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Pivotal Results of the Phase 3 PROTECT Trial of Sparsentan vs Irbesartan in Patients With Immunoglobulin A Nephropathy

Brad Rovin,[1] Jonathan Barratt,[2] Ulysses Diva,[3] Radko Komers,[3] Vlado Perkovic[4] on behalf of the DUPRO steering committee and PROTECT investigators

[1]Division of Nephrology, Ohio State University Wexner Medical Center, Columbus, OH, USA; [2]Department of Cardiovascular Sciences, University of Leicester, Leicester, UK; [3]Travere Therapeutics, Inc., San Diego, CA, USA; [4]Faculty of Medicine & Health, University of New South Wales, Sydney, NSW, Australia

Contact information:
Brad Rovin, Brad.Rovin@osumc.edu

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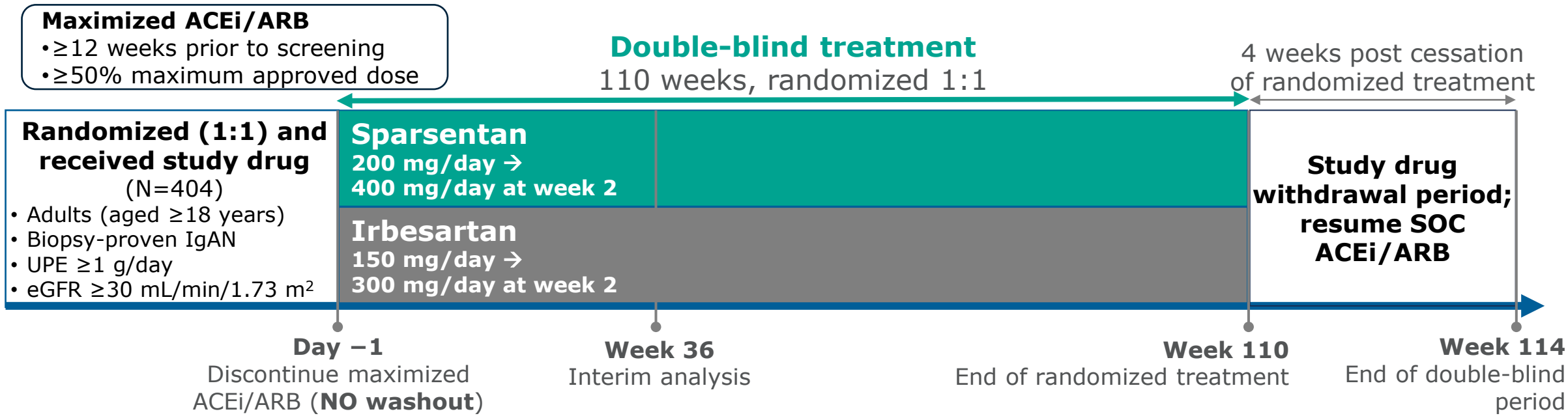
The PROTECT Study

- **Objective:** Test the efficacy and safety of sparsentan vs active control (irbesartan) in patients with IgAN
- **Rationale:**
  - In IgAN, the endothelin system is activated along with the RAAS
  - Both systems mediate kidney injury through multiple mechanisms including inflammation and fibrosis
  - Therefore, we postulated that treatment with sparsentan, a dual endothelin (ET_AR) and angiotensin (AT_1R) receptor antagonist, will be more effective in reducing proteinuria and preserving kidney function in patients with IgAN than treatment with an angiotensin receptor blocker (ARB) alone

Trial* Design

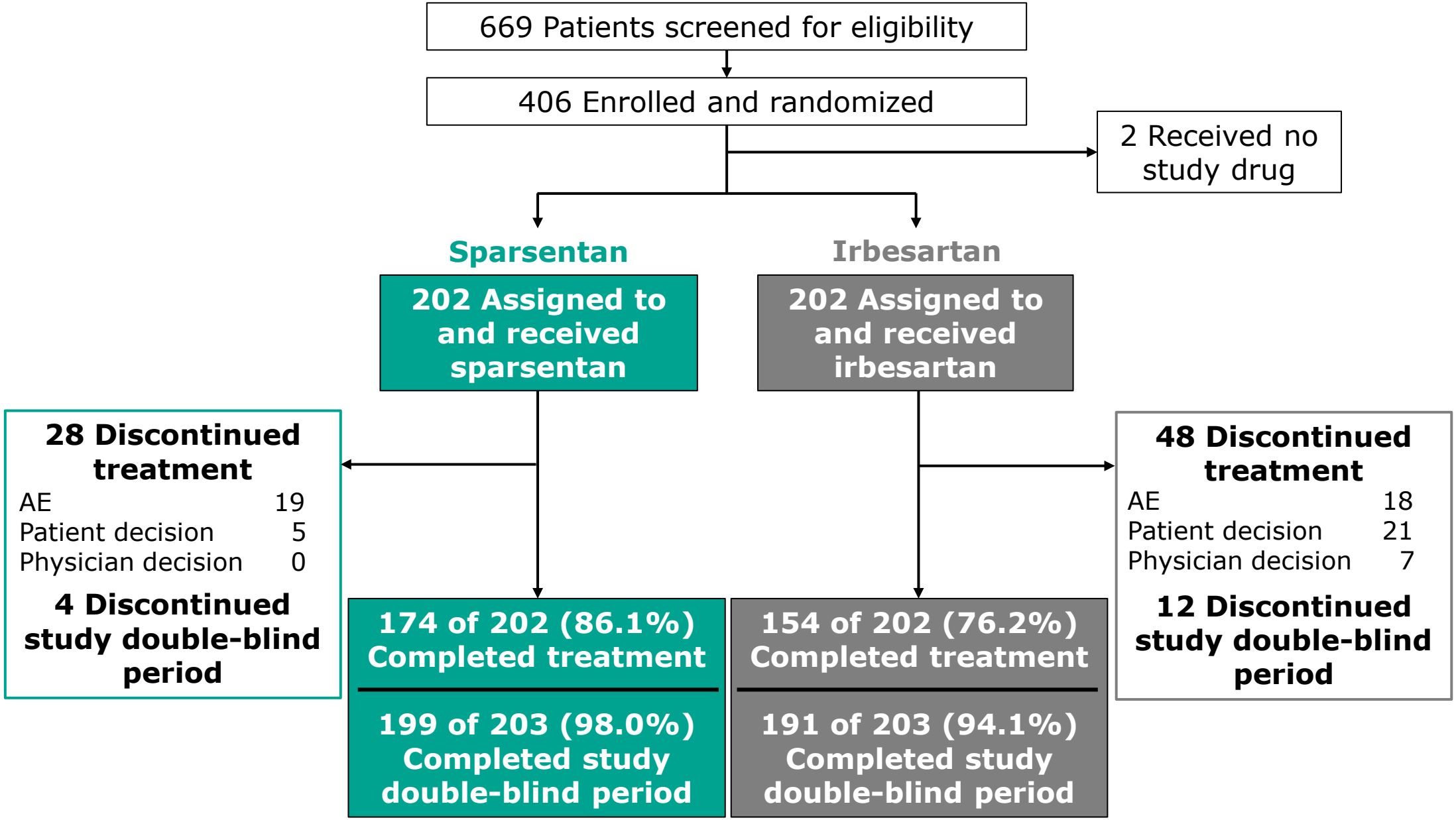


Primary Efficacy Endpoint
Change in UPCR from baseline to week 36

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

***NCT03762850**

Patient Disposition



Baseline Demographics and Clinical Characteristics

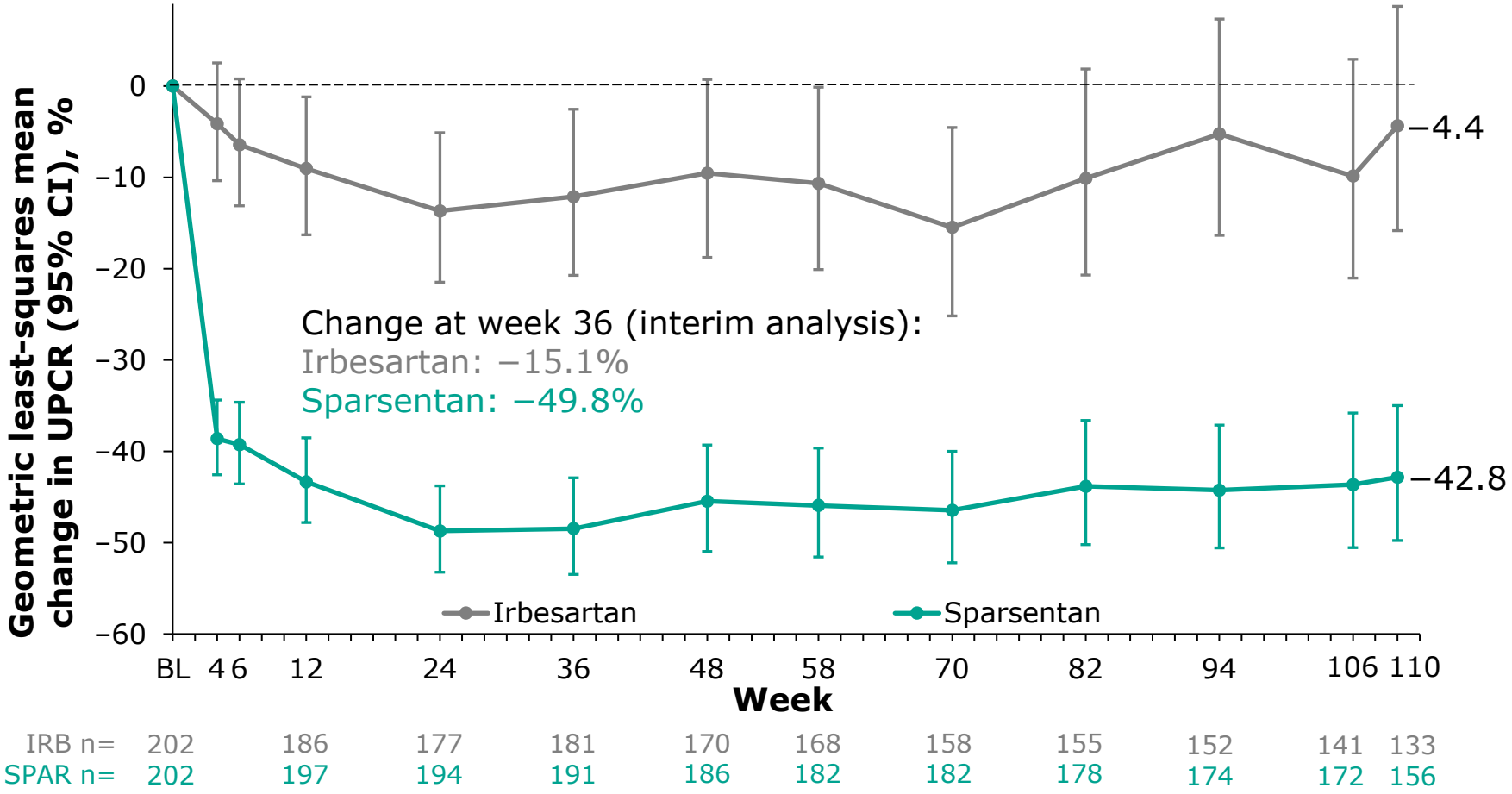
	Sparsentan n=202	Irbesartan n=202
Age at IgAN diagnosis, mean (SD), years	40.2 (13.4)	39.0 (12.4)
Age at informed consent, mean (SD), years	46.6 (12.8)	45.4 (12.1)
Male sex, n (%)	139 (69)	143 (71)
Blood pressure, mean (SD), mm Hg		
Systolic	128.0 (14.4)	129.9 (12.4)
Diastolic	81.6 (10.6)	83.2 (10.6)
Maximum labeled ACEi or ARB dose at screening, n (%)	130 (64)	125 (62)
eGFR, mean (SD), mL/min/1.73 m²	56.8 (24.3)	57.1 (23.6)
Urine protein excretion, median (IQR), g/day	1.8 (1.2-2.9)	1.8 (1.3-2.6)
Urine protein-creatinine ratio, median (IQR), g/g	1.3 (0.8-1.8)	1.2 (0.9-1.7)
Hematuria, n (%)	111 (55)	114 (56)

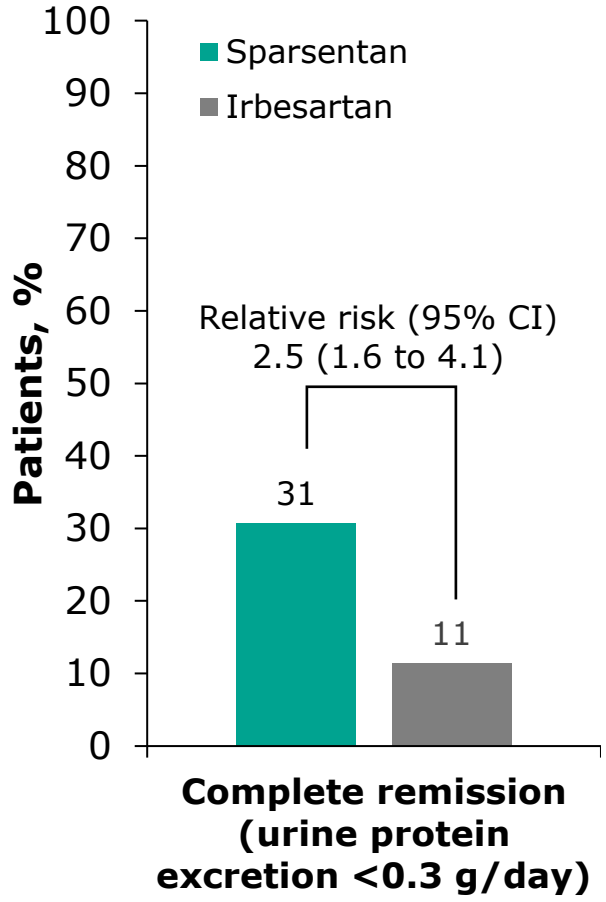
Study drug dose

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

Proteinuria

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



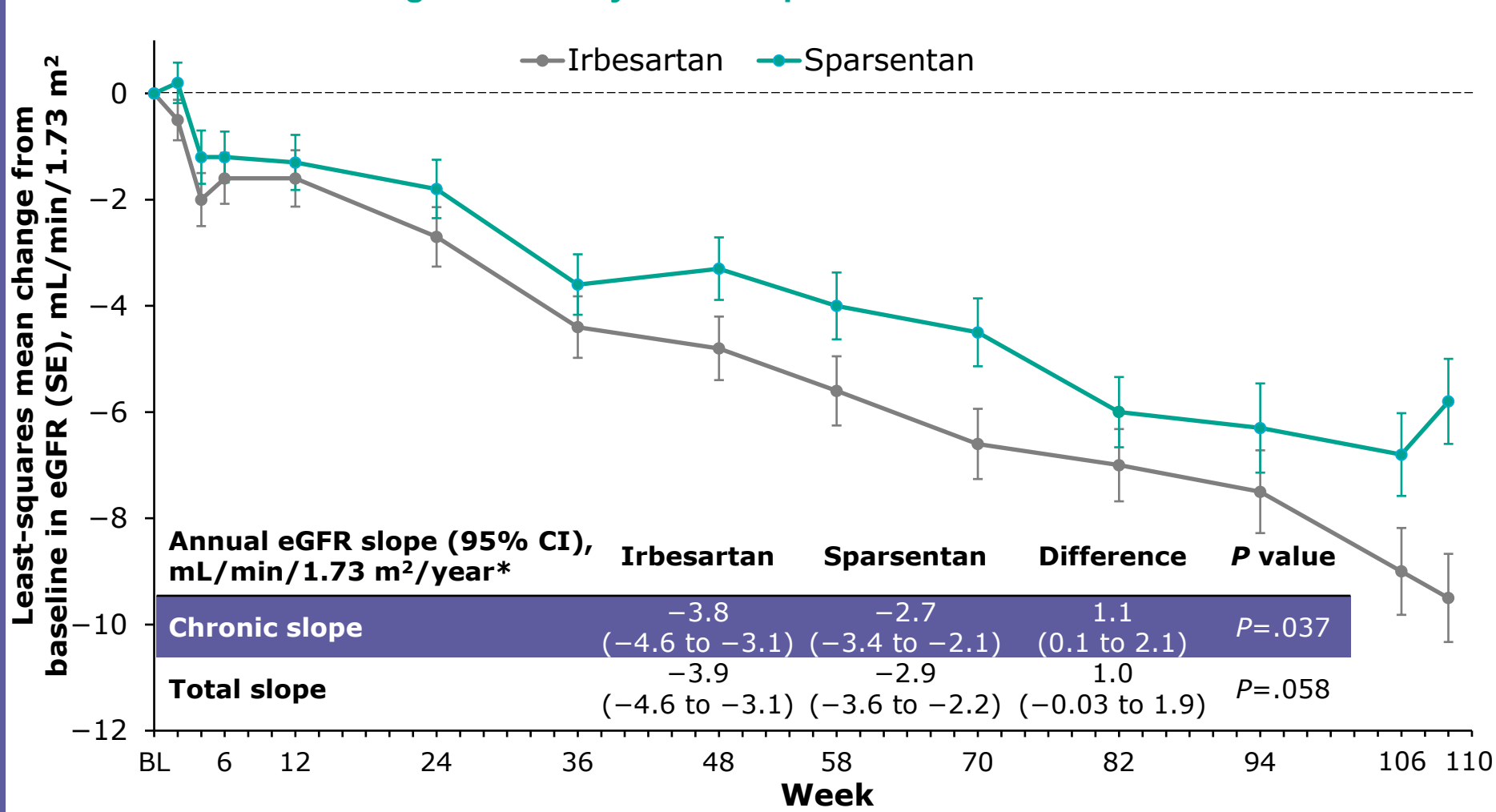


- Significant proteinuria reduction was sustained over 110 weeks
- More patients achieved complete proteinuria remission (<0.3 g/day) with sparsentan vs irbesartan

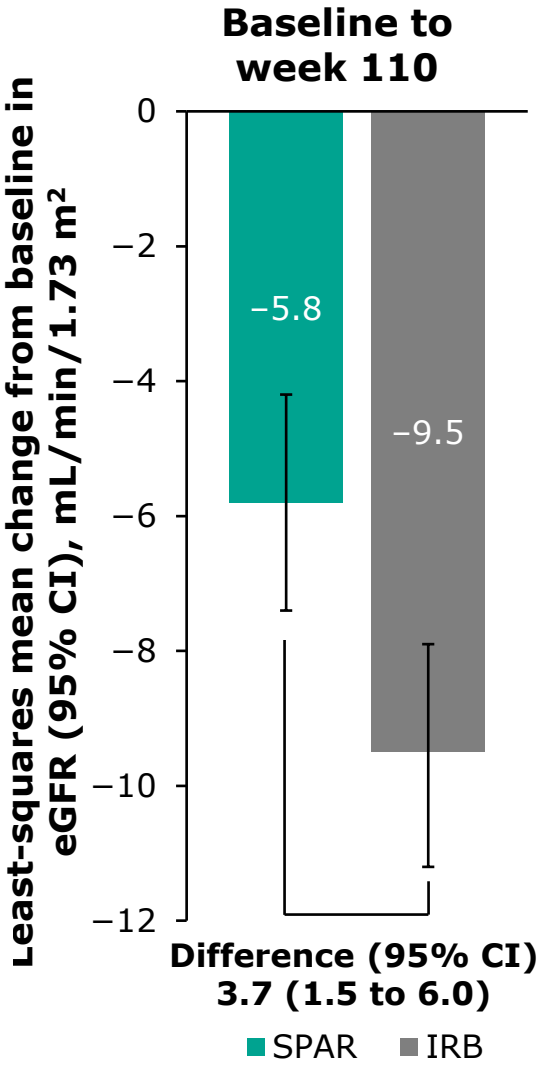
RESULTS

Kidney Function

Confirmation of long-term kidney function preservation



Annual eGFR slope (95% CI), mL/min/1.73 m²/year*	Irbesartan	Sparsentan	Difference	*P* value
Chronic slope	−3.8 (−4.6 to −3.1)	−2.7 (−3.4 to −2.1)	1.1 (0.1 to 2.1)	*P*=.037
Total slope	−3.9 (−4.6 to −3.1)	−2.9 (−3.6 to −2.2)	1.0 (−0.03 to 1.9)	*P*=.058

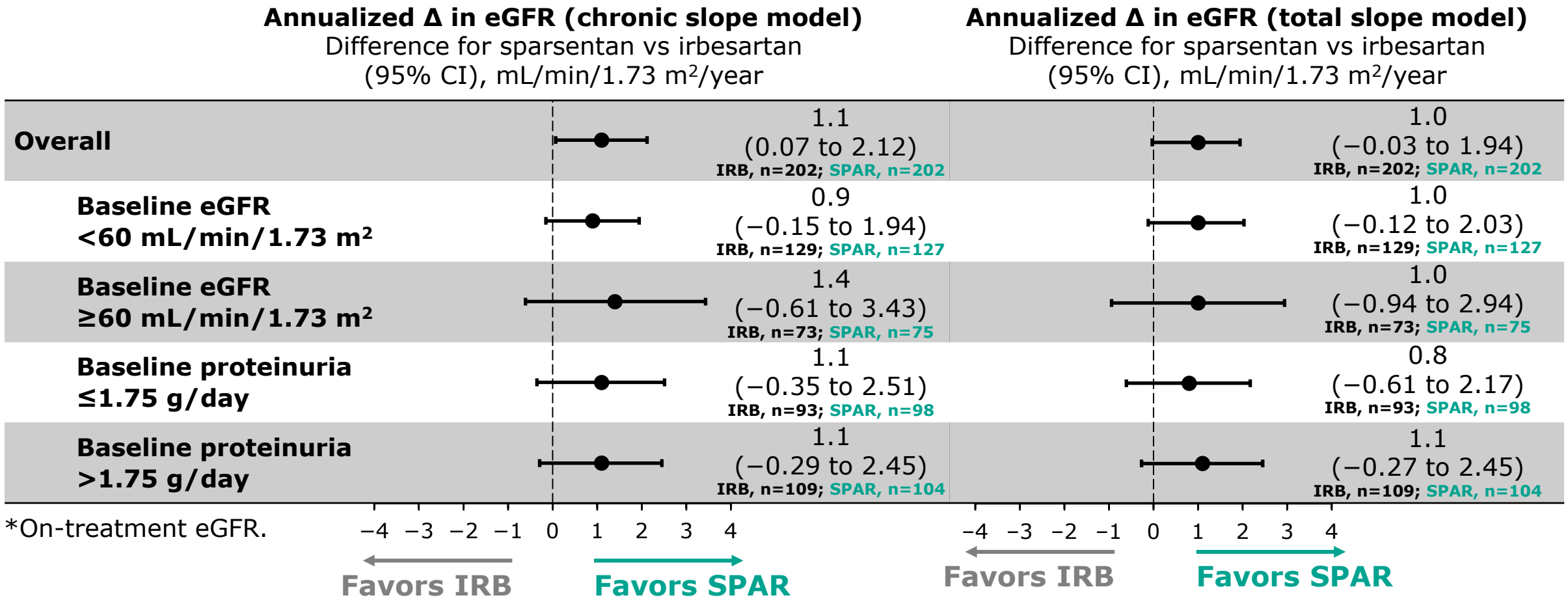


*Analysis includes eGFR data for patients on treatment; off-treatment and missing data imputed using the multiple imputation procedure.

RESULTS

Key eGFR* Slope Subgroup Analyses by Baseline eGFR and Proteinuria

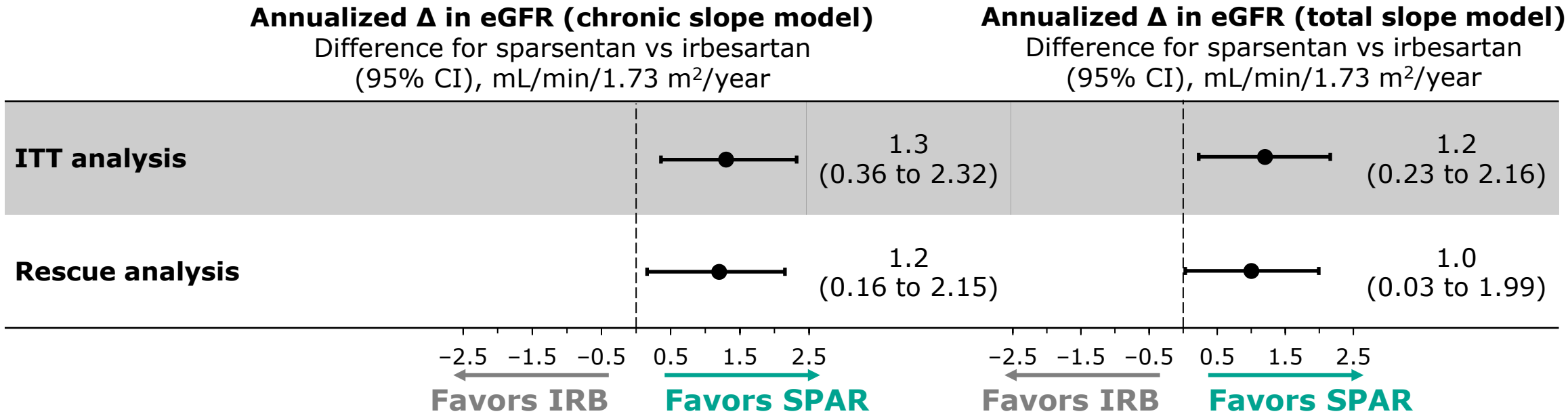
Subgroup analyses demonstrate consistent treatment effect across disease severity



*On-treatment eGFR.

eGFR Slope Sensitivity Analyses

Sensitivity analyses confirm long-term kidney function preservation



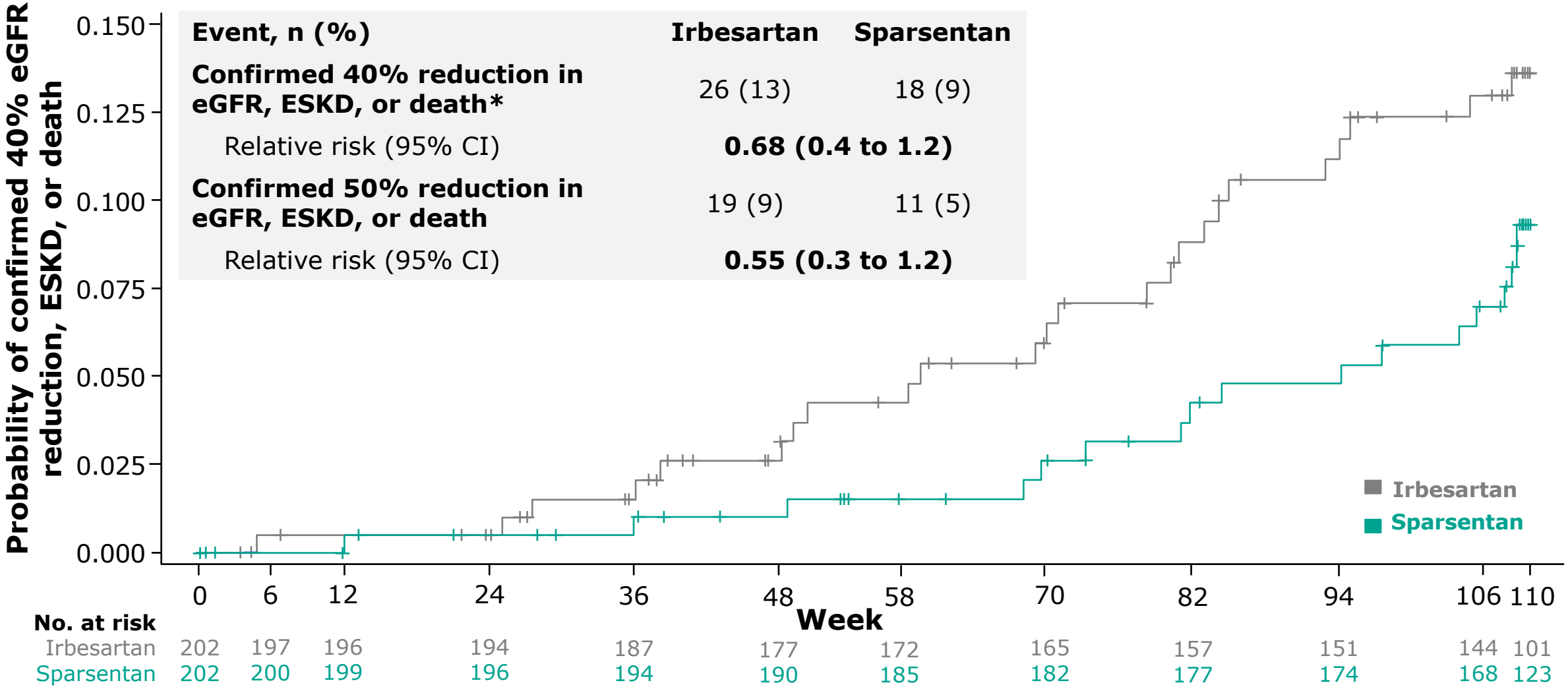
- ITT analysis includes all eGFR measurements through study end irrespective of premature treatment discontinuations
- Rescue analysis excludes eGFR measurements after initiation of rescue immunosuppression for renal disease (3% with SPAR and 8% with IRB)

Progression to Composite Kidney Failure Endpoint

PROTECT IgAN

Fewer sparsentan-treated patients progressed to composite endpoint vs irbesartan

Event, n (%)	Irbesartan	Sparsentan
Confirmed 40% reduction in eGFR, ESKD, or death*	26 (13)	18 (9)
Relative risk (95% CI)	**0.68 (0.4 to 1.2)**	
Confirmed 50% reduction in eGFR, ESKD, or death	19 (9)	11 (5)
Relative risk (95% CI)	**0.55 (0.3 to 1.2)**	

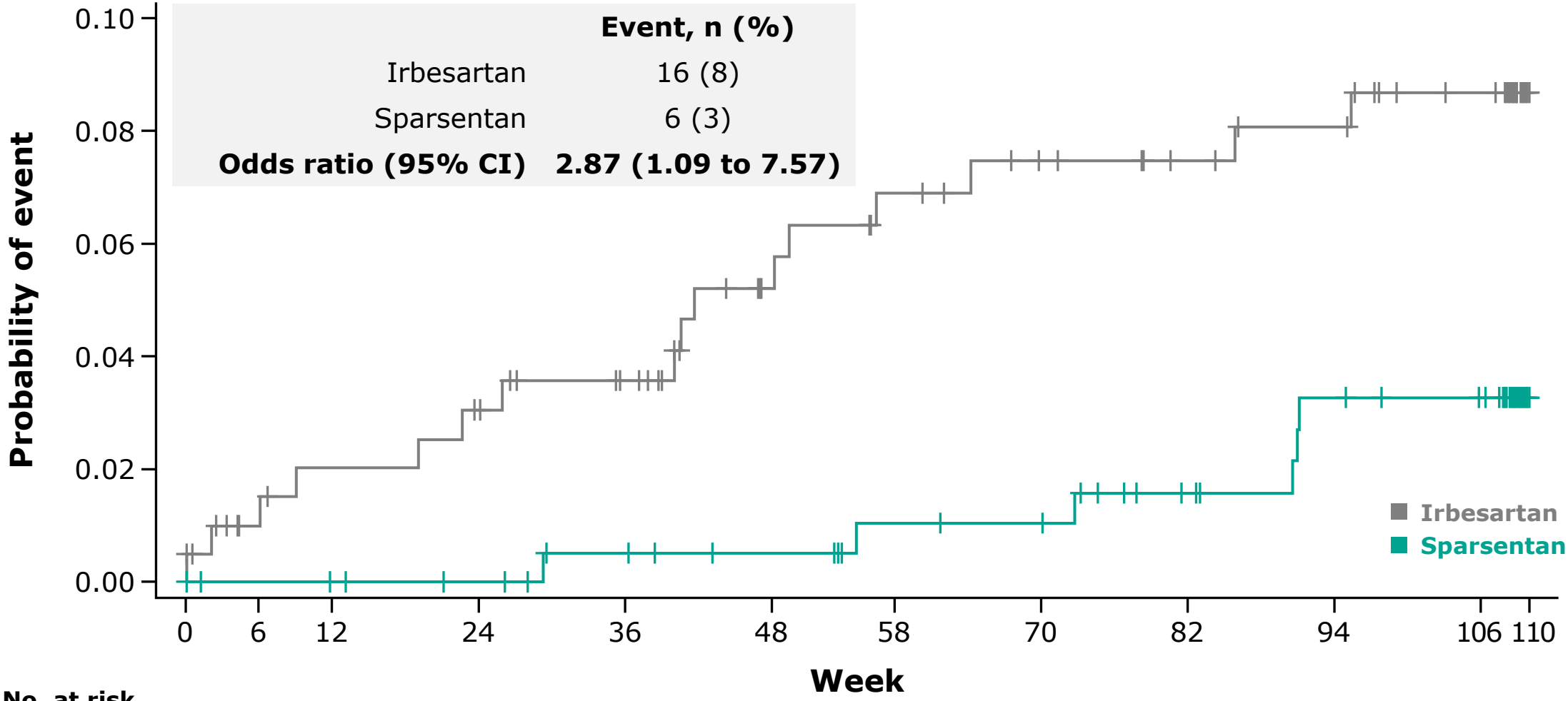


Vertical bars indicate censored patients. *Patients with confirmed 40% reduction in eGFR (IRB, n=22 [11%]; SPAR, n=18 [9%]), ESKD (IRB, n=11 [5%]; SPAR, n=9 [4%]), or death (IRB, n=1 [<1%]; SPAR, n=0).

Initiation of Immunosuppressive Therapy

Fewer sparsentan-treated patients initiated immunosuppressive therapy vs irbesartan

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



No. at risk

Irbesartan	202	194	191	188	182	169	164	159	155	152	145	108
Sparsentan	202	200	199	197	193	190	186	185	178	173	170	123

Vertical bars indicate censored patients. Median time to initiation of systemic IST with renal indication was not estimable for either treatment group.

Safety

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× ULN that was comparable with IRB; no cases of drug-induced liver injury with sparsentan**

CONCLUSIONS

- Sparsentan met the primary endpoint of proteinuria change at 36 weeks in the interim analysis, with sustained antiproteinuric effects shown in the final analysis
- Clinical benefit of sparsentan was confirmed by eGFR chronic slope, which showed statistically significant treatment effects vs maximally titrated irbesartan within a rigorously conducted trial, including in the ITT analysis
- The data suggest a clinically meaningful difference between sparsentan and irbesartan in total slope and other eGFR-based endpoints, including a composite kidney failure endpoint
- Patients treated with sparsentan over 2 years exhibited one of the slowest annual rates of kidney function decline seen in IgAN trials
- All top-line efficacy endpoints favored sparsentan, and sparsentan was well tolerated with a safety profile comparable to irbesartan, supporting long-term use

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Efficacy and safety of sparsentan versus irbesartan in patients with IgA nephropathy (PROTECT): 2-year results from a randomised, active-controlled, phase 3 trial

Brad H Rovin, Jonathan Barratt*, Hiddo J L Heerspink, Charles E Alpers, Stewart Bieler, Dong-Wan Chae, Ulysses A Diva, Jürgen Floege, Loreto Gesualdo, Jula K Inrig, Donald E Kohan, Radko Komers, Laura Ann Kooienga, Richard Lafayette, Bart Maes, Robert Małecki, Alex Mercer, Irene L Noronha, Se Won Oh, Chen Au Peh, Manuel Praga, Priscila Preciado, Jai Radhakrishnan, Michelle N Rheault, William E Rote, Sydney C W Tang, Vladimir Tesar, Howard Trachtman, Hernán Trimarchi, James A Tumlin, Muh Geot Wong, Vlado Perkovic, on behalf of the DUPRO steering committee and PROTECT Investigators†*

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