

eGFR decline in patients with IgAN treated with Nefecon or placebo: Results from the 2-year NeflgArd Phase 3 trial

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Introduction

- Nefecon is a novel, oral, targeted-release capsule formulation of budesonide, specifically designed to treat IgAN by inhibiting IgA formation in the Peyer's-patch-rich distal ileum¹
- Results from the full 2-year Phase 3 NefIgArd study evidenced an eGFR treatment benefit vs placebo and durable reduction in proteinuria after 9 months of treatment and 15 months of observational follow-up²
 - Time-weighted average of eGFR over 2 years showed a statistically significant treatment benefit in favor of Nefecon 16 mg/day (difference 5.05 mL/min/1.73 m² [95% CI 3.24, 7.38]; p<0.0001) versus placebo; eGFR treatment benefit was maintained over the 15-month follow-up
 - A significant 41% reduction in time-averaged UPCR from 12 to 24 months was seen in the Nefecon group compared with placebo (95% CI 32, 49; p<0.0001)
- Here, we present data from the complete NefIgArd study for the composite endpoint of time to confirmed 30% eGFR reduction or kidney failure

CI, confidence interval; eGFR, estimated glomerular filtration rate; IgA, immunoglobulin A; IgAN, immunoglobulin A nephropathy; UPCR, urine protein-creatinine ratio.

1. Barratt J, et al. *Kidney Int Rep* 2020;5:1620-1624. 2. Lafayette R, et al. *Lancet* 2023;402:859-870

Methods

NeflgArd: A Phase 3, two-part, randomized, double-blind, placebo-controlled trial^{1,2}

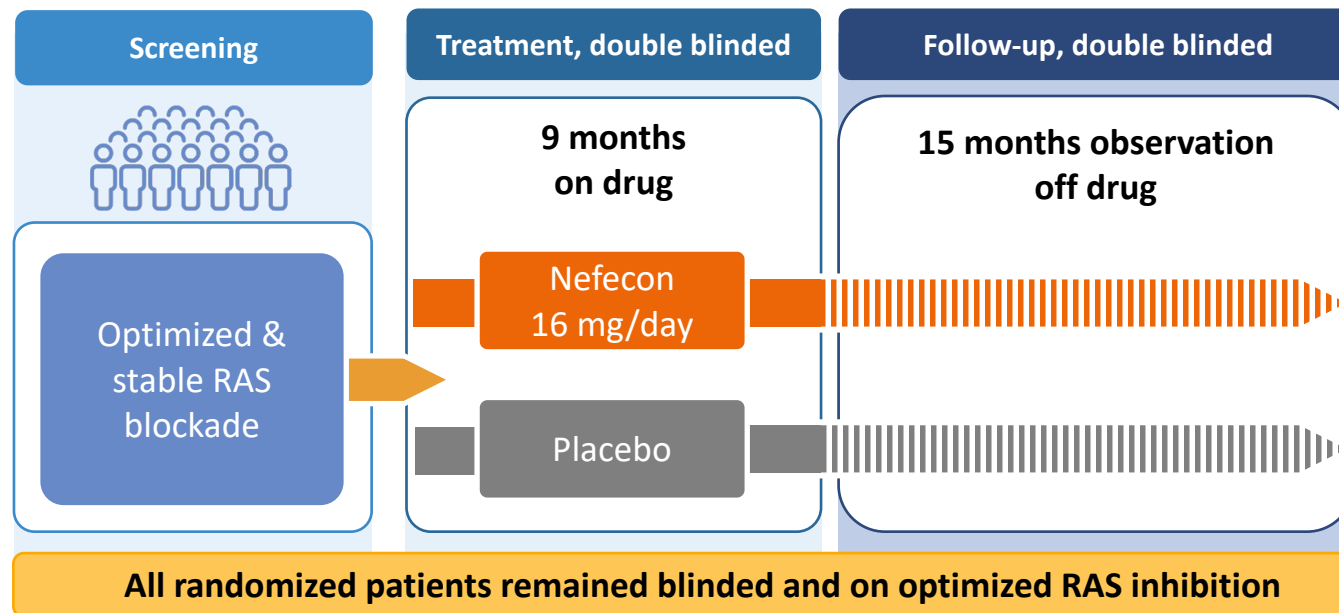
Aim of the analysis: To assess the effect of Nefecon 16 mg/day on eGFR decline in patients with IgAN over the 9-month treatment period and 15-month observational follow-up period of the Phase 3 NeflgArd trial

Key inclusion criteria:

- ≥18 years old with biopsy-confirmed primary IgAN
- eGFR 35-90 mL/min/1.73 m²
- UPCR ≥0.8 g/g or proteinuria ≥1 g/24h, despite optimized RAS inhibition

Key exclusion criteria

- Secondary form of IgAN or non-IgAN glomerulonephritis
- Kidney transplantation
- Systemic diseases that may cause mesangial IgA deposition
- Poorly controlled BP (≥140/90 mmHg)
- Poorly controlled T1D or T2D



Primary efficacy endpoint: Time-weighted average of eGFR over 2 years

Secondary efficacy endpoint: Composite endpoint of time from randomization to confirmed 30% reduction in eGFR* or confirmed kidney failure (dialysis for ≥1 month, kidney transplantation, sustained [≥1 month] eGFR <15 mL/min/1.73 m², or kidney-related death)

*Confirmed by two values over ≥4 weeks

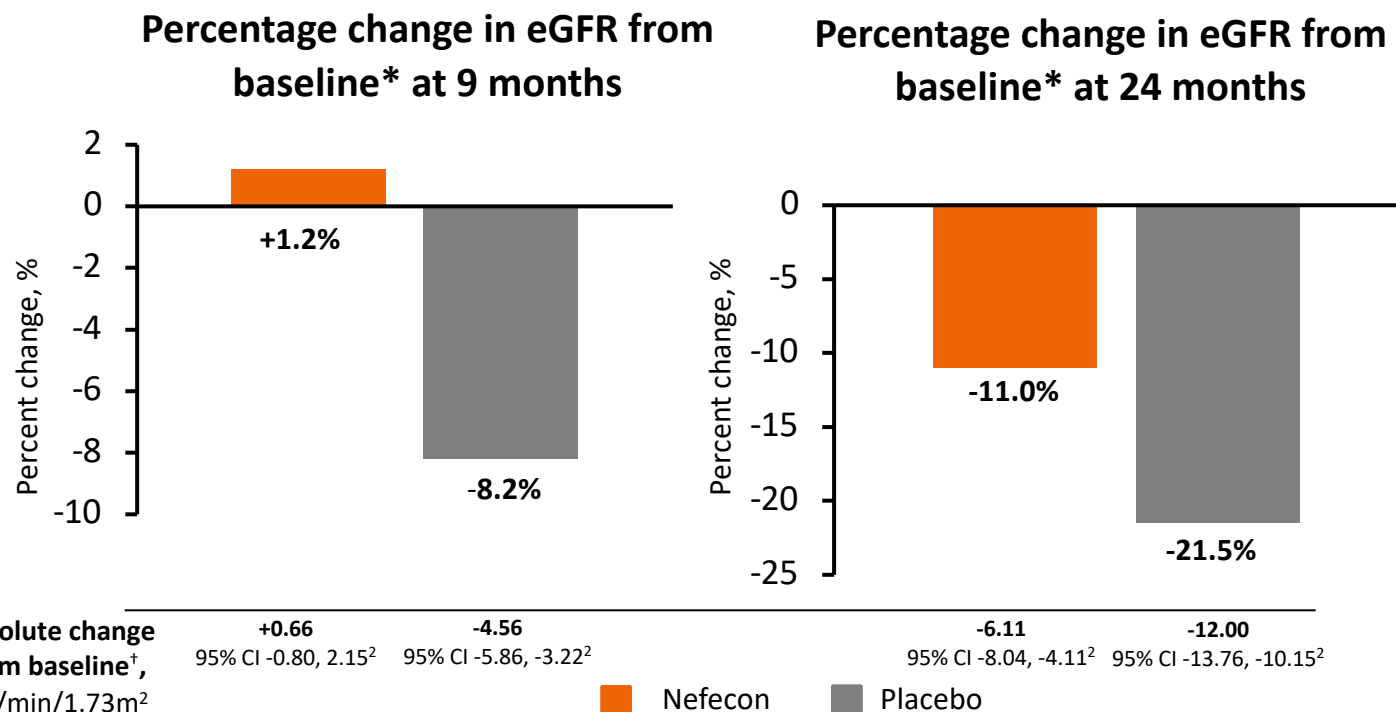
BP, blood pressure; eGFR, estimated glomerular filtration rate; IgA, immunoglobulin A; IgAN, immunoglobulin A nephropathy; RAS, renin-angiotensin system; T1D, type 1 diabetes; T2D, type 2 diabetes; UPCR, urine protein-creatinine ratio.

1. Lafayette R, et al. *Lancet* 2023;402:859-870. 2. Lafayette R, et al. *Lancet* 2023;402:859-870 (online appendix).

eGFR at 9 and 24 months

Sustained eGFR effect observed at 24 months^{1,2}

9 months of treatment with Nefecon (16 mg/day) in 364 patients resulted in approximately **50% less deterioration of kidney function** versus placebo at 24 months



Efficacy findings^{1,2}

- **Time-weighted average of eGFR over 2 years:**
 - Nefecon: -2.47 mL/min per 1.73 m²
 - Placebo: -7.52 mL/min per 1.73 m²
 - Difference: 5.05 mL/min per 1.73 m² (95% CI 3.24, 7.38, p<0.0001)
- **After 9 months:**
 - eGFR increase in Nefecon-treated patients: 0.66 mL/min/1.73m²
 - eGFR decrease in placebo-treated patients: 4.56 mL/min/1.73m²
- **After 24 months:**
 - eGFR decrease in Nefecon-treated patients: 6.11 mL/min/1.73m²
 - eGFR decrease in placebo-treated patients: 12.00 mL/min/1.73m²

*Percentage change in eGFR from baseline = (geometric LS mean of ratio of postbaseline value/baseline value for each treatment arm - 1) x 100.

[†]Estimated absolute change from baseline = baseline geometric mean for total x (geometric LS mean of postbaseline value/baseline value for each treatment arm - 1).

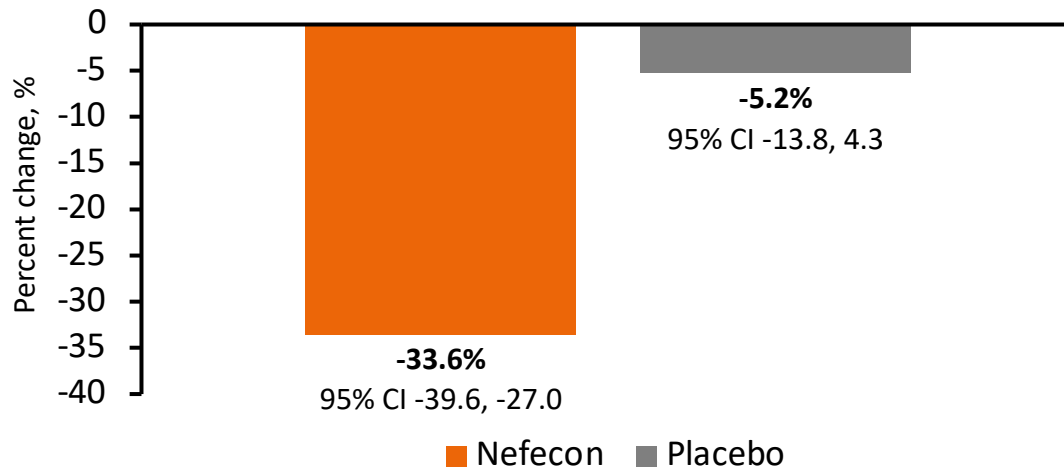
CI, confidence interval; eGFR, estimated glomerular filtration rate; LS, least squares.

1. Calliditas Therapeutics. Nef-301 Summary of Full Phase 3 Trial Results, 13 March 2023 – presentation. Available at: <https://www.calliditas.se/en/investors/financial-reports-and-presentations>. Accessed 24 October 2023. 2. Lafayette R, et al. *Lancet* 2023;402:859-870.

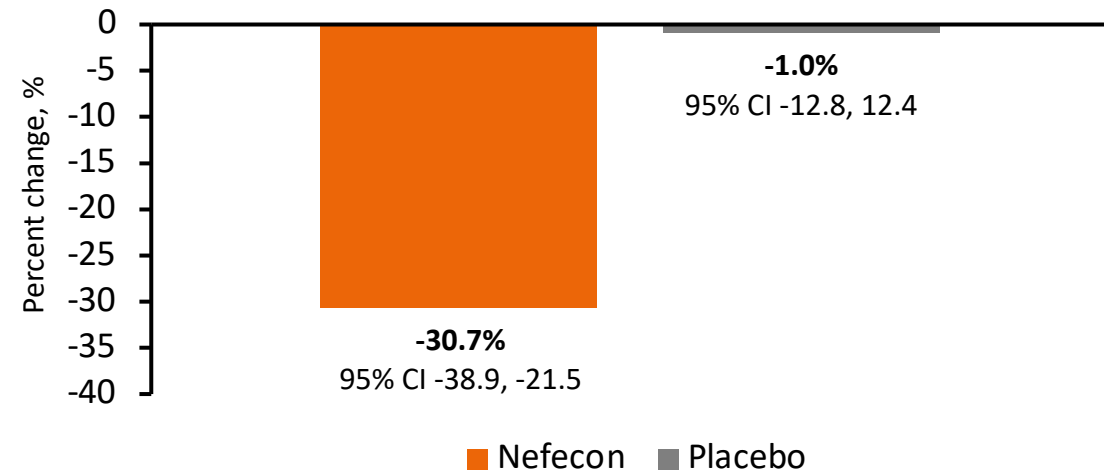
Secondary endpoint: UPCR at 9 and 24 months

A 30% reduction in UPCR with Nefecon compared with placebo was observed after the 9-month treatment period, which was sustained for up to 2 years

Percentage change in UPCR from baseline* at 9 months



Percentage change in UPCR from baseline* at 24 months

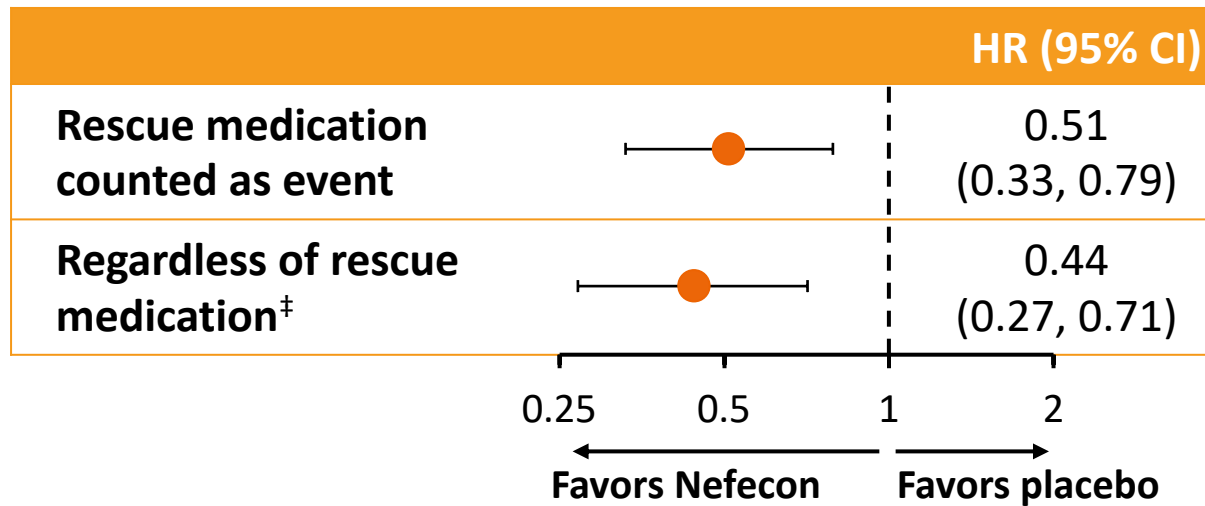


*Baseline is defined as the geometric mean of the two consecutive measurements prior to randomization. Percentage change in UPCR from baseline = (geometric LS mean of ratio of postbaseline value/baseline value for each treatment arm -1) x 100. CI, confidence interval; LS, least squares; UPCR, urine protein-creatinine ratio. Lafayette R, et al. *Lancet* 2023;402:859-870.

Secondary endpoint: Time to 30% reduction in eGFR or kidney failure

Time to composite endpoint of confirmed 30% eGFR reduction from baseline or kidney failure*

- Nefecon 16 mg/day versus placebo: **HR 0.45** (95% CI 0.26, 0.75), $p=0.0014$ (1-sided)[†]



	Patients who experienced an event, % (n/N)
Nefecon	11.5% (21/182)
Placebo	21.4% (39/182)

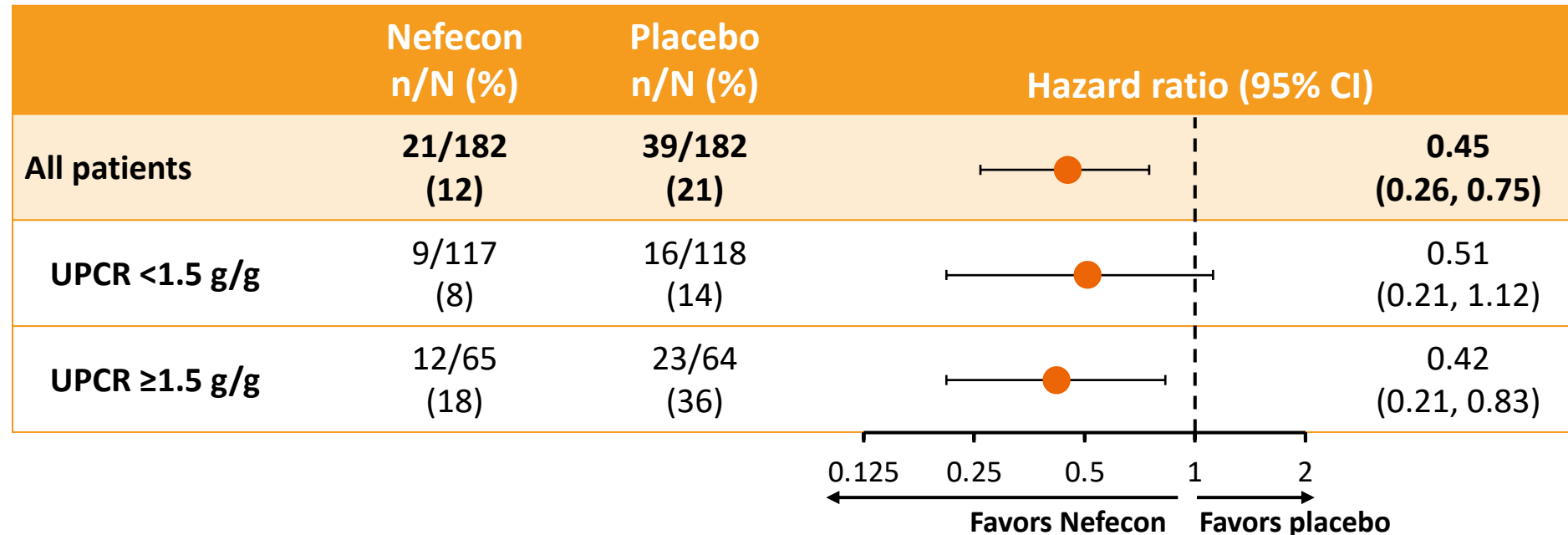
The time to a confirmed 30% eGFR reduction or kidney failure event was **significantly delayed** with Nefecon vs placebo

*A 30% reduction in eGFR was confirmed by two values over ≥ 4 weeks. To prevent informative censoring, death from a renal-related event, patients who experienced dialysis for at least 1 month, kidney transplantation or kidney failure (defined as a sustained eGFR < 15 mL/min/1.73 m² prior to a 30% reduction) were included as having had a clinical event occurring at that time.

[†]In an IPCW analysis, patients who received rescue medication or other prohibited immunosuppressive medications were censored at the time of their last eGFR measurement before receiving the medication. [‡]Post hoc analysis using a standard Cox model. CI, confidence interval; eGFR, estimated glomerular filtration rate; HR, hazard ratio; IPCW, inverse probability of censoring weights.

Secondary endpoint: Time to 30% reduction in eGFR or kidney failure by UPCR subgroup

*Post hoc analysis: Time to confirmed 30% eGFR reduction or kidney failure in the absence of rescue medication stratified by UPCR subgroup**



Nefecon treatment effect on risk of 30% reduction in eGFR or kidney failure was consistent irrespective of baseline UPCR category

*In an IPCW analysis, patients who received rescue medication or other prohibited immunosuppressive medications were censored at the time of their last eGFR measurement before receiving the medication. A 30% reduction in eGFR was confirmed by two values over ≥4 weeks, and kidney failure was defined as dialysis for ≥1 month, kidney transplantation, sustained (≥1 month) eGFR <15 mL/min/1.73 m², or kidney-related death.

CI, confidence interval; eGFR, estimated glomerular filtration rate; HR, hazard ratio; IPCW, inverse probability of censoring weights; UPCR, urine protein-creatinine ratio.

Summary of TEAEs during treatment period*

TEAEs ($\geq 5\%$ in the Nefecon 16-mg/day arm)¹

Adverse event, N (%)	Nefecon 16 mg (N=182)	Placebo (N=182)
Peripheral edema ^{†,‡}	31 (17)	7 (4)
Hypertension [§]	22 (12)	6 (3)
Muscle spasms	22 (12)	7 (4)
Acne	20 (11)	2 (1)
Headache	19 (10)	14 (8)
Nasopharyngitis	17 (9)	19 (10)
Face edema [‡]	14 (8)	1 (0.5)
Dyspepsia	13 (7)	4 (2)
Arthralgia	12 (7)	4 (2)
URTI	10 (5)	10 (5)
Insomnia	10 (5)	7 (4)
Fatigue	10 (5)	7 (4)
Rash	10 (5)	7 (4)
Increase in weight	10 (5)	5 (3)

During the 9-month treatment period, **Nefecon 16 mg/day was well tolerated**, with a safety profile as expected for a **locally acting oral budesonide product**²

*Includes only adverse events that started during treatment up to 14 days after the last treatment dose (i.e., the last dose the patient received including the tapering period, regardless of treatment duration). Five patients (n=2 in the Nefecon group and n=3 in the placebo group) did not start study treatment.

[†]One patient receiving Nefecon experienced a TEAE graded as severe. [‡]One patient receiving Nefecon experienced a TEAE classed as serious. [§]Two patients receiving Nefecon experienced a TEAE classed as serious. TEAE, treatment-emergent adverse event; URTI, upper respiratory tract infection.

1. Lafayette R, et al. *Lancet* 2023;402:859-870 (online appendix). 2. Lafayette R, et al. *Lancet* 2023;402:859-870.

Conclusions

- The time from randomization to confirmed 30% reduction in eGFR or kidney failure was significantly delayed with Nefecon vs placebo
 - HR 0.45 (95% CI 0.26, 0.75) p=0.0014 (1-sided)
- The Nefecon vs placebo treatment effect was similar irrespective of handling of rescue medication
 - Rescue medication counted as an event: HR 0.51 (95% CI 0.33, 0.79)
 - Regardless of rescue medication: HR 0.44 (95% CI 0.27, 0.71)
- The treatment effect of Nefecon vs placebo was consistent irrespective of baseline UPCR category
 - UPCR <1.5 g/g: HR 0.51 (95% CI 0.21, 1.12)
 - UPCR ≥1.5 g/g: HR 0.42 (95% CI 0.21, 0.83)
- These findings strongly indicate preserved kidney function with Nefecon and provide support for Nefecon as a disease-modifying therapy in patients with IgAN

Acknowledgments

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