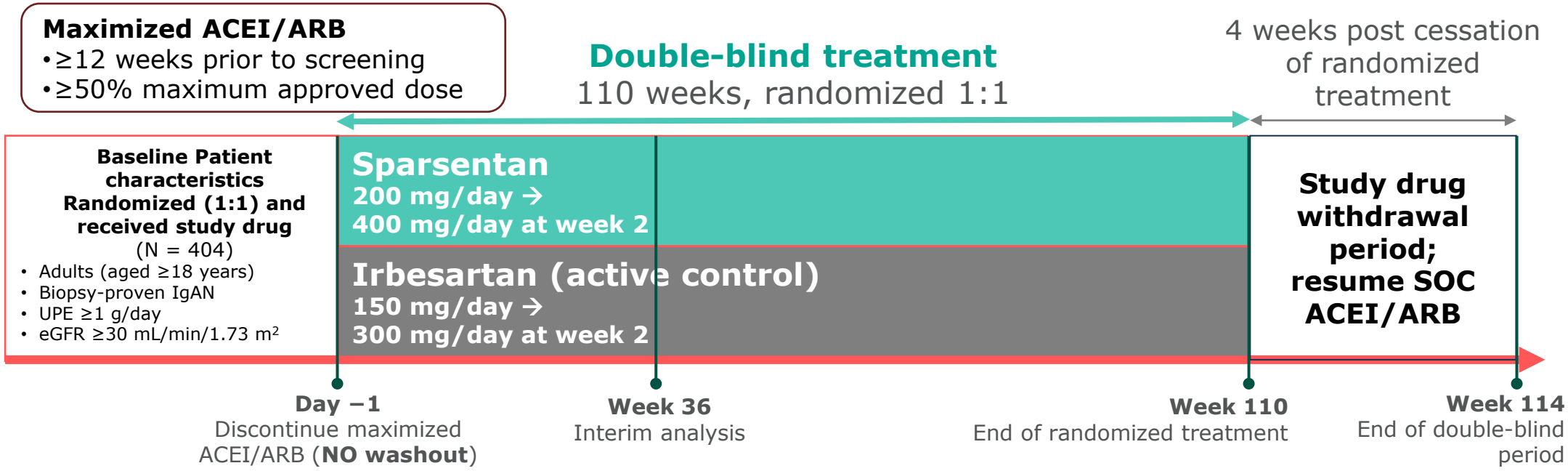
PROTECT Phase 3 Trial

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



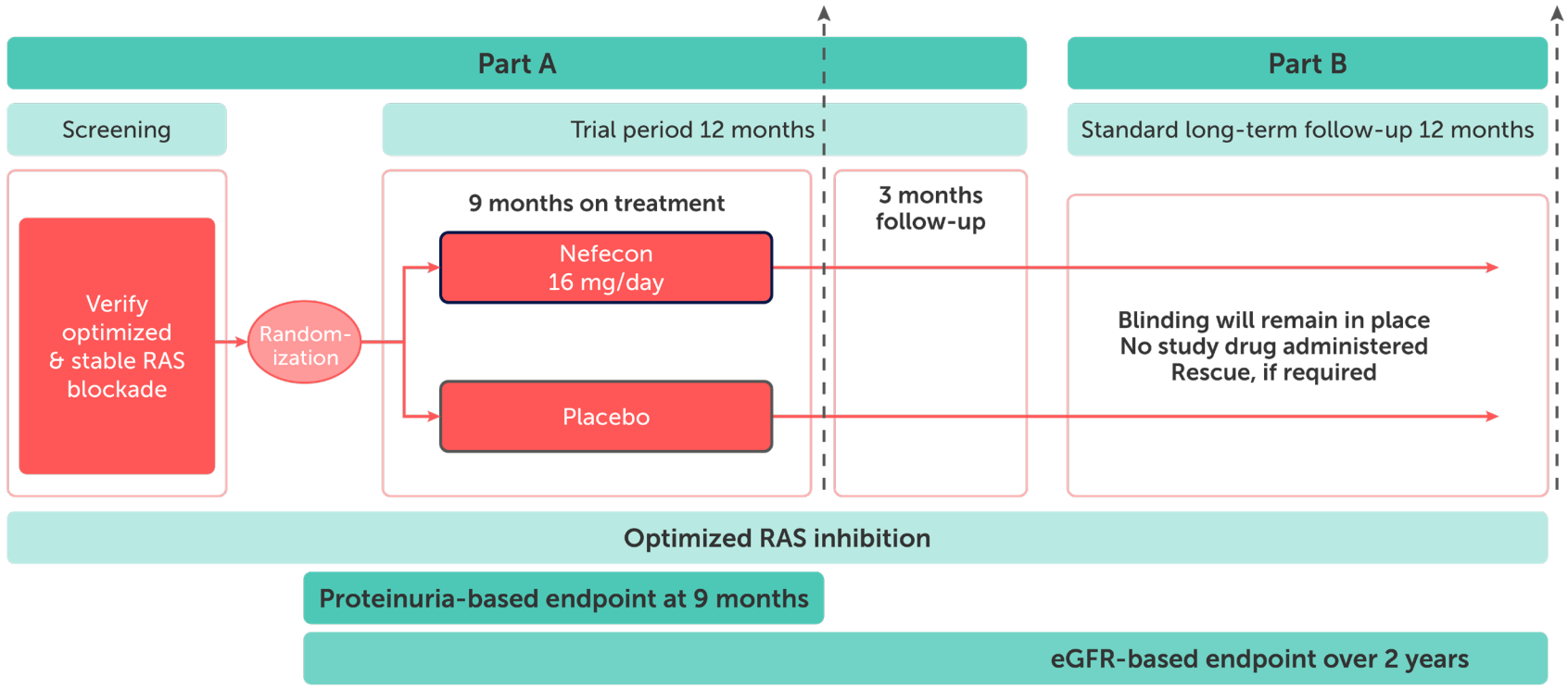
Primary Efficacy Endpoint	Key Secondary Efficacy Endpoints
Change in UPCR from baseline to week 36	eGFR slope: • **Chronic** (weeks 6-110) • **Total** (day 1-week 110)

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.* 2023;402(10417):2077-2090.

NeflgArd Phase 3 Trial

Randomized, Double-Blind, Placebo-Controlled Clinical Trial
Evaluate the efficacy and safety of nefecon vs placebo in patients with IgAN



Nefecon (approved): Delayed-release budesonide [immunosuppressant]

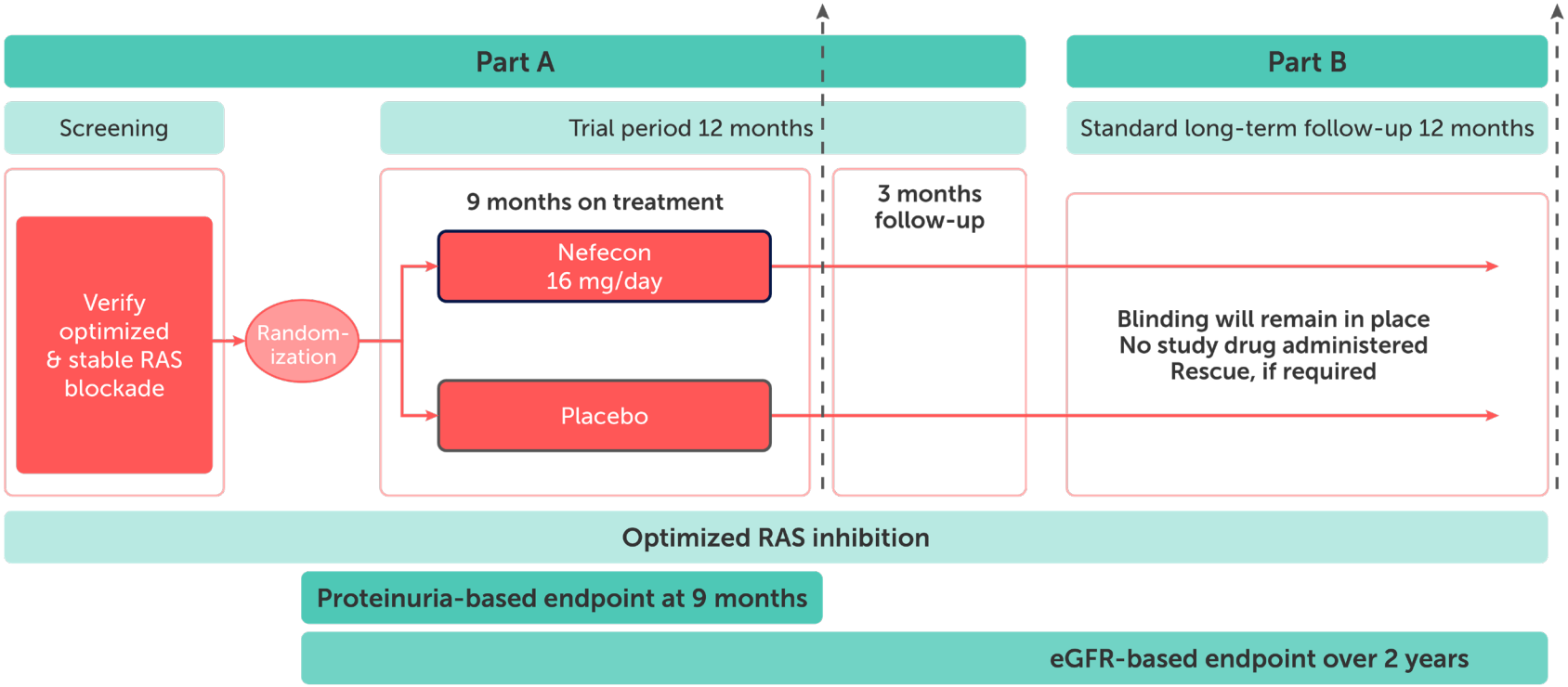
Lafayette R, et al. *Lancet*. 2023;402(10405):859-870.

NeflgArd Phase 3 Trial

Randomized, Double-Blind, Placebo-Controlled Clinical Trial
Evaluate the efficacy and safety of nefecon vs placebo in patients with IgAN

Baseline patient Characteristics
Randomized (1:1)

- 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

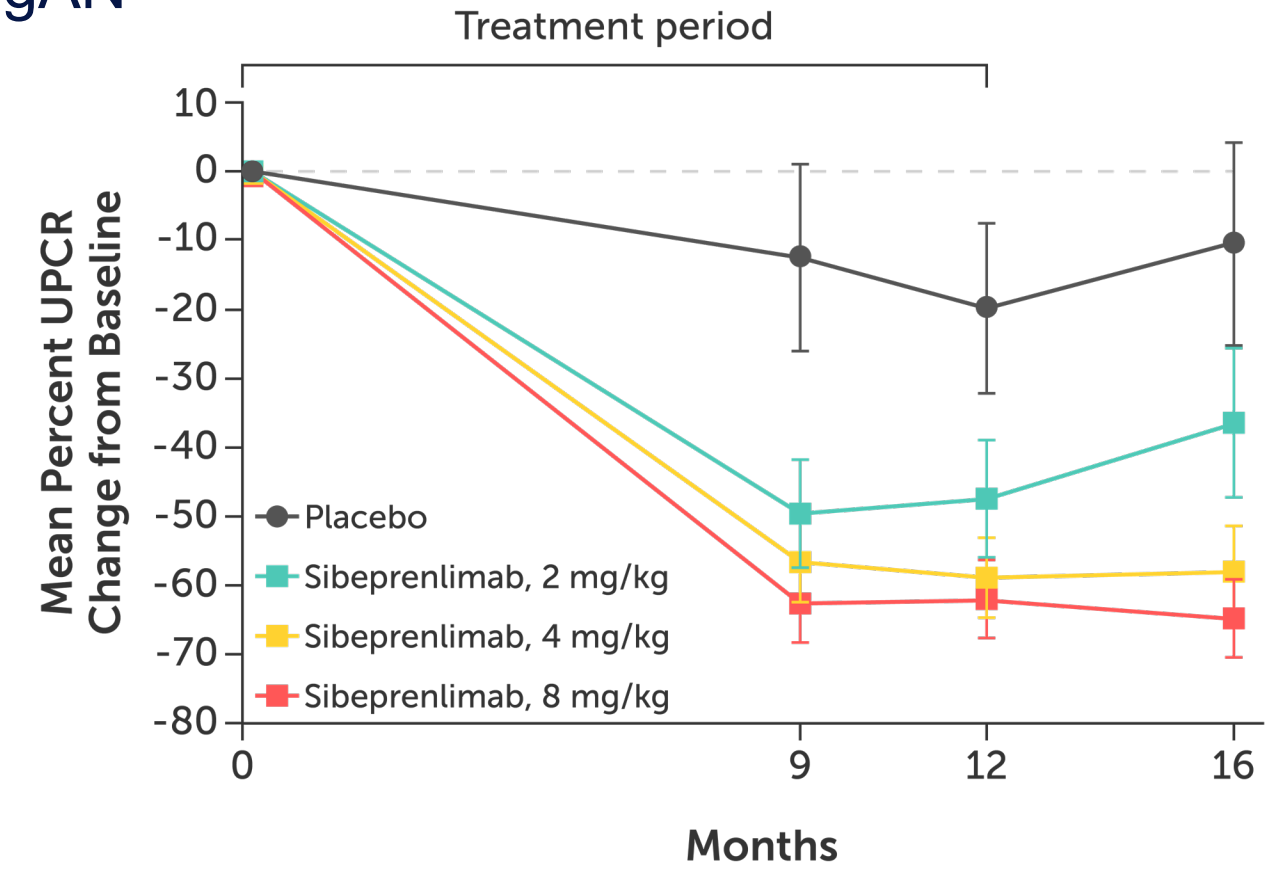


Nefecon (approved): Delayed-release budesonide [immunosuppressant]

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

ENVISION Phase 2 Trial

Evaluate the efficacy and safety of sibeprenlimab (investigational) vs placebo in patients with IgAN

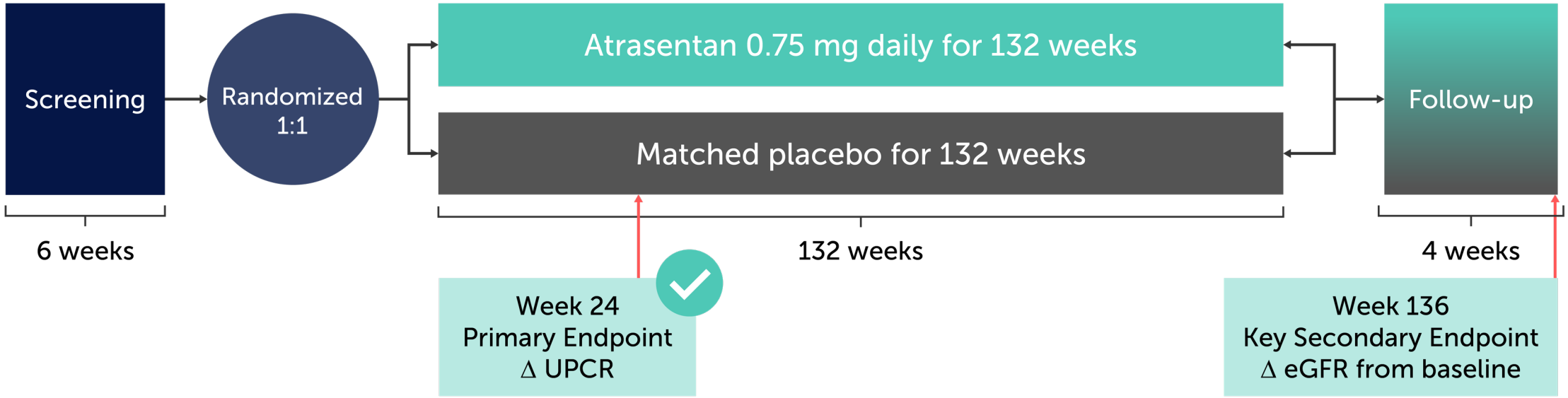


Sibeprenlimab: APRIL inhibitor [monoclonal antibody]

Mathur M, et al. *N Engl J Med*. Published online November 2, 2023. doi:10.1056/NEJMoa2305635

ALIGN Phase 3 Study (Ongoing)

Evaluate the efficacy and safety of atrasentan (investigational) vs placebo in patients with IgAN

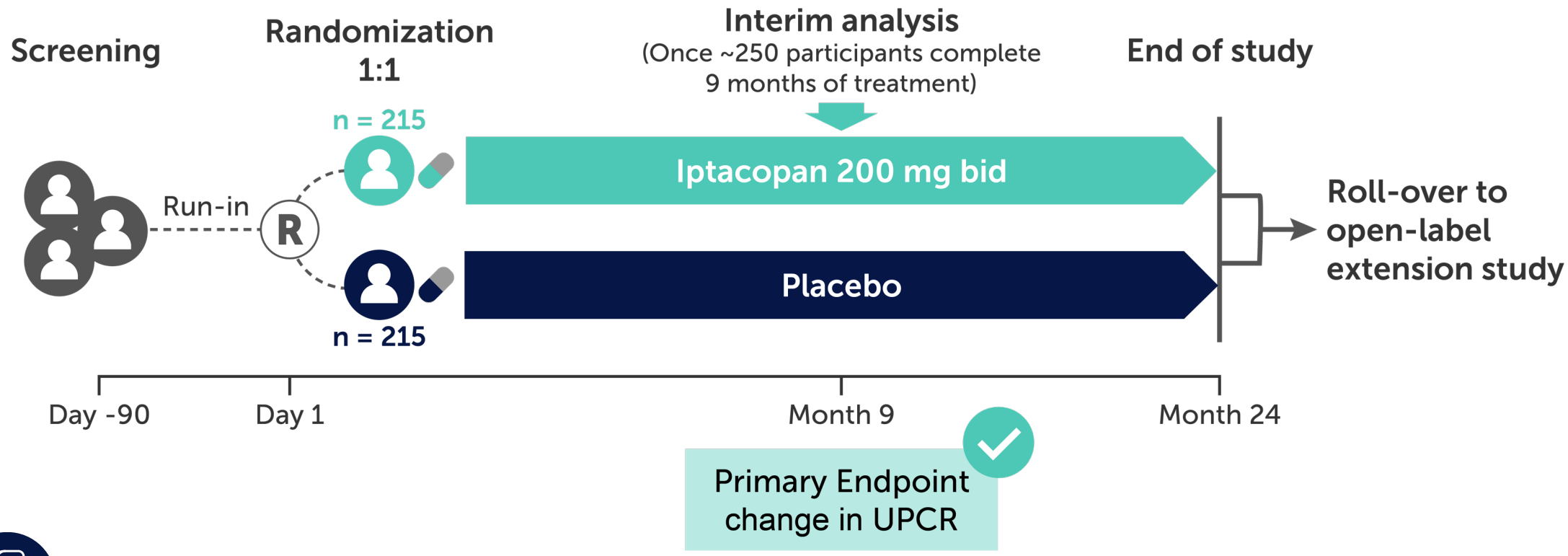


Atrasentan: Selective endothelin A receptor antagonist

Kohan DE, et al. *Kidney Int Rep*. 2023;8(11):2198-2210.

APPLAUSE Phase 3 Study

Evaluate the efficacy and safety of iptacopan (investigational) vs placebo in patients with IgAN



Iptacopan: Selective complement factor B inhibitor

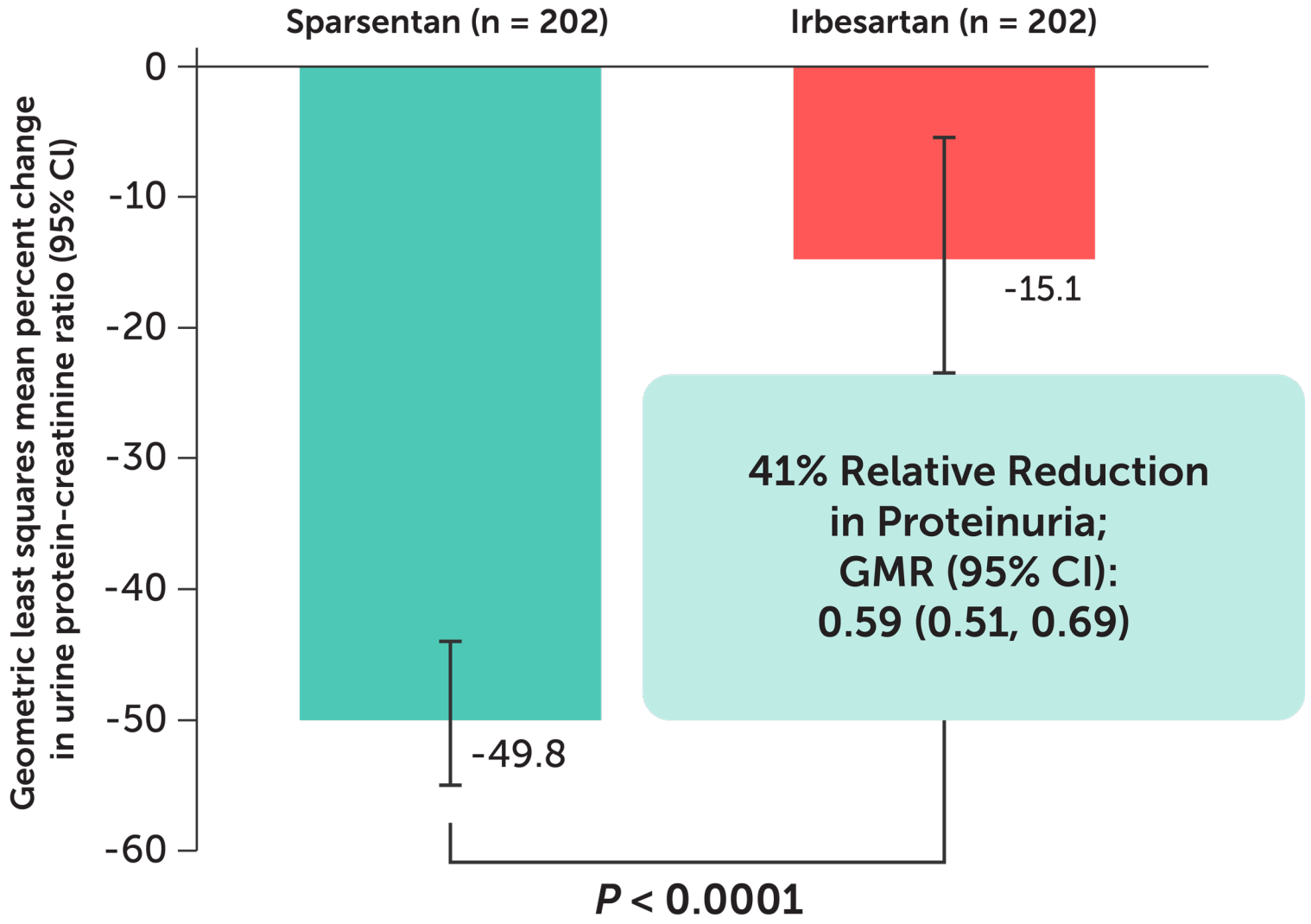
Rizk DV, et al. *Kidney Int Rep*. 2023;8(5):968-979.

Additional Ongoing Trials

Trial	Agent	Mechanism of Action
ORIGIN Phase 3	Atacicept (investigational)	Dual APRIL and BLyS inhibitor
BEYOND Phase 3	Zigakibart (investigational)	APRIL inhibitor

Lafayette R, et al. *Nephrol Dial Transplant*. 2023;38(Supplement_1):abst 3848.

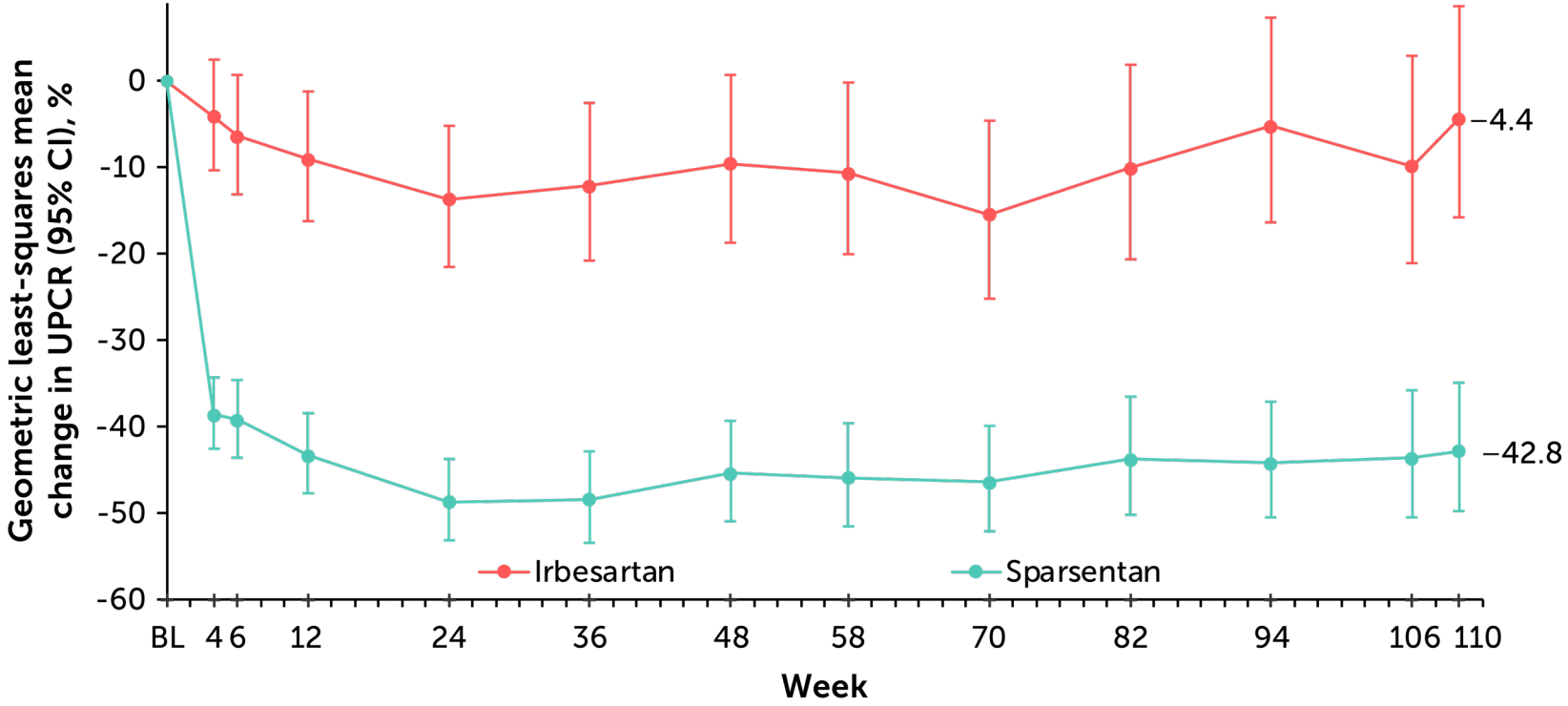
PROTECT Interim Analysis: Percent Change in Proteinuria at Week 36 (Primary Efficacy Endpoint)



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

PROTECT Trial: Sustained Proteinuria Reduction

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



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

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

PROTECT: 2-Year Topline Confirmatory Endpoints

Annual eGFR slope (95% CI), mL/min/1.73 m²/year	Chronic slope	Total slope
Irbesartan	−3.8 (−4.6 to −3.1)	−3.9 (−4.6 to −3.1)
Sparsentan	−2.7 (−3.4 to −2.1)	−2.9 (−3.6 to −2.2)
Difference	1.1 (0.1 to 2.1)	1.0 (−0.03 to 1.9)
P value	*P* = 0.037	*P* = 0.058

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

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

1 mL/min/1.73 m^2/year average difference between sparsentan and irbesartan

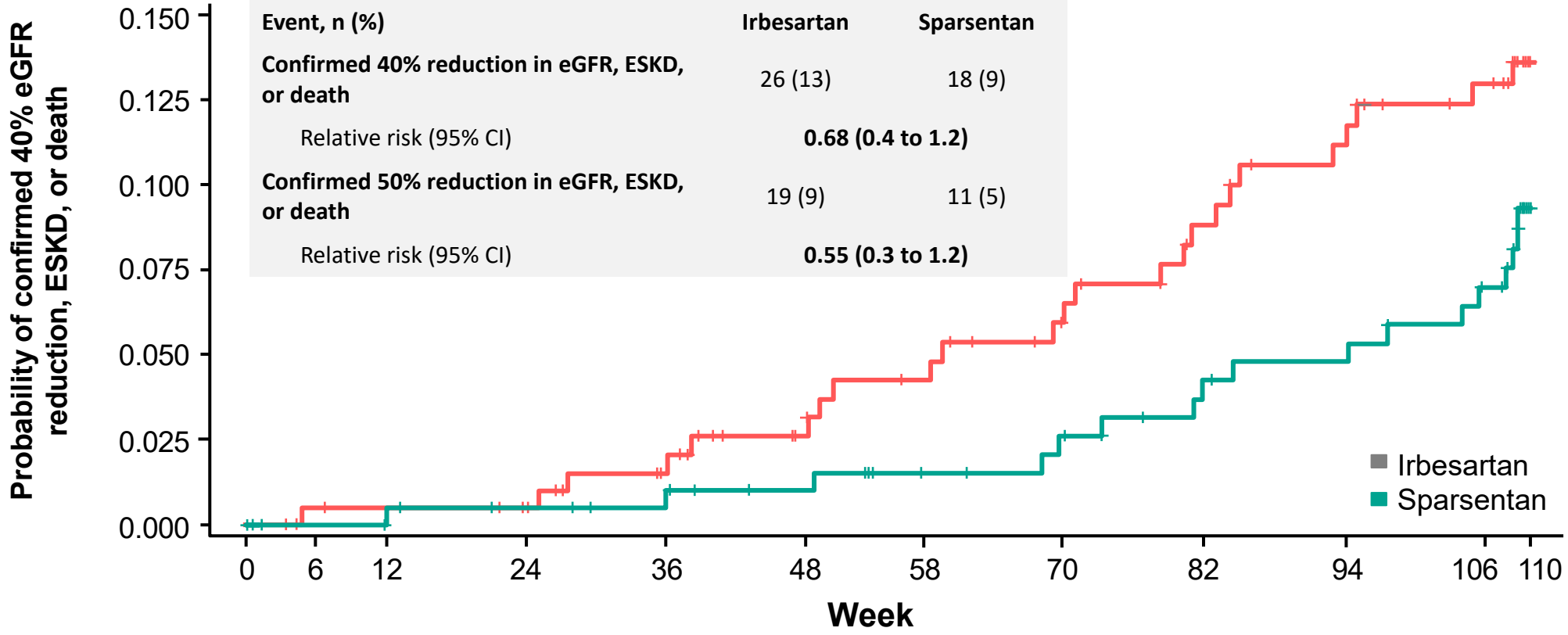
Fewer patients initiated immunosuppressive therapy in the sparsentan group compared to the irbesartan group in the PROTECT trial

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

PROTECT Trial: Progression to Composite Kidney Failure Endpoint

Fewer patients treated with sparsentan progressed to composite endpoint vs irbesartan

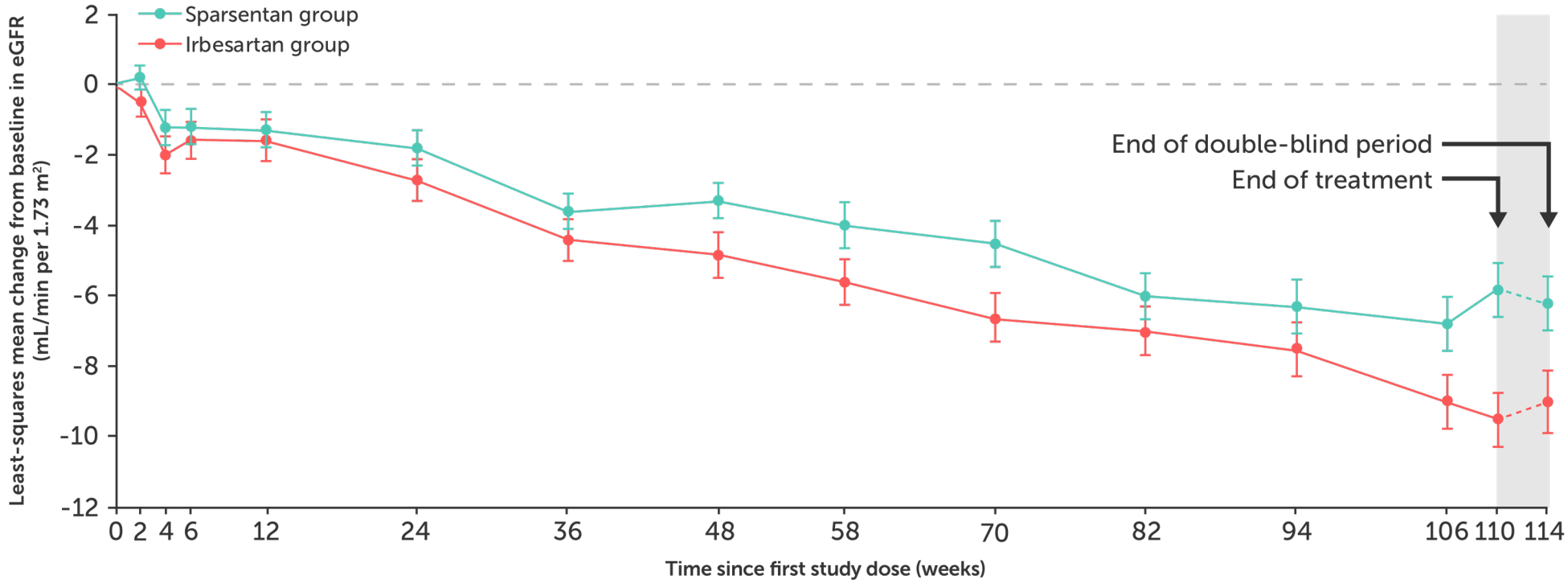
Event, n (%)	Irbesartan	Sparsentan
Confirmed 40% reduction in eGFR, ESKD, or death	26 (13)	18 (9)
Relative risk (95% CI)	**0.68 (0.4 to 1.2)**	
Confirmed 50% reduction in eGFR, ESKD, or death	19 (9)	11 (5)
Relative risk (95% CI)	**0.55 (0.3 to 1.2)**	



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

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.* 2023;402(10417):2077-2090.

PROTECT Trial: Safety

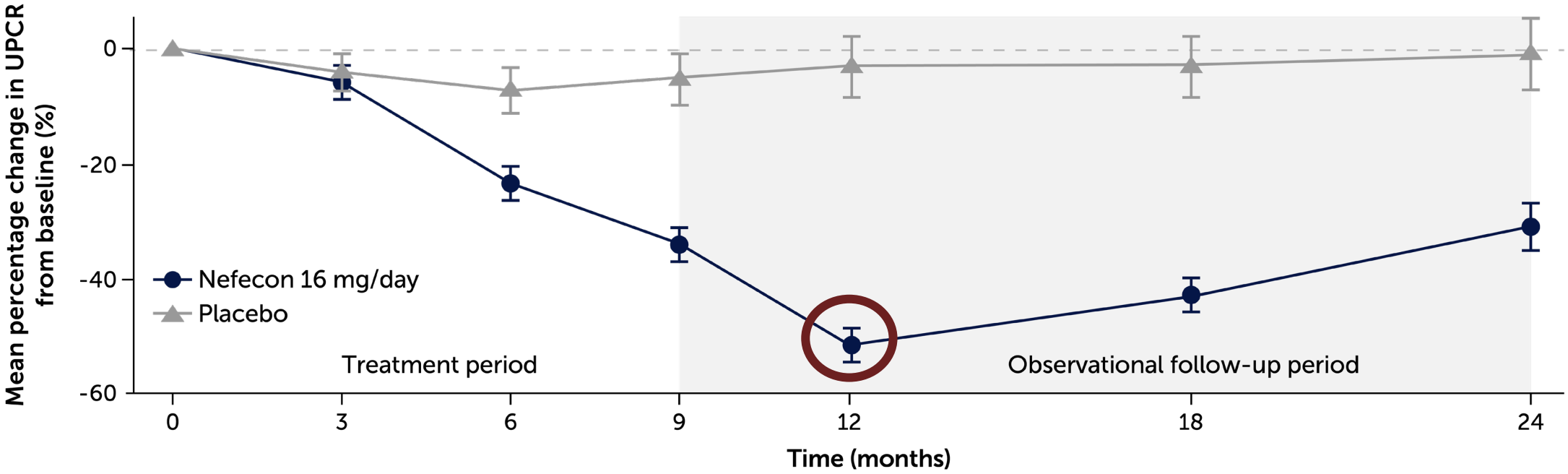
Sparsentan was well tolerated with a consistent safety profile comparable to irbesartan

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)

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

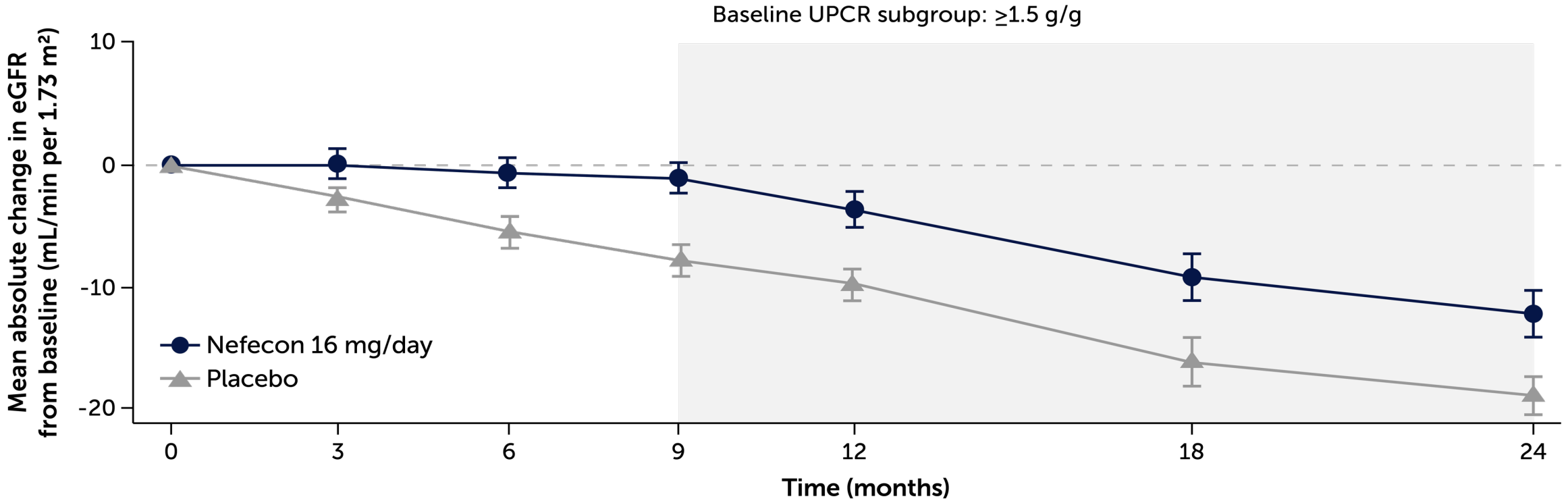
NeflgArd Trial: UPCR Change

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



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

NefIgArd Trial: eGFR Change



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

NefIgArd Trial: Safety

Adverse events, n (%)	Nefecon 16 mg/day (n = 182)	Placebo (n = 182)
Peripheral edema	31 (17)	7 (4)
Hypertension	22 (12)	6 (3)

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