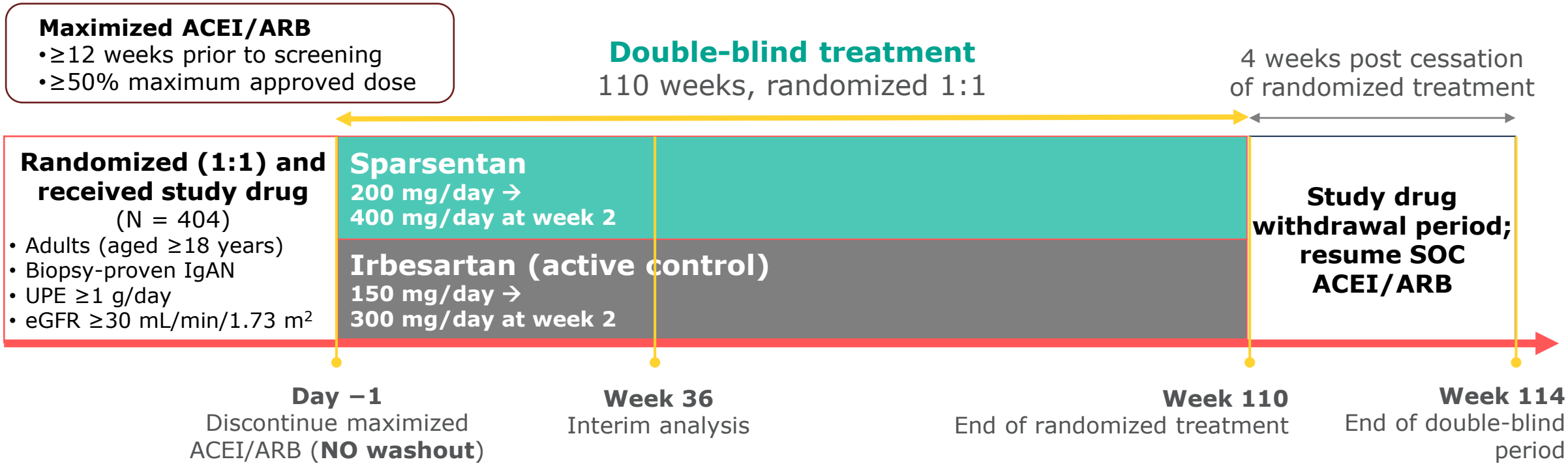
# PROTECT Trial Design

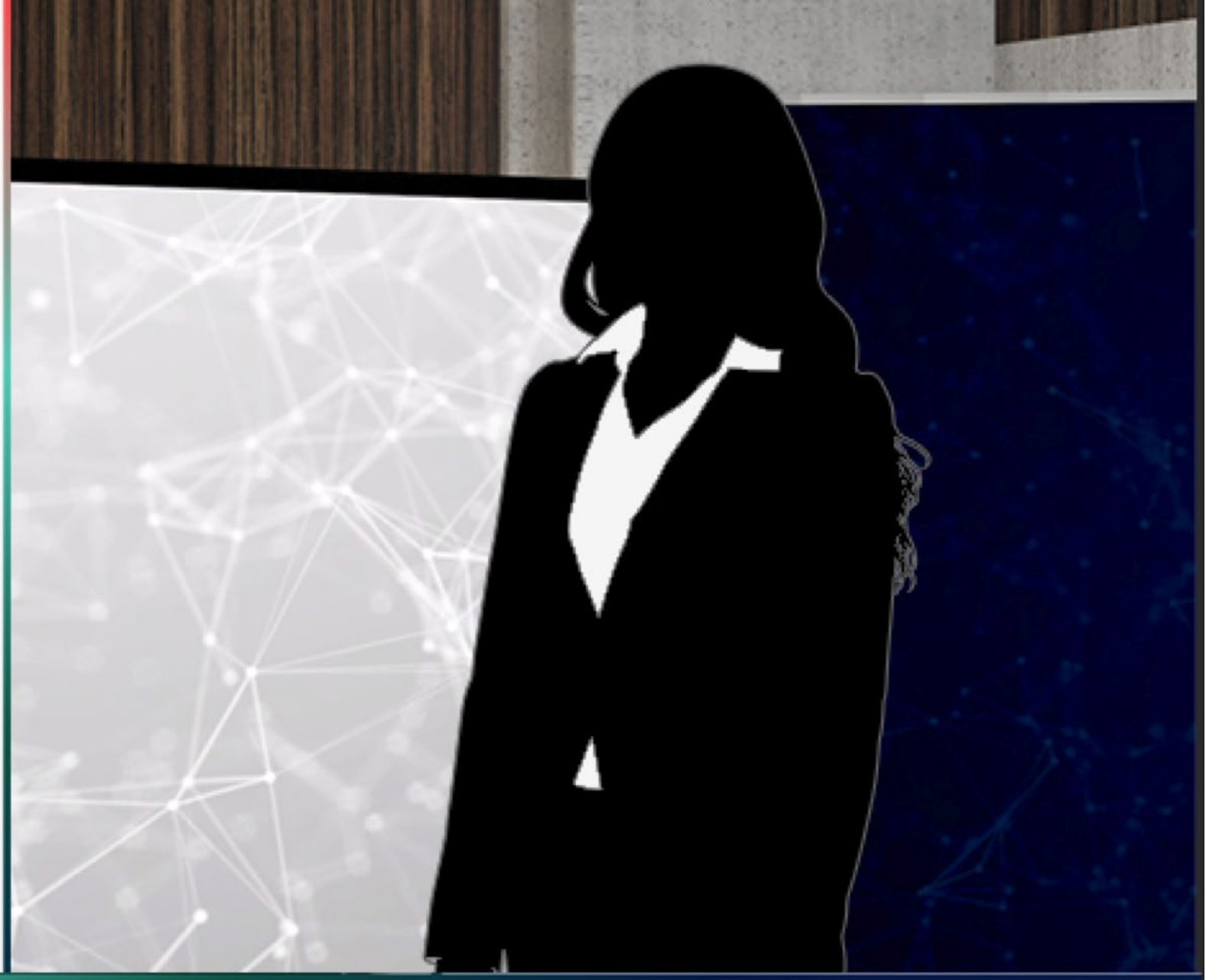



| Primary Efficacy Endpoint | Key Secondary Efficacy Endpoints |
|---|---|
| Change in UPCR from baseline to week 36 | eGFR slope:<br>• **Chronic** (weeks 6-110)<br>• **Total** (day 1-week 110) |

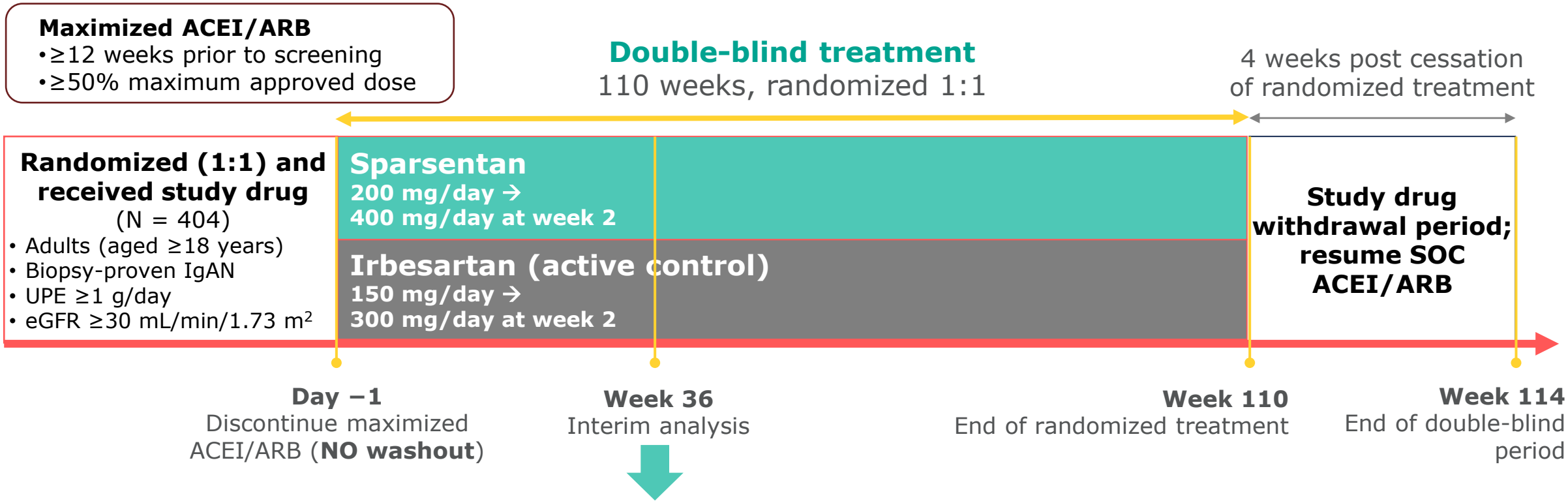
Rovin BH, et al. *Lancet.* Published online November 3, 2023. doi:10.1016/S0140-6736(23)02302-4

# Sparsentan Novel Mechanism of Action

- Orally active **dual endothelin** ($ET_AR$) **angiotensin receptor antagonist** ($AT_1R$)



# PROTECT Trial Design




- Sparsentan received accelerated regulatory approval for treatment of IgAN
  - Patients in the sparsentan group had a **41% relative** reduction in proteinuria versus irbesartan at 36 weeks interim analysis ($P < 0.0001$)

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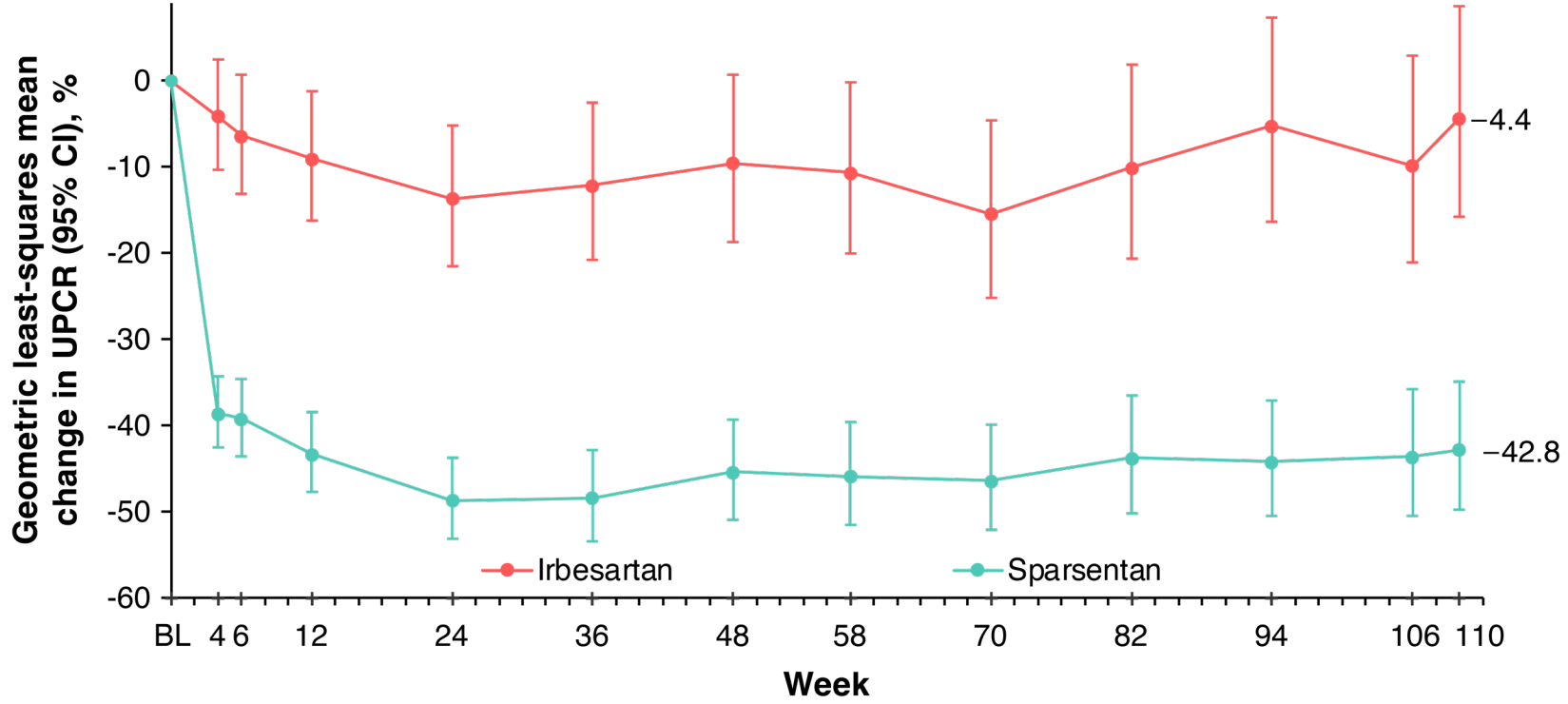
# PROTECT Trial: Sustained Proteinuria Reduction

**~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

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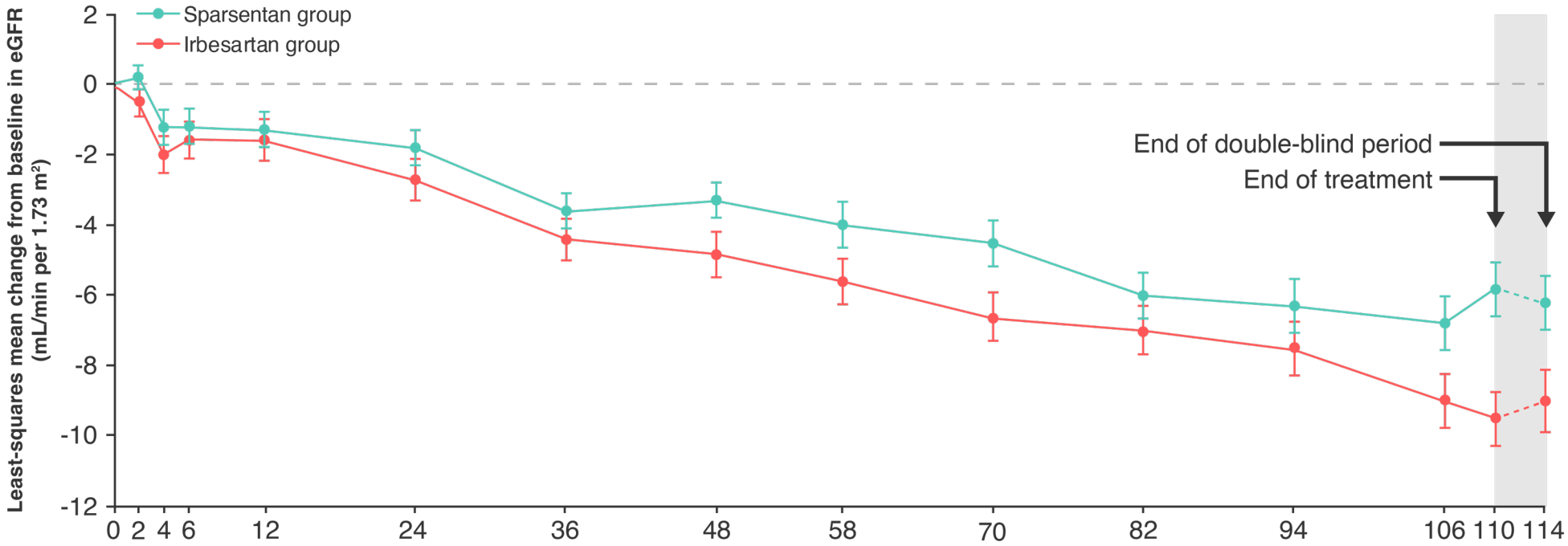
# PROTECT Trial: Kidney Function (eGFR)

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




**Number of participants**

| | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Irbesarten group | 202 | 196 | 191 | 193 | 188 | 176 | 179 | 173 | 162 | 160 | 159 | 154 | 144 | 138 | 148 |
| Sparsentan group | 202 | 197 | 197 | 193 | 196 | 191 | 189 | 184 | 180 | 182 | 176 | 173 | 170 | 159 | 170 |

**eGFR by visit up to week 114**

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

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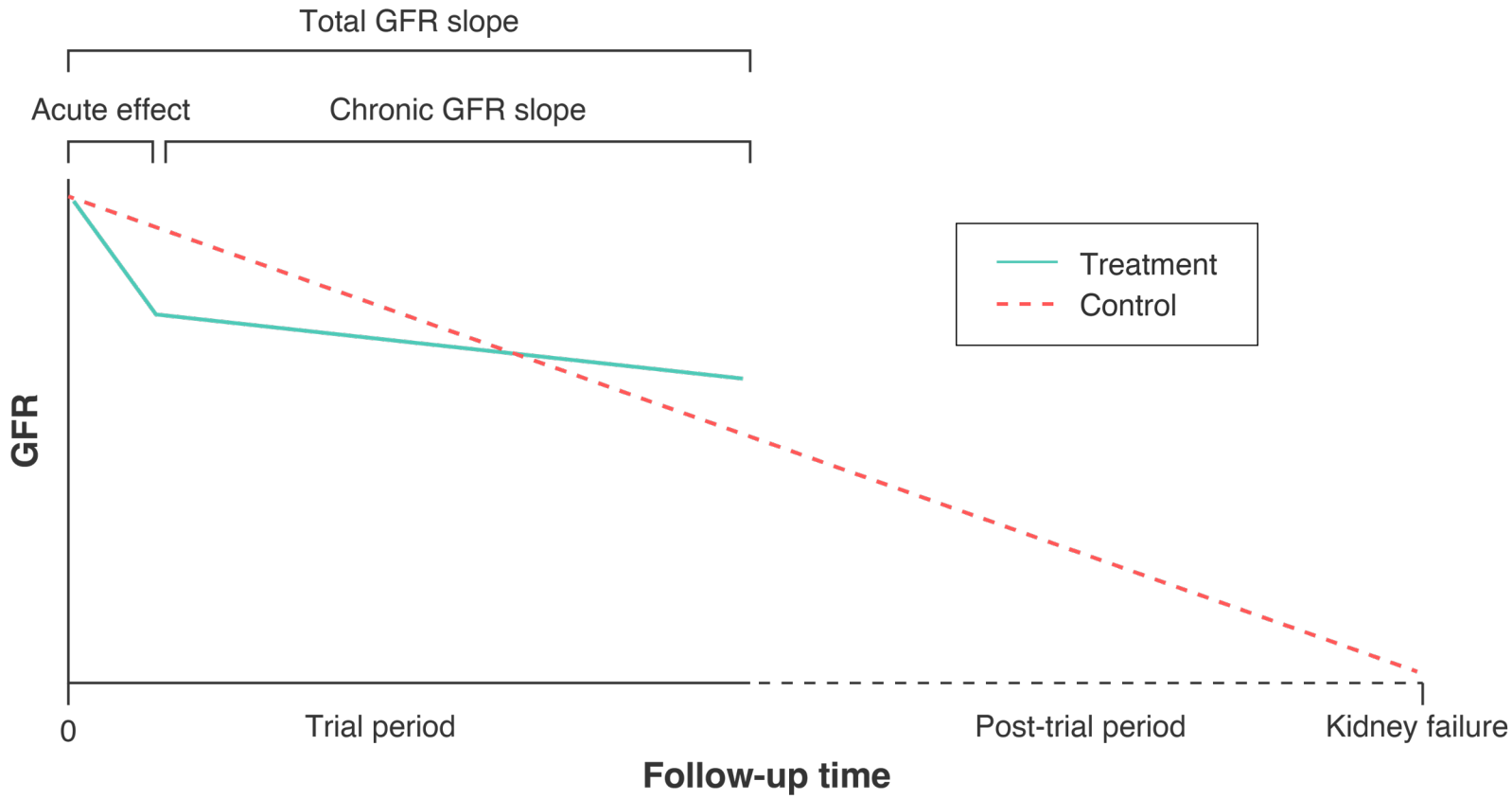
# eGFR Slopes: Total vs Chronic

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

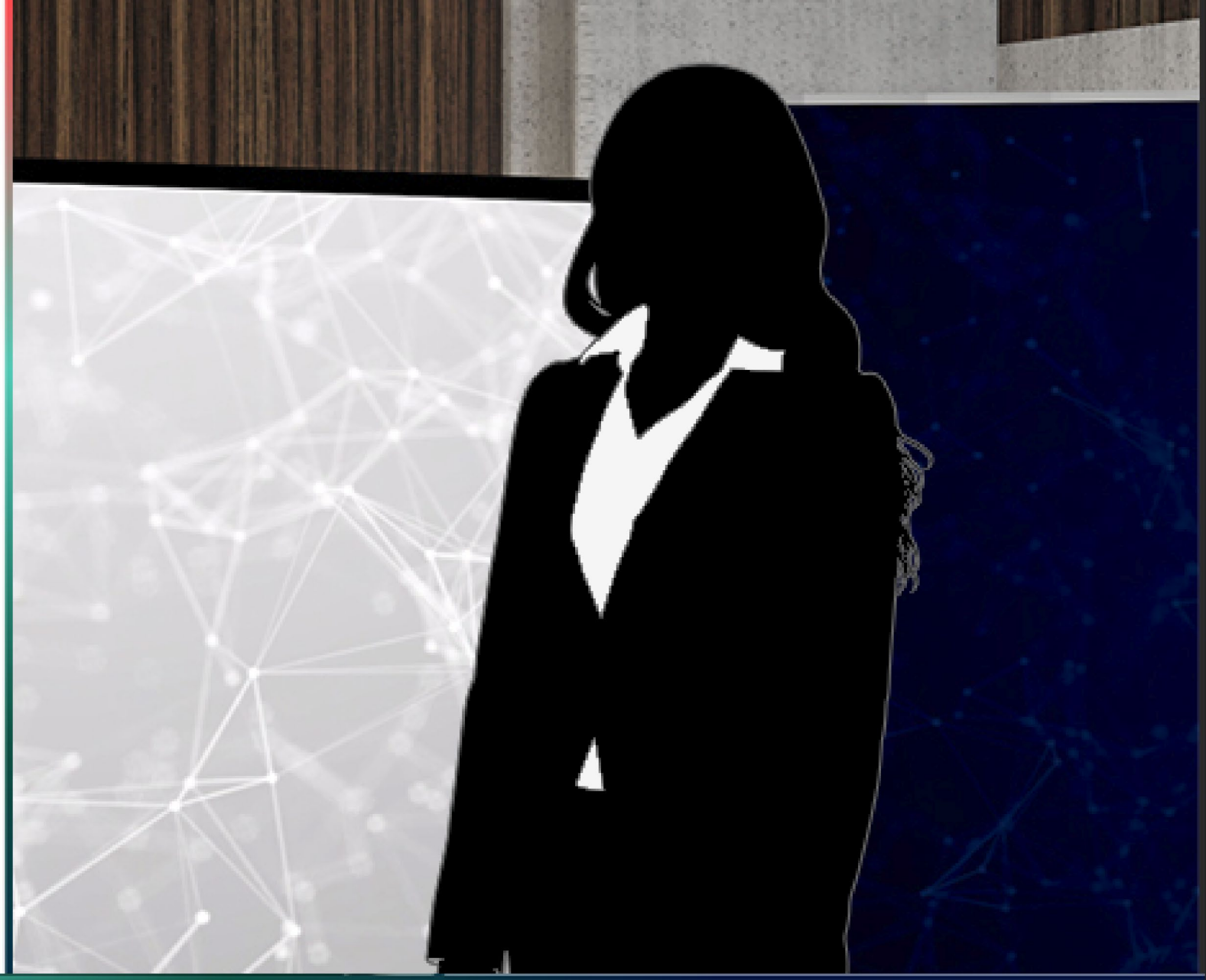



Inker LA, et al. *Nat Med*. 2023;29(7):1867-1876. Lees JS, Mark PB. *Nat Rev Nephrol*. 2023;19(10):625-626.

# PROTECT: 2-Year Topline Confirmatory Endpoints

| Annual eGFR slope (95% CI), mL/min/1.73 $m^2$/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



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# Quote by Jonathan Barratt, MD

*“And for a 30-year-old patient living with IgA nephropathy who's got another 50 years or so of life, that 1 mL/min/1.73 $m^2$/year translates to a significant delay in the time to them reaching 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
- Peripheral edema was similar in both groups, with no increases in body weight

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