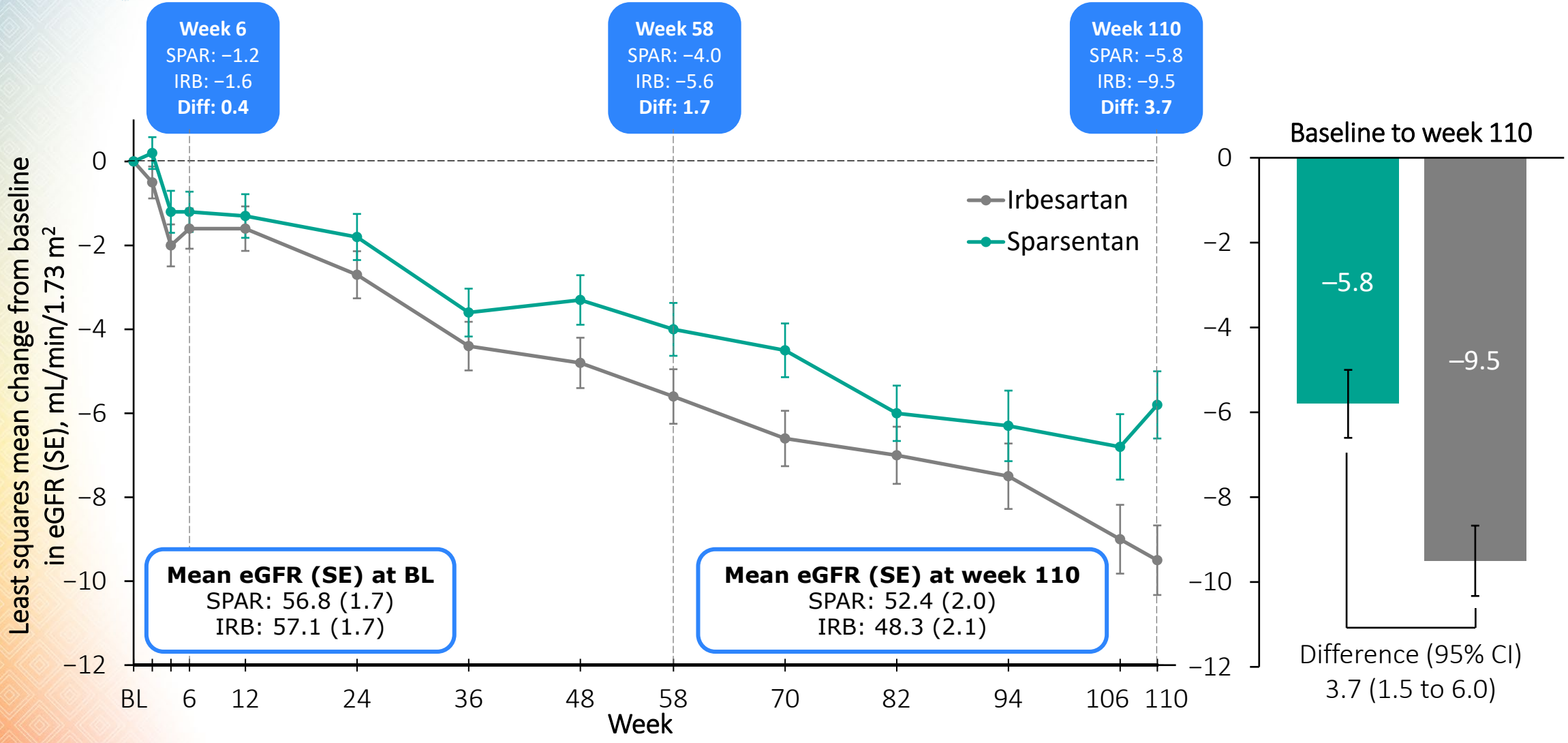
SPARSENTAN PRESERVES KIDNEY FUNCTION MORE THAN IRBESARTAN



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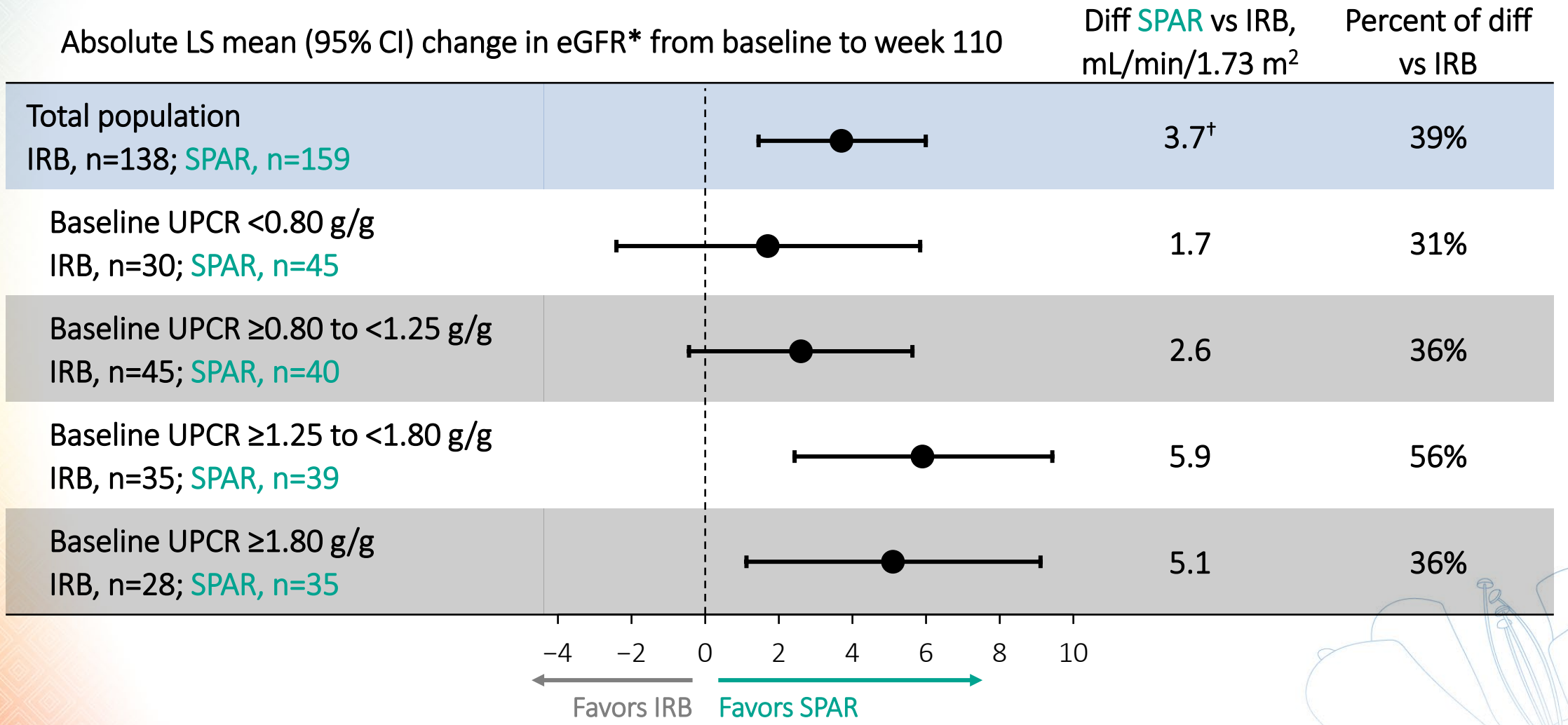
THE 110-WEEK eGFR BENEFITS OF SPARSENTAN ARE CONSISTENT ACROSS BASELINE UPCR SUBGROUPS



*On-treatment eGFR. †*P*=.001.

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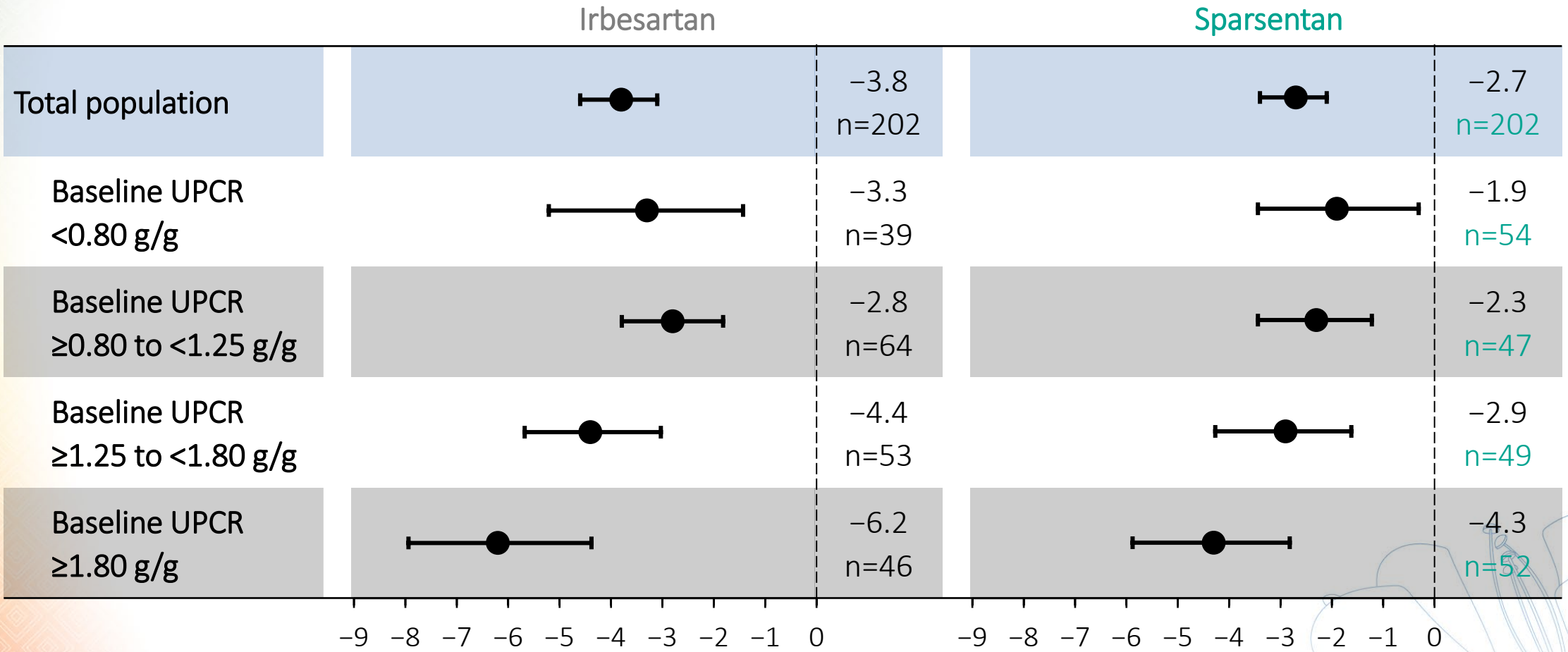
THE eGFR SLOPE BENEFITS OF SPARSENTAN ARE CONSISTENT ACROSS BASELINE UPCR SUBGROUPS

Annualized change in eGFR* (chronic slope model) with sparsentan or irbesartan (95% CI), mL/min/1.73 m^2/year



*On-treatment eGFR.

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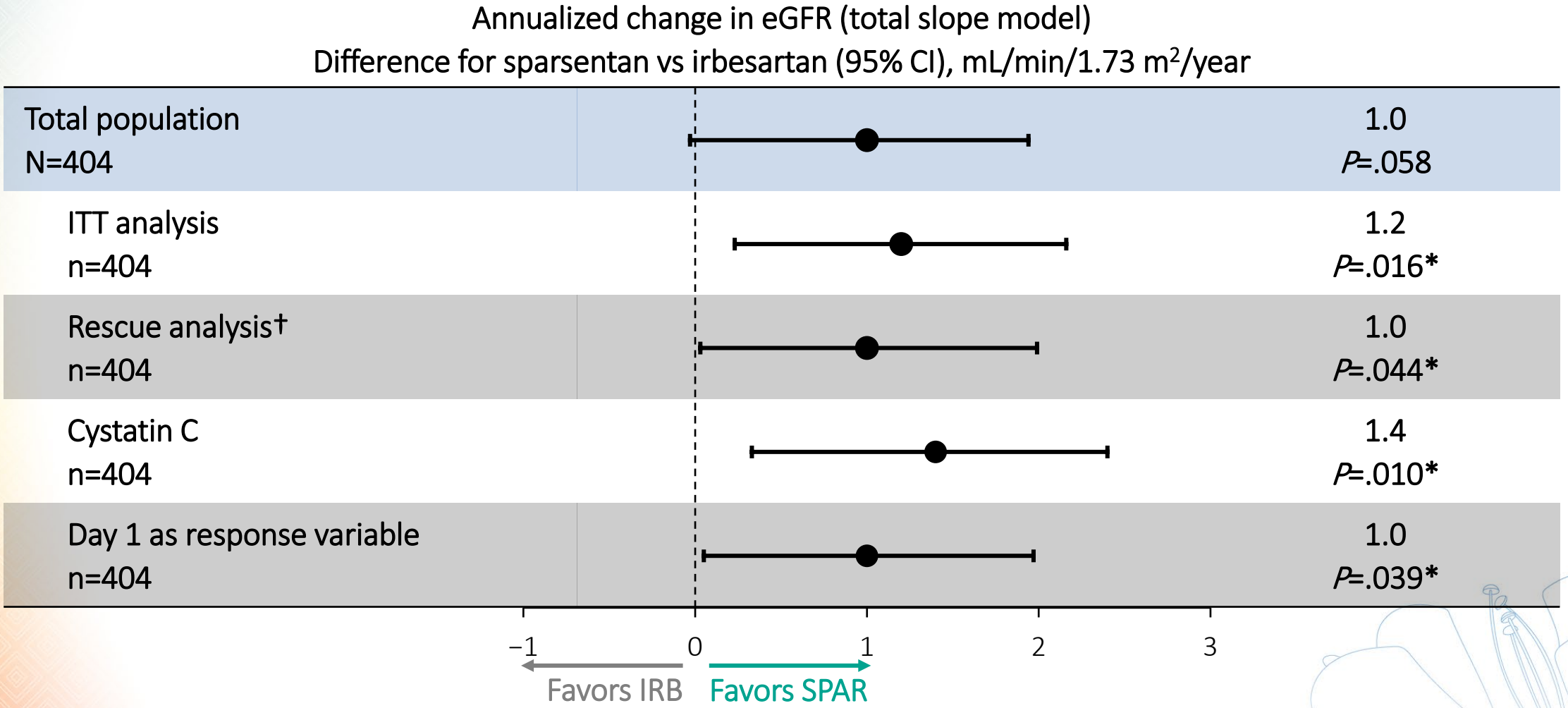
eGFR SLOPE SENSITIVITY ANALYSES CONFIRM LONG-TERM BENEFITS OF SPARSENTAN VS IRBESARTAN



*Nominal *P* values. †Rescue analysis excludes eGFR measurements after initiation of rescue immunosuppression for renal disease.

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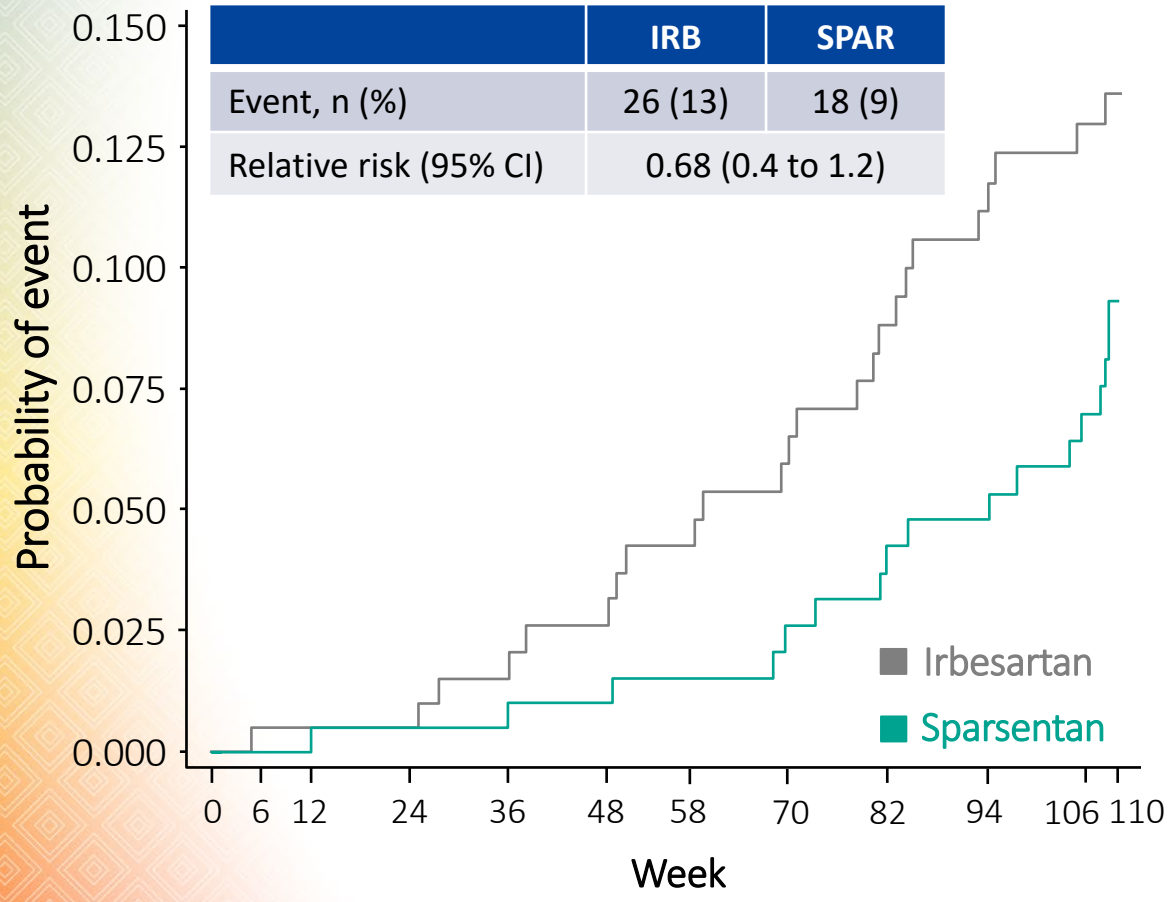
SPARSENTAN REDUCES PROGRESSION TO COMPOSITE KIDNEY FAILURE ENDPOINT

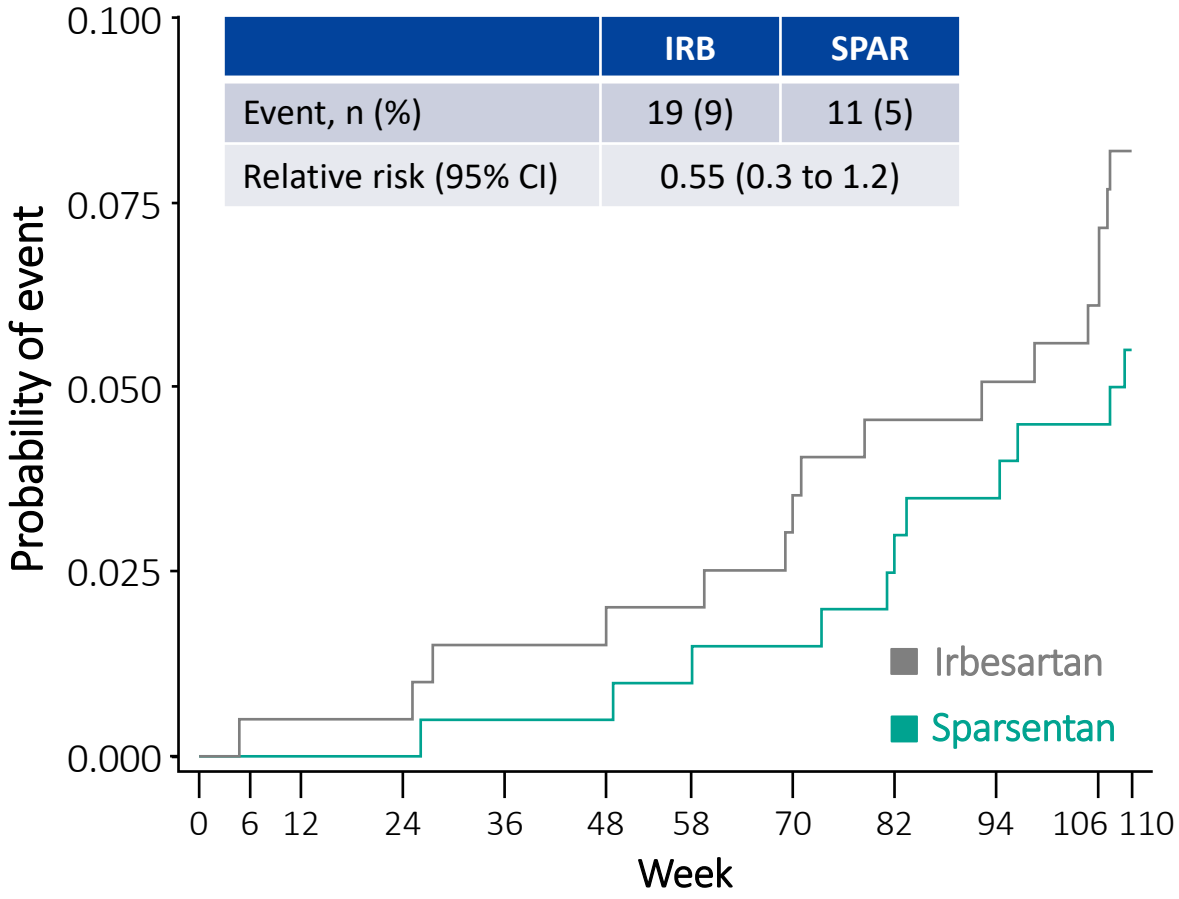
Confirmed 40% eGFR reduction, ESKD, or death

	IRB	SPAR
Event, n (%)	26 (13)	18 (9)
Relative risk (95% CI)	0.68 (0.4 to 1.2)	



Confirmed 50% eGFR reduction, ESKD, or death

	IRB	SPAR
Event, n (%)	19 (9)	11 (5)
Relative risk (95% CI)	0.55 (0.3 to 1.2)	



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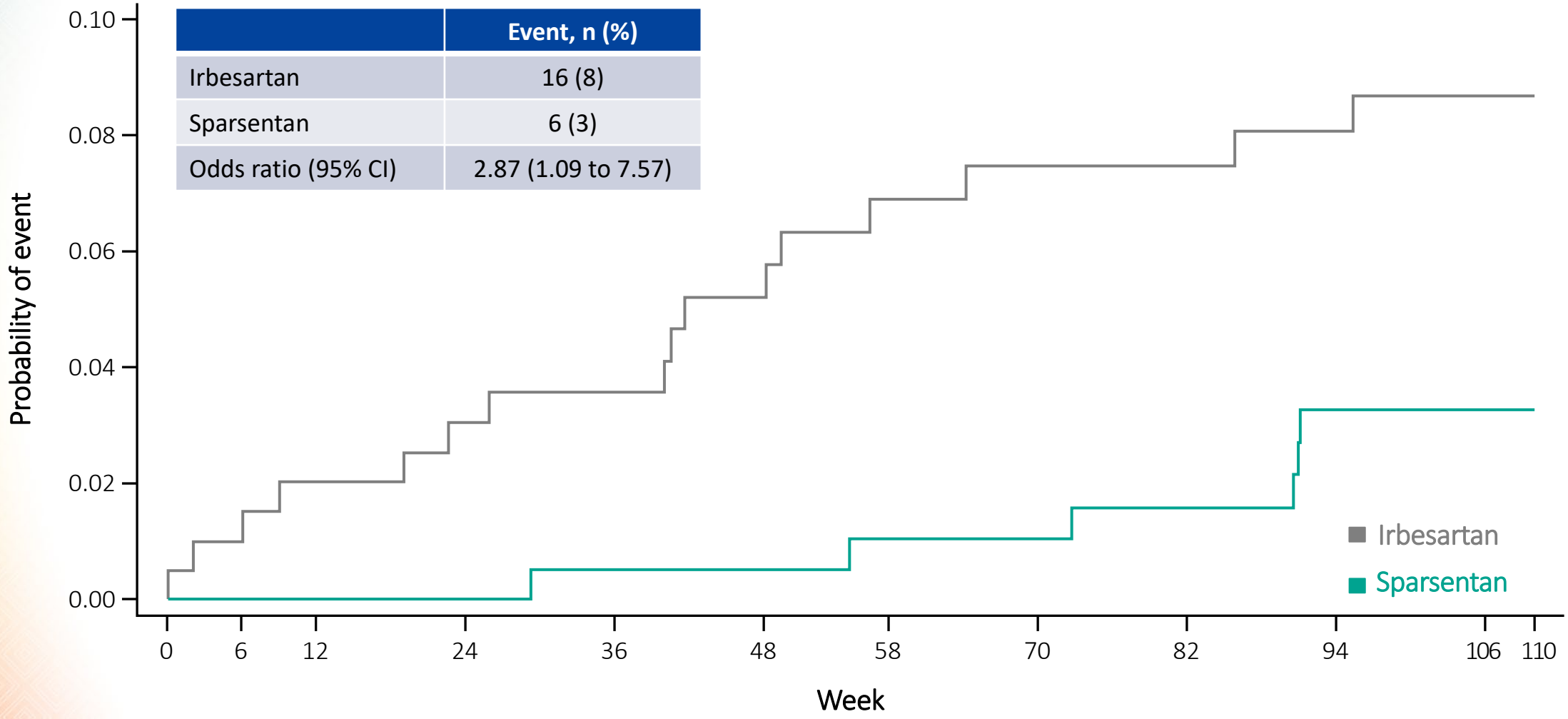
SPARSENTAN-TREATED PATIENTS REQUIRED LESS RESCUE IMMUNOSUPPRESSIVE THERAPY

	Event, n (%)
Irbesartan	16 (8)
Sparsentan	6 (3)
Odds ratio (95% CI)	2.87 (1.09 to 7.57)



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SPARSENTAN WAS WELL TOLERATED WITH A CONSISTENT SAFETY PROFILE COMPARABLE TO IRBESARTAN

Patients with TEAEs, n (%)	Sparsentan (n=202)	Irbesartan (n=202)
Any TEAEs	187 (93)	177 (88)
Most common TEAEs (≥10% of patients in either group)		
COVID-19	53 (26)	46 (23)
Hyperkalemia	32 (16)	26 (13)
Peripheral edema	31 (15)	24 (12)
Dizziness	30 (15)	13 (6)
Headache	27 (13)	26 (13)
Hypotension	26 (13)	8 (4)
Hypertension	22 (11)	28 (14)
Transaminase elevations	5 (2)	7 (3)
Serious TEAEs	75 (37)	71 (35)
Serious TEAEs in ≥5 patients in either group		
COVID-19	42 (21)	38 (19)
Chronic kidney disease	6 (3)	6 (3)
TEAEs leading to treatment discontinuation	21 (10)	18 (9)
TEAEs leading to death	0	1 (<1)

- Peripheral edema was similar in both groups, with no increases in body weight
- Low incidence of ALT/AST >3 times the ULN that was comparable with IRB; no cases of drug-induced liver injury with sparsentan

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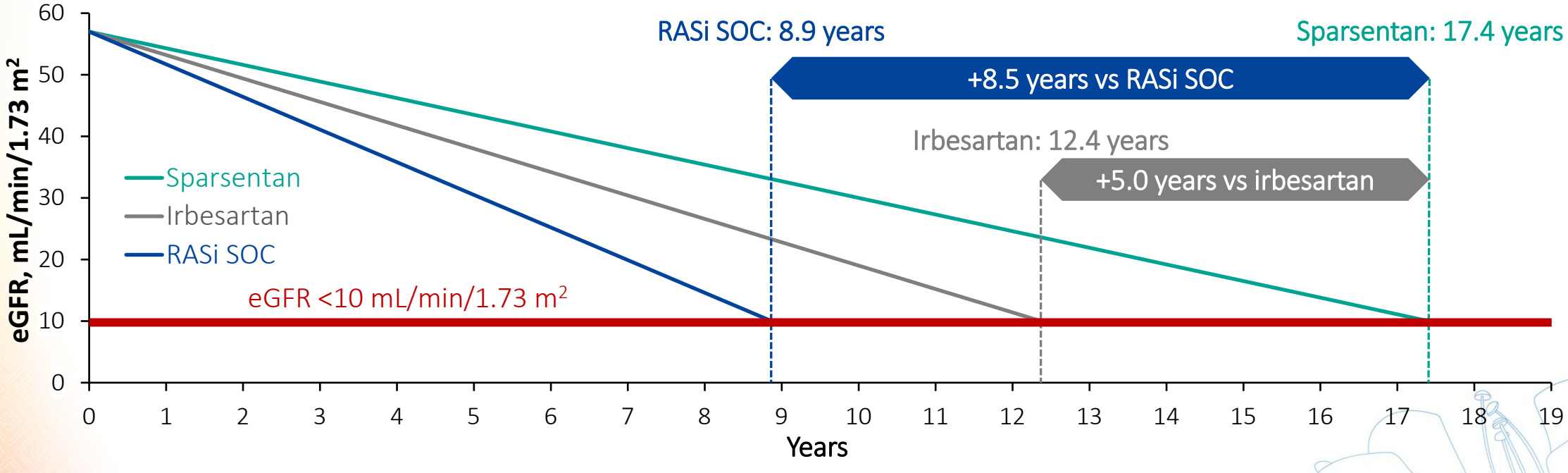
eGFR SLOPE RESULTS PROJECT DELAY IN TIME TO DIALYSIS WITH SPARSENTAN TREATMENT

Improved eGFR slope suggests that sparsentan could delay the need for dialysis or transplant

	Sparsentan	Irbesartan	RASi SOC (ACEi/ARB)
eGFR chronic slope, mL/min/1.73 m^2/year	−2.7	−3.8	−5.3*
Difference in eGFR slope vs sparsentan		1.1	2.6



Baseline (0 years) eGFR = 57 mL/min/1.73 m^2 based on the mean eGFR of all patients (N=404) reported in this study.

*Mean of observed slopes for maximized ACEi/ARB as reported in 5 clinical trials.[1-5]

1. Lafayette R, et al. *Lancet*. 2023;402(10405):859-870. 2. Lv J, et al. *JAMA*. 2022;327(19):1888-1898. 3. Wheeler DC, et al. *Kidney Int*. 2021;100(1):215-224.
4. Manno C, et al. *Nephrol Dial Transplant*. 2009;24(12):3694-3701. 5. Li PK, et al. *Am J Kidney Dis*. 2006;47(5):751-760.

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SPARSENTAN EFFICACY IN IgAN

- Sparsentan treatment causes a sustained reduction in proteinuria and a clear benefit in eGFR over 110 weeks as well as reduced hazard of renal failure
- eGFR decline in proteinuria subgroups all favor sparsentan
- Patients treated with sparsentan over 2 years exhibited one of the slowest annual rates of kidney function decline seen in phase 3 clinical trials of patients with IgAN
- Immunosuppressive therapy was initiated sooner and more frequently with irbesartan vs sparsentan

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SPARSENTAN SAFETY AND TOLERABILITY

- Sparsentan is well tolerated, with a consistent safety profile comparable to irbesartan
- Key adverse events of interest (eg, clinical edema, high aminotransferases) occur at similar frequencies in sparsentan- and irbesartan-treated patients

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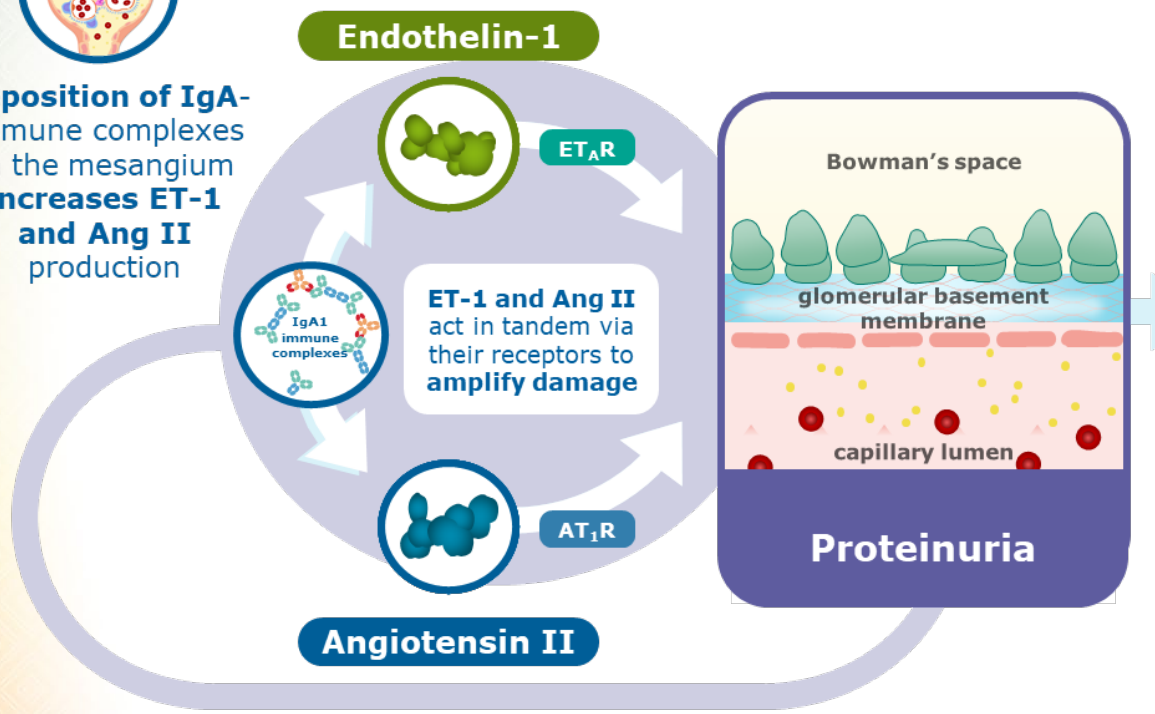
QUESTIONS?

ENDOTHELIN-1 AND ANGIOTENSIN II ARE KEY PLAYERS IN DRIVING KIDNEY INJURY, PROTEINURIA, AND DISEASE PROGRESSION IN IgAN[1-6]

Deposition of IgA-immune complexes in the mesangium **increases ET-1 and Ang II** production



Glomeruli
- Podocyte cytoskeletal alterations
- Podocyte apoptosis
- Increased glomerular permeability
- Mesangial cell proliferation
- Extracellular matrix expansion
- Glomerulosclerosis

Tubulointerstitial Compartment
- Tubular Na^+ transport
- Inflammation
- Fibrosis

Vasculature
- Vasoconstriction
- Endothelial dysfunction

Kidney failure

Together, **ET-1 and Ang II pathophysiologic effects** on glomeruli, tubulointerstitium, and vasculature **drive progression to kidney failure**

Proteinuria has a central role in disease pathophysiology

Increasing proteinuria further amplifies ET-1 and Ang II, exacerbating this cycle of damage

1. Komers R, Plotkin H. *Am J Physiol Regul Integr Comp Physiol*. 2016;310(10):R877-R884. 2. Raina R, et al. *Kidney Dis*. 2020;6(1):22-34.
3. Dhaun N, et al. *Br J Pharmacol*. 2012;167(4):720-731. 4. Wyatt RJ, Julian BA. *N Engl J Med*. 2013;368(25):2402-2414.
5. Kohan DE, Barton M. *Kidney Int*. 2014;86(5):896-904. 6. Benigni A, et al. *Pediatr Nephrol*. 2021;36(4):763-775.

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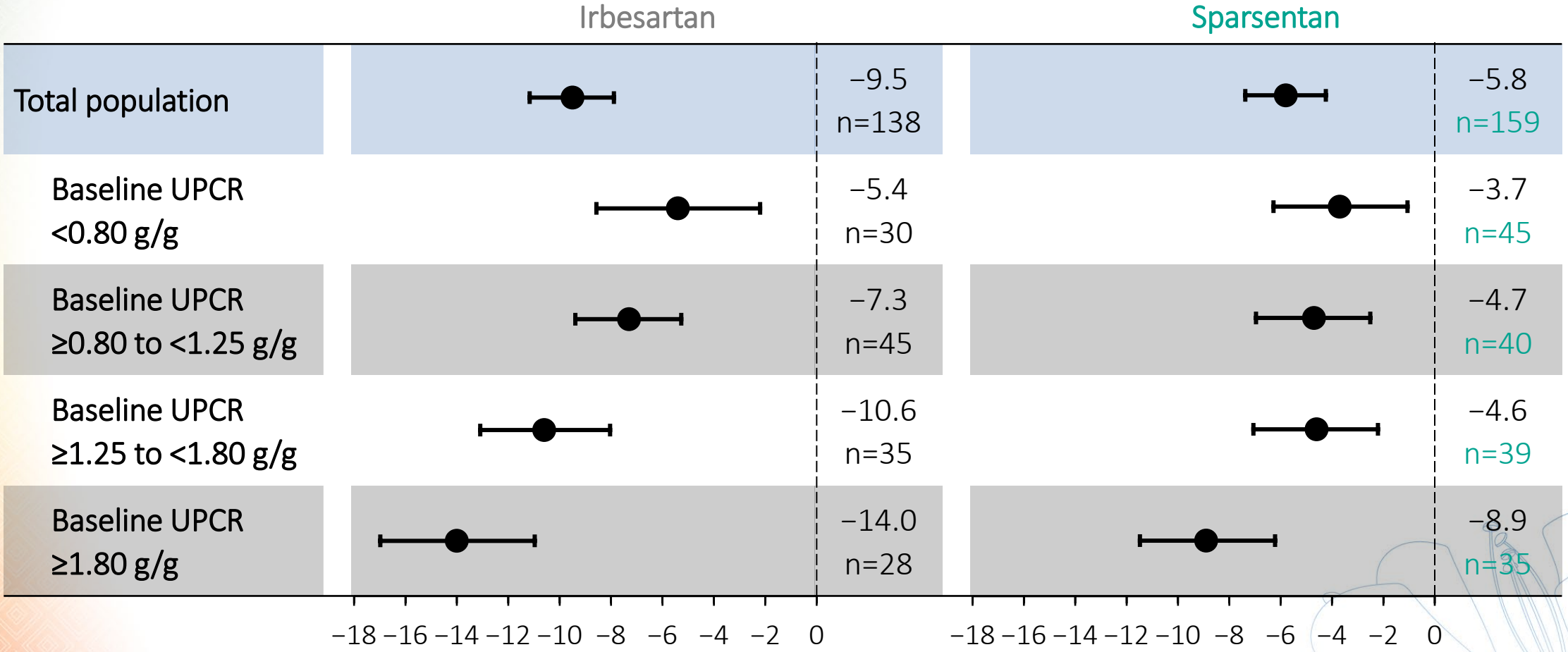
THE 110-WEEK eGFR BENEFITS OF SPARSENTAN ARE CONSISTENT ACROSS BASELINE UPCR SUBGROUPS

Absolute LS mean (95% CI) change in eGFR* from baseline to week 110, mL/min/1.73 m^2



*On-treatment eGFR.

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