60TH ERA CONGRESS MILAN & VIRTUAL JUNE 15-18, 2023

# Durable proteinuria reduction over 2 years with Nefecon treatment: A secondary analysis of the full NefIgArd Phase 3 trial results

calliditas THERAPEUTICS

R. LAFAYETTE[1], J. KRISTENSEN[2], A. STONE[3], J. FLOEGE[4], V. TESAŘ[5], H. TRIMARCHI[6], H. ZHANG[7], N. EREN[8], A. PALIEGE[9], H. REICH[10], B. H. ROVIN[11], AND J. BARRATT[12], on behalf of the NefIgArd trial investigators.

[1]Division of Nephrology, Department of Medicine, Stanford University, Stanford, CA, USA; [2]Calliditas Therapeutics AB, Stockholm, Sweden; [3]Stone Biostatistics, Ltd., Crewe, UK; [4]Department of Nephrology and Clinical Immunology, Rheinisch Westfälische Technische Hochschule Aachen University Hospital, Aachen, Germany; [5]Department of Nephrology, First Faculty of Medicine and General University Hospital, Charles University, Prague, Czech Republic; [6]Nephrology Service, Hospital Británico de Buenos Aires, Buenos Aires, Argentina; [7]Renal Division, Peking University First Hospital, Peking University Institute of Nephrology, Beijing, China; [8]Department of Nephrology, Kocaeli University, Kocaeli, Turkey; [9]Division of Nephrology, Department of Internal Medicine III, University Hospital Carl Gustav Carus, Technische Universität Dresden, Dresden, Germany; [10]Division of Nephrology, University Health Network, Department of Medicine, University of Toronto, Toronto, ON, Canada; [11]Division of Nephrology, the Ohio State University Wexner Medical Center, Columbus, OH, USA; [12]College of Medicine Biological Sciences and Psychology, University of Leicester, Leicester, UK

## INTRODUCTION

Immunoglobulin A nephropathy (IgAN) is a chronic autoimmune kidney disease characterized by IgA deposition in the glomeruli.[1]

Proteinuria is a common clinical manifestation of IgAN, and persistent proteinuria is a risk factor for progression to kidney failure. Changes in proteinuria can be measured to determine the efficacy of IgAN treatments.[2,3]

Previous findings from the Phase 2b NEFIGAN trial showed that patients treated with Nefecon 16mg/day for 9 months, with a 3-month follow up, showed a reduction in urine protein-to-creatinine ratio (UPCR) compared with placebo.[4]

In the interim analysis of the Phase 3 NefIgArd trial (N=199), patients treated with Nefecon 16 mg/day in addition to optimized standard of care (SOC) had reduced proteinuria versus placebo and an estimated glomerular filtration rate (eGFR) treatment benefit of 3.87 mL/min/1.73 $m^2$ after a 9-month course of treatment.[3] These findings led to the FDA and EMA approval of Nefecon in patients with primary IgAN.[3,5]

Here, we present results from the entire 2-year NefIgArd study consisting of the full dataset of 364 patients with primary IgAN.

## AIM

To assess the durability of effect of Nefecon 16 mg/day over 9 months of treatment and subsequent 15 months of follow-up on proteinuria reduction vs placebo in patients with IgAN in the full Phase 3 NefIgArd trial.

## METHODS

NefIgArd was a 2-part randomized, double-blind, placebo-controlled study. Patients received Nefecon 16 mg/day or placebo, in addition to optimized SOC for 9 months, with a 2-week tapering period, followed by a 15-month blinded observational follow-up with continued optimized SOC.

**Key inclusion criteria:**

- Patients aged ≥18 years with biopsy-confirmed primary IgAN
- UPCR ≥0.8 g/g or proteinuria ≥1 g/24 h, despite optimized renin–angiotensin system blockade
- eGFR of 35–90 mL/min/1.73 $m^2$

**Key exclusion criteria:**

- Other glomerulopathies and nephrotic syndrome
- Kidney transplant
- Systemic diseases that may cause mesangial IgA deposition
- Poorly controlled blood pressure (≥140/90 mmHg)

## METHODS (CONT.)

Pre-defined secondary efficacy endpoints: **time-averaged urine protein-to-creatinine ratio (UPCR)** and **urine albumin-to-creatinine ratio (UACR) between 12 and 24 months** following the first dose of the study drug and expressed as ratios vs baseline.

UPCR and UACR data were based on a 24-hour urine protein collection and were log-transformed prior to analysis using a mixed-effects model for repeated measures (MMRM) including all timepoints from 3 months onwards.

UPCR and UACR values at 12, 18, and 24 months were given equal weight to obtain the geometric mean treatment effect during follow-up.

## RESULTS

Baseline characteristics were **well balanced** for the Nefecon 16 mg and placebo groups (Table 1).

**Table 1:** Patient demographics and baseline characteristics in the NefIgArd full analysis set.

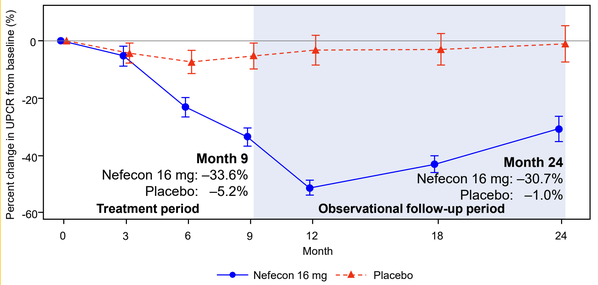
| | Nefecon 16 mg (n=182) | Placebo (n=182) |
|---|---|---|
| Age (years), median (range) | 43 (21–69) | 42 (20–73) |
| Sex (n, % male) | 117 (64) | 123 (68) |
| Race (n, % White) | 138 (76) | 137 (75) |
| Race (n, % Asian) | 43 (24) | 40 (22) |
| Systolic BP, median (range) | 126 (121, 132) | 124 (117, 130) |
| Diastolic BP, median (range) | 79 (76, 84) | 79 (74, 84) |
| UPCR (g/gram), median (IQR) | 1.28 (0.9, 1.8) | 1.25 (0.9, 1.7) |
| UACR (g/gram), median (IQR) | 0.99 (0.7, 1.4) | 0.98 (0.7, 1.4) |
| eGFR CKD-EPI (mL/min/1.73 $m^2$), median (IQR) | 56.1 (46, 71) | 55.1 (46, 68) |

*BP, blood pressure; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; eGFR; estimated glomerular filtration rate; IQR, interquartile range; UACR, urine albumin-to-creatinine ratio; UPCR, urine protein-to-creatinine ratio.*

## RESULTS (CONT.)

At 24 months, UPCR was reduced by 30.7% from baseline in the Nefecon group compared with 1% in the placebo group (comparative reductions at the end of the 9-month treatment period were 33.6% and 5.2%, respectively; Figure 1).

**Figure 1:** Percentage change in UPCR (g/gram) from baseline (full analysis set).




*UPCR, urine protein-to-creatinine ratio.*

The pre-defined secondary analysis of durability of proteinuria reduction showed:

- UPCR was significantly reduced by 41% over 12–24 months in the Nefecon group compared with placebo (95% CI 32–49%, p<0.0001; Table 2)
- UACR was also significantly reduced by 46% over 12–24 months in the Nefecon group compared with placebo (95% CI 37–55%, p<0.0001; Table 2).

**Table 2:** Ratio of UPCR and UACR averaged over 12–24 months compared with baseline using MMRM (full analysis set).

| | % change vs placebo (95% CI) p-value[a] | % change from baseline (95% CI), Nefecon 16 mg (n=182) | % change from baseline (95% CI), placebo (n=182) |
|---|---|---|---|
| UPCR | 41% (32–49%) p<0.0001 | –40% (–46%, –34%) | 1% (–9%, 12%) |
| UACR | 46% (37–55%) p<0.0001 | –48% (–54%, –42%) | –4% (–15%, 8%) |

[a]*Corresponding percentage reduction and 95% CI is derived from (1–ratio of geometric least squares means) × 100.*

*CI, confidence interval; MMRM, mixed-effects model for repeated measures; UACR, urine albumin-to-creatinine ratio; UPCR, urine protein-to-creatinine ratio.*

## CONCLUSIONS

**These secondary analyses show that after 9 months of Nefecon 16 mg/day treatment, a clinically relevant reduction in proteinuria (as measured by UPCR and UACR) was seen in patients with primary IgAN.**

**This effect was durable, being maintained throughout the 15 months' off-drug observation period.**

**These results lend further support to the clinical benefit of Nefecon as well as provide further evidence of a disease-modifying effect.**

## ACKNOWLEDGEMENTS

We would like to thank the patients and their families, as well as the teams of healthcare professionals and academics involved in this work, without whom none of it would be possible.

Editorial assistance was provided by Olivia Scragg and Geraint Owens of Chameleon Communications International, UK, which was funded by Calliditas Therapeutics, in accordance with Good Publication Practice guidelines (https://www.ismpp.org/gpp-2022).

## REFERENCES

1. Wyatt RJ, Julian BA. IgA nephropathy. *N Engl J Med 2013;368:2402-2414*

2. Smerud HK et al. New treatment for IgA nephropathy: enteric budesonide targeted to the ileocecal region ameliorates proteinuria. *Nephrol Dial Transplant 2011;26:3237-3242*

3. Barratt J et al. Results from part A of the multi-center, double-blind, randomized, placebo-controlled NefIgArd trial, which evaluated targeted-release formulation of budesonide for the treatment of primary immunoglobulin A nephropathy. *Kidney Int 2022;103: 391-402*

4. Fellstrom BC et al. Targeted-release budesonide versus placebo in patients with IgA nephropathy (NEFIGAN): a double-blind, randomised, placebo-controlled phase 2b trial. *Lancet 2017;389:21172127*

5. PR Newswire. European Commission approves Kinpeygo® for adults with primary IgA nephropathy. 2022. (https://www.prnewswire.com/news-releases/european-commission-approves-kinpeygo-for-adults-with-primary-iga-nephropathy-301587501.html).Kinpeygo [European Summary of Product Characteristics]. Bad Vilbel: STADA Arzneimittel AG; 2022

## CONTACT INFORMATION

Please contact Professor Richard Lafayette (czar@stanford.edu) for more information.