Patients With IgAN at the Nephrology Clinic		
↓ Kidney function	↑ Proteinuria	++ Hematuria

Quote by Richard Lafayette, MD

“I think a lot of primary care doctors and even nephrologists sometimes feel if you've got modest proteinuria and hematuria, relatively stable blood pressure and kidney function, that that's good enough. But now we know that these patients can really progress. And we have to get to our diagnosis, which in IgA nephropathy, is a kidney biopsy.”

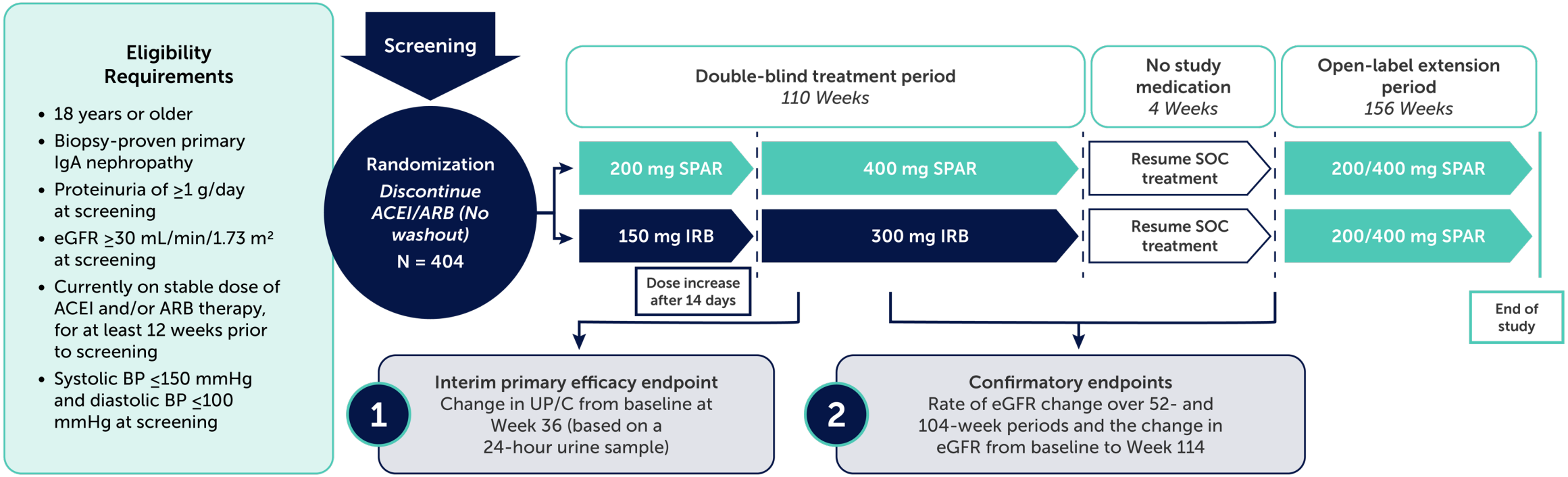
The lack of symptoms in patients with FSGS with **asymptomatic proteinuria** makes it difficult to diagnose early, which can have serious consequences for their health

39-Year-Old Patient With Biopsy: Confirmed IgAN Diagnosis

- Medical History: Immunosuppressive therapy → side effects
- Labs:
  - Proteinuria: 3 g/day
  - eGFR: 35 mL/min/1.73 m^2
- Current medications: maximally tolerated ACE inhibitor
- Blood pressure: 130/80 mmHg
- Repeat biopsy: M0 E0 S1 T1

PROTECT Phase 3 Trial Design in IgAN

Objective: Evaluate the efficacy and safety of sparsentan vs the active control irbesartan in patients with IgAN

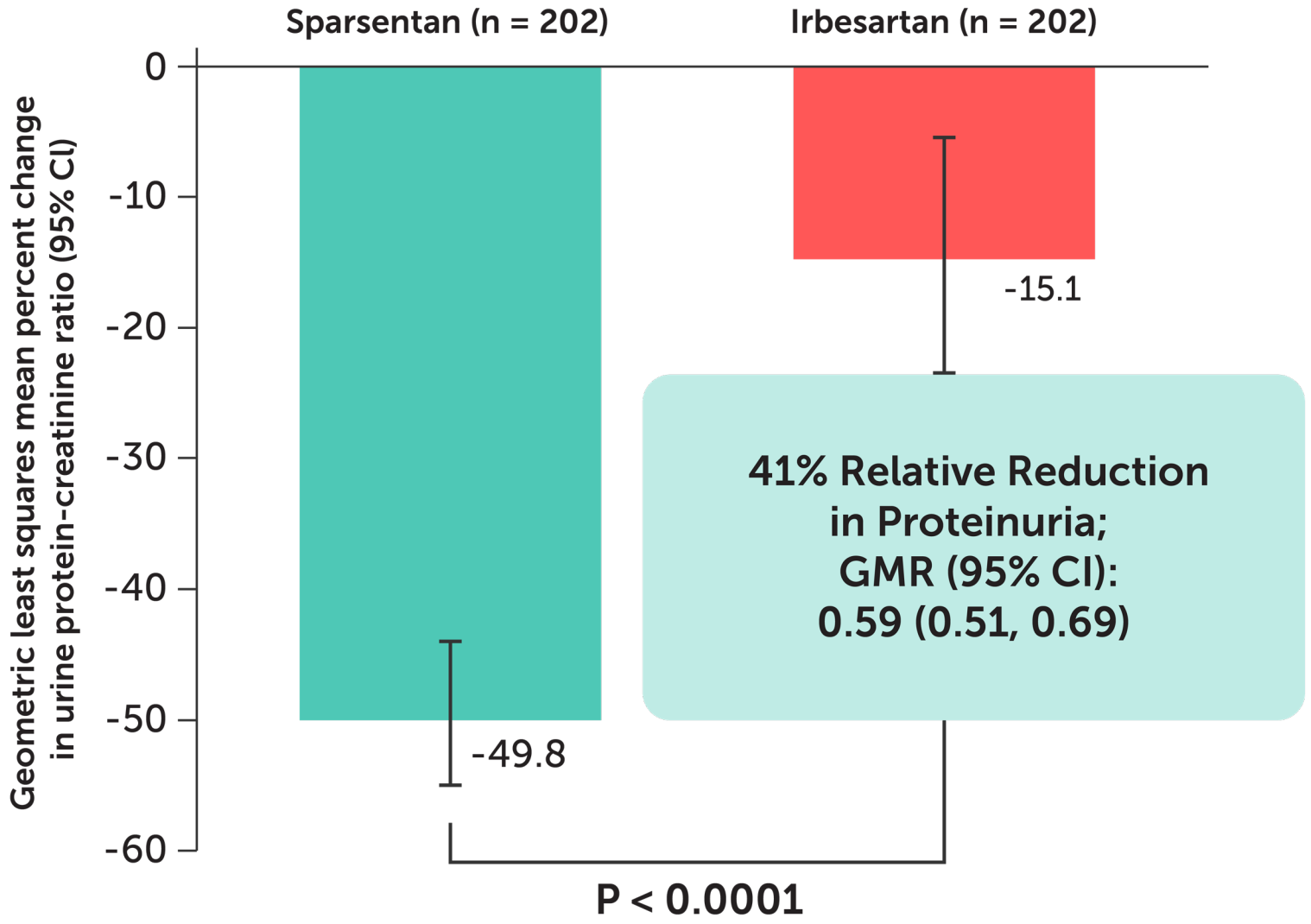


Sparsentan: Orally active dual endothelin angiotensin receptor antagonist (DEARA) selectively targeting the endothelin A receptor (ET_AR) and the angiotensin II subtype 1 receptor (AT_1R) [Non-immunosuppressant]

IRB: irbesartan; SPAR: sparsentan.

Rovin BH, et al. *Lancet.* Published online November 3, 2023. doi:10.1016/S0140-6736(23)02302-4

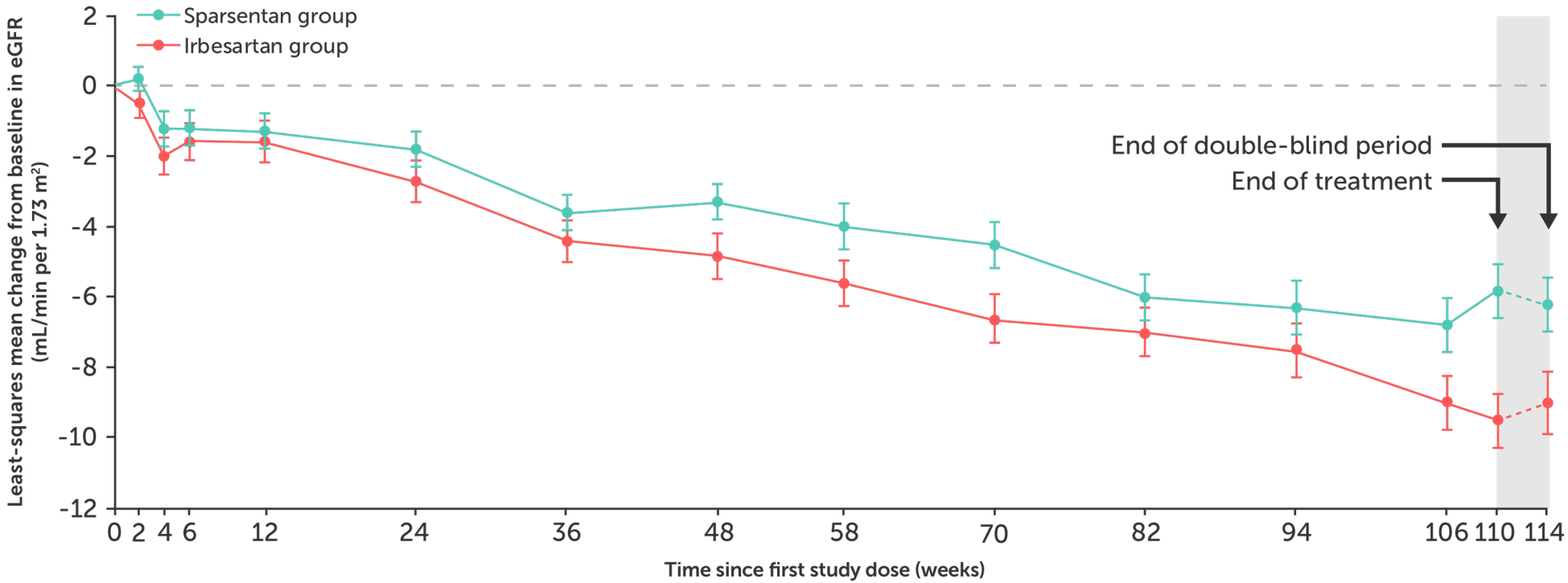
PROTECT Interim Analysis: Percent Change in Proteinuria at Week 36 (Primary Efficacy Endpoint)



Heerspink HJL, et al. *Lancet*. 2023;401(10388):1584-1594.

PROTECT Trial: Kidney Function (eGFR)

Patients treated with sparsentan over 2 years exhibited one of the **slowest** annual rates of kidney function decline seen in IgAN trials



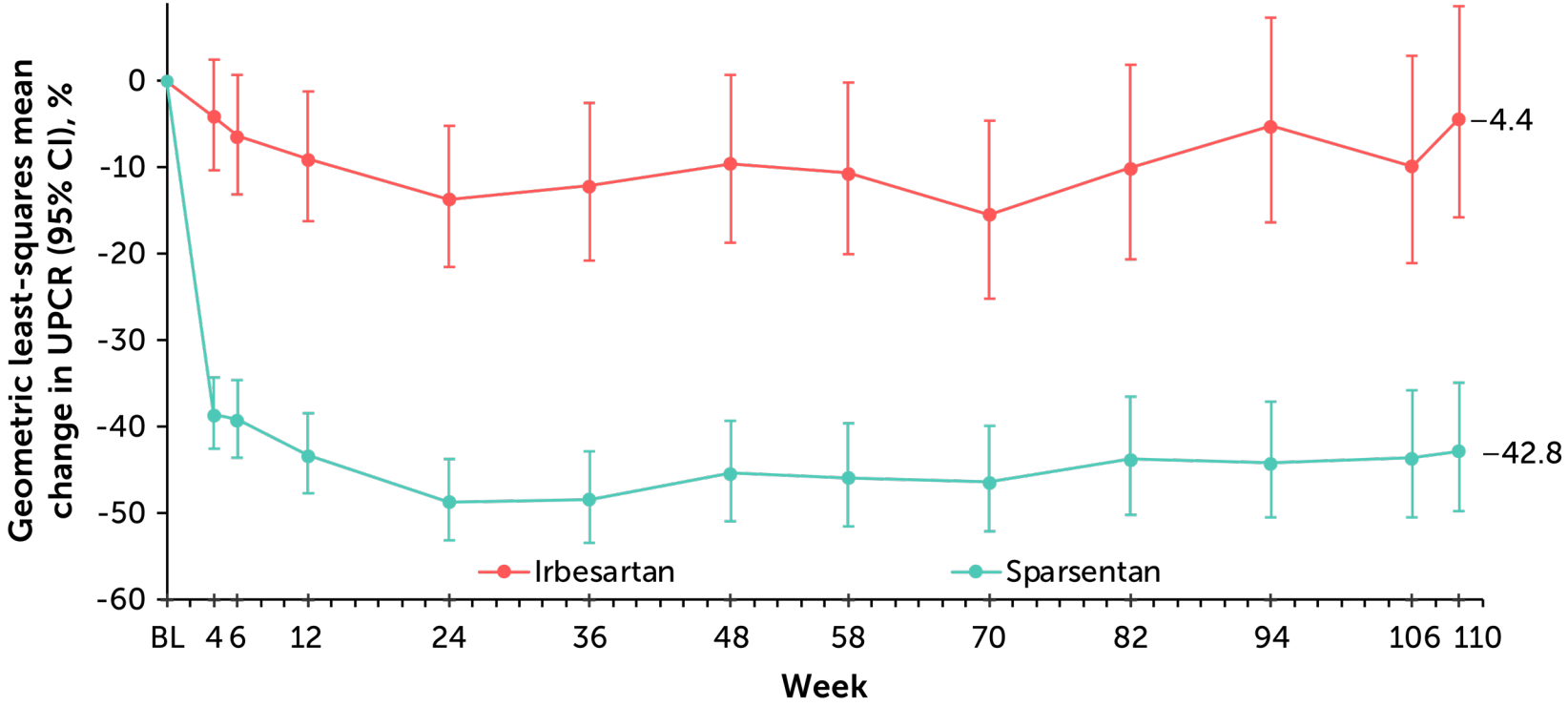
eGFR by visit up to week 114

Difference (95% CI)
3.7 (1.5 to 6.0)

Rovin BH, et al. *Lancet.* Published online November 3, 2023. doi:10.1016/S0140-6736(23)02302-4

PROTECT Trial: Sustained Proteinuria Reduction

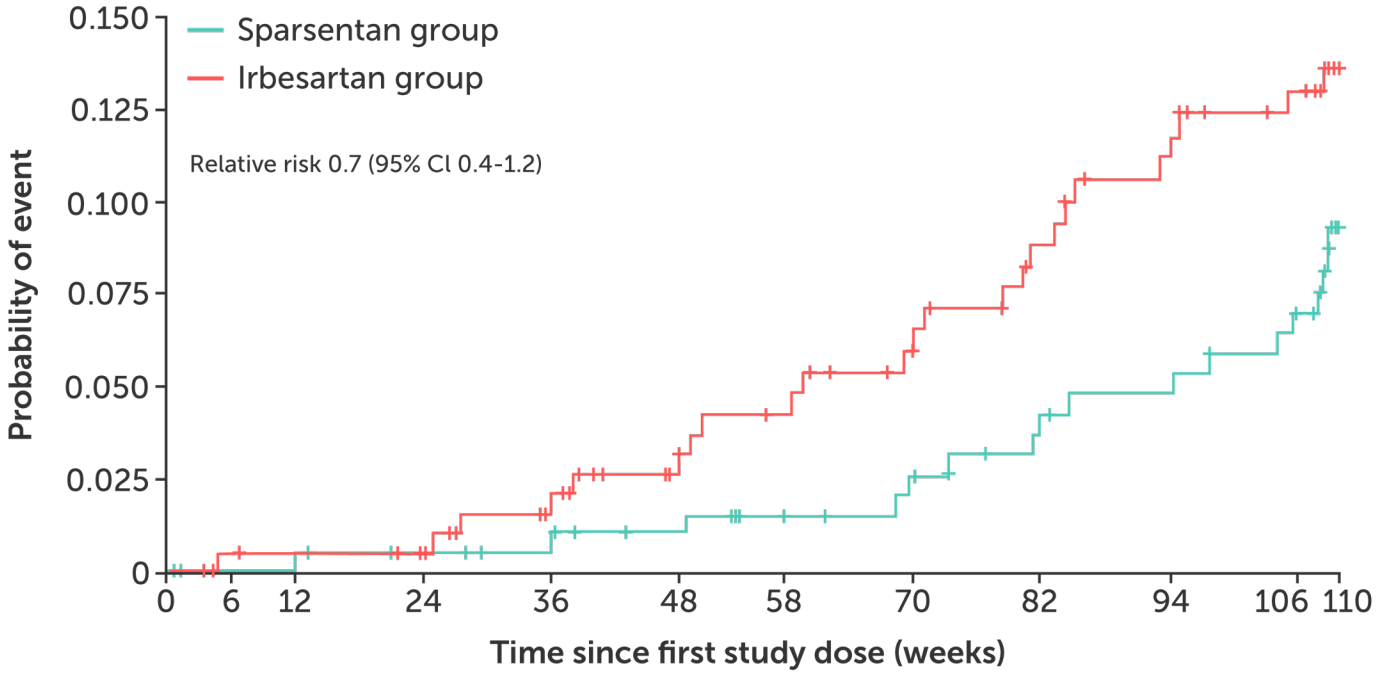
~**43%** proteinuria reduction with sparsentan compared to ~4% for irbesartan-treated patients sustained over **110 weeks**



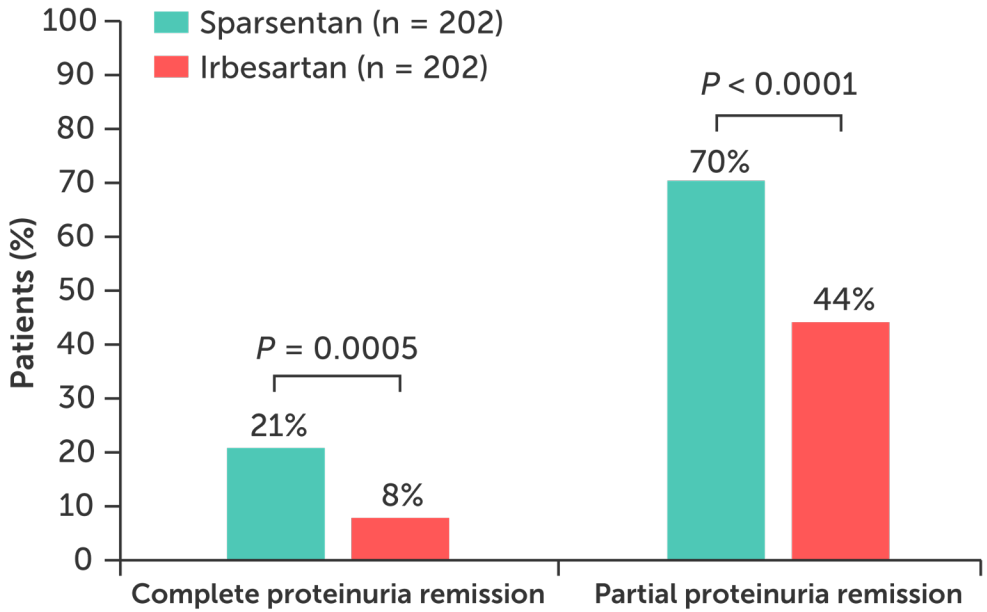
Rovin BH, et al. *Lancet.* Published online November 3, 2023. doi:10.1016/S0140-6736(23)02302-4

PROTECT Trial: 2-Year Final Analysis

Fewer sparsentan-treated patients progressed to composite kidney failure endpoint vs irbesartan



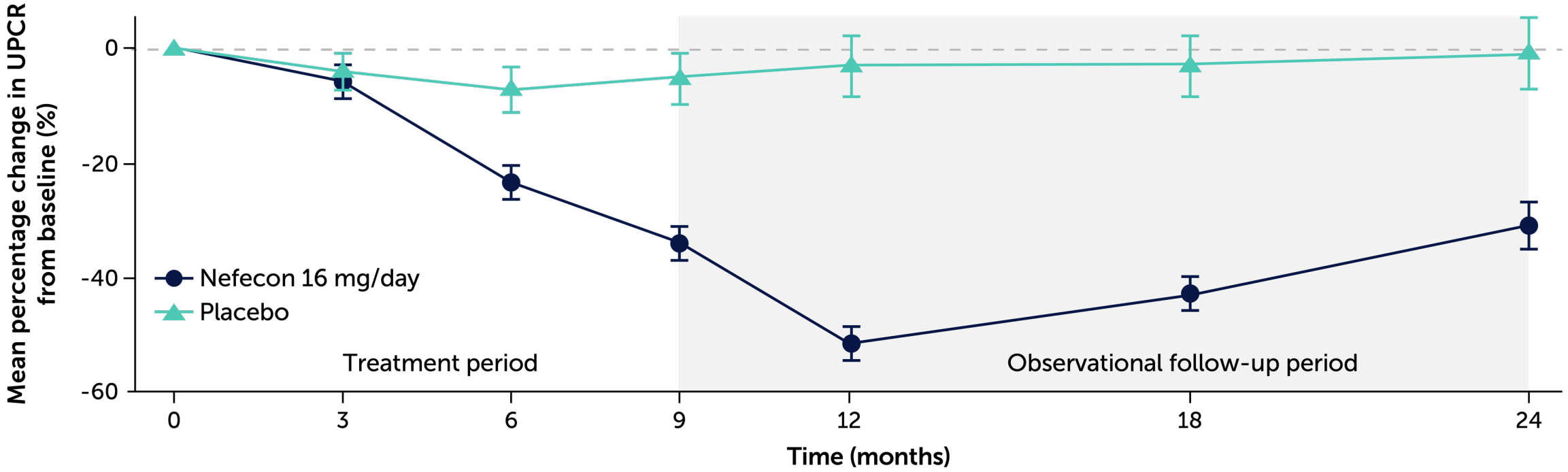
Most patients achieved complete proteinuria remission (<0.3 g/day) with sparsentan vs irbesartan



Rovin BH, et al. *Lancet.* Published online November 3, 2023. doi:10.1016/S0140-6736(23)02302-4

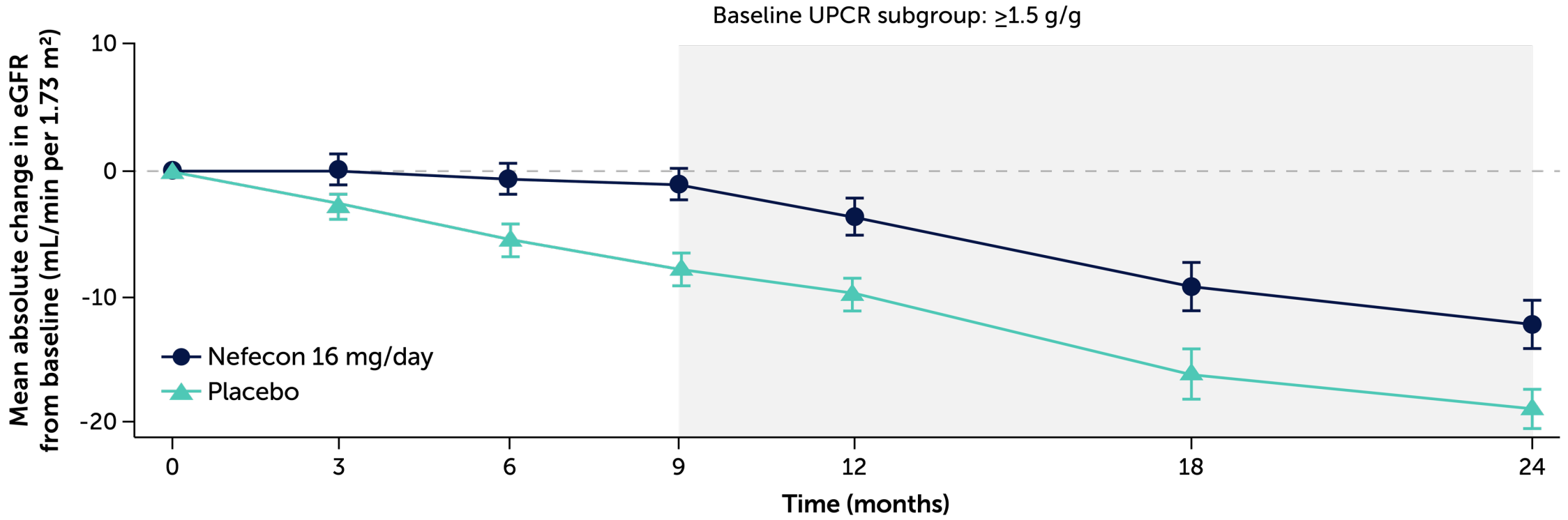
NeflgArd Phase 3 Trial in IgAN: Proteinuria Reduction Randomized, Placebo-Controlled Trial

Nefecon: Oral steroid that reduces inflammation (delayed-release budesonide)



Lafayette R, et al. *Lancet*. 2023;402(10405):859-870.

NefIgArd Trial in IgAN: eGFR Change



Lafayette R, et al. *Lancet*. 2023;402(10405):859-870.

PROTECT Trial: Safety

Sparsentan was well tolerated with a consistent safety profile comparable to irbesartan

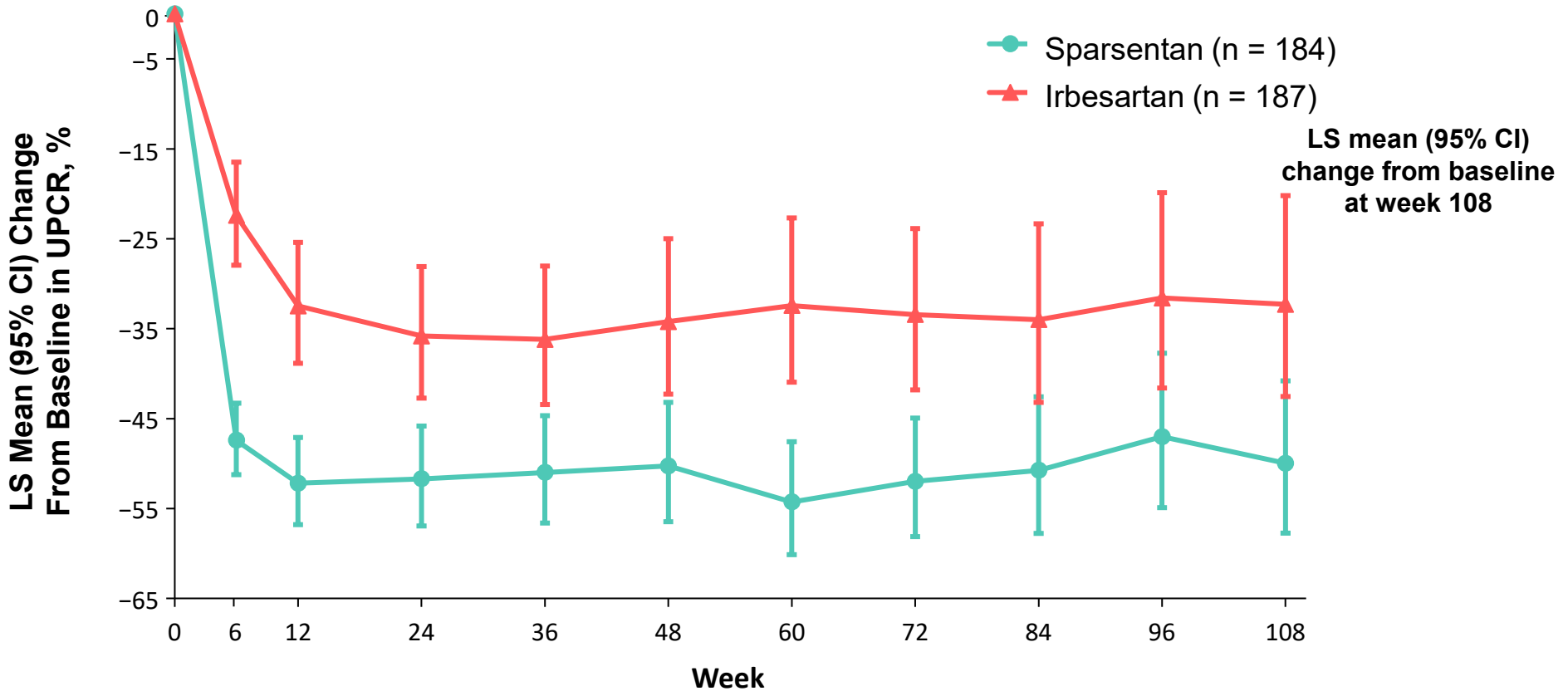
Patients with TEAEs, n (%)	Sparsentan (n = 202)	Irbesartan (n = 202)
Any TEAEs	**187 (93)**	**177 (88)**
Most common TEAEs (≥10% of patients in either group)		
COVID-19	53 (26)	46 (23)
Hyperkalemia	32 (16)	26 (13)
Peripheral edema	31 (15)	24 (12)
Dizziness	30 (15)	13 (6)
Headache	27 (13)	26 (13)
Hypotension	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)

- No cases of drug-induced liver injury with sparsentan
- Peripheral edema was similar in both groups, with no increases in body weight

Rovin BH, et al. *Lancet.* Published online November 3, 2023. doi:10.1016/S0140-6736(23)02302-4

DUPLEX Phase 3 Trial in FSGS

Sparsentan resulted in rapid decline in UPCR that was sustained through 108 weeks



Rheault MN, et al. *N Engl J Med*. Published online November 3, 2023. doi:10.1056/NEJMoa2308550

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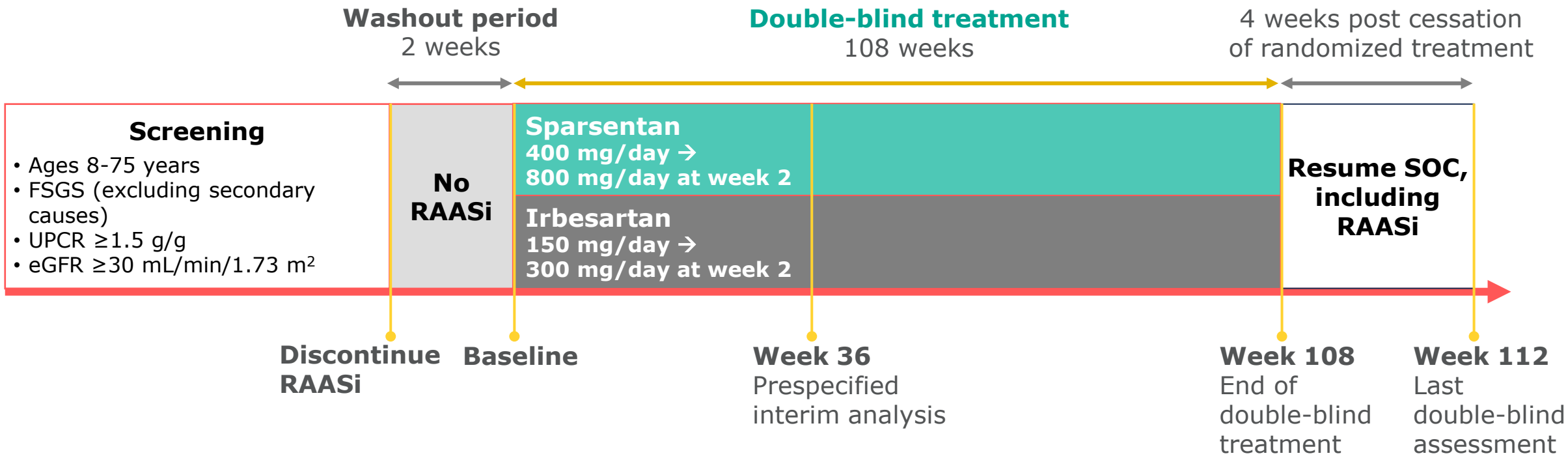
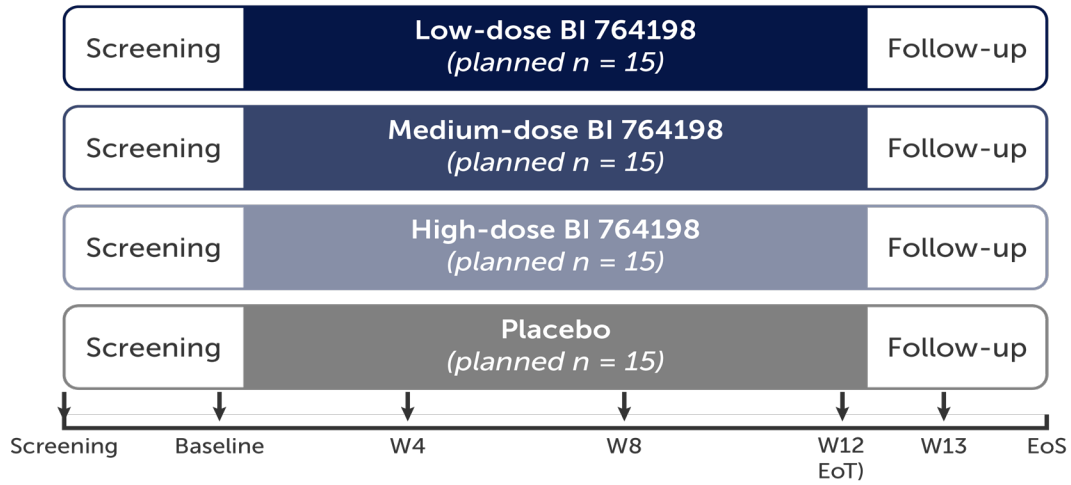


Rheault MN, et al. *N Engl J Med*. Published online November 3, 2023. doi:10.1056/NEJMoa2308550

TRPC6 Inhibitor 764198 BI Phase 2 Trial in FSGS



Tractman H, et al. *Kidney Int Rep*. Published online September 29, 2023. doi:10.1016/j.ekir.2023.09.026

39-Year-Old Patient With Biopsy-Confirmed IgAN Diagnosis

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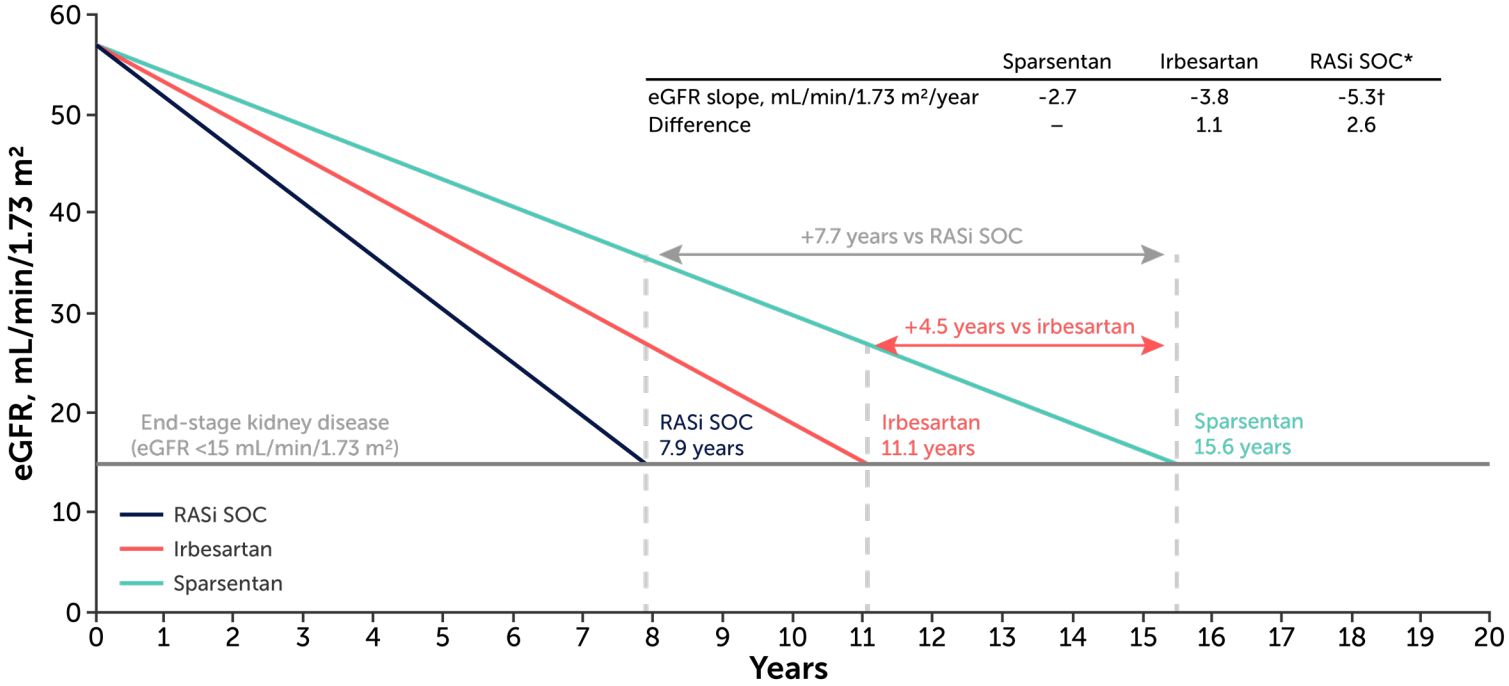
- Current medications: maximally tolerated ACE inhibitor
- Blood pressure: 130/80 mmHg
- Repeat biopsy: M0 E0 S1 T1

Treatment Considerations for Patients With IgAN

- **Blood pressure** optimization
- **Dietary** modifications
- **Sparsentan:** orally active dual endothelin (ET_AR) angiotensin receptor antagonist (AT_1R) to lower proteinuria (non-immunosuppressant)
- **SGLT2-inhibitor**
- **Nefecon**: delayed-release budesonide for inflammation (immunosuppressant)

PROTECT Study in IgAN: Potential Long-Term Impact of Improved eGFR Slope

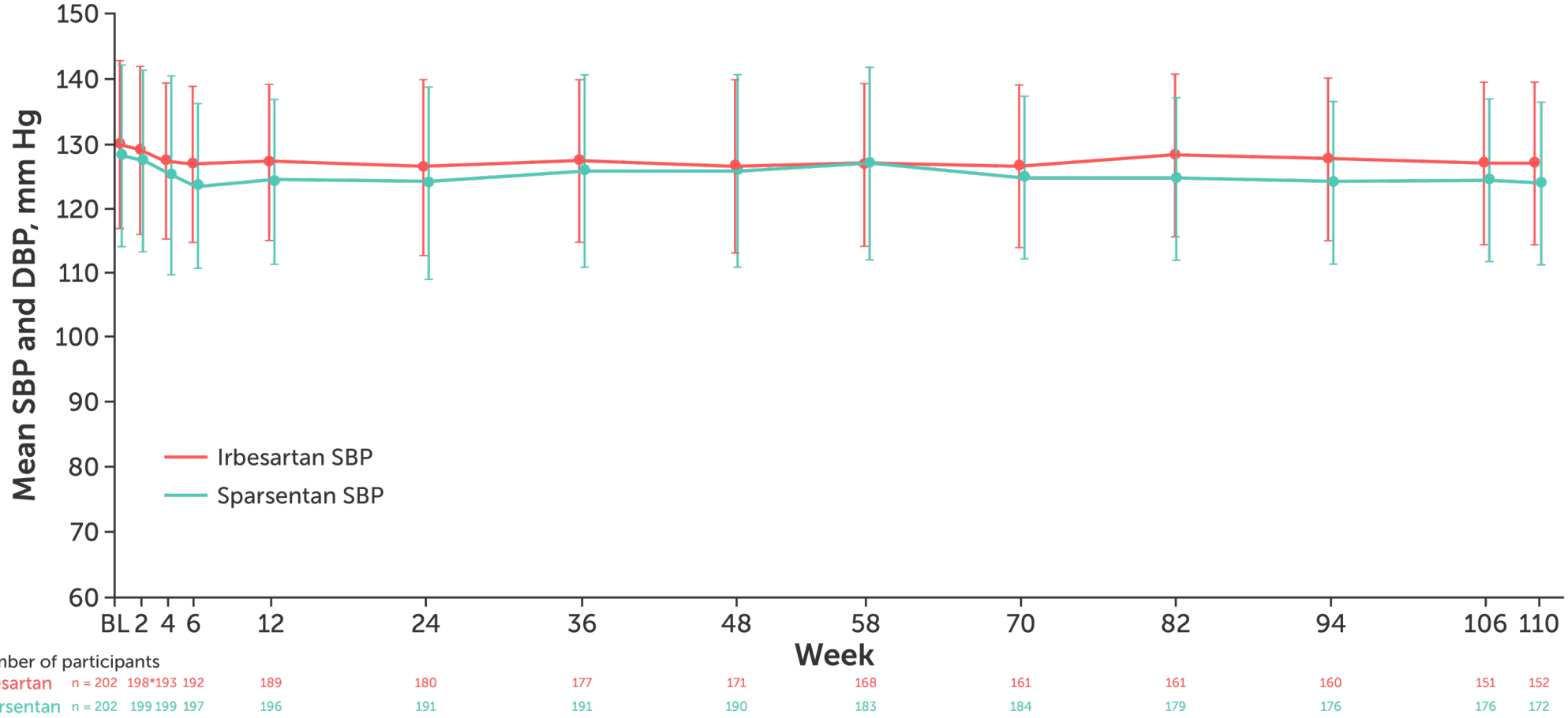
① mL/min/1.73 m^2/year difference in eGFR slope



ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; eGFR, estimated glomerular filtration rate; RASi, renin-angiotensin system inhibitor; SOC, standard of care.
Baseline eGFR was set to=57 mL/min/1.73 m² (0 years), reflecting the mean eGFR of all patients (N=404) reported in this study.
* ACEI and/or ARB
† Mean of observed chronic or total slopes for SOC ACEI/ARB as reported in 5 randomized controlled trials in IgAN

Rovin BH, et al. *Lancet.* Published online November 3, 2023. doi:10.1016/S0140-6736(23)02302-4

PROTECT Study in IgAN: Mean Systolic and Diastolic Blood Pressure at Each Visit



BL, baseline; DBP, diastolic blood pressure; SBP, systolic blood pressure.
Error bars indicate standard deviation
* Irbesartan value for DBP, n = 197.

Rovin BH, et al. *Lancet.* Published online November 3, 2023. doi:10.1016/S0140-6736(23)02302-4