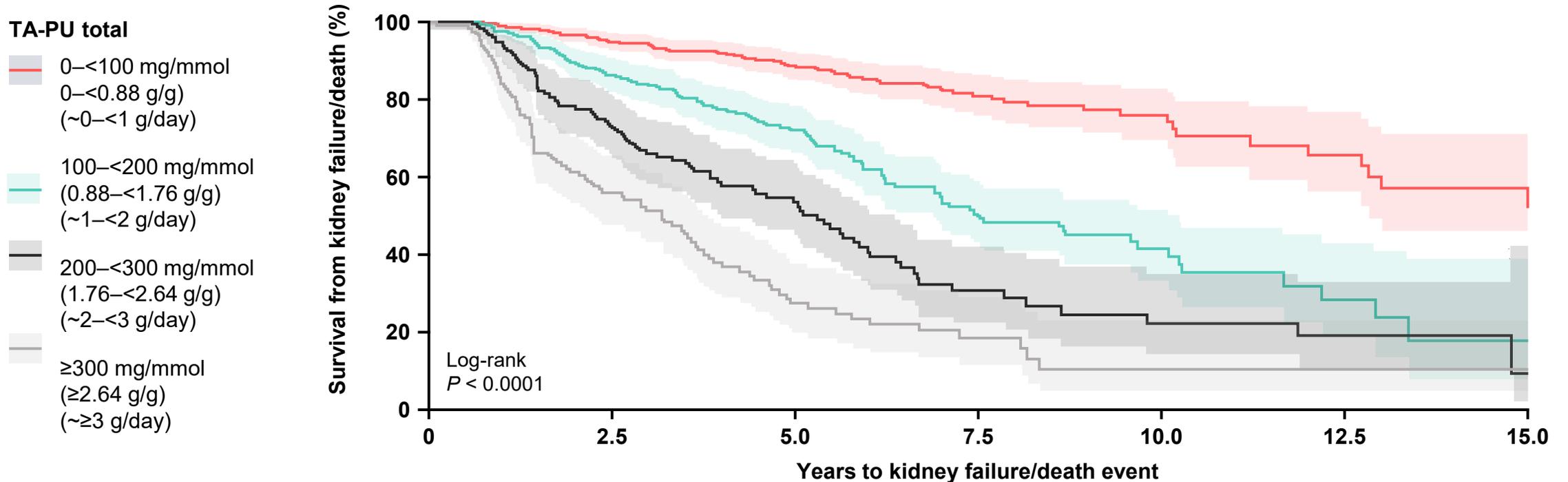


There Is No “Safe” Proteinuria Threshold: An Analysis of the UK National RADAR IgA Nephropathy Cohort

Development of kidney failure and mortality by severity of proteinuria*



0–<100 mg/mmol	406	336	217	103	46	24	9
100–<200 mg/mmol	262	204	126	54	21	8	2
200–<300 mg/mmol	129	89	49	18	10	4	1
≥300 mg/mmol	123	60	22	8	1	1	1

*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.

Supportive Care in IgAN

- Healthy lifestyle
- Low blood pressure
- Avoid smoking
- Avoid nephrotoxic drugs

- Treatments:
 - RAAS inhibitors
 - SGLT2 inhibitors
 - Immunomodulatory drugs



Quote by Federico Alberici, MD

Glucocorticoids may be effective in reducing proteinuria, although their effect usually is transient...and the duration of treatment is limited by the potential side effects.



Mr. G, 35-Year-Old Man

HISTORY

- BMI 32 kg/m²
- History of long-term CKD
- eGFR: 50 mL/min 5 years previous
- Smoker, high blood pressure
- eGFR: 36 mL/min
- UPCR 2 g/g with hematuria
- Negative HIV, HBV, HCV serologies
- Normal serum electrophoresis



Oxford Classification: MEST-C Score

Mesangial proliferation	M
Endocapillary hypercellularity	E
Segmental glomerulosclerosis	S
Tubular interstitial inflammation and fibrosis	T
Presence of crescents	C

Mr. G MEST-C Score

- M-0
- E-0
- S-1
- T-1
- C-0



International IgAN Prediction Tool

https://qxmd.com/calculate/calculator_499/international-igan-prediction-tool-at-biopsy-adults

Calculate by QxMD

All Calculators Become a Contributor Support

Calculator About References

International IgAN Prediction Tool at biopsy - Adults

Determine prognosis in adults with IgA nephropathy

Questions

1. Estimated GFR at biopsy
2. Systolic blood pressure
3. Diastolic blood pressure
4. Proteinuria at biopsy
5. Age at biopsy
6. Race
7. Use of ACE inhibitor or ARB at the time of...
8. MEST M-score

1. Estimated GFR at biopsy

ml/min/1.73m2

Min value: 15

Next Question →

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0/13 completed

Risk in this patient was about 35% of a 50% decline in eGFR, or end-stage renal disease after 5 years



Mr. G, 35-Year-Old Man

3 YEARS LATER

- eGFR: 32 mL/min
- UPCR 2 g/g with hematuria
- Repeat kidney biopsy



MEST-C Score

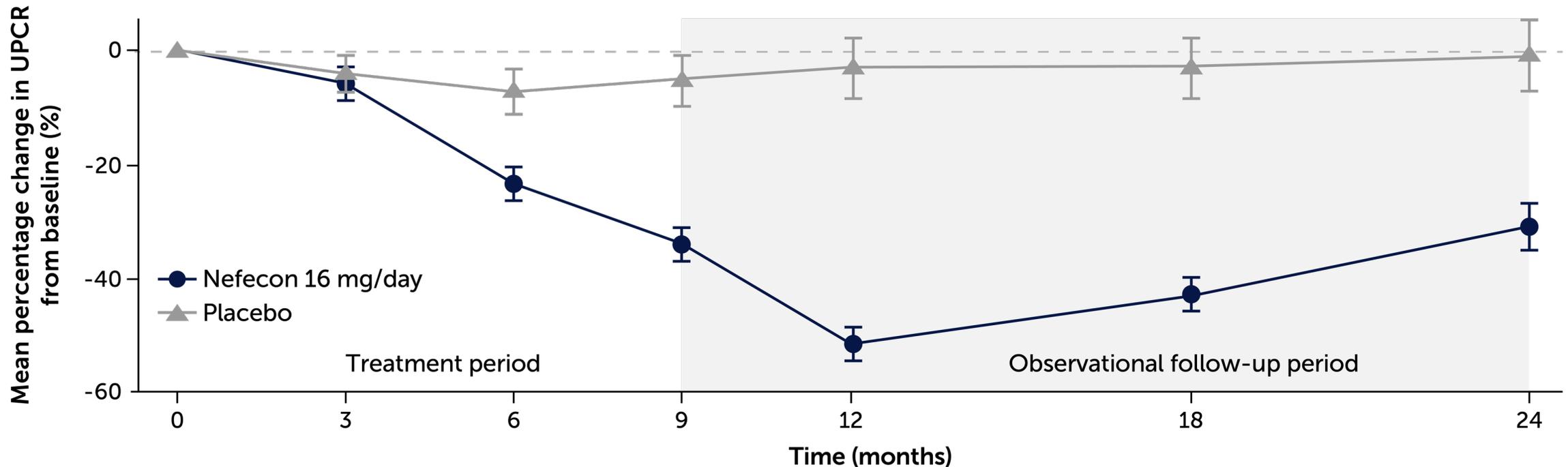
- M-0
- E-0
- S-1
- T-2
- C-0

Reduce Proteinuria



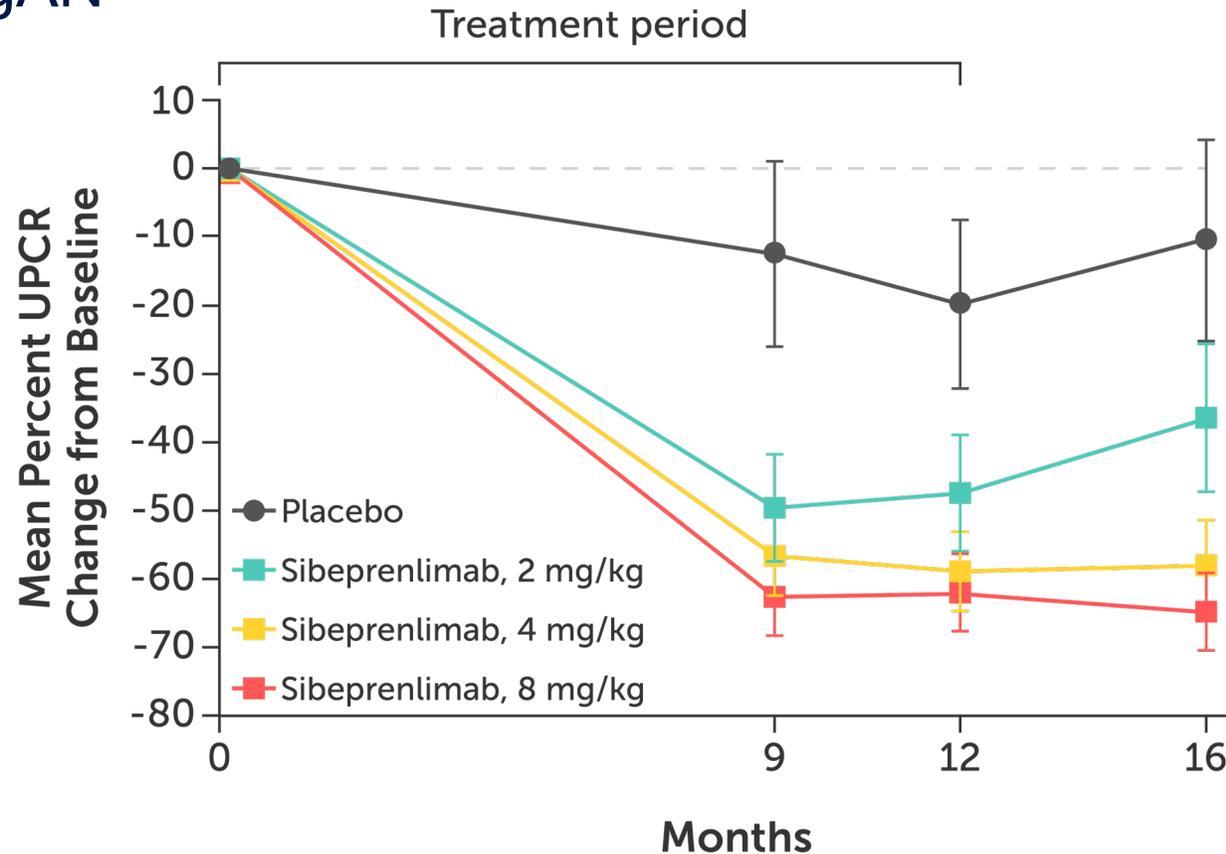
NeflgArd Phase 3 Trial in IgAN: Proteinuria Reduction Randomized, Placebo-controlled Trial

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



ENVISION Phase 2 Trial

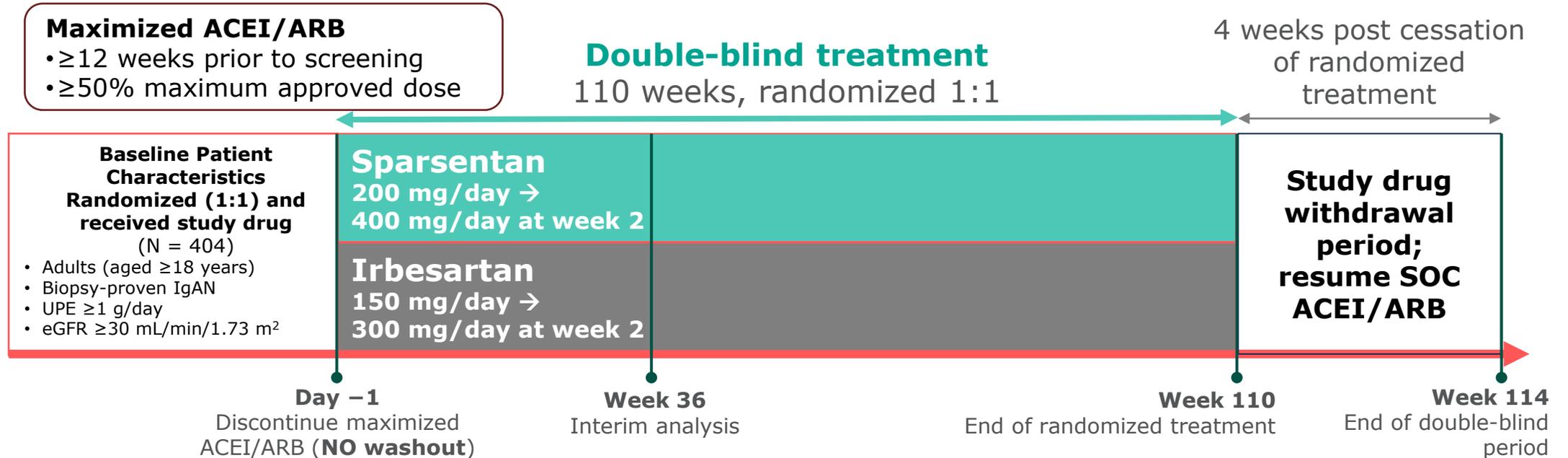
Evaluate the efficacy and safety of sibeprenlimab (investigational) vs placebo in patients with IgAN



Sibeprenlimab: APRIL inhibitor [monoclonal antibody]

PROTECT Phase 3 Trial

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



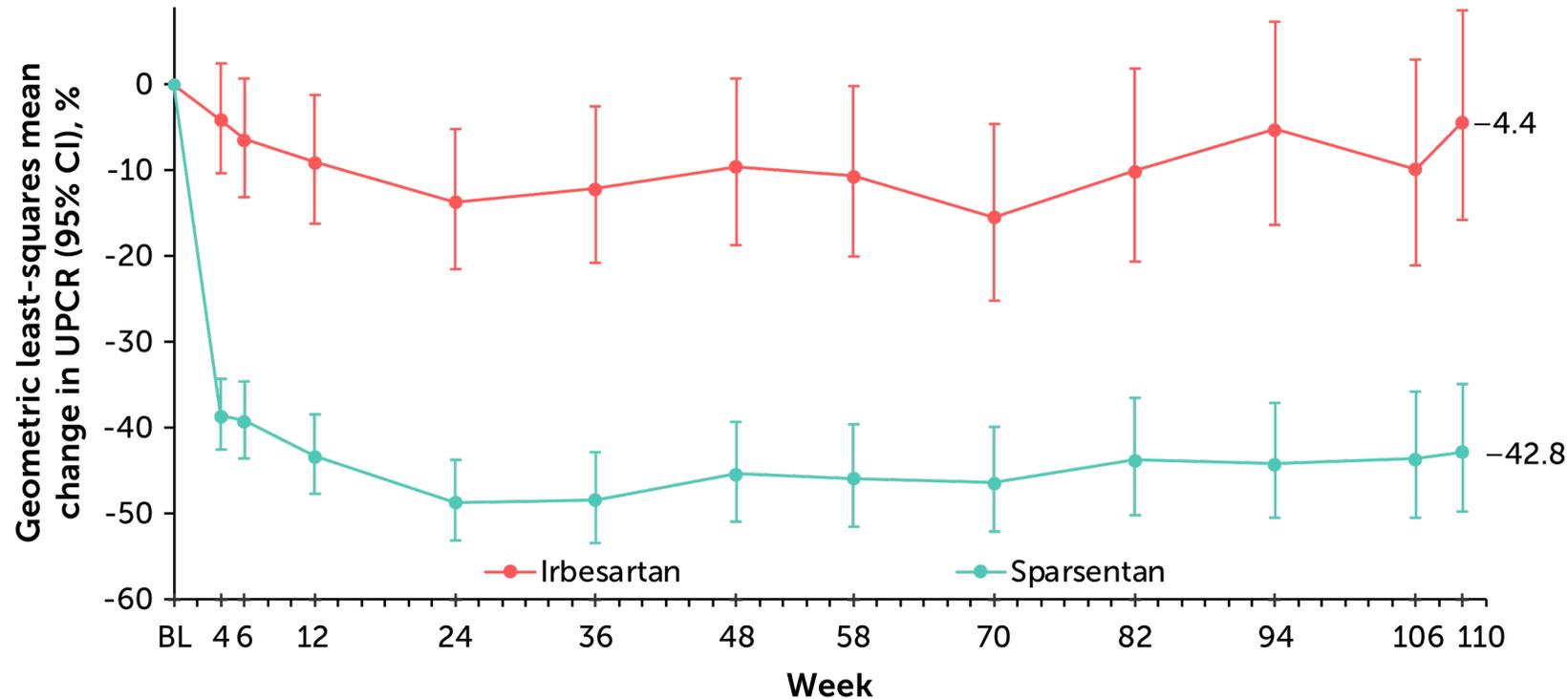
Primary Efficacy Endpoint	Key Secondary Efficacy Endpoints
Change in UPCR from baseline to week 36	eGFR slope: <ul style="list-style-type: none"> • Chronic (weeks 6-110) • Total (day 1-week 110)



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 (AT₁R) [non-immunosuppressant]

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

1 ML/MIN/1.73 M²/YEAR
AVERAGE DIFFERENCE
BETWEEN **SPARSENTAN**
AND IRBESARTAN



Quote by Khalil El Karoui, MD, PhD

To optimize the conservative therapy in patients with chronic lesions and no inflammatory lesions, I think that the best way in patients already treated with ARB blockers and SGLT2 inhibitors is to propose **sparsentan**.

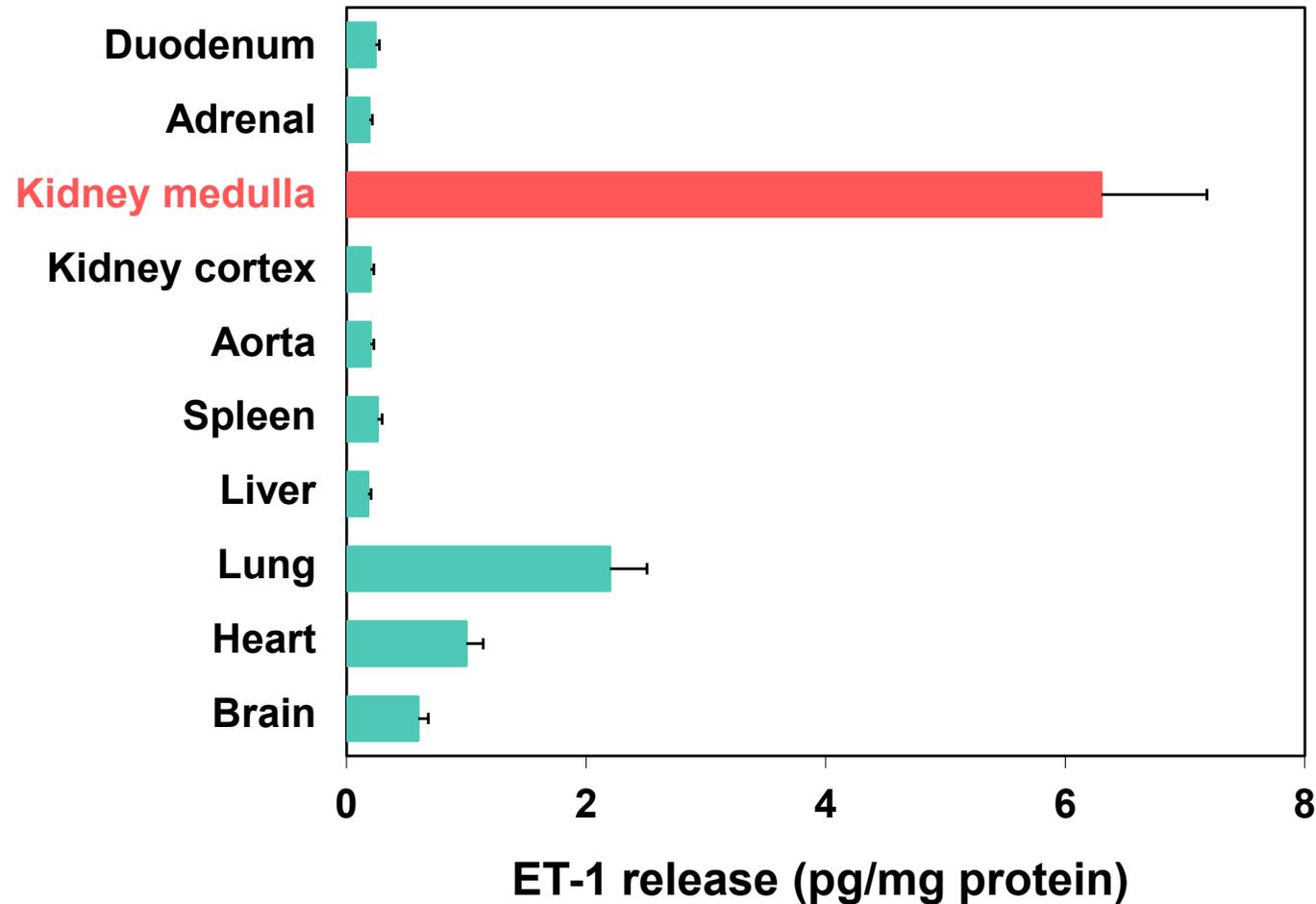


Sparsentan

- Single molecule
- Dual endothelin and angiotensin II receptor antagonist

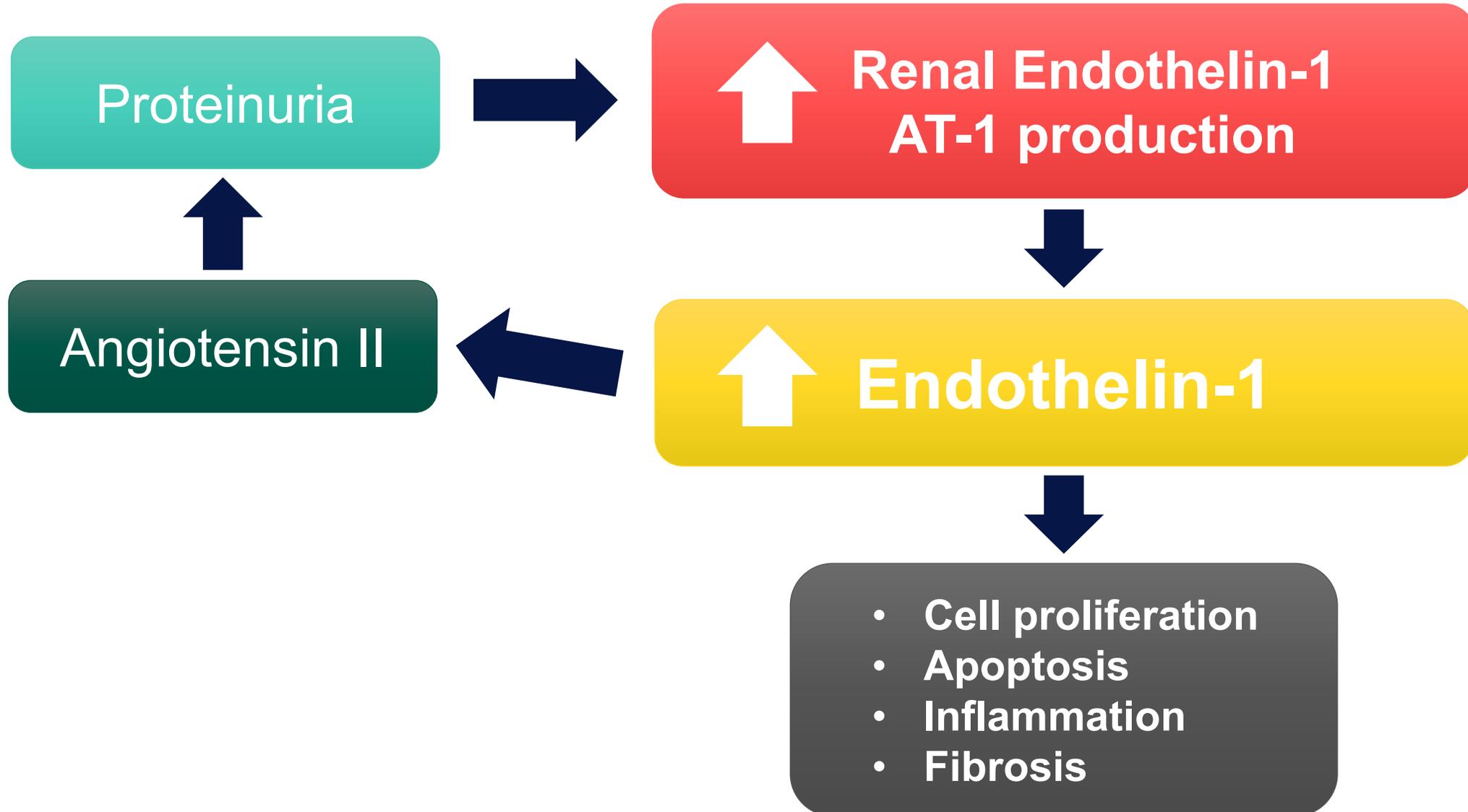


Endothelin-1 (ET-1) Production by the Kidney



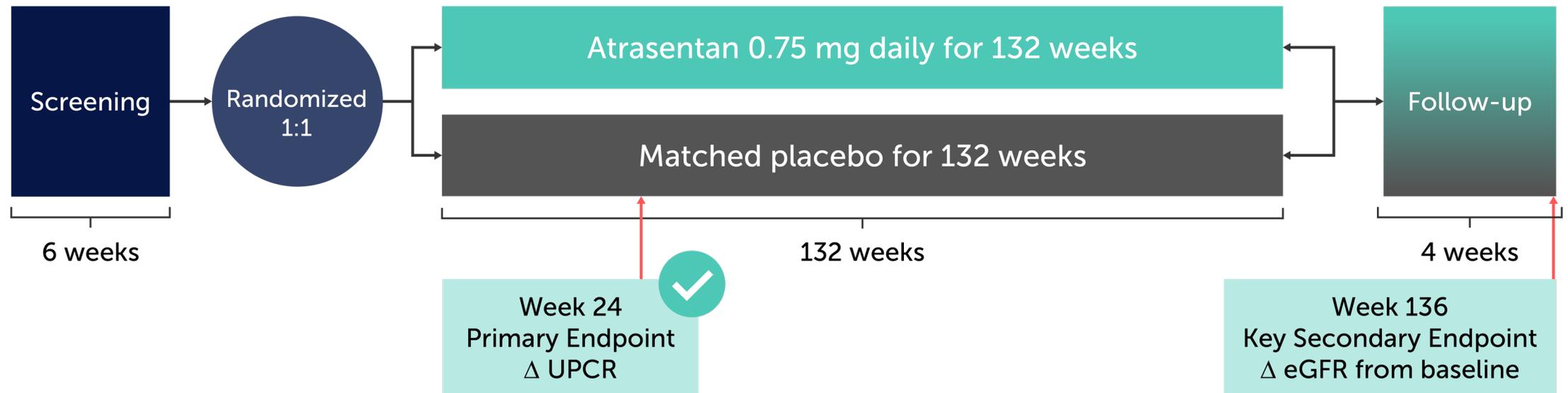
Renal ET-1 expression
in kidney disease

Pathophysiology of IgAN



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



Meeting highlights from the Committee for Medicinal Products for Human Use (CHMP) 19-22 February 2024

Share

23 February 2024

EMA's human medicines committee (CHMP) recommended 10 medicines for approval at its February 2024 meeting.

News

Human

Medicines

Referrals

Vaccines

Page contents

Positive recommendations on new medicines

Positive recommendation on a new biosimilar medicine

Positive recommendations on new generic medicines

Re-examination of recommendations for new medicines

Positive recommendations on extensions of indications

Outcome of arbitration procedures

10 new medicines recommended for approval

The CHMP recommended granting a conditional marketing authorization for sparsentan for the treatment of primary immunoglobulin A nephropathy, a disease where the kidneys gradually stop working and eventually fail, requiring patients to undergo dialysis or have a kidney transplant.



Take-Home Message

- Proteinuria is the most powerful predictor of prognosis in patients with IgAN
- The lower the proteinuria, the better
- Lowest proteinuria possible for each patient
- Increasing proteinuria significantly increases risk of disease progression



Take-Home Message

- Dual blockade effects of both the endothelin receptor and angiotensin receptor with **sparsentan** will optimize therapy for our patients

