FR-OR57

PROTECT Subgroup Analysis: Sparsentan Provides Clinical Benefits vs Irbesartan in Patients With IgA Nephropathy With Proteinuria Above and Below 1 g/g

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- **HT** reports receiving grants from AstraZeneca, Bayer, BioCryst Pharmaceuticals, Calliditas Therapeutics, Chinook Therapeutics, Dimerix, George Clinical, Novartis, Omeros, Otsuka Pharmaceuticals, and Vera Therapeutics; consulting fees from AstraZeneca, BioCryst Pharmaceuticals, Calliditas Therapeutics, Chinook Therapeutics, Dimerix, George Clinical, Novartis, Omeros, Travere Therapeutics, Inc., and Vera Therapeutics; honoraria from AstraZeneca, BioCryst Pharmaceuticals, Calliditas Therapeutics, Chinook Therapeutics, George Clinical, Novartis, and Travere Therapeutics, Inc.; travel support from BioCryst Pharmaceuticals, Calliditas Therapeutics, and Chinook Therapeutics; and membership 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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- **PP** is a former employee and stockholder of Travere Therapeutics, Inc.

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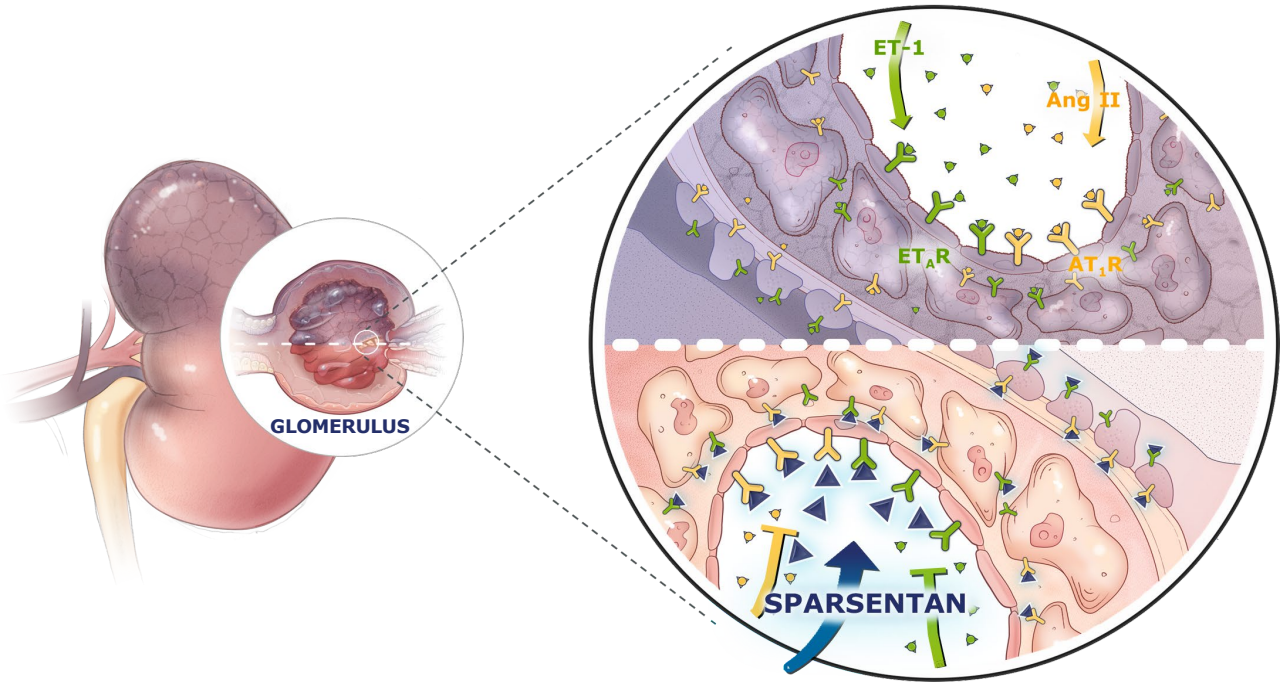
- **JR** reports receiving grant funding for clinical trials from Travere Therapeutics, Inc., paid to his institution; consulting fees from Travere Therapeutics, Inc.; advisory board membership for Travere Therapeutics, Inc.; and a leadership role at KDIGO 2021 Clinical Practice Guideline for the Management of Glomerular Diseases.

Background

- Sparsentan (SPAR) is a non-immunosuppressive, single-molecule, dual endothelin angiotensin receptor antagonist (DEARA)[1] approved in the US and EU for adults with IgAN[2,3]



Sparsentan targets glomerular injury and slows kidney function decline[1,2]

EFFECTS:

- Anti-inflammatory[4-7*]
- Anti-proliferative[4,5,7*]
- Anti-fibrotic[6,7*]
- Anti-proteinuric[8]

*These effects are based on pre-clinical animal modeling data.

Ang II, angiotensin II; AT_1R, angiotensin II type 1 receptor; DEARA, dual endothelin angiotensin receptor antagonist; ET-1, endothelin 1; ET_AR, endothelin-1 type A receptor; IgAN, immunoglobulin A nephropathy; SPAR, sparsentan.

1. Kohan DE, et al. *Clin Sci (Lond)*. 2024;138(11):645-662. **2.** FILSPARI (sparsentan). Prescribing Information. September 2024. Travere Therapeutics, Inc. San Diego, CA, USA. **3.** FILSPARI (sparsentan). SmPC. April 2024. CSL Vifor. Paris, France. **4.** Jenkinson C, et al. Poster presented at: ISN World Congress of Nephrology; April 12-15, 2019; Melbourne, Australia. SAT-010. **5.** Reily C, et al. *Am J Physiol Renal Physiol*. 2024;326:F862-F875. **6.** Nagasawa H, et al. *Nephrol Dial Transplant*. 2024;39:1494-1503. **7.** Jenkinson C, et al. Presentation at: International Symposium on IgANephropathy; September 27-29, 2018; Buenos Aires, Argentina. **8.** Rovin BH, et al. *Lancet*. 2023;402(10417):2077-2090.

Background (continued)

- In the pivotal Phase 3 PROTECT trial, SPAR showed sustained proteinuria reduction and better kidney function preservation vs the maximum labeled dose of irbesartan (IRB)[1]
- In patients with IgAN, reduced proteinuria is associated with improved kidney survival[2]
- Even patients with proteinuria <1 g/day are at risk for developing kidney failure within 10 years of diagnosis[3]

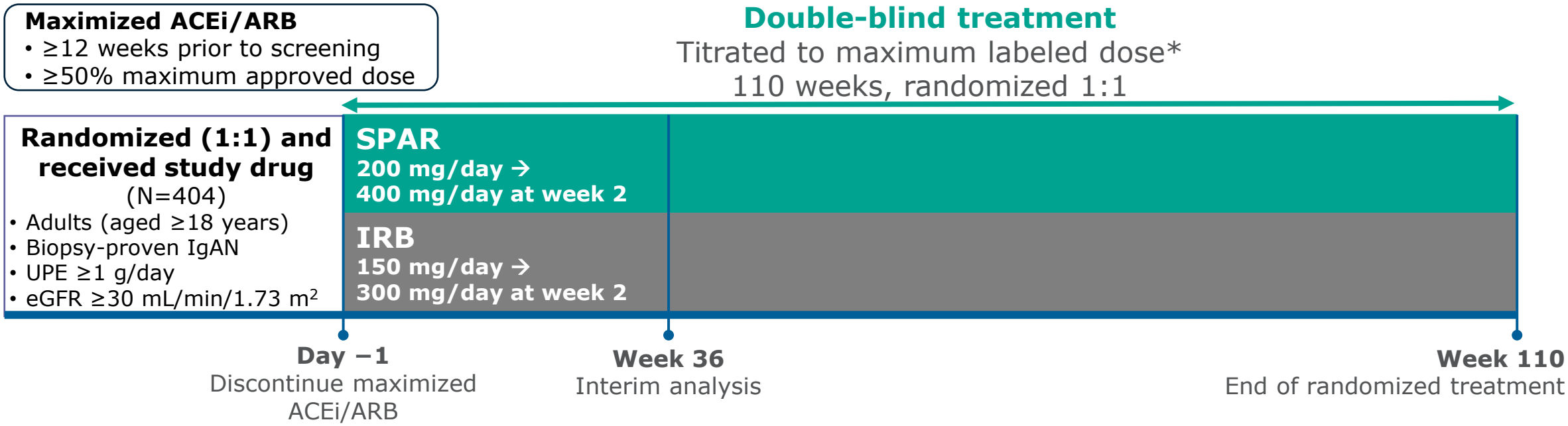
Objective

- Determine the treatment effects of SPAR vs maximum labeled dose IRB in patients with IgAN in PROTECT between patient subgroups with baseline 24 h UPCR <1.0 and ≥1.0 g/g

IgAN, immunoglobulin A nephropathy; IRB, irbesartan; SPAR, sparsentan; UPCR, urine protein-to-creatinine ratio.

1. Rovin BH, et al. *Lancet*. 2023;402(10417):2077-2090. **2.** Thompson A, et al. *Clin J Am Soc Nephrol*. 2019;14(3):469-481.
3. Pitcher D, et al. *Clin J Am Soc Nephrol*. 2023;18(6):727-738.

PROTECT Trial Design (NCT03762850)



- Inclusion criterion of **UPE ≥1 g/day** at screening
- This analysis evaluates subgroups of **UPCR <1 vs ≥1 g/g** at baseline

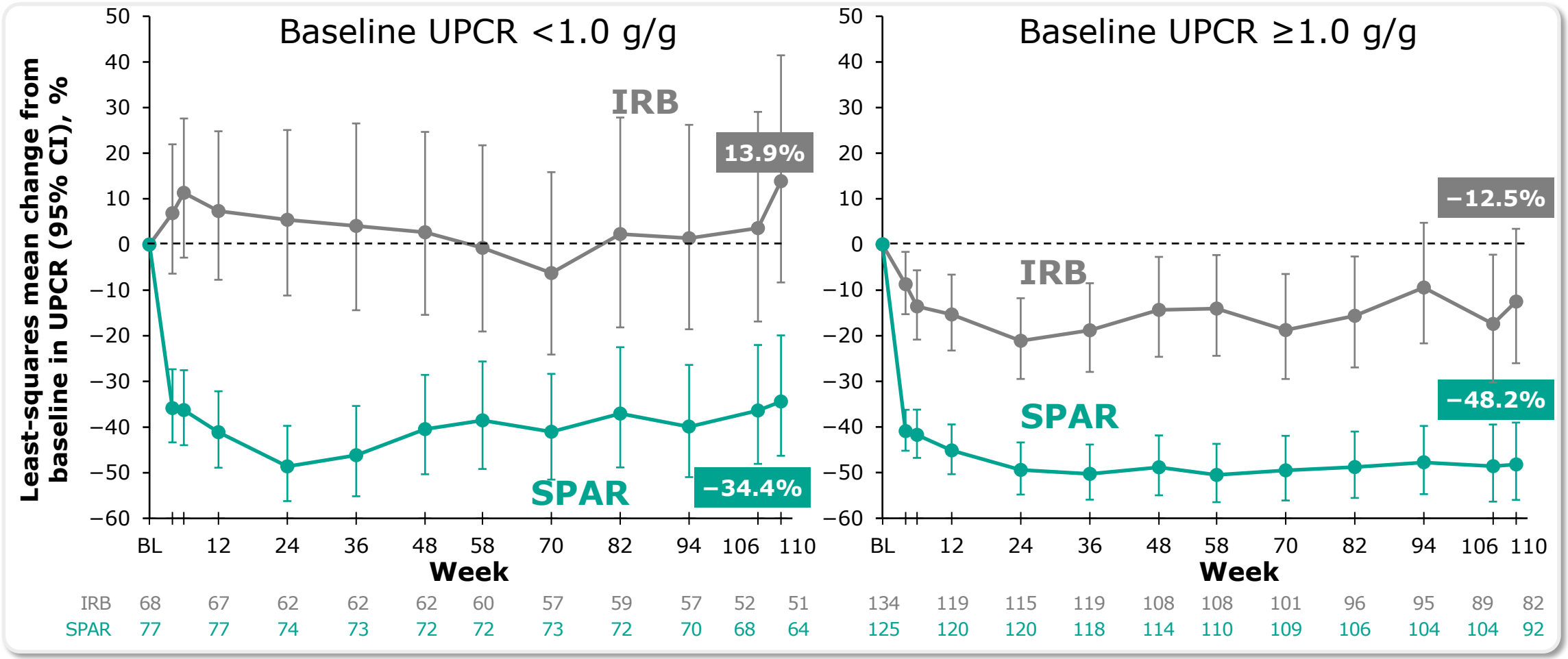
ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; eGFR, estimated glomerular filtration rate; IgAN, immunoglobulin A nephropathy; IRB, irbesartan; SPAR, sparsentan; UPCR, urine protein-to-creatinine ratio; UPE, urine protein excretion.
*95% and 97% of patients titrated to maximum labeled dose of sparsentan and irbesartan, respectively.

Patient Demographics and Baseline Characteristics Were Well Balanced Between Treatment Arms

	Baseline UPCR <1.0 g/g (n=145)		Baseline UPCR ≥1.0 g/g (n=259)	
Baseline characteristics	**SPAR (n=77)**	**IRB (n=68)**	**SPAR (n=125)**	**IRB (n=134)**
Age at informed consent, mean (SD), years	46.2 (12.31)	47.2 (12.21)	46.8 (13.07)	44.5 (12.02)
Male, n (%)	63 (82)	58 (85)	76 (61)	85 (63)
eGFR, mean (SD), mL/min/1.73 m²	57.6 (24.78)	61.3 (25.59)	56.3 (24.13)	54.9 (22.27)
UPCR, median (IQR), g/g	0.72 (0.54-0.82)	0.76 (0.62-0.88)	1.69 (1.29-2.14)	1.52 (1.24-1.96)
UPE, median (IQR), g/day	1.15 (0.95-1.40)	1.31 (1.04-1.57)	2.51 (1.77-3.30)	2.32 (1.77-3.02)

eGFR, estimated glomerular filtration rate; IRB, irbesartan; SPAR, sparsentan; UPCR, urine protein-to-creatinine ratio; UPE, urine protein excretion.

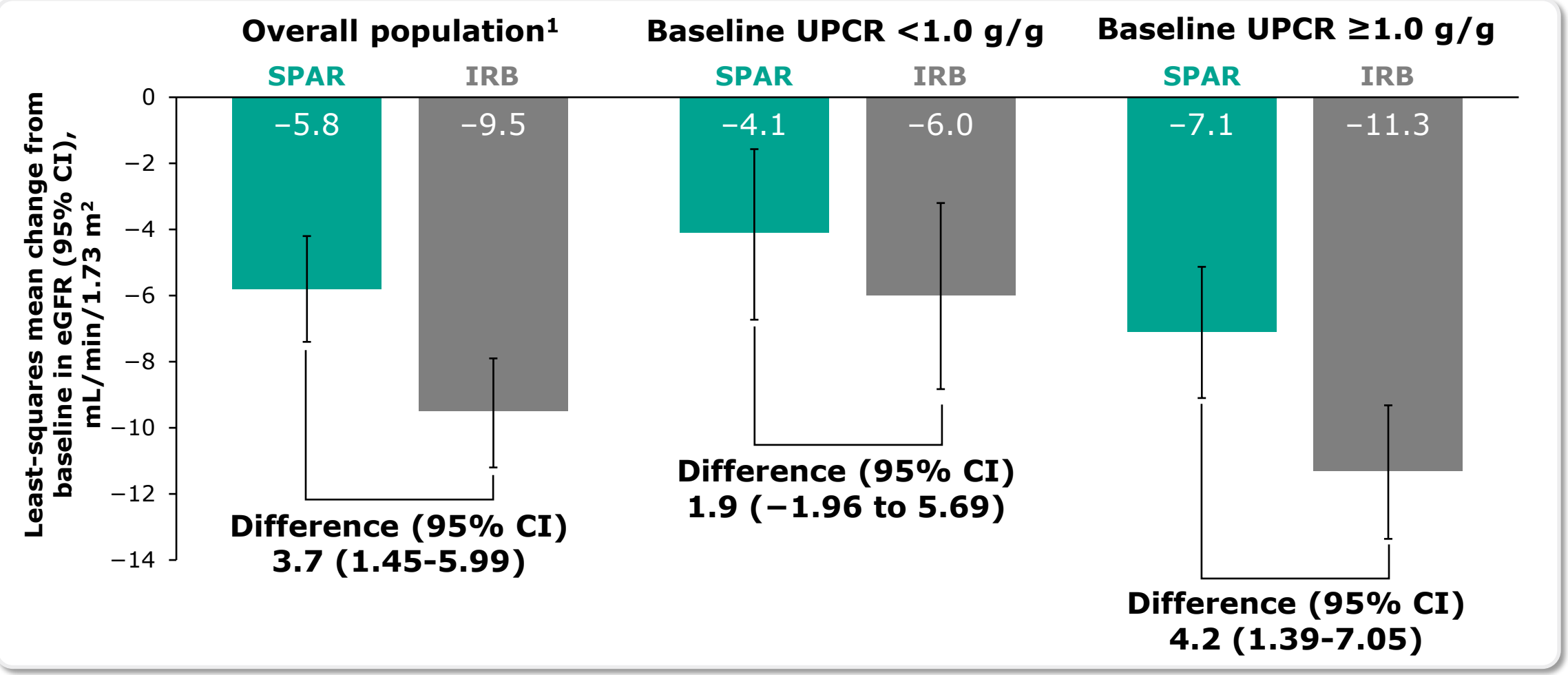
SPAR Showed Rapid and Sustained Reductions in Proteinuria Through Week 110, Superior to Maximum Labeled Dose IRB, Regardless of Baseline UPCR Level



IRB, irbesartan; SPAR, sparsentan; UPCR, urine protein-to-creatinine ratio.

RESULTS

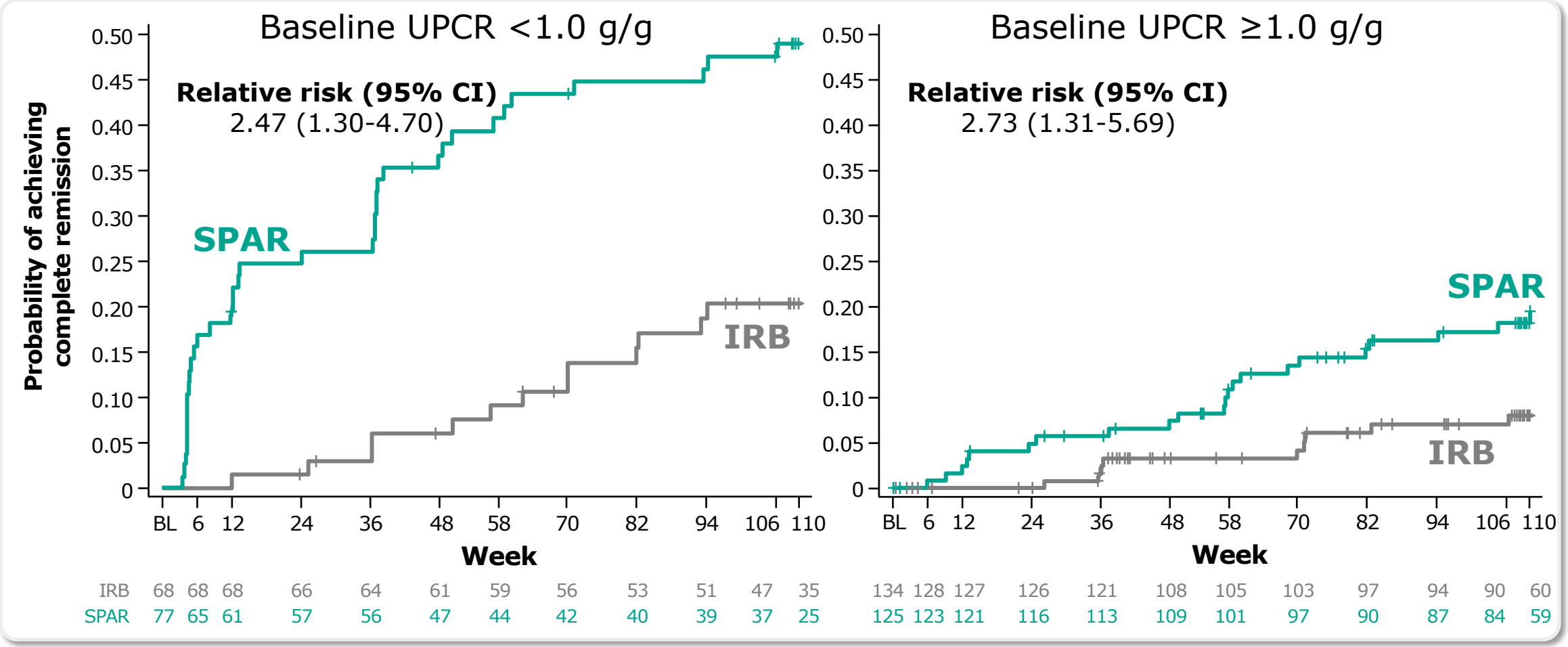
Absolute Change in eGFR From Baseline to Week 110 Was Lower With SPAR vs Maximum Labeled Dose IRB, Regardless of Baseline UPCR Level



eGFR, estimated glomerular filtration rate; IRB, irbesartan; SPAR, sparsentan; UPCR, urine protein-to-creatinine ratio.

1. Rovin BH, et al. *Lancet*. 2023;402(10417):2077-2090.

Complete Proteinuria Remission (<0.3 g/day) Was Achieved Earlier and More Frequently With SPAR vs IRB Regardless of Baseline UPCR Level



IRB, irbesartan; SPAR, sparsentan; UPCR, urine protein-to-creatinine ratio.

SPAR Was Well-Tolerated With a Consistent Safety Profile Across Baseline Proteinuria Subgroups, Comparable to Maximum Labeled Dose IRB

	Baseline UPCR <1.0 g/g (n=145)		Baseline UPCR ≥1.0 g/g (n=259)	
	SPAR (n=77)	IRB (n=68)	SPAR (n=125)	IRB (n=134)
Patients with any TEAE, n (%)	69 (90)	58 (85)	118 (94)	119 (89)
Discontinued treatment due to AE, n (%)	6 (8)	2 (3)	13 (10)	16 (12)
Most common AEs (≥15% in any group), n (%)				
COVID-19*	26 (34)	18 (26)	27 (22)	28 (21)
Dizziness	12 (16)	2 (3)	18 (14)	11 (8)
Headaches	8 (10)	7 (10)	19 (15)	19 (14)
Hyperkalemia	11 (14)	9 (13)	21 (17)	17 (13)
Hypertension	7 (9)	8 (12)	15 (12)	20 (15)
Hypotension	5 (6)	1 (1)	21 (17)	7 (5)
Peripheral edema	9 (12)	7 (10)	22 (18)	17 (13)

*PROTECT was conducted during the COVID-19 pandemic.
AE, adverse event; IRB, irbesartan; SPAR, sparsentan; TEAE, treatment-emergent adverse event; UPCR, urine protein-to-creatinine ratio.

CONCLUSIONS

- Rapid, superior proteinuria reduction was observed, and complete proteinuria remission was achieved earlier and more frequently with sparsentan vs maximum labeled dose irbesartan, regardless of baseline UPCR level
- Treatment with sparsentan showed greater kidney function preservation vs maximum labeled dose irbesartan in patients above or below 1 g/g
- Sparsentan's nephroprotective treatment effects are consistent across baseline proteinuria levels in patients with IgAN
- Given the draft KDIGO guidelines, which recommend treatment of patients with IgAN >0.5 g/day, these data support the use of sparsentan in patients traditionally considered low risk (<1 g/g)

IgAN, immunoglobulin A nephropathy; KDIGO, Kidney Disease Improving Global Outcomes; UPCR, urine protein-to-creatinine ratio.

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Questions?