A 29-Year-Old Woman

"Never been sick," no history of microhematuria

Sept 2020:

- Edema
- 1 episode of macrohematuria
- BP 140/90 mmHg

Labs:

- eGFR > 90 mL/min/1.73 m^2
- Se-ALB 23 g/L
- ACR: 900 g/mol Cr
- PU 4 g/d

Clinical Case: 1-2 Years Later...

A 29-Year-Old Woman

11/2020: Start prednisolone 60 mg/d (1 mg/kg), MMF 2x1 g/d

2/2021: Stop immunosuppression

2/2022: Add dapagliflozin 10 mg/d

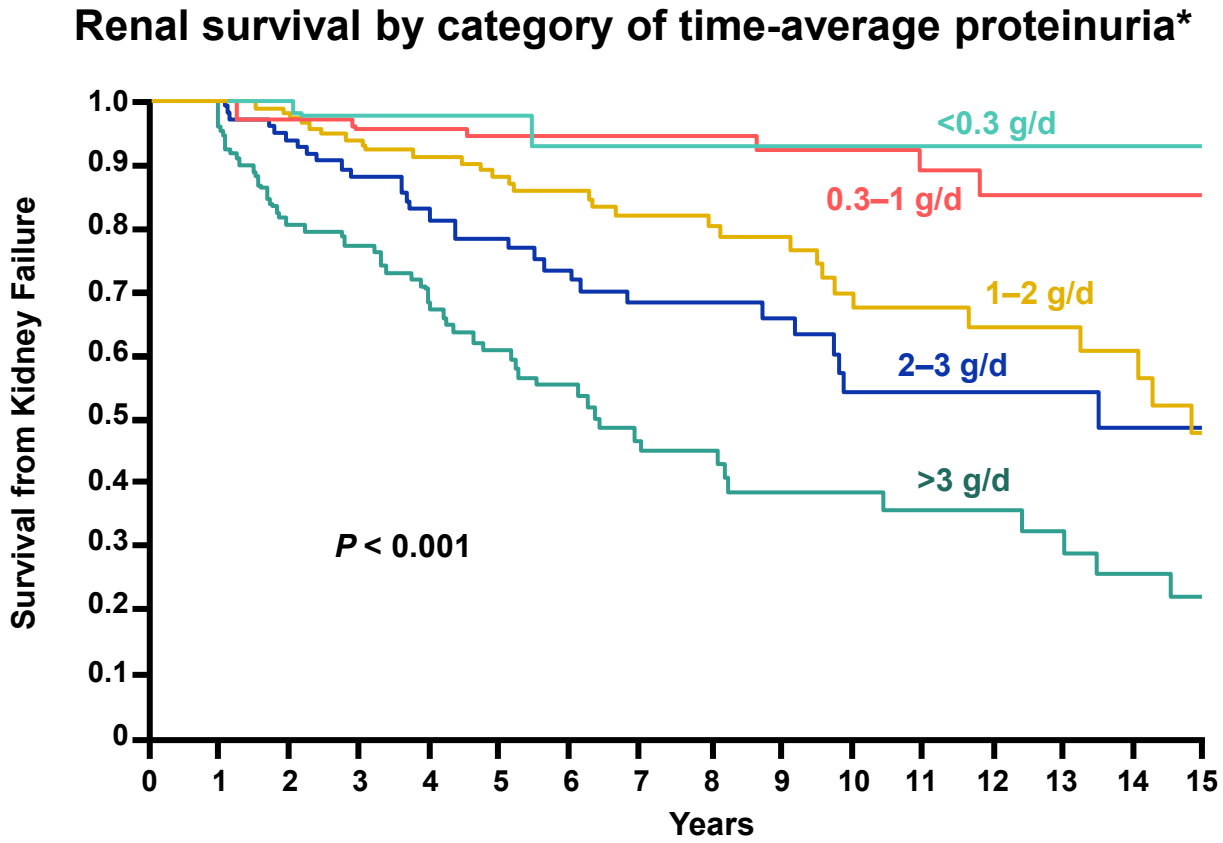
8/2022: Kidney biopsy

- M1, E1, S1, T0, C1

09/2023:

- Early access program sparsentan 400 mg/d
- ACR: 350 → 200 g/mol Cr after 3 months

Sustained Proteinuria >1 g/d Has Been Shown to Be the Strongest Predictor of the Rate of Progression

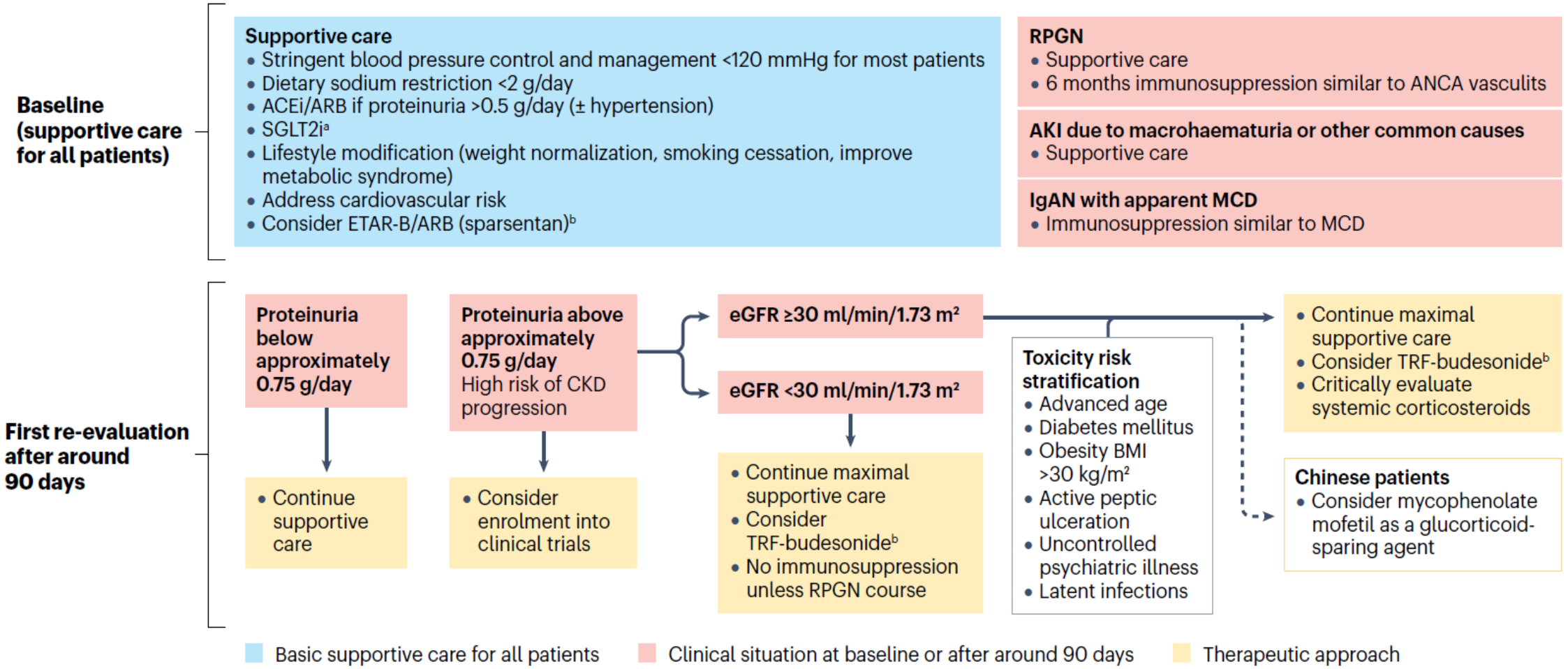


Each incremental g/d >1 g is associated with a 10- to 25-fold more rapid rate of decline in kidney function and similar differences in kidney survival

* N = 542 patients with biopsy-proven primary IgA nephropathy in the Toronto Glomerulonephritis Registry, mean follow-up of 6.5 years. IgA, immunoglobulin A.

Reich HN, et al. *J Am Soc Nephrol* 2007;18(12):3177-3183.

Nature Reviews Disease Primers: IgA Nephropathy

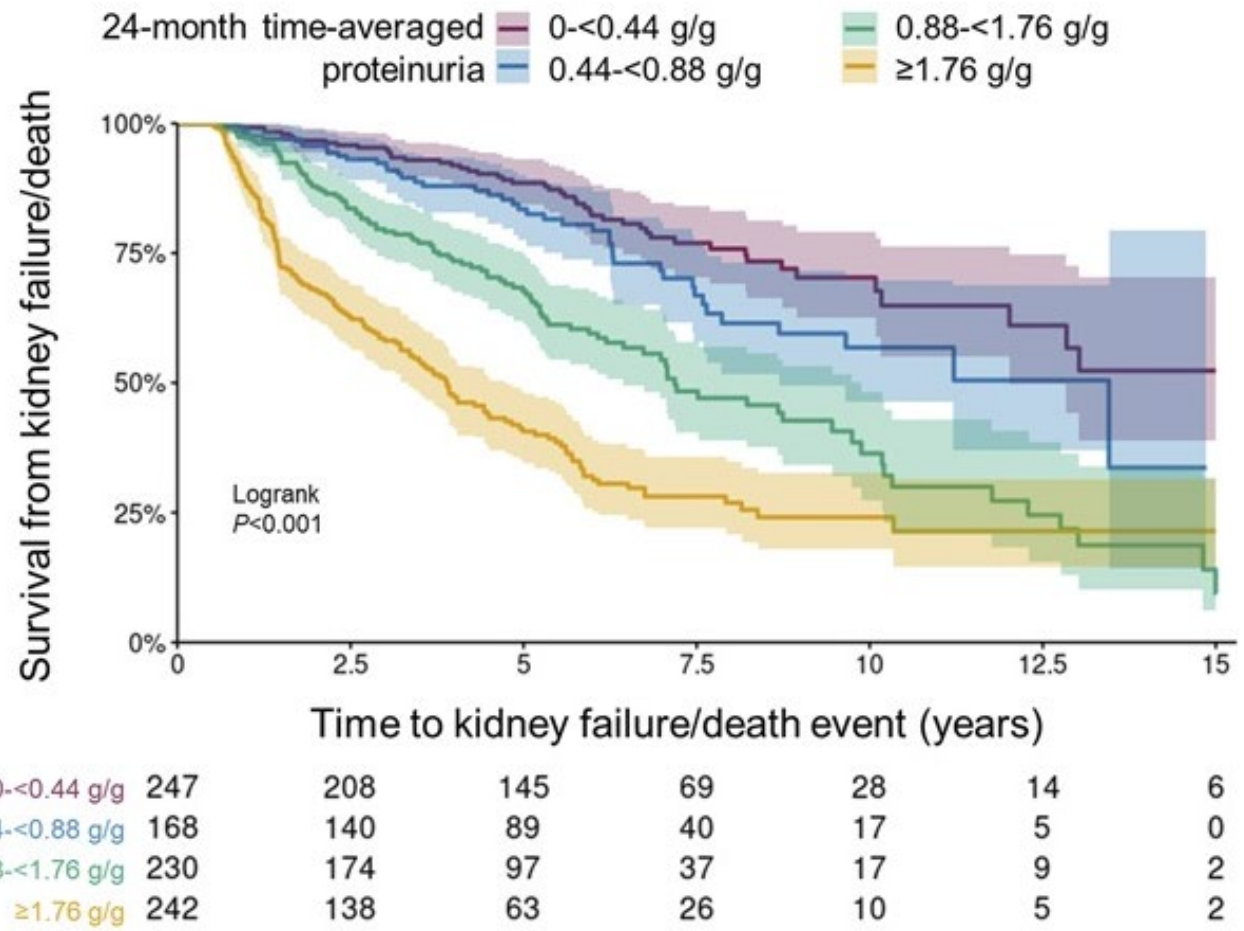


ACEi, angiotensin converting enzyme inhibitor; AKI, acute kidney injury; ARB, angiotensin receptor blocker; BMI, body mass index; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; ETAR, endothelin A receptor blocker; MCD, minimal change disease; RPGN, rapidly progressing glomerulonephritis; SGLT2i, sodium-glucose cotransporter 2 inhibitor; TRF; targeted-release formation.

Stamellou E, et al. *Nat Rev Dis Primers*. 2023;9(1):67.

There Is No “Safe” Proteinuria Threshold: An Analysis of the UK National RaDaR IgA Nephropathy Cohort

Development of kidney failure and mortality by severity of proteinuria*

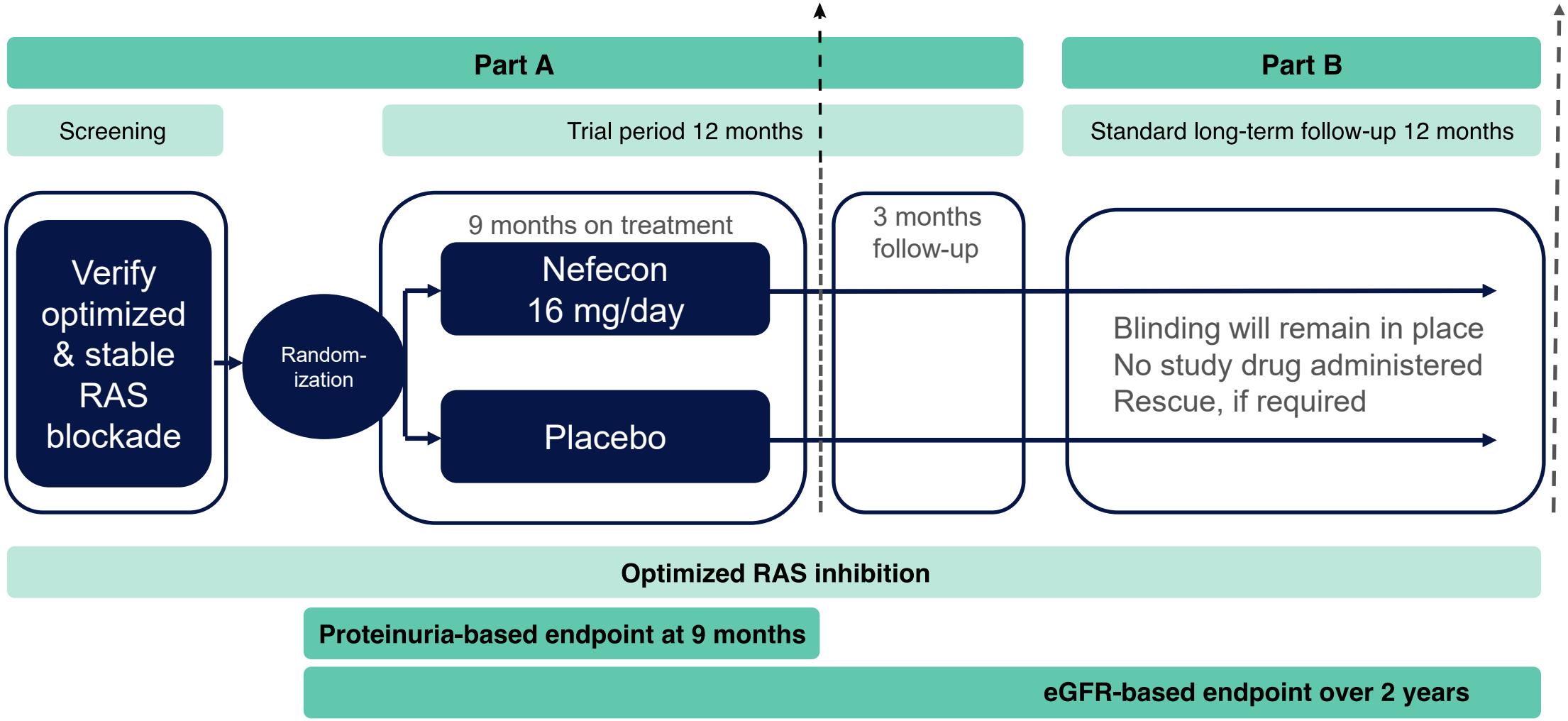


*Kaplan-Meier curves for patients categorized by TA-PU. TA-PU, time-averaged proteinuria.

Pitcher D, et al. *Clin J Am Soc Nephrol.* 2023;18(6):727-738.

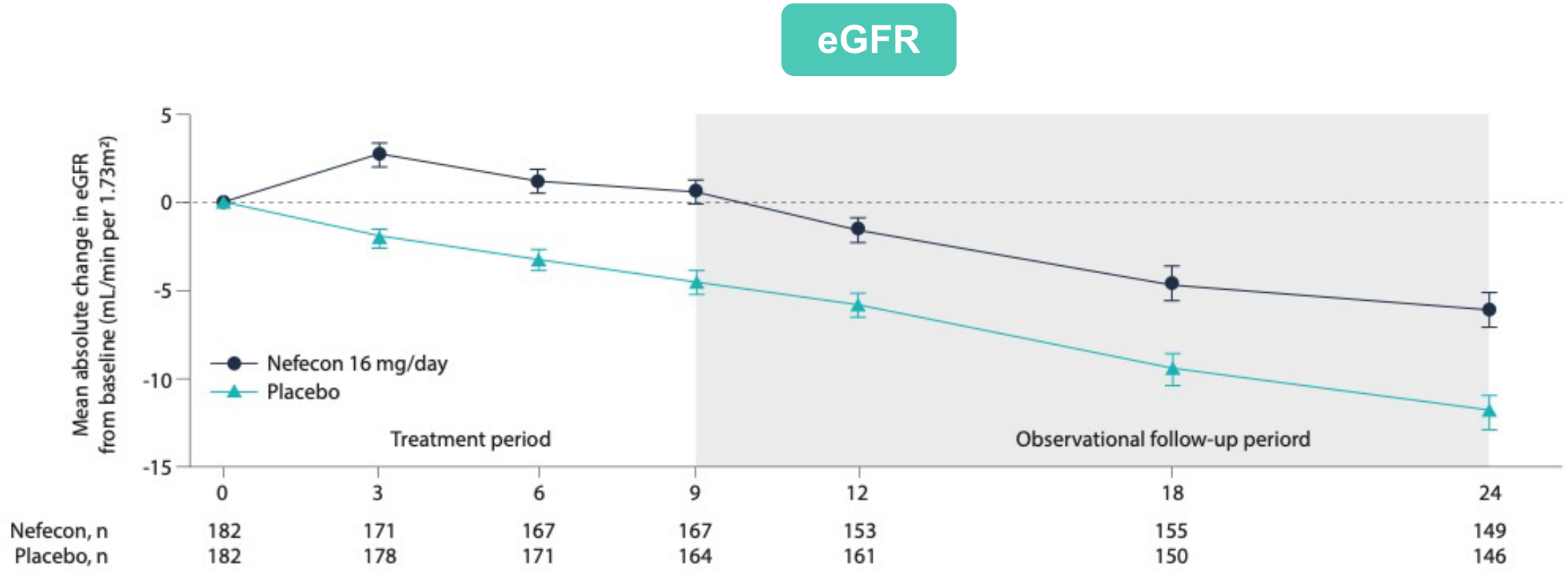
NeflgArd Phase 3 Trial in IgAN

Randomized, Double-Blind, Placebo-Controlled Clinical Trial



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

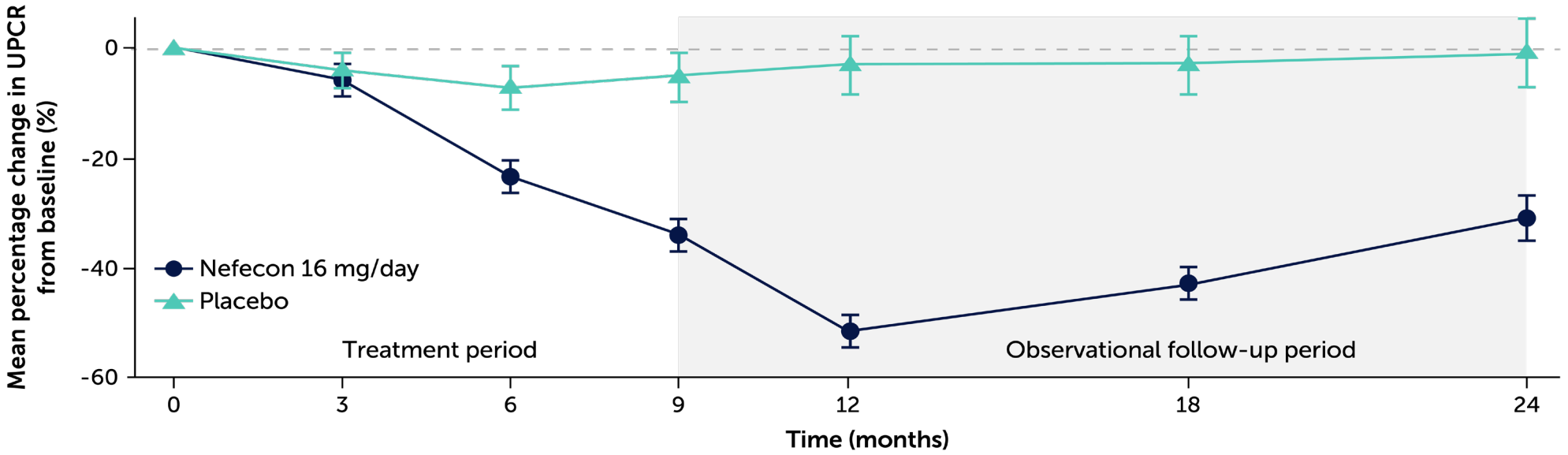
Targeted-Release Budesonide (Nefecon) in IgAN: Neflgard Phase 3 Trial



eGFR, estimated glomerular filtration rate.

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

Targeted-Release Budesonide (Nefecon) in IgAN: Neflgard Phase 3 Trial



Nefecon, n	182	173	169	166	157	155	145
Placebo, n	182	176	169	164	160	151	142
Mean percentage change (95% CI) from baseline, %							
Nefecon 16 mg/day		-5·2 (-11·8 to 1·9)	-23·1 (-29·5 to -16·1)	-33·6 (-39·6 to -27·0)	-51·3 (-56·2 to -45·9)	-43·1 (-49·0 to -36·6)	-30·7 (-38·9 to -21·5)
Placebo		-4·3 (-10·9 to 2·9)	-7·3 (-15·0 to 1·2)	-5·2 (-13·8 to 4·3)	-3·2 (-12·8 to 7·5)	-2·9 (-13·0 to 8·3)	-1·0 (-12·8 to 12·4)

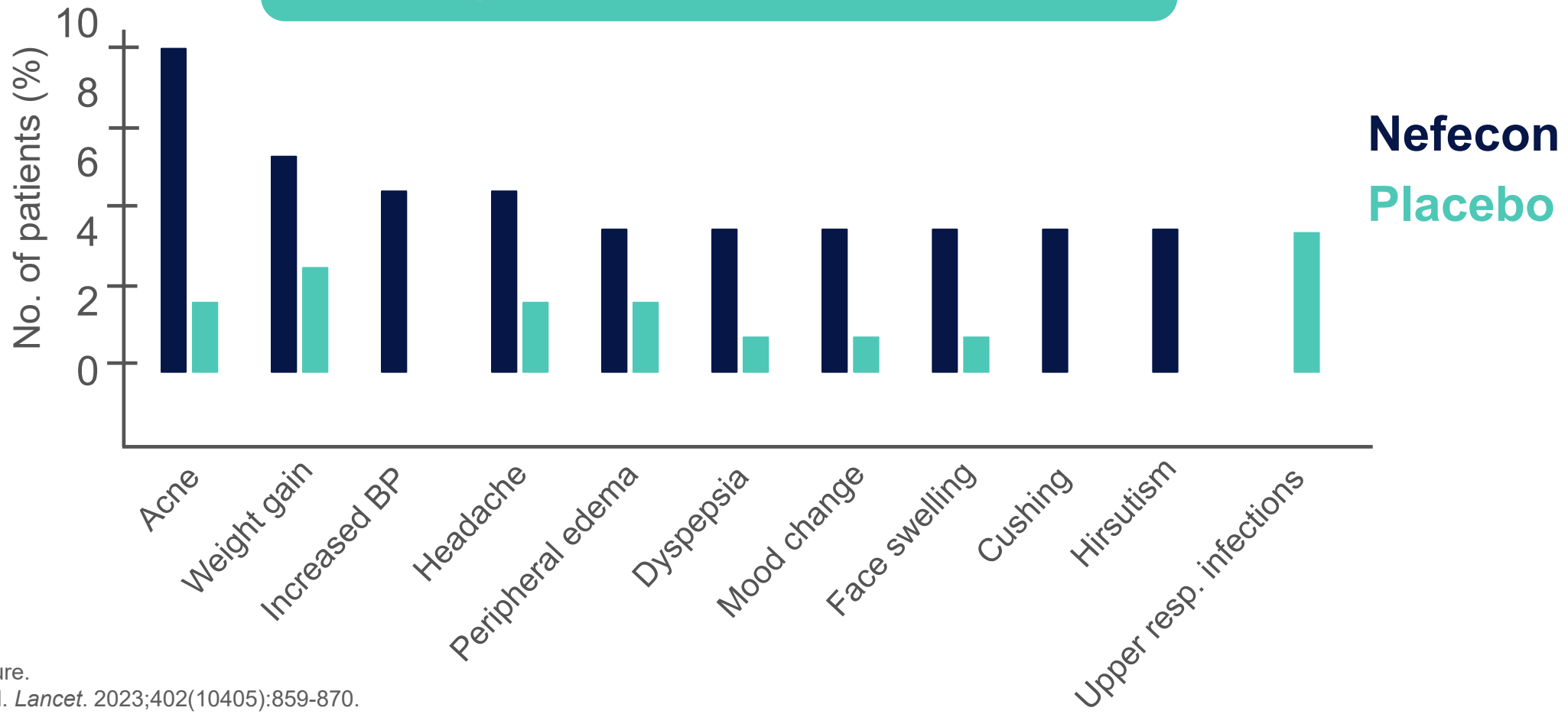
UPCR, urine protein creatinine ratio.

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

Neflgard Phase 3 Trial: Adverse Events

- Treatment-emergent adverse events in >4% patients (full analysis set, n = 197)

- **No serious infections or deaths**
- **No significant increase in diabetes**

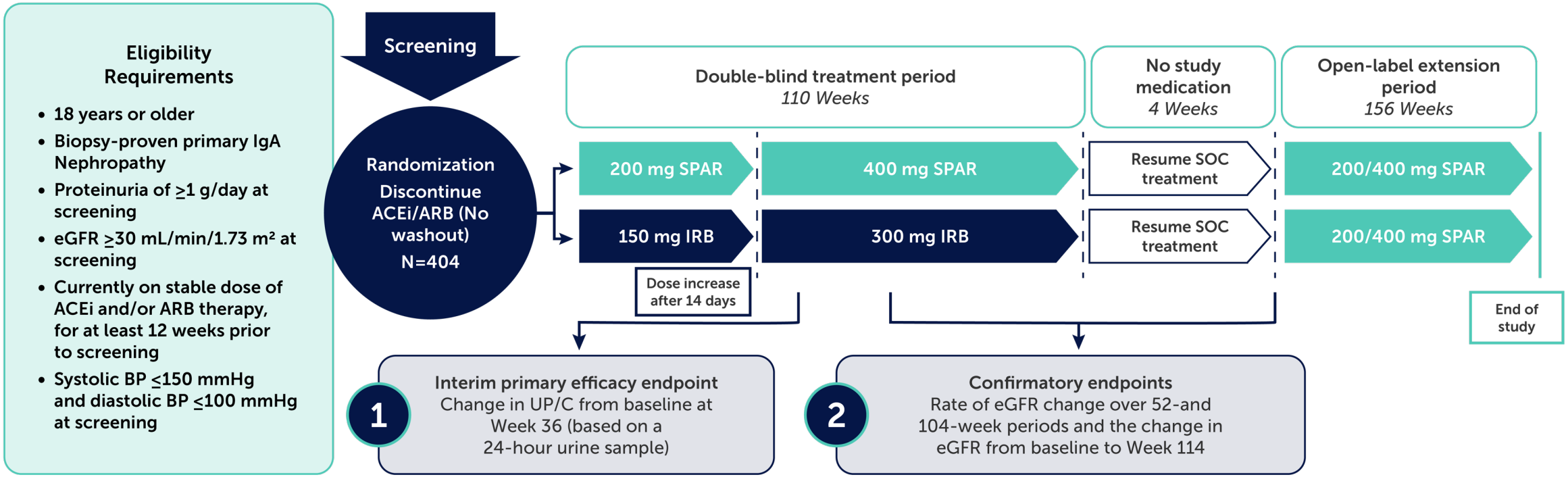


BP, blood pressure.

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

PROTECT Trial Design in IgAN

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



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

Sparsentan

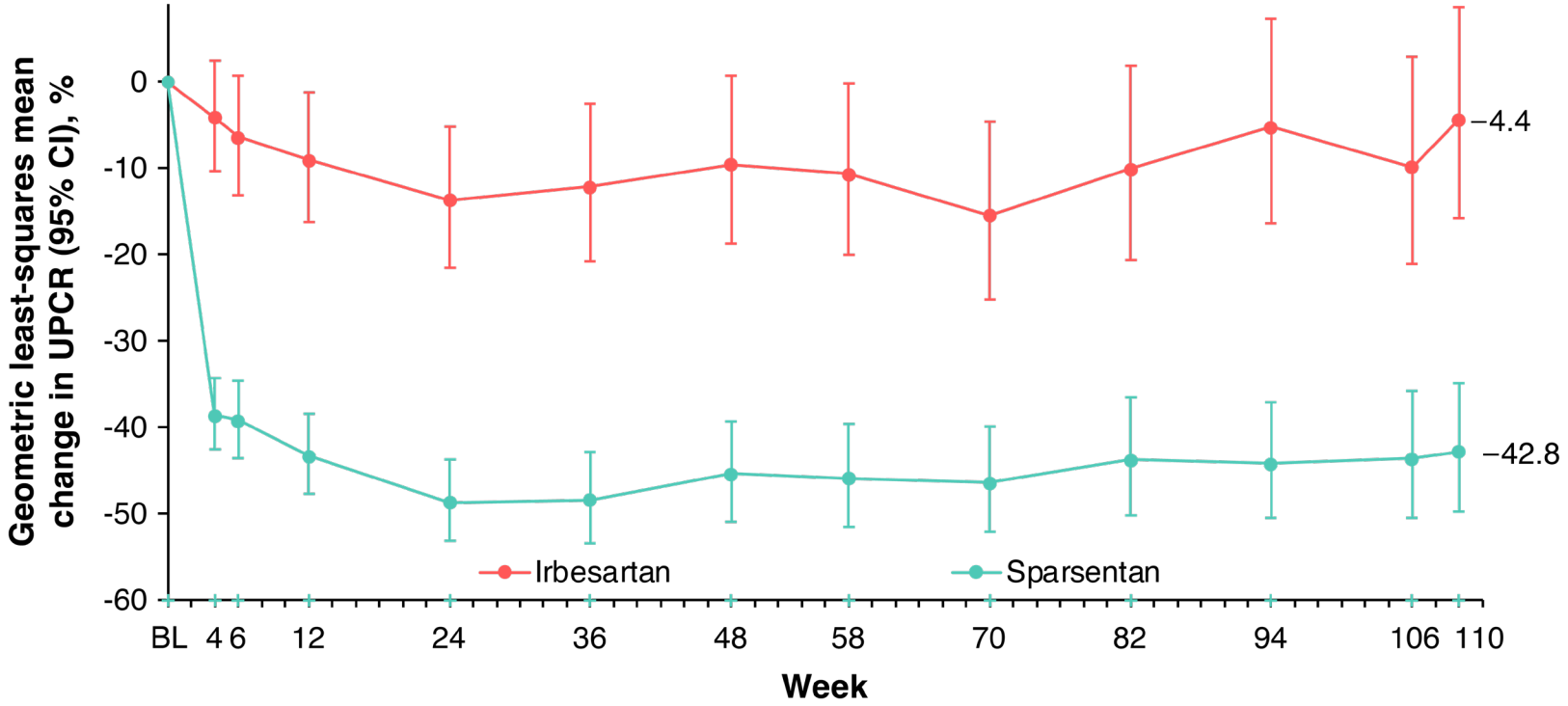
- Orally active dual endothelin angiotensin receptor antagonist (DEARA)
- Selectively targeting the endothelin A receptor (ET_AR) and the angiotensin II subtype 1 receptor (AT_1R)
- Non-immunosuppressant

PROTECT Trial: Sustained Proteinuria Reduction

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

Primary endpoint met
Interim analysis week 36

- Sparsentan achieved mean reduction in proteinuria from baseline of 49.8%, compared to 15.1% for irbesartan



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

UPCR, urine protein creatinine ratio.

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

1 ML/MIN/1.73 M^2/YEAR
AVERAGE DIFFERENCE
BETWEEN **SPARSENTAN**
AND IRBESARTAN

PROTECT Trial: Safety

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

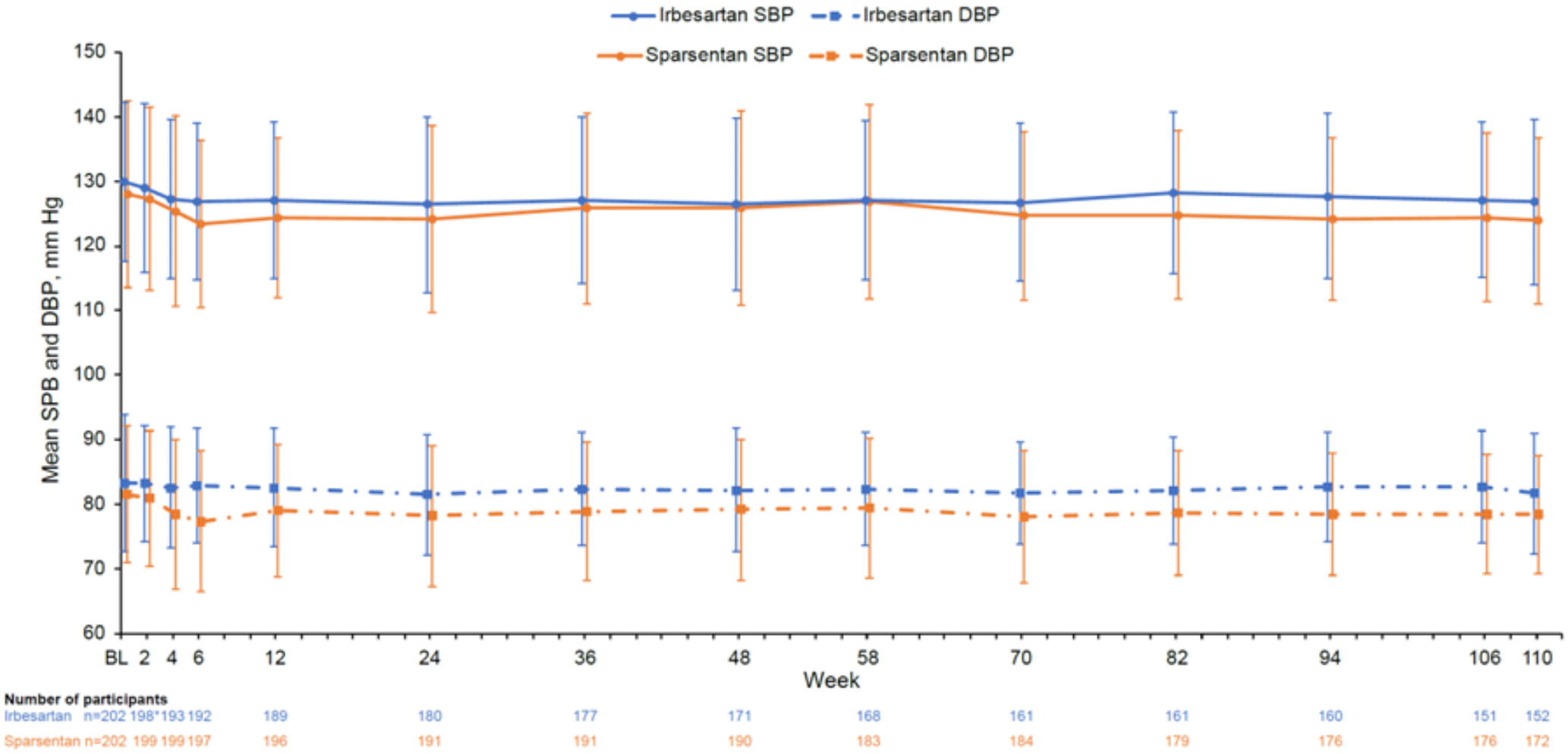
Patients with TEAEs, n (%)	Sparsentan (n = 202)	Irbesartan (n = 202)
Any TEAEs	**187 (93)**	**177 (88)**
Most common TEAEs (≥10% of patients in either group)		
COVID-19	53 (26)	46 (23)
Hyperkalemia	32 (16)	26 (13)
Peripheral edema	31 (15)	24 (12)
Dizziness	30 (15)	13 (6)
Headache	27 (13)	26 (13)
Hypotension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

TEAE, treatment-emergent adverse event.

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

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



BL, baseline; DBP, diastolic blood pressure; SBP, systolic blood pressure.* Irbesartan value for DBP, n = 197.

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

Quote by Jürgen Floege, MD

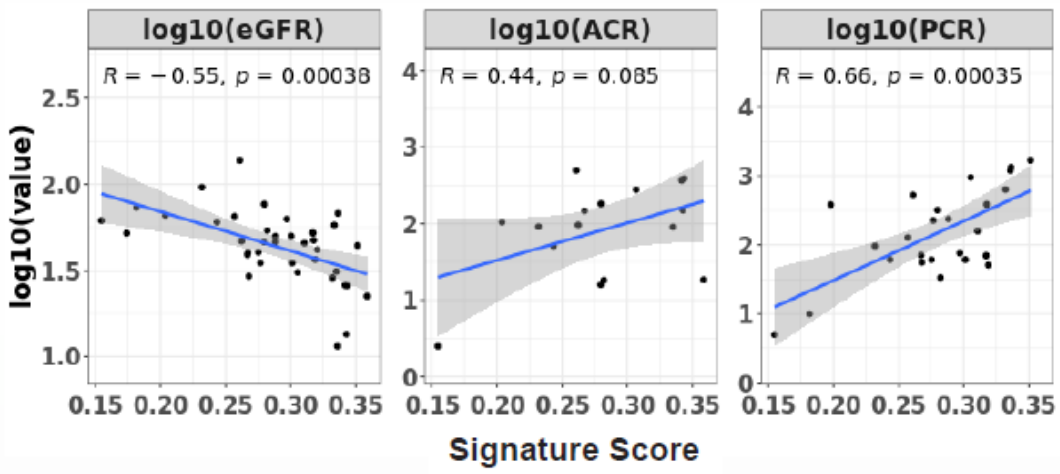
“This is a landmark study because it sets a new standard in treatment, and the GFR loss in IgA nephropathy patients can be lowered so much that future trials will indeed have somewhat of a difficult stand in improving this even further…”

ET-1 Signatures Correlate With Kidney Function

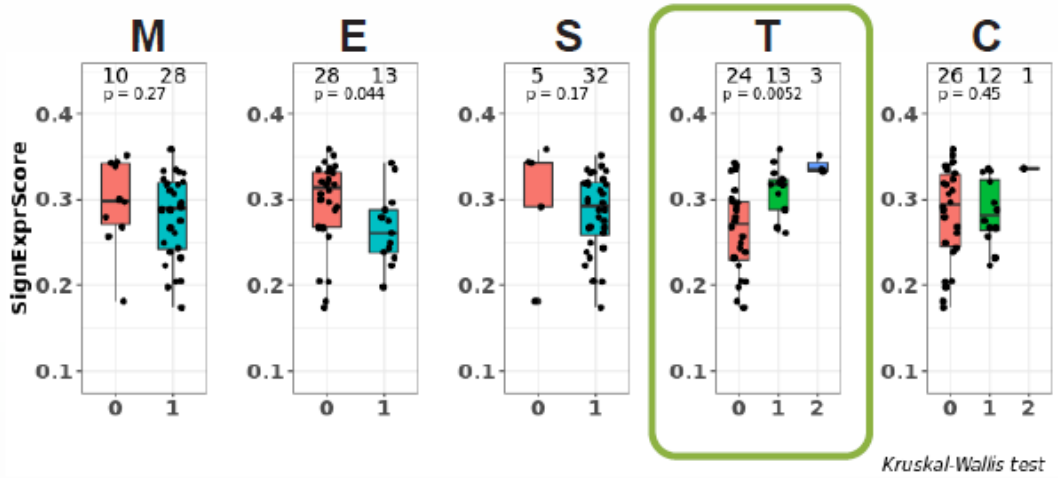
- A 31 gene atrasentan response signature derived from failed repair of proximal tubule cells in the gddY IgAN model is significantly correlated with eGFR and UPCR in the IgAN cohort
- The signatures score is significantly higher in samples from subjects with an elevated T score

Atrasentan (investigational): Selective endothelin A receptor antagonist

The atrasentan signature score from kidney biopsies is correlated with kidney function in the IgAN cohort



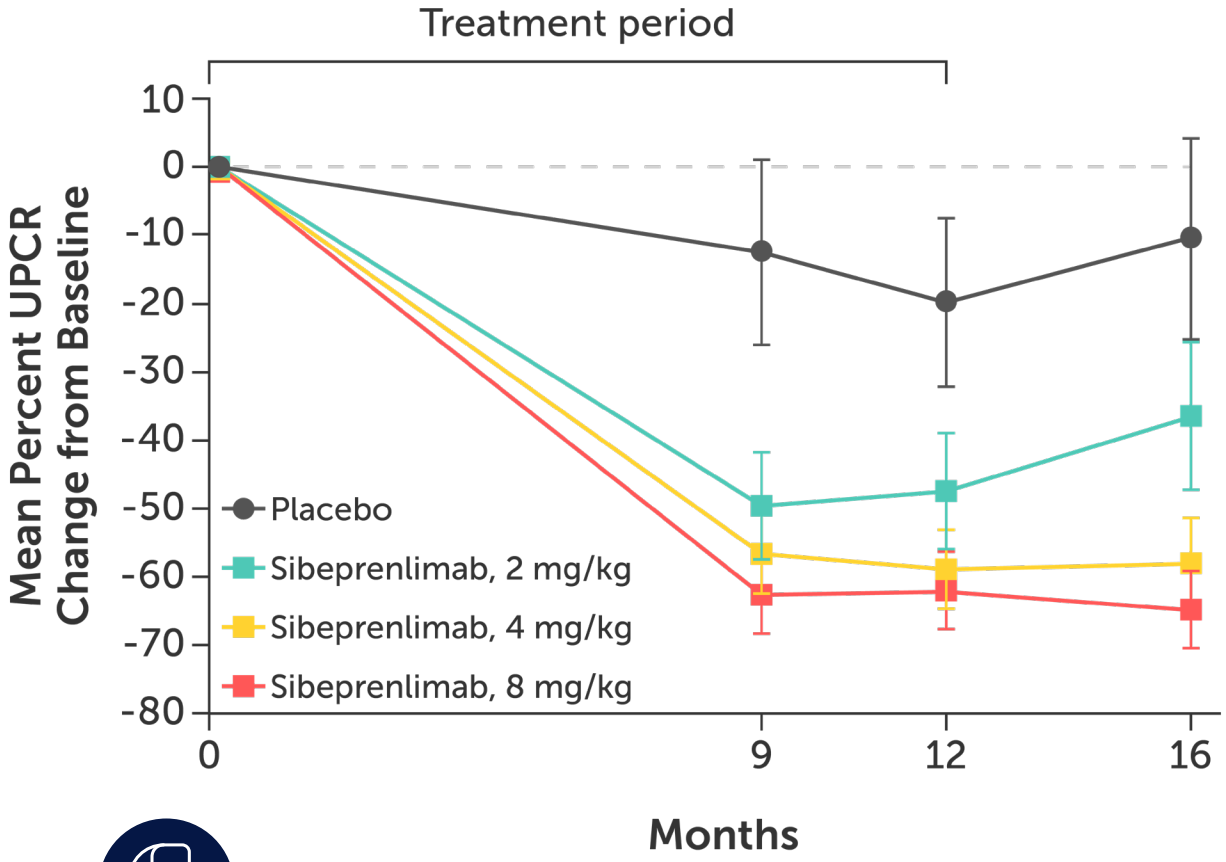
Increased atrasentan signature score is associated with tubular atrophy and interstitial fibrosis



Presented at Kidney Week 2022. https://www.nurturebiobank.org
Figure (left) adapted from Kidney Medicine Project. https://www.kpmp.org/about-kpmp

ENVISION Phase 2 Trial

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



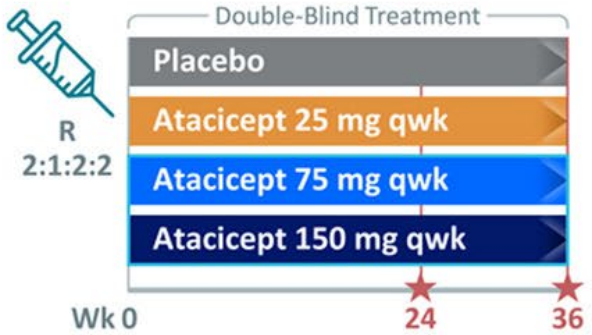
Sibeprenlimab: APRIL inhibitor [monoclonal antibody]

UPCR, urine protein creatinine ratio.

Mathur M, et al. *N Engl J Med*. 2024;390(1):20-31.

A Phase 2b, Randomized, Double-Blind, Placebo-Controlled Clinical Trial of Atacicept for Treatment of IgAN

Methods and population

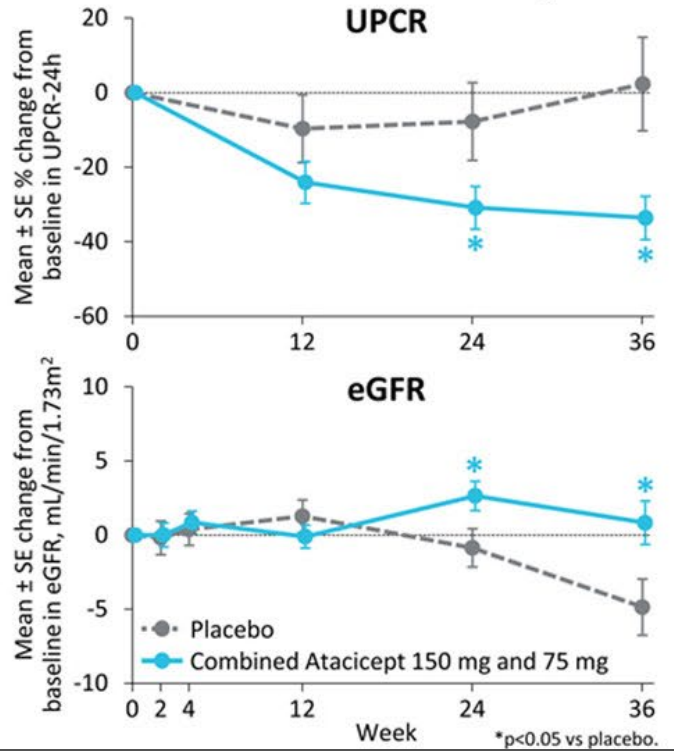


- 116 adults from 13 countries
- Biopsy-proven IgAN within 10 years prior to screening
- ≥12 weeks on maximally tolerated, stable dose of RAASi
- SGLT2i use was allowed

Key baseline characteristics

- Mean UPCR-24h **1.6** g/g
- Mean eGFR **63** mL/min/1.73m²

Outcomes with combined 75 mg and 150 mg group vs placebo



1° endpoint met at 24 weeks:

UPCR reduction **Δ25%** **p=0.037**

Key 2° endpoints at 36 weeks

UPCR reduction **Δ35%** **p=0.004**

eGFR difference **11%** **p=0.022** **5.7** mL/min/1.73m²

Gd-IgA1 reduction **Δ60%** **p<0.0001**

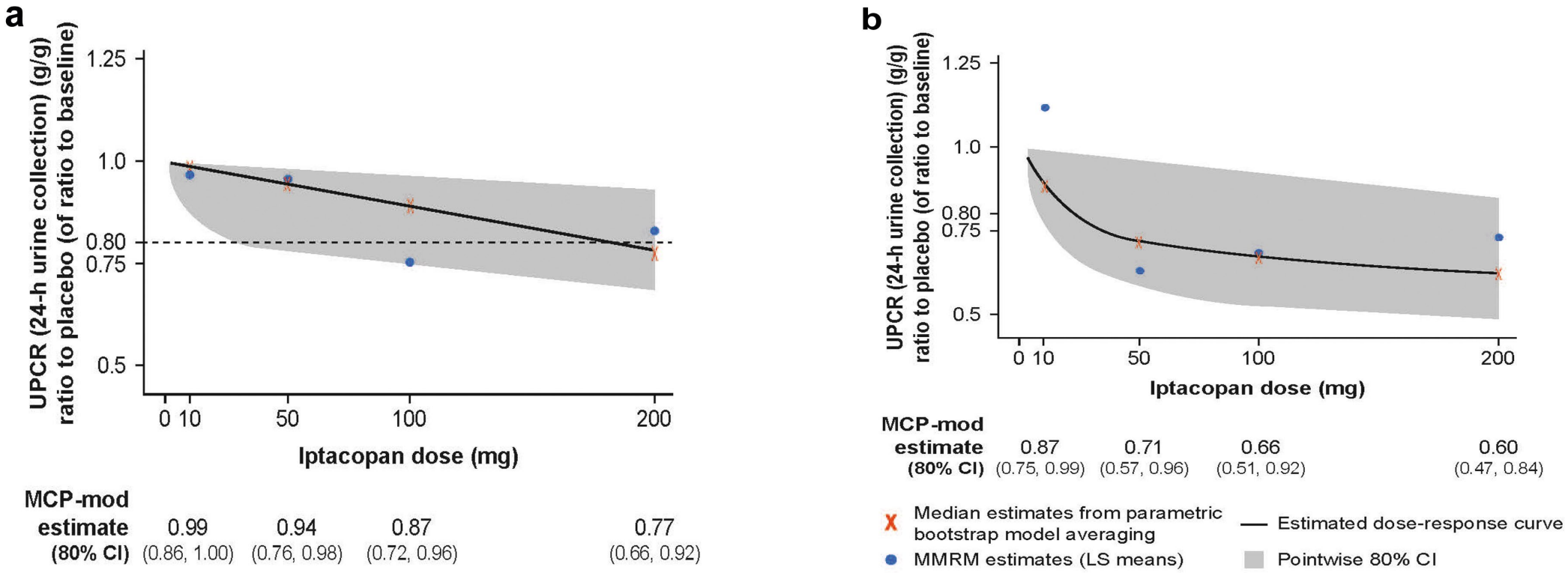
Safety profile of all atacicept doses similar to placebo

- Treatment with atacicept, a dual BAFF/APRIL inhibitor, in addition to current standard of care, resulted in clinically and statistically significant UPCR reductions at weeks 24 and 36 and eGFR stabilization at week 36, supporting a pivotal phase 3 trial

eGFR, estimated glomerular filtration rate; RAASi, renin-angiotensin-aldosterone system inhibitor; SGLT2i, sodium-glucose cotransporter 2 inhibitor; UPCR, urine protein creatinine ratio.

Lafayette R, et al. *Kidney Int*. 2024;105(6):1306-1315.

Results of a Randomized, Double-Blind, Placebo-Controlled, Phase 2 Study Propose Iptacopan as an Alternative Complement Pathway Inhibitor for Iga Nephropathy



MCP-mod, multiple comparison procedure–modeling; MMRM, mixed model of repeated measures; UPCR, urine protein creatinine ratio.

Zhang H, et al. *Kidney Int.* 2024;105(1):189-199.

Quote by Jürgen Floege, MD

“What is the best therapy to reduce proteinuria? And as I said earlier, ideally to induce full remission of the disease, that is no proteinuria, below 0.3 g/day, no microhematuria, and a stable eGFR.”

Key Takeaway: IgAN Is 2 Diseases

- Lifelong CKD
  - Persistent treatment
    - RAS blockers
    - Sparsentan
    - SGLT2 inhibitors
- Immune disease
  - Intermittent or low-dose continuous therapy

Quote by Uyen Huynh-Do, MD

Key Takeaway

"We can treat the causes of IgA, tackling inflammation, and treat the consequences, which is CKD. So in addition to RAS blockade and SGLT2 inhibitor, we have now the dual angiotensin and endothelin antagonist **sparsentan**."