Long-term renal benefit over 2 years with Nefecon verified: The NefIgArd Phase 3 full trial results

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INTRODUCTION

- **Nefecon** is a novel, oral, targeted-release budesonide formulation specifically designed to treat IgAN by **acting locally in the distal ileum**[1,2]
- It was the first ever treatment **approved by the FDA and EMA** for adult patients with primary IgAN at risk of rapid disease progression[2,3]
- In the **interim analysis** of the Phase 3 NefIgArd trial (N=199), treatment with Nefecon resulted in a significant reduction in UPCR (27%, p=0.0003) and significant eGFR treatment benefit of 3.87 mL/min/1.73 m² compared with placebo after 9 months[3]
- Here, we present primary data from the **complete 2-year study**, comprising 9 months of treatment and 15 months of follow-up[1,2]

METHODS AND BASELINE CHARACTERISTICS

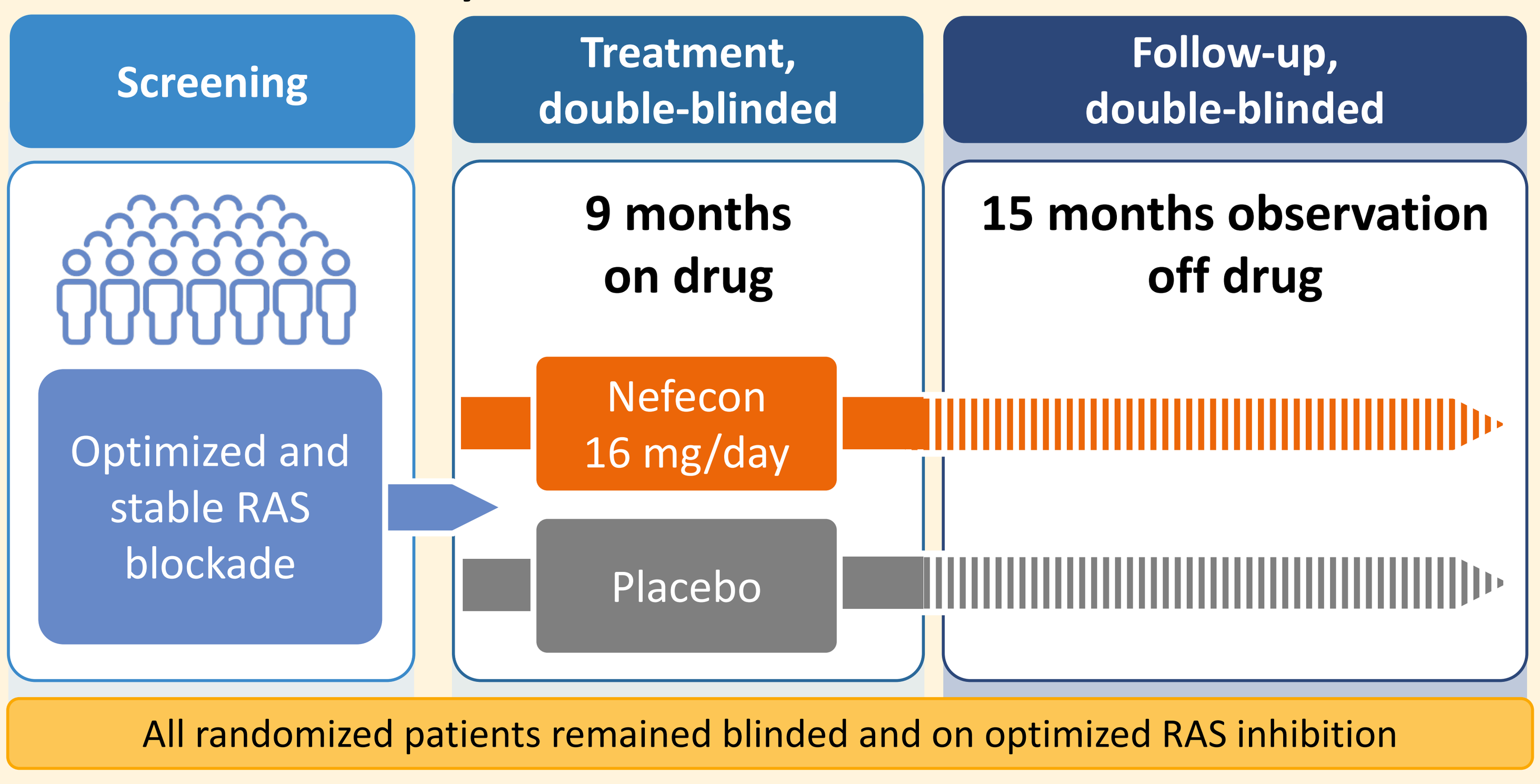
Full 2-year Phase 3 trial results

- Designed to assess whether 9 months of Nefecon treatment leads to a **significant reduction in kidney function decline** over 2 years
- Read out positive data in March 2023; global study with **364 patients**
- **FDA Priority Review granted:** August 2023

Inclusion/exclusion criteria

- The study **included** patients aged ≥18 years with: biopsy-proven primary IgAN; UPCR ≥0.8 g/g or proteinuria ≥1 g/24 h despite optimized RAS inhibitor blockade; and eGFR 35-90 mL/min/1.73 m²
- **Exclusion criteria** included: poorly controlled diabetes or blood pressure (≥140/90 mmHg); any secondary form of IgAN or non-IgAN glomerulonephritis; and having undergone a kidney transplant

Figure 1: NefIgArd: A two-part, global, randomized, double-blind, placebo-controlled study



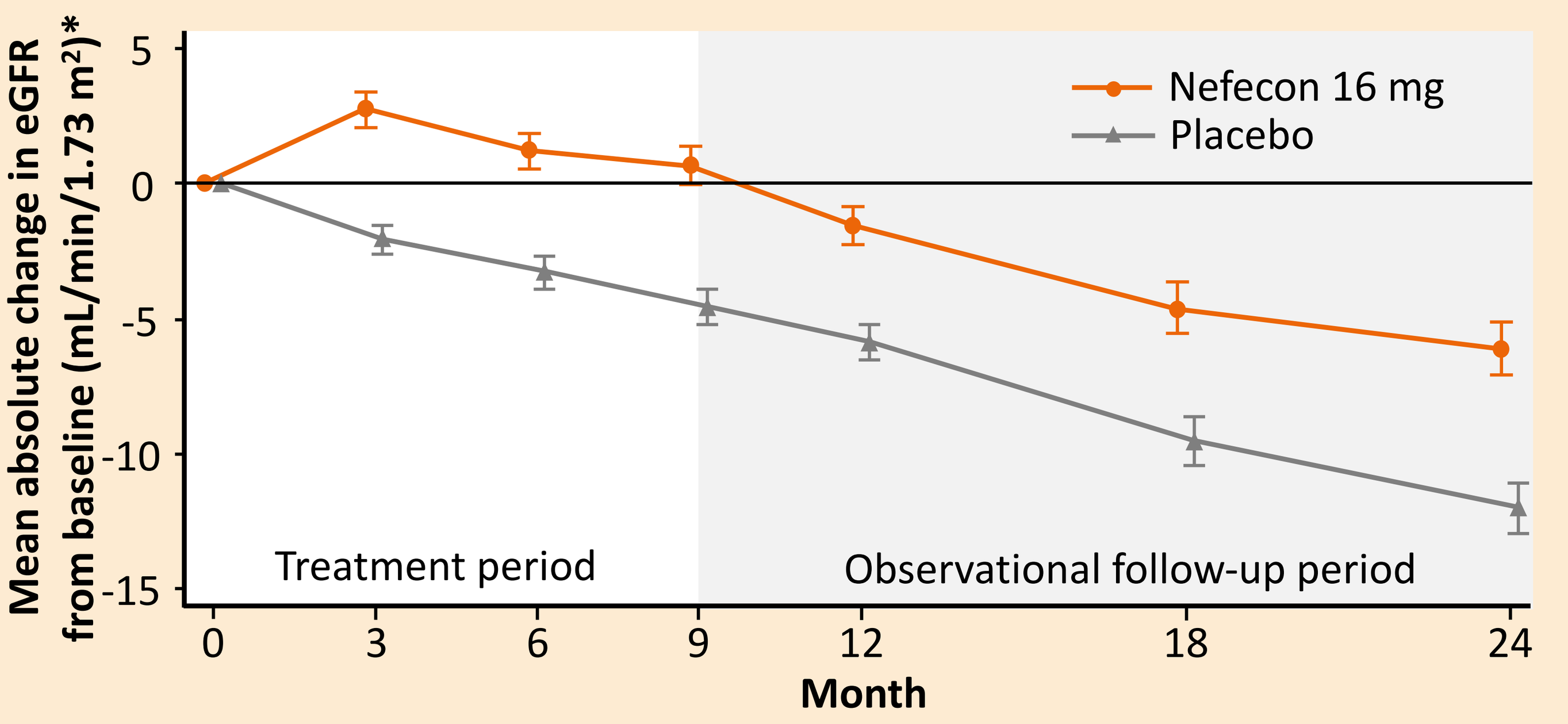
Primary efficacy endpoint
Time-weighted average change from baseline in eGFR over the 2-year period

Table 1: Key demographics and baseline characteristics

	Nefecon 16 mg/day (n=182)	Placebo (n=182)
Median age, years (range)	43 (21-69)	42 (20-73)
<45 years, n (%)	98 (53.8)	104 (57.1)
Sex, n (%)		
Male	117 (64.3)	123 (67.6)
Female	65 (35.7)	59 (32.4)
Race, n (%)		
White	138 (75.8)	137 (75.3)
Asian	43 (23.6)	40 (22.0)
Black or African American	0 (0.0)	0 (0.0)
Other	1 (0.5)	5 (2.7)
Median (IQR) blood pressure, mmHg		
Systolic	126 (121-132)	124 (117-130)
Diastolic	79 (76-84)	79 (74-84)
Median (IQR) UPCR (g/g)	1.28 (0.90-1.76)	1.25 (0.88-1.74)
Median (IQR) UACR (g/g)	0.99 (0.68-1.40)	0.98 (0.66-1.42)
Median (IQR) eGFR CKD-EPI (mL/min/1.73 m²)	56.1 (45.5-71.0)	55.1 (46.0-67.7)
Microhematuria at randomization, n (%)		
Yes	123 (67.6)	127 (69.8)
No	59 (32.4)	55 (30.2)
Median (IQR) years since IgAN diagnosis	2.4 (0.6-6.9)	2.6 (0.6-6.5)
Systemic CS or immunosuppressant use before randomization, n (%)		
Yes	15 (8.2)	19 (10.4)
No	167 (91.8)	163 (89.6)

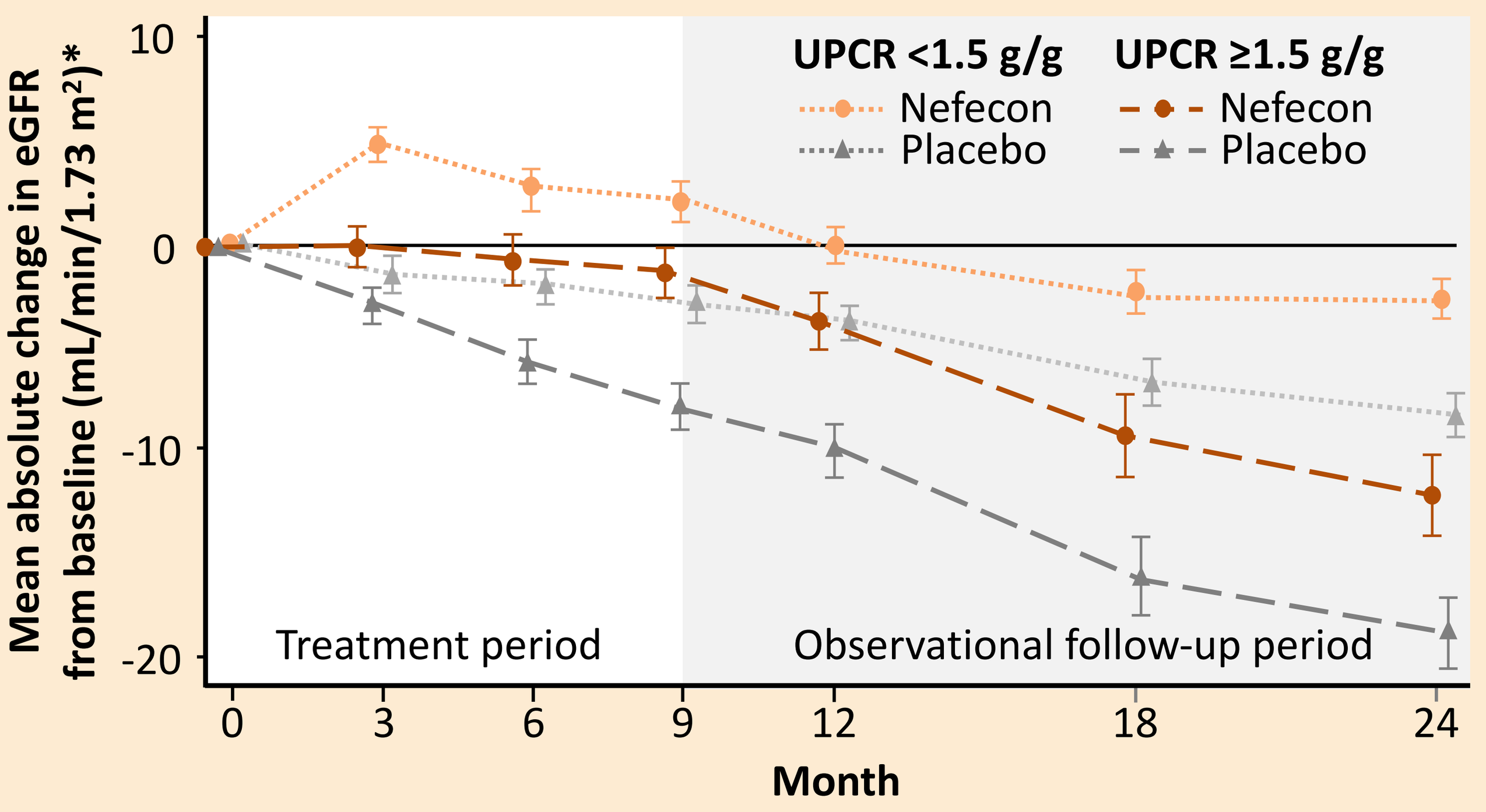
RESULTS

Figure 2: Average change from baseline in eGFR over the 2-year period



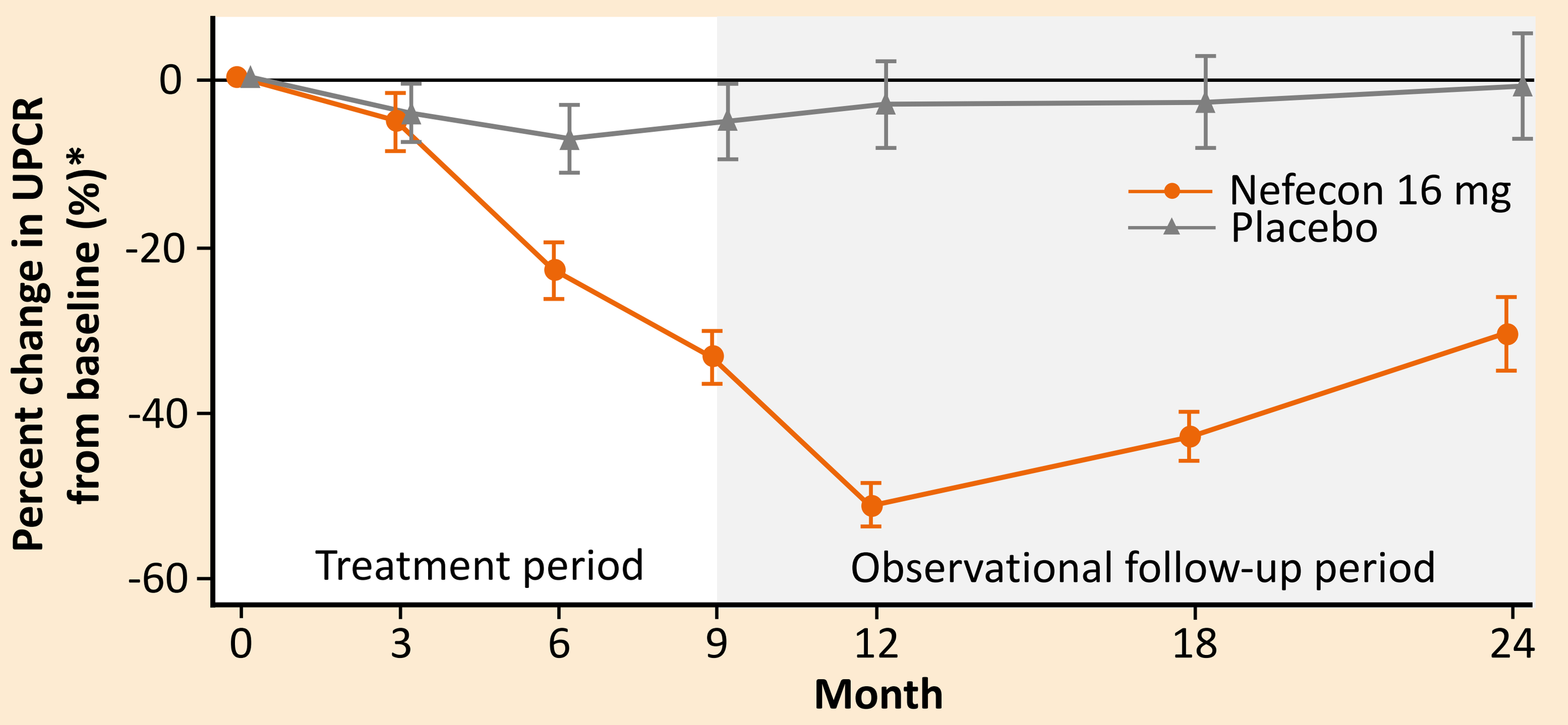
Month	9	12	24
Nefecon 16 mg, mL/min/1.73 m²	+0.66	-1.52	-6.11
Placebo, mL/min/1.73 m²	-4.56	-5.85	-12.0
Absolute difference, mL/min/1.73 m² (95% CI)	5.21 (3.35, 7.58)	4.33 (2.44, 6.66)	5.89 (3.35, 9.15)

Figure 3: Absolute change in eGFR over time by baseline UPCR subgroup



- The **primary endpoint** of time-weighted average of eGFR over 2 years showed a **statistically significant eGFR treatment benefit** in favor of Nefecon 16 mg/day of **5.05 mL/min/1.73 m²** (95% CI 3.24, 7.38; p<0.0001) compared with placebo
- **eGFR benefit** at the end of the 9-month treatment period with Nefecon was maintained over the **15-month observational follow-up**
- The eGFR benefit with Nefecon vs placebo was **consistent irrespective of baseline UPCR**

Figure 4: Mean % change in UPCR from baseline



Month	9	12	24
Nefecon 16 mg, %	-34	-51	-31
Placebo, %	-5	-3	-1
Corresponding percentage reduction, % (95% CI)	30 (20, 39)	50 (42, 57)	30 (16, 41)

Nefecon was associated with a **41% reduction** from baseline in the **time-averaged UPCR** between 12 and 24 months compared with placebo

Table 2: TEAEs during treatment period[†] (full analysis set; ≥5% in the Nefecon arm and higher than placebo)

TEAE, n (%)	Nefecon 16 mg (n=195)	Placebo (n=194)
Peripheral edema	31 (17.0)	7 (3.8)
Hypertension	22 (12.1)	6 (3.3)
Muscle spasms	22 (12.1)	7 (3.8)
Acne	20 (11.0)	2 (1.1)
Headache	19 (10.4)	14 (7.7)
Face edema	14 (7.7)	1 (0.5)
Dyspepsia	13 (7.1)	4 (2.2)
Arthralgia	12 (6.6)	4 (2.2)
Weight increased	10 (5.5)	5 (2.7)
Fatigue	10 (5.5)	7 (3.8)
Rash	10 (5.5)	7 (3.8)
Insomnia	10 (5.5)	7 (3.8)

CONCLUSIONS

- The NefIgArd study **met its 2-year primary endpoint**, demonstrating that 9 months of treatment with Nefecon on top of optimized SoC provided a statistically significant and clinically relevant **preservation of eGFR** and **durable reduction in proteinuria** compared with optimized SoC alone
- The size of the eGFR benefit was maintained over the 15-month off-drug, observational follow-up period, supporting the **disease-modifying effect** of Nefecon 16 mg treatment
- Nefecon 16 mg was **well tolerated**, and the safety profile was as expected for a **locally acting oral budesonide product**

Scan to view Nefecon presentations, posters, and materials

REFERENCES

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ABBREVIATIONS

CI, confidence interval; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; CS, corticosteroid; eGFR, estimated glomerular filtration rate; EMA, European Medicines Agency; FDA, US Food and Drug Administration; IIgANN, International IgA Nephropathy Network; IgAN, immunoglobulin A nephropathy; IQR, interquartile range; RAS, renin–angiotensin system; SoC, standard of care; TEAE, treatment-emergent adverse event; UACR, urine albumin-to-creatinine ratio; UPCR, urine protein-to-creatinine ratio.

DISCLOSURES

RL received support for the present study from Calliditas; reports institutional grants from Calliditas, ChemoCentryx, Omeros, Otsuka, Pfizer, Roche, Travere Therapeutics, Vera Therapeutics, and Visterra; and has served on advisory boards for Cara Therapeutics. **JK** is a consultant for Calliditas. **AS** received support for the present study and reports consulting fees from AstraZeneca and Calliditas outside the submitted work. **JF** has received consultancy fees or honoraria from AstraZeneca, Bayer, Boehringer Ingelheim, Calliditas, Chinook, GSK, Novartis, Omeros, Otsuka, and Travere Therapeutics and serves on data safety monitoring boards for Novo Nordisk and Visterra. **VT** has reported consultancy fees or honoraria from Calliditas, Novartis, Omeros, Otsuka, and Travere Therapeutics. **HT** has served on advisory boards for Calliditas and received grants, honoraria, consultancy fees, or travel support from Alexion, AstraZeneca, Biocryst, Calliditas, Chinook, George Clinical, Novartis, Omeros, Otsuka, Travere Therapeutics, and Vera Therapeutics. **HZ** has received consulting fees or honoraria from Calliditas, Chinook, Novartis, Omeros, and Otsuka. **AP** received honoraria and travel grants from Alexion, AstraZeneca, Bayer, Boehringer Ingelheim, GlaxoSmithKline, Otsuka, STADA Arzneimittel AG, and Vifor Pharma. **HNR** received support to serve as a member of the steering committee and funding for the execution of the study from Calliditas; has received grant support from the Kidney Foundation of Canada, Canadian Institutes of Health Research, and John and Leslie Pearson; has received fellowship support from the Louise Fast Foundation; reports consulting fees, honoraria, or travel support from Calliditas, Chinook, Novartis, Omeros, Pfizer, and Travere Therapeutics; served in advisory boards and steering committees for Chinook, Novartis, Omeros, Pfizer, and Travere Therapeutics; has been an investigator for Alnylam Pharmaceuticals, Calliditas, ChemoCentryx, Chinook, Omeros, Pfizer; and is Director of the Glomerulonephritis Fellowship, funded by the Louise Fast Foundation. **BHR** received support for the present study from Calliditas; reports consulting fees from Alpine Immune Sciences, Alexion, Calliditas, Novartis, Omeros, Otsuka/Visterra, Q32 Bio, Travere Therapeutics, and Vera Therapeutics; and is Co-Chair of Glomerular Diseases Guidelines for KDIGO. **JB** is a consultant to Calliditas and reports grants as well as consultancy and personal fees from Arzneimittel AG, Everest Medicines, Calliditas, and STADA. **NE** declares no competing interests.

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*Error bars represent standard error. †Includes AEs that started during treatment, up to 14 days after the last treatment dose.

Nefecon has not been approved by the Japanese Pharmaceuticals and Medical Devices Agency.

Calliditas Therapeutics