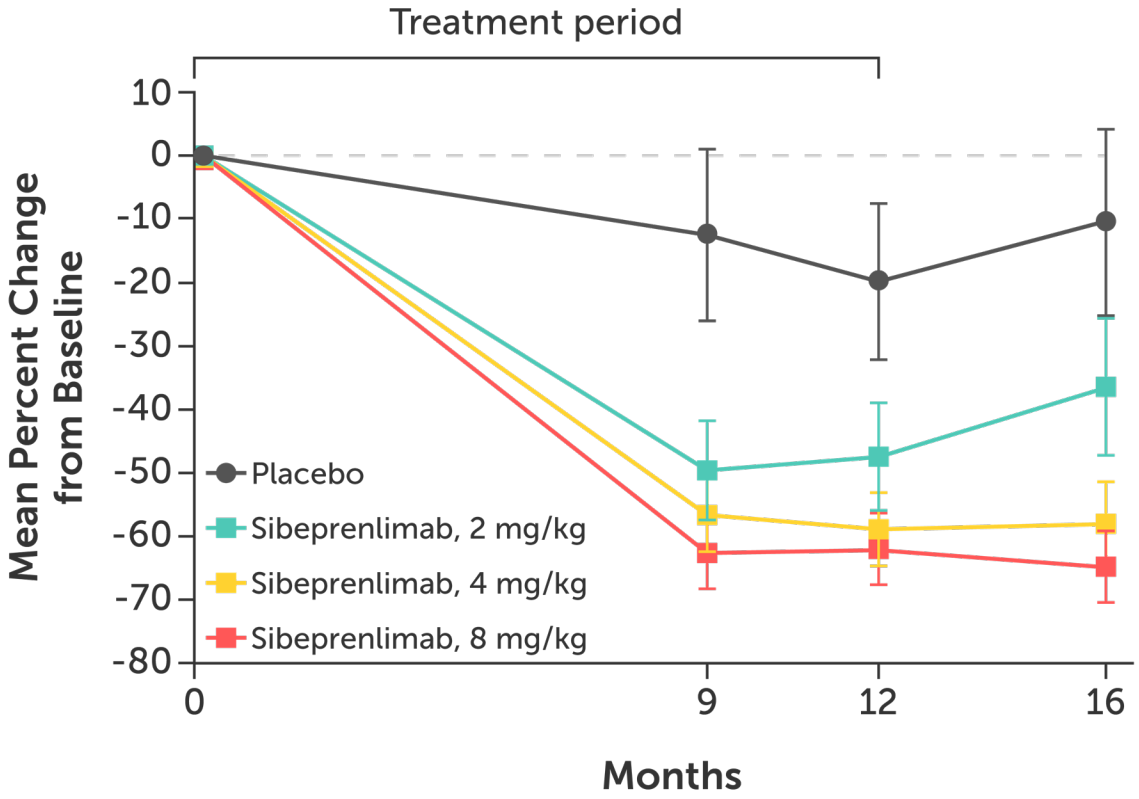
B-Cell Modulators (Investigational)

- **Povetacicept**
  - Dual APRIL/BAFF antagonist
- **Sibeprenlimab**
  - APRIL inhibitor

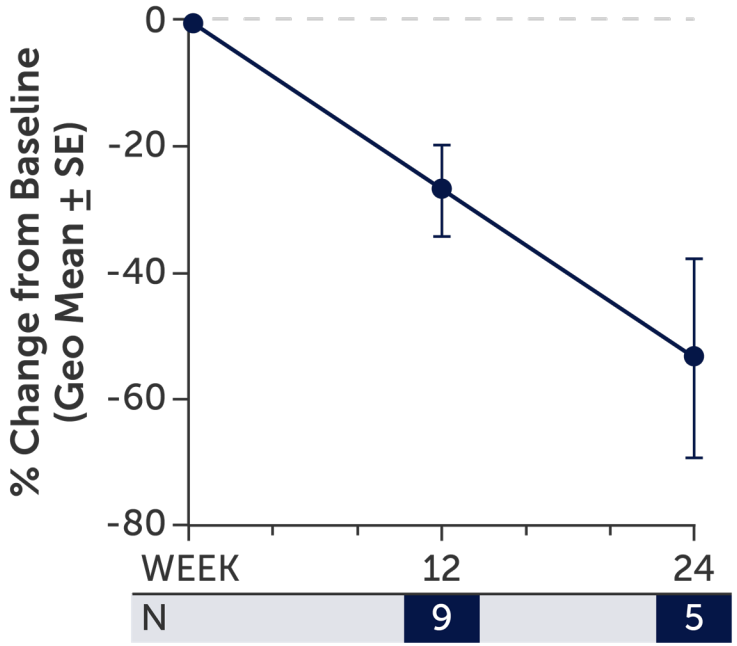
→ Galactose-deficient IgA1 antibody reduction

B-Cell Modulators (Investigational): UPCR Change

ENVISION Phase 2 Trial
Sibeprenlimab in patients with IgAN



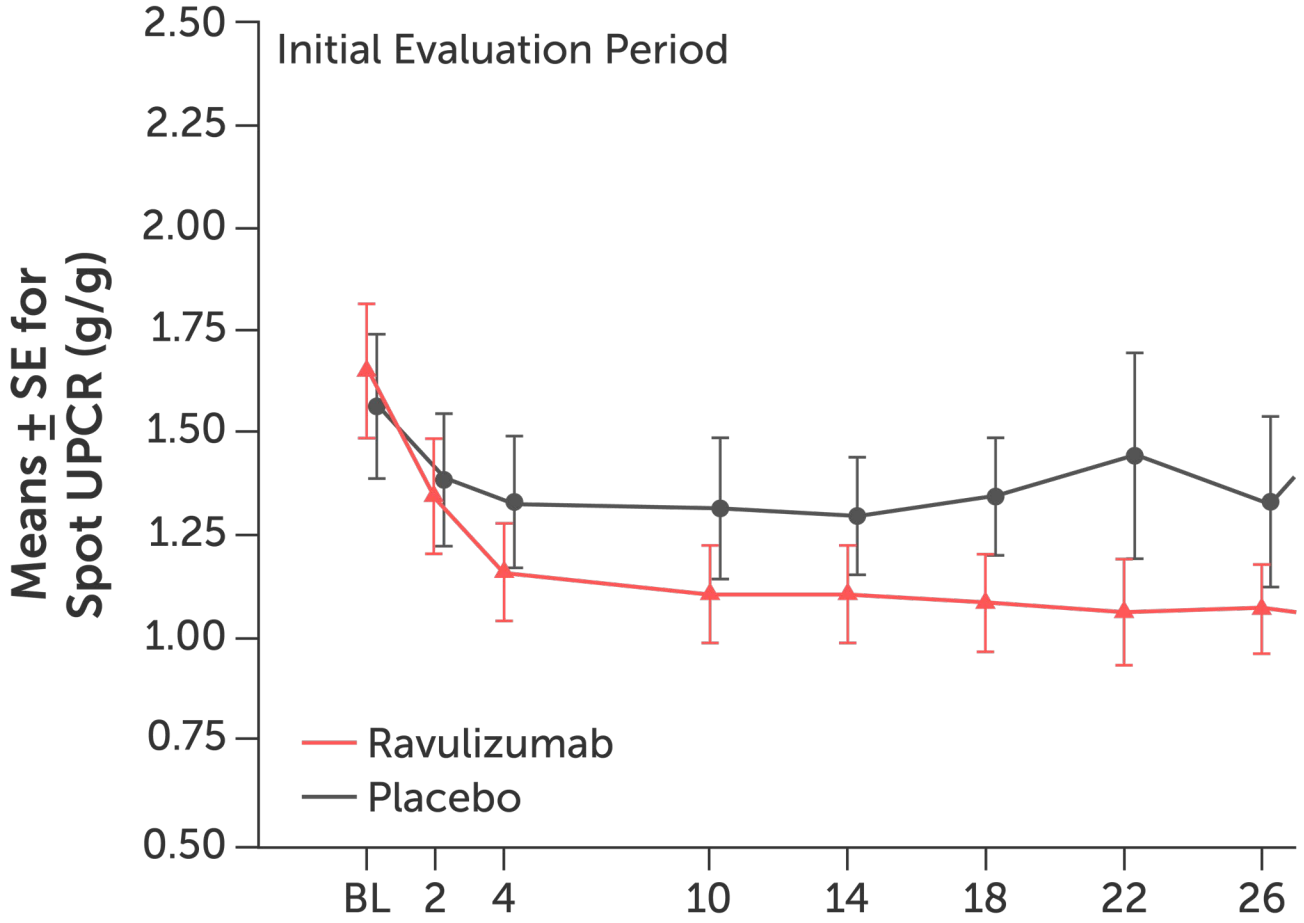
RUBY-3 Phase 1a/2b Trial
Povetacicept in patients with IgAN



Tumlin J, et al. Poster presented at ASN Kidney Week 2023; Philadelphia, PA; November 2, 2023. Abstract TH-PO1125.
Mathur M, et.al. *Kidney Int Rep*. 2022;7(5):993-1003.

Ravulizumab (Investigational) Phase 2 Trial in IgAN

Binds to C5 to inhibit terminal complement activity



Barratt J, et al. Poster presented at ASN Kidney Week 2023; Philadelphia, PA; November 2, 2023. Abstract TH-PO1127.

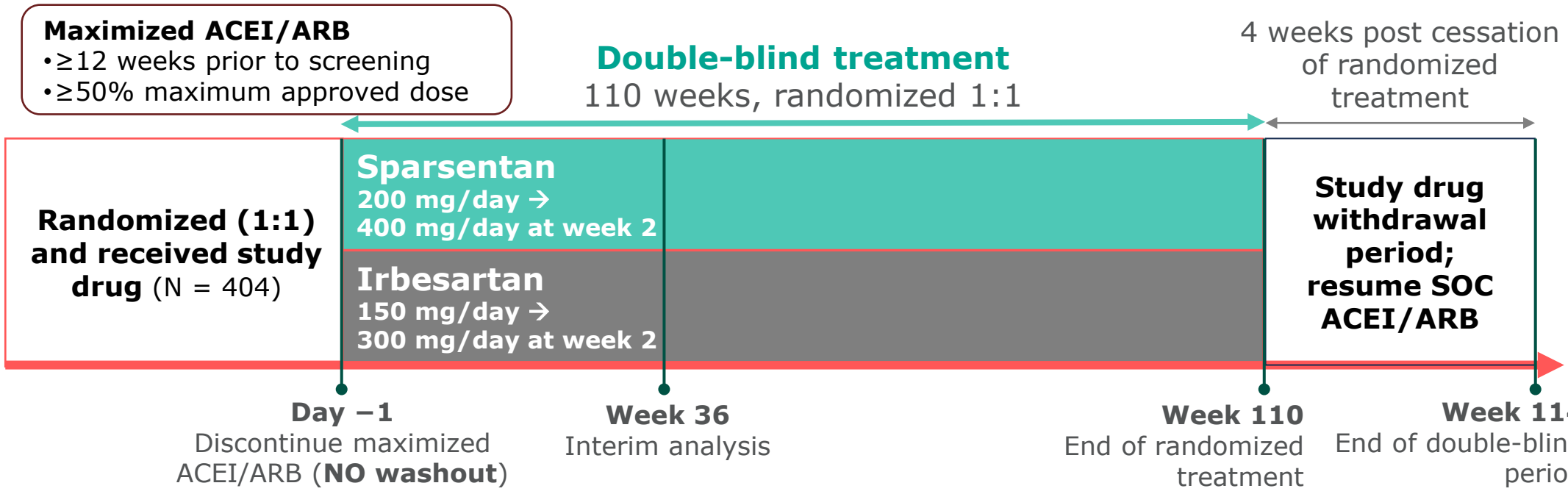
PROTECT Phase 3 Trial: Baseline Characteristics

- Adults (aged ≥18 years)
- Biopsy-proven IgAN
- Proteinuria ≥1 g/day
- eGFR ≥30 mL/min/1.73 m^2
- Different racial backgrounds and across CKD stages

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

PROTECT Phase 3Trial Design

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

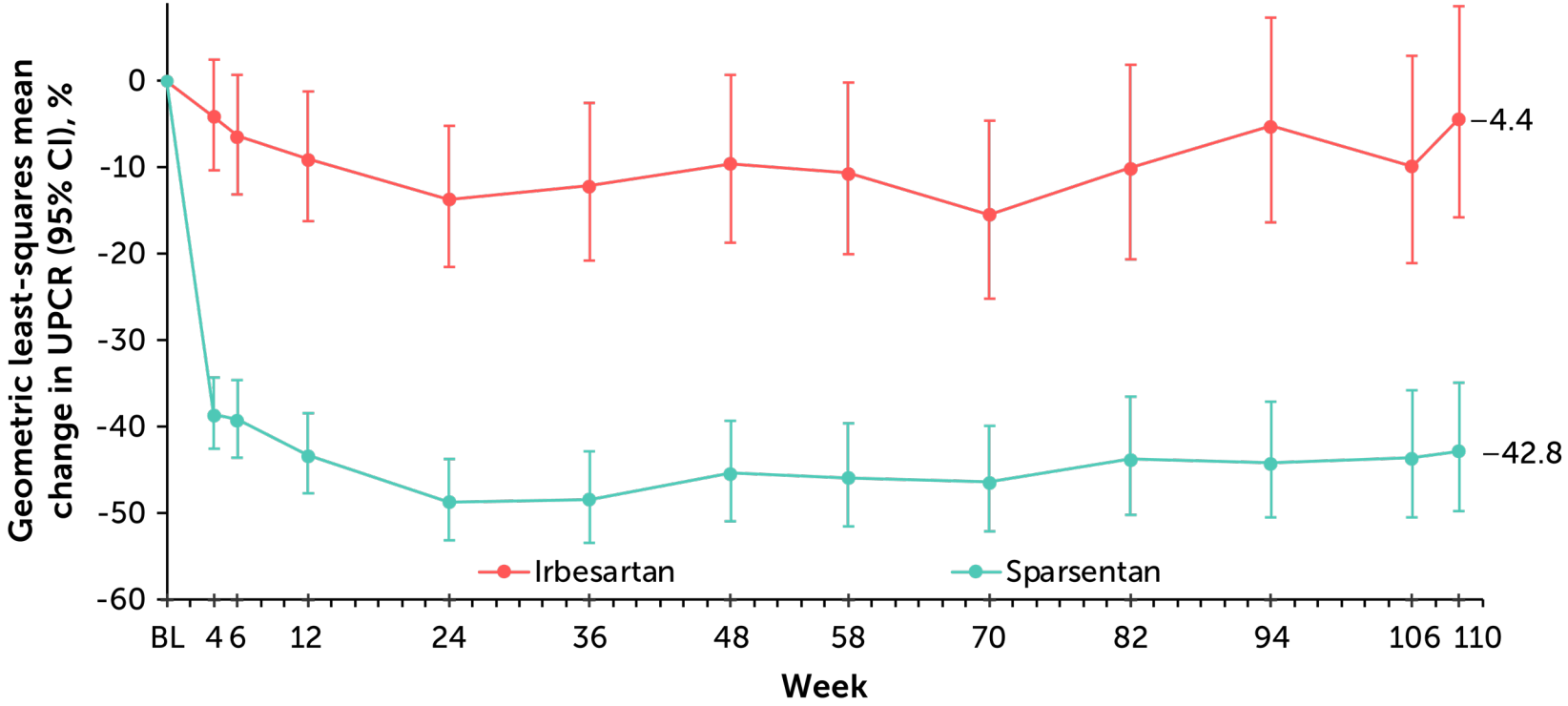


Sparsentan (approved): Orally active dual endothelin angiotensin receptor antagonist (DEARA) selectively targeting the endothelin A receptor (ET_AR) and the angiotensin II subtype 1 receptor (AT_1R) [Non-immunosuppressant]

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

PROTECT Trial: Sustained Proteinuria Reduction

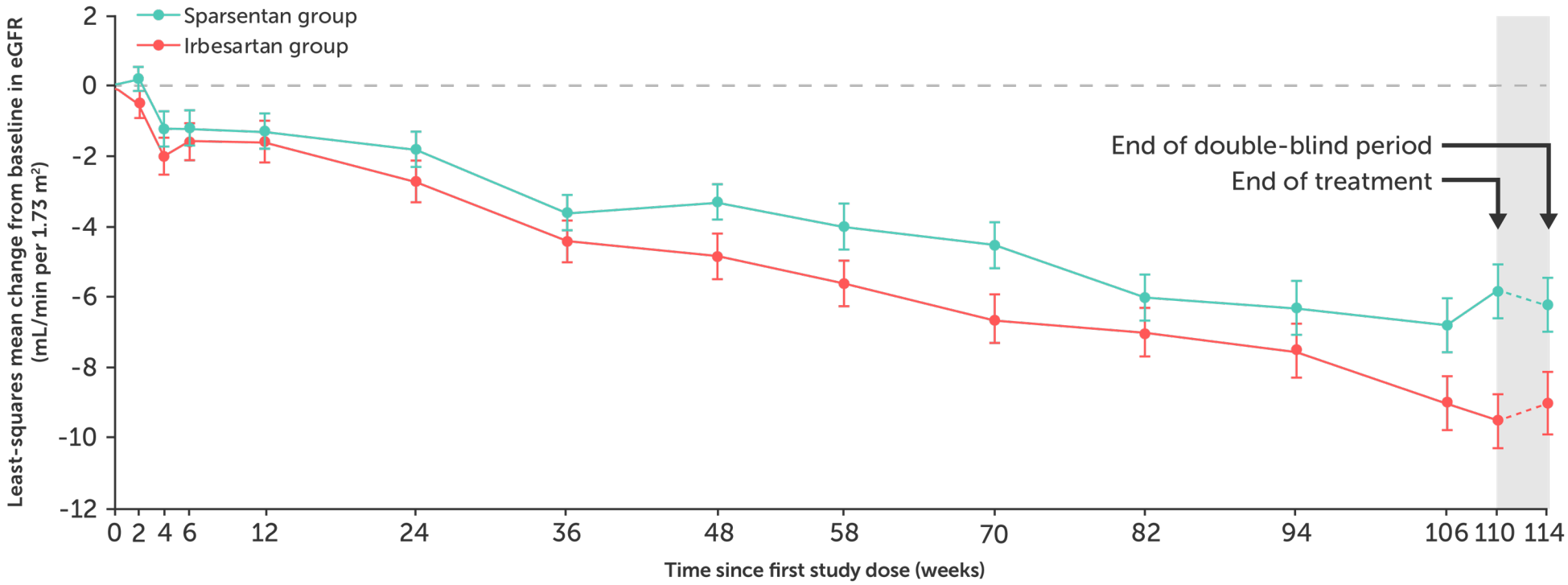
~43% proteinuria reduction with sparsentan compared to ~4% for irbesartan-treated patients sustained over 110 weeks



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

PROTECT Trial: 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



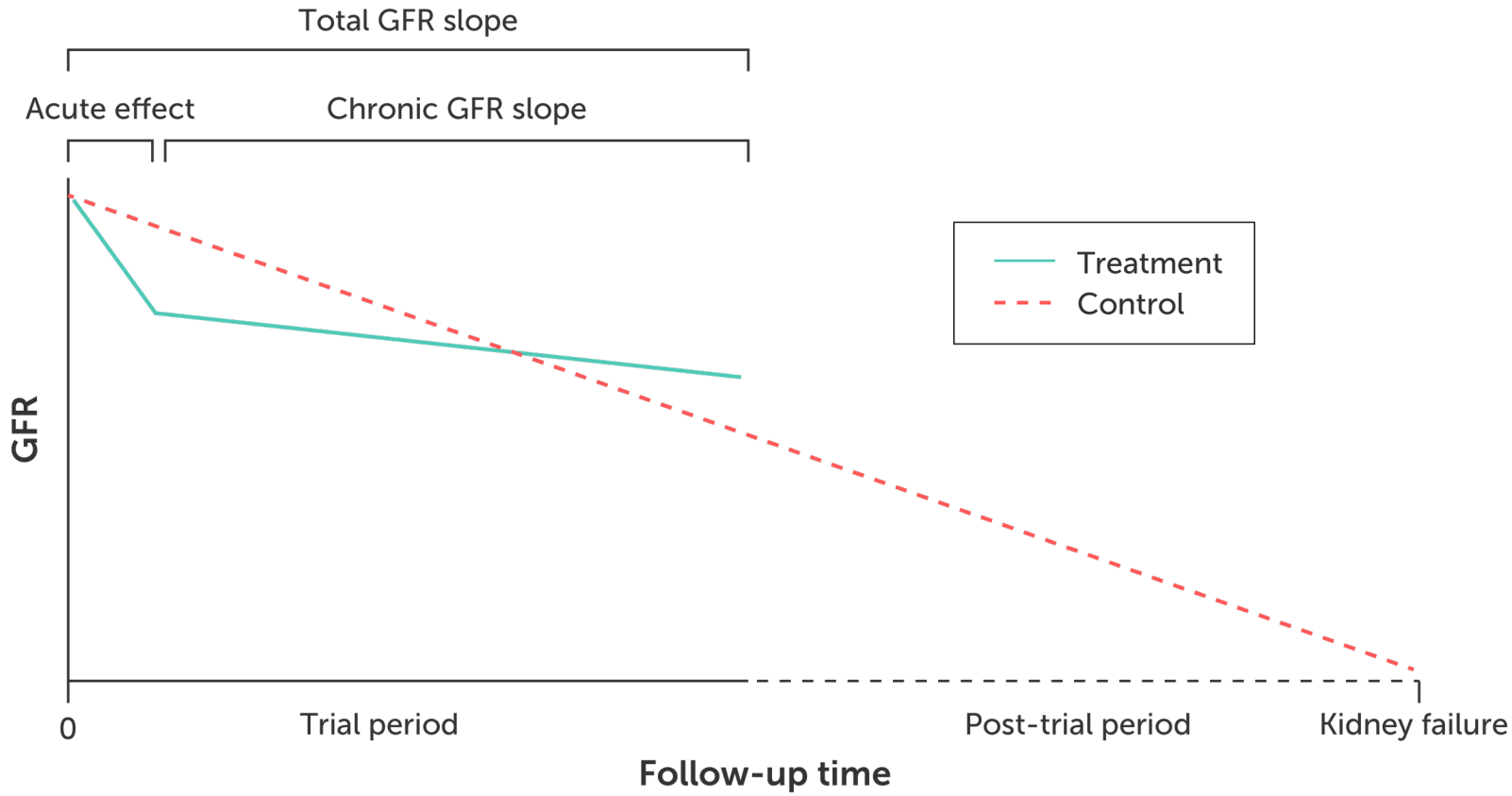
eGFR by visit up to week 114

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

eGFR Slopes: Total vs Chronic

- Total or chronic slopes during the trial period re measures of CKD progression
  - Steeper negative GFR slope indicates ↑ likelihood of future kidney failure



Inker LA, et al. *Nat Med*. 2023;29(7):1867-1876. Lees JS, Mark PB. *Nat Rev Nephrol*. 2023;19(10):625-626.

Quote by Jonathan Barratt, PhD

"When we look at the effect on GFR, we look at the endpoint on hard kidney endpoints, kidney failure, significant loss of kidney function…"

"…there is a highly consistent effect of sparsentan in reducing kidney endpoints in the PROTECT trial, which I think is really reassuring that this drug is protecting kidney function in patients with IgA nephropathy."

Quote by Jonathan Barratt, PhD

“On average, the difference between the irbesartan and sparsentan was ***1 mL/min/1.73 m^2/year****. And for a 30-year-old, that's a significant impact on delaying the time to dialysis.”*

PROTECT Trial: Safety

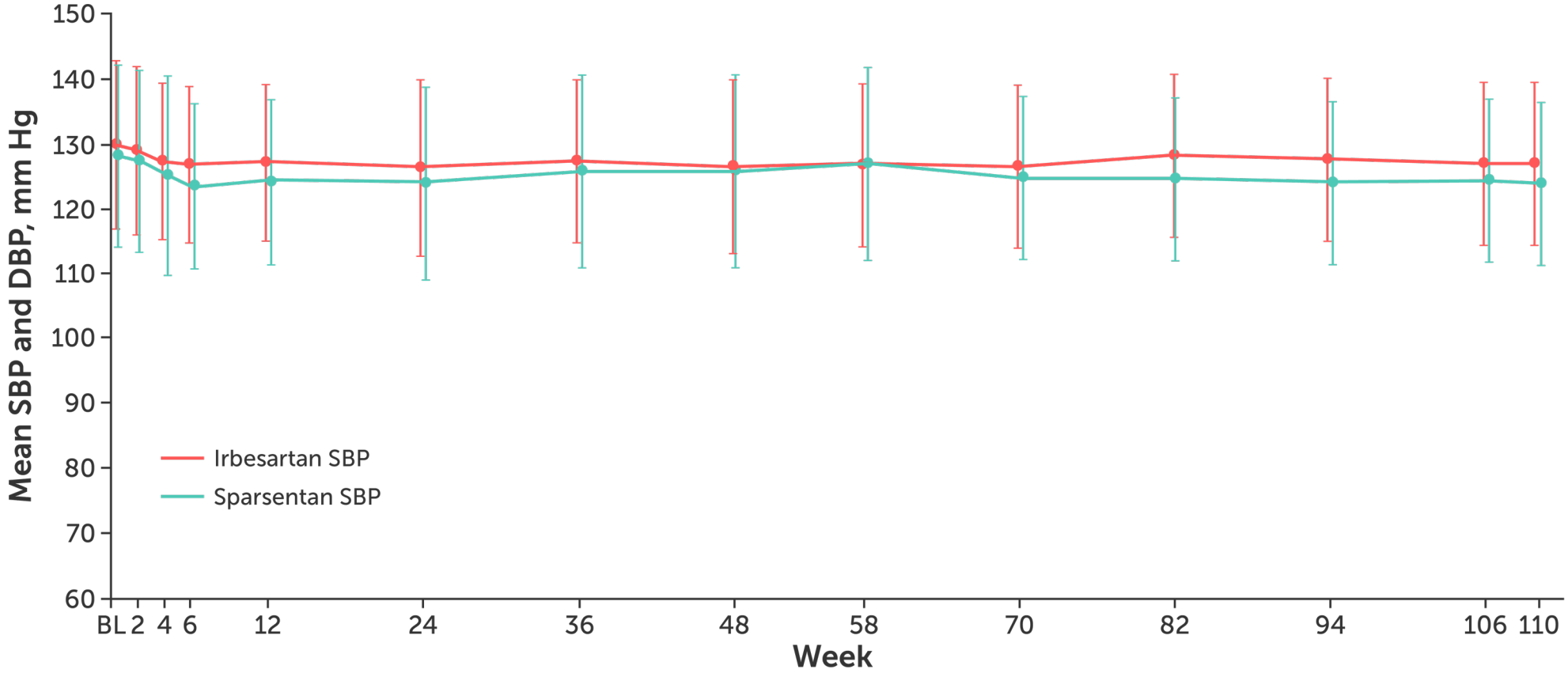
Sparsentan was well tolerated with a consistent safety profile comparable to irbesartan

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

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

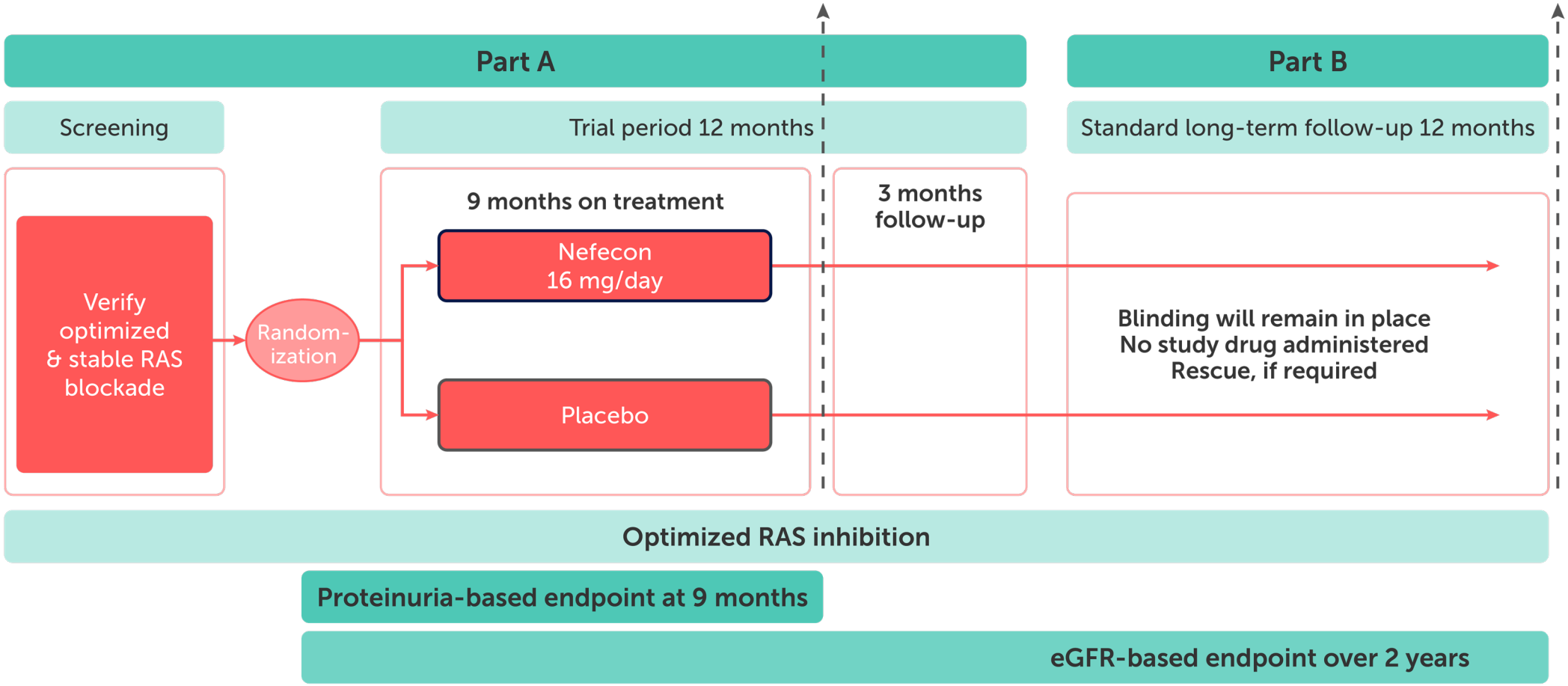
NeflgArd Phase 3 Trial: Baseline Characteristics

- Adults ≥18 years
- Biopsy-verified IgAN
- eGFR ≥35 mL/min/1.73 m^2 and ≤90 mL/min/1.73 m^2
- UPCR ≥1 g/24 hr

ClinicalTrials.gov identifier: NCT03643965.

NeflgArd Phase 3 Trial in IgAN

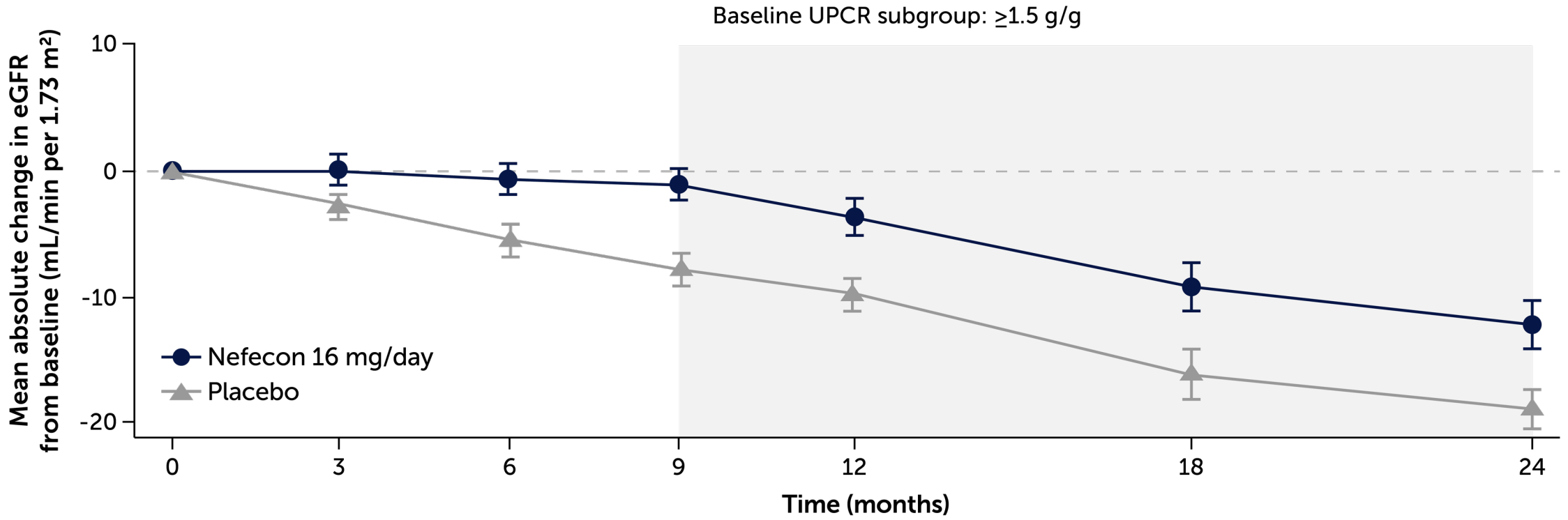
Randomized, Double-Blind, Placebo-Controlled Clinical Trial



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

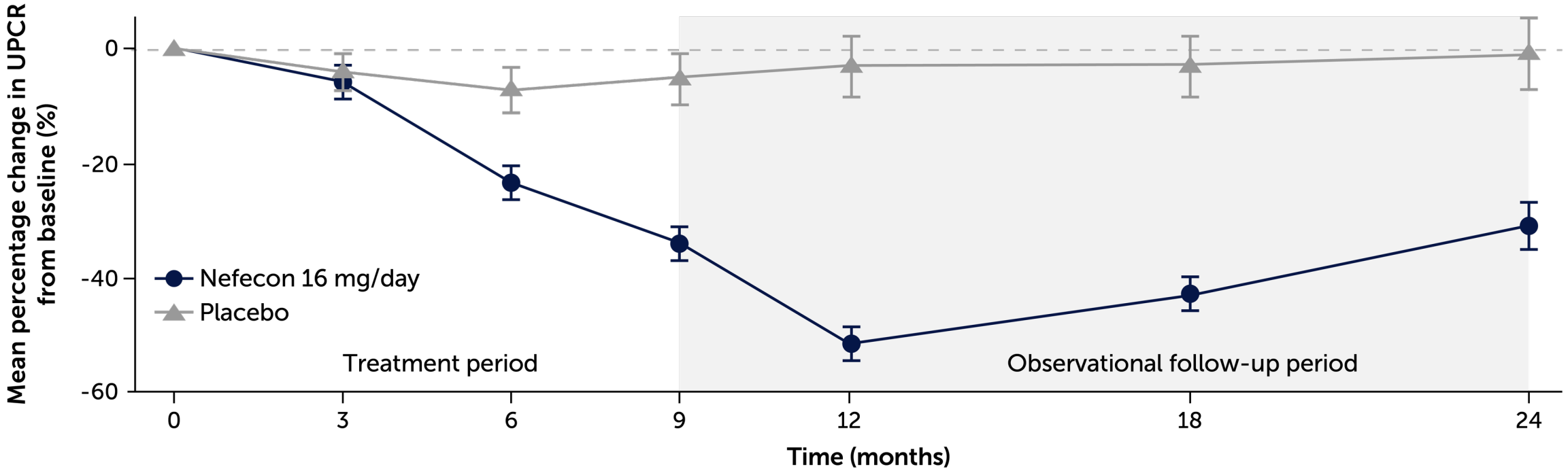
NeflgArd Phase 3 Trial in IgAN: eGFR Change

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



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

NeflgArd Trial: UPCR Change



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

NeflgArd Trial: Safety

	9-month treatment period		15-month observational follow-up period	
	Nefecon 16 mg/day (n = 182)	Placebo (n = 182)	Nefecon 16 mg/day (n = 175)	Placebo (n = 174)
All treatment-emergent adverse events	159 (87%)	125 (69%)	127 (73%)	124 (71%)
Any treatment-emergent serious adverse events	18 (10%)	9 (5%)	14 (8%)	14 (8%)
Any treatment-emergent adverse events leading to death	1 (1%)	0	1 (1%)	0
Any treatment-emergent adverse events leading to discontinuation of study treatment	17 (9%)	3 (2%)	NA	NA

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

Quote by Jürgen Floege, MD

“The mainstay still is a comprehensive supportive care regimen. And I think also in that respect, PROTECT has set a new standard. If you really optimize your ARB or ACE inhibitor, you can do something.”

“We will yet have to learn how the addition of an SGLT2 inhibitor modifies all this.”