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

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ERA LEADING EUROPEAN NEPHROLOGY

Introduction

- Nefecon is a targeted-release budesonide formulation specifically designed to treat IgAN[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 Phase 3 NefIgArd trial, treatment with Nefecon resulted in a significant reduction in UPCR (27%, p=0.0003) and significant treatment benefit on eGFR compared with placebo after 9 months[3]
- Here, we present primary data from the full long-term data set, comprising 9 months of treatment and 15 months of follow-up (2 years in total)[1,2]

eGFR, estimated glomerular filtration rate; EMA, European Medicines Agency; FDA, Food and Drug Administration; IgA, immunoglobulin A; IgAN, Immunoglobulin A nephropathy; UPCR, urine protein-to-creatinine ratio.

1. Barratt J, et al. *Kidney Int Rep*. 2020;5:1620-1624. 2. Barratt J, et al. *Kidney Int*. 2023;103:391-402. 3. Calliditas Therapeutics press release. March 12, 2023. https://www.calliditas.se/en/calliditas-announces-primary-endpoint-successfully-met-in-phase-3-nefigard-trial-evaluating-nefecon-in-iga-nephropathy/ (accessed May 19, 2023).

Method

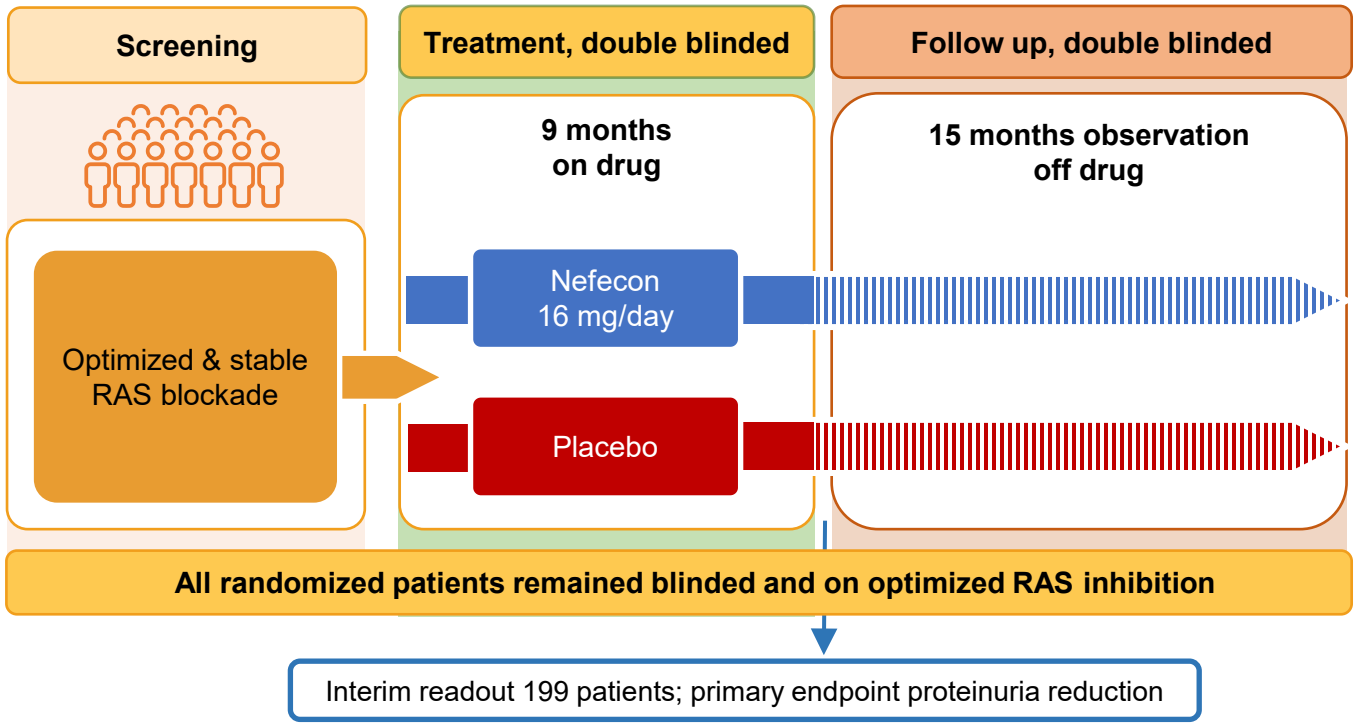
Interim readout

- November 2020 readout; global study with 199 patients
- Primary endpoint: proteinuria; key secondary endpoint: eGFR
- Basis for accelerated/conditional approval in USA/Europe, respectively

Full Phase 3 trial

- Designed to confirm the long-term renal benefit of observed proteinuria reduction
- Primary endpoint eGFR
- Read out positive data in March 2023; global study with 364 patients
- Estimated FDA filing July 2023

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



Base inclusion/exclusion criteria:

- Study included patients ≥18 years old with biopsy-proven IgAN; >1 g of proteinuria; eGFR >35–<90 mL/min/1.73 m², and well-controlled blood pressure of <140/90 mmHg
- Among the exclusion criteria were systemic diseases, having undergone a kidney transplant, and the presence of other glomerulopathies

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

eGFR, estimated glomerular filtration rate; FDA, Food and Drug Administration; IgAN, immunoglobulin A nephropathy; RAS, renin–angiotensin system.

Results: Patient overview

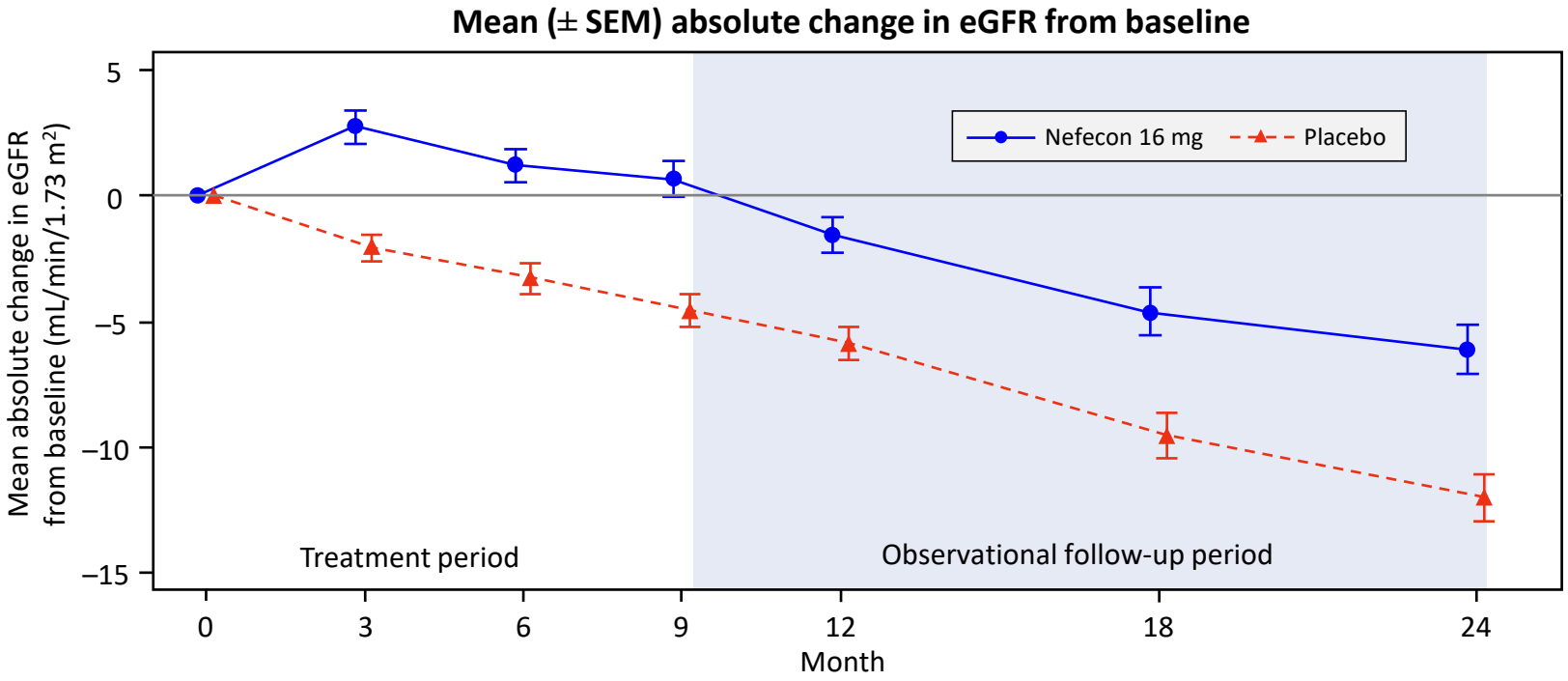
	Nefecon 16 mg/day (n=182)	Placebo (n=182)
Median (range) age, years	43 (21-69)	42 (20-73)
<45 years, n (%)	98 (53.8)	104 (57.1)
Sex, n (%)		
Male	117 (64.3)	123 (67.6)
Female	65 (35.7)	59 (32.4)
Race, n (%)		
White	138 (75.8)	137 (75.3)
Asian	43 (23.6)	40 (22.0)
Black or African American	0 (0.0)	0 (0.0)
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 (0.9-1.76)	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 m^2)	56.14 (45.50-70.97)	55.11 (45.96-67.74)
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)

CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; CS, corticosteroid; eGFR, estimated glomerular filtration rate; IgAN, immunoglobulin A nephropathy; IQR, interquartile range; UACR, urine albumin-to-creatinine ratio; UPCR, urine protein-to-creatinine ratio.

Results: Efficacy (1)

Primary endpoint: time-weighted average change from baseline in eGFR over the 2-year period

- 5.05 mL/min/1.73 m^2 eGFR treatment benefit in favor of Nefecon vs placebo over 2 years ($p<0.0001$)
- eGFR benefit at the end of the 9-month treatment period with Nefecon was maintained during the 15-month observational follow-up

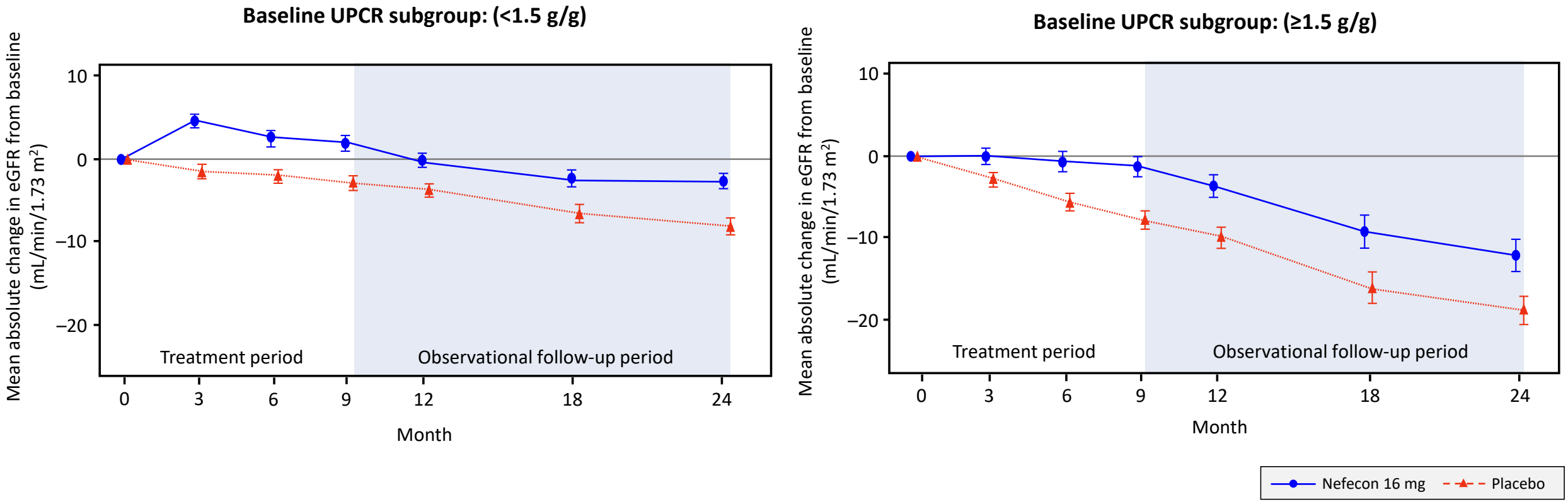


Nefecon 16 mg/day, mL/min/1.73 m^2	+0.66	−1.52	−6.11
Placebo, mL/min/1.73 m^2	−4.56	−5.85	−12.00
Absolute difference, mL/min/1.73 m^2 (95% CI)	5.21 (3.35–7.58)	4.33 (2.44–6.66)	5.89 (3.35–9.15)

CI, confidence interval; eGFR, estimated glomerular filtration rate; SEM, standard error of the mean; UPCR, urine protein-to-creatinine ratio.

Results: Efficacy (2)

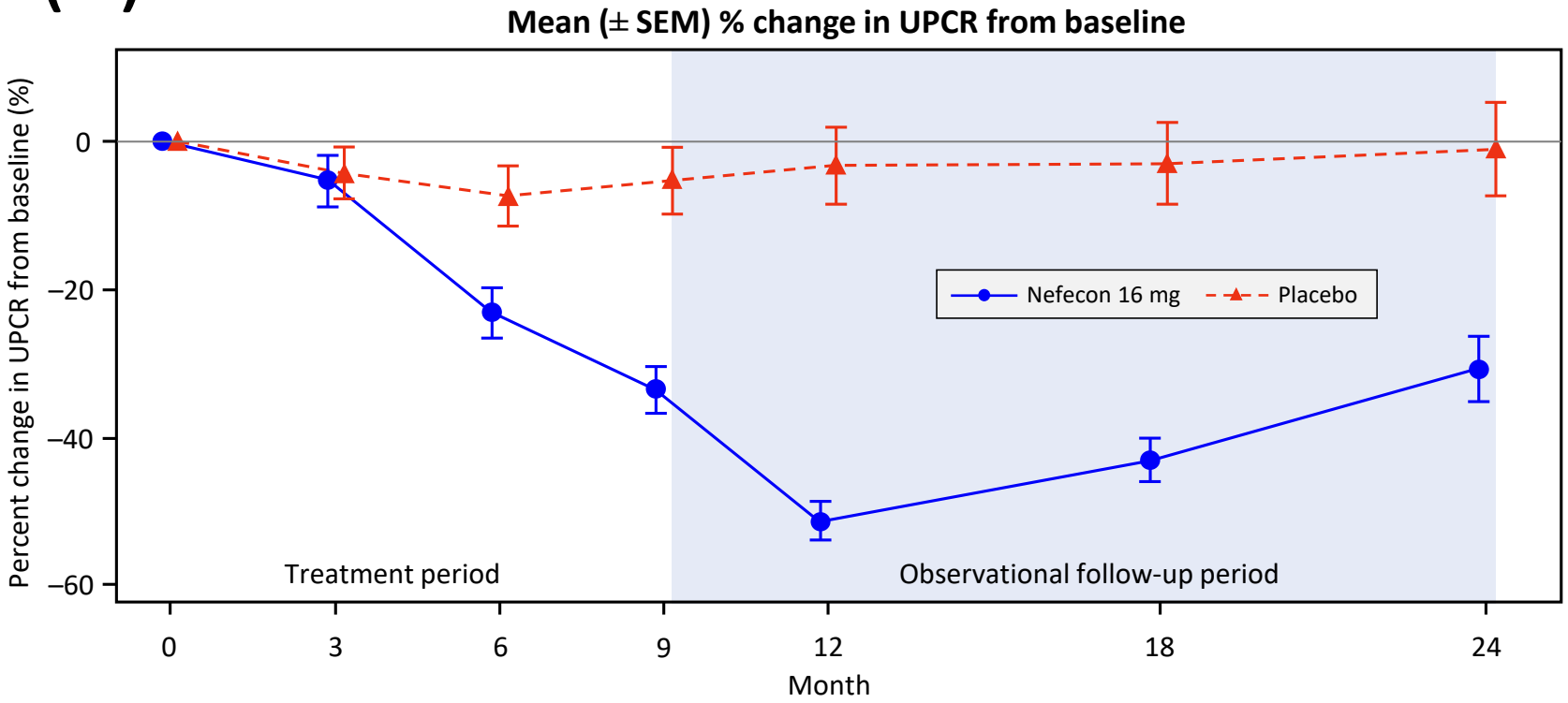
- The eGFR benefit with Nefecon vs placebo was consistent regardless of baseline UPCR



eGFR, estimated glomerular filtration rate; UPCR, urine protein-to-creatinine ratio.

Results: Efficacy (3)

- At 2 years, the percentage reduction in UPCR in the Nefecon vs placebo arm was similar to the end of the 9-month treatment period



Nefecon 16 mg/day, %	–33.6	–51.3	–30.7
Placebo, %	–5.2	–3.2	–1.0
Corresponding percentage reduction, % (95% CI)	30 (20–39)	50 (42–57)	30 (16–41)

CI, confidence interval; SEM, standard error of the mean; UPCR, urine protein-to-creatinine ratio.

Results: TEAEs by preferred term (USPI definition)

Safety analysis set (≥5% Nefecon-treated patients and ≥2% higher than placebo)

Adverse reaction, n (%)	Nefecon 16 mg (n=195)	Placebo (n=194)
Peripheral edema[a]	33 (16.9)	10 (5.2)
Hypertension	23 (11.8)	6 (3.1)
Muscle spasms	23 (11.8)	8 (4.1)
Acne	22 (11.3)	2 (1.0)
URTI	16 (8.2)	12 (6.2)
Face edema[b]	15 (7.7)	1 (0.5)
Weight increased	13 (6.7)	6 (3.1)
Dyspepsia	13 (6.7)	4 (2.1)
Arthralgia	12 (6.2)	4 (2.1)
WBC increased	11 (5.6)	1 (0.5)

[a]Includes preferred terms of edema peripheral and peripheral swelling. [b]Includes preferred terms of face edema and swelling face.
TEAE, treatment-emergent adverse event; URTI, upper respiratory tract infection; USPI, United States prescribing information; WBC, white blood cell.

Discussion

- 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 compared with optimized SoC
- The size of the eGFR benefit was maintained over the 15-month off-drug, observational follow-up period, supporting a disease-modifying effect of Nefecon 16 mg treatment
- Nefecon 16 mg was generally well tolerated, and the AE profile was consistent with that reported in the previous interim analysis

AE, adverse event; eGFR, estimated glomerular filtration rate; SoC, standard of care.

Acknowledgments

- 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 Maariya Shahzad 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)

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

Nefecon treatment likely modulates downstream pathways of kidney inflammation and fibrosis in IgA nephropathy

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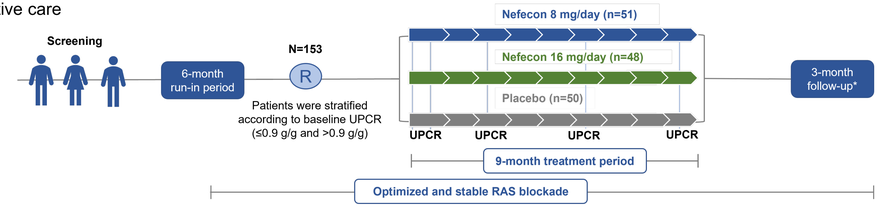
calliditas THERAPEUTICS

INTRODUCTION

- IgA nephropathy (IgAN) is characterized by the accumulation of immunoglobulin A1 (IgA1)-containing immune complexes (IgA1-ICs) in the renal mesangium, leading to breakdown of the glomerular filtration barrier; this allows unfiltered proteins to come into contact with cells lining the tubules, causing progressive tubulointerstitial inflammation and scarring, which is a predictor of disease progression in IgAN[1,2]
- The NEFIGAN trial (NCT01738035) tested the safety and efficacy of a novel targeted-release formulation of budesonide (Nefecon) designed to deliver budesonide to the gut-associated lymphoid tissue (GALT)-rich distal ileum in patients with IgAN in addition to optimized supportive care

Study Design



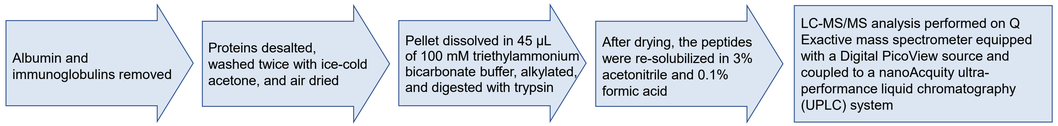
**Patients who received 16 mg/day Nefecon during months 0–9 were tapered to 8 mg/day for 2 weeks while all other patients (ie, those who received Nefecon 8 mg/day or placebo during months 0–9) received placebo to maintain masking. No further trial medication was administered after tapering*

- The headline result of the study was that Nefecon 16 mg/day, added to optimized renin-angiotensin system blockade, reduced proteinuria and stabilized estimated glomerular filtration rate in patients with IgAN. These findings have now been replicated in the NefIgArd study, which reported in 2021 and provided the basis for the recent FDA and EMA approval of Nefecon as a treatment for patients with IgAN at high risk of progressive disease. The results of the completed trial will be presented separately at this conference
- In this study, we determined the composition of urinary proteins from patients treated with placebo and 16 mg of Nefecon in the NEFIGAN trial using liquid chromatography with tandem mass spectrometry (LC-MS/MS)

METHOD

- Urine samples from 18 patients from each of the placebo and 16 mg/day arms of the NEFIGAN trial collected at start of treatment (SOT) and end of treatment (EOT) were analyzed. Patients were only included if they had received at least 8 months of treatment and the urine sample was taken up to 2 days after the completion of tapering

Preparation and LC-MS/MS analysis of urine



- For protein identification and quantification, raw data were processed with FragPipe (V16) having at least 2 peptides per protein
- The protein intensities reported in the combined_protein.txt file generated by the FragPipe were:
  1. Log_2-transformed and internally normalized against a group of peptides found in all samples
  2. The normalized protein abundance at SOT was subtracted from the abundance from the EOT for each patient
  3. A probabilistic dropout model was fitted to the data to estimate fold changes between the treatment and placebo groups at EOT
  4. The proteins were ranked using the t-statistic and a gene set enrichment analysis was performed to determine the gene sets significantly affected by the treatment compared with the placebo group

RESULTS

Gene ontology analysis revealed that treatment with 16 mg of Nefecon led to a significant enrichment of multiple pathways (n=57) involved in a number of processes previously shown to be important in the pathogenesis of kidney injury in IgAN (Tables 1-4)

Table 1: Epigenetic pathways

ID	Description	Enrichment score	qvalue
GO:0045814	negative regulation of gene expression, epigenetic	0.77822	0.000023
GO:0097549	chromatin organization involved in negative regulation of transcription	0.77822	0.000023
GO:0060968	regulation of gene silencing	0.74540	0.000132
GO:0060147	regulation of posttranscriptional gene silencing	0.76836	0.000132
GO:0060964	regulation of gene silencing by miRNA	0.76836	0.000132
GO:0060966	regulation of gene silencing by RNA	0.76836	0.000132
GO:0031047	gene silencing by RNA	0.69949	0.000173
GO:0035194	posttranscriptional gene silencing by RNA	0.71719	0.000405
GO:0016458	gene silencing	0.65049	0.000730
GO:0035195	gene silencing by miRNA	0.71011	0.001105
GO:0040029	regulation of gene expression, epigenetic	0.69539	0.001510
GO:0016441	posttranscriptional gene silencing	0.69427	0.001522
GO:0010608	posttranscriptional regulation of gene expression	0.46586	0.019032

Table 2: Microvesicle formation

ID	Description	Enrichment score	qvalue
GO:0099503	secretory vesicle	0.41340	0.002955
GO:0030312	external encapsulating structure	0.44636	0.007910
GO:0016192	vesicle-mediated transport	0.38002	0.011345

Table 3: Kidney remodeling

ID	Description	Enrichment score	qvalue
GO:0048771	tissue remodeling	0.73277	0.001004
GO:0062023	collagen-containing extracellular matrix	0.48024	0.001510
GO:0031012	extracellular matrix	0.44636	0.007910
GO:0006508	proteolysis	0.39559	0.019032
GO:0010466	negative regulation of peptidase activity	0.47351	0.022175
GO:1903035	negative regulation of response to wounding	0.60180	0.028780
GO:0010951	negative regulation of endopeptidase activity	0.47271	0.033849
GO:0009888	tissue development	0.38878	0.041148
GO:0009611	response to wounding	0.44240	0.041559

Table 4: Local immune and inflammatory responses

ID	Description	Enrichment score	qvalue
GO:0045638	negative regulation of myeloid cell differentiation	0.77415	0.000029
GO:0006953	acute-phase response	0.83084	0.000132
GO:0045596	negative regulation of cell differentiation	0.59467	0.000506
GO:0006954	inflammatory response	0.50626	0.001602
GO:0001775	cell activation	0.41658	0.001975
GO:0002682	regulation of immune system process	0.41526	0.003481
GO:0032101	regulation of response to external stimulus	0.45829	0.004380
GO:0006955	immune response	0.38373	0.006983
GO:0045321	leukocyte activation	0.40302	0.011254
GO:0034097	response to cytokine	0.43277	0.011740
GO:0002526	acute inflammatory response	0.61731	0.015653
GO:0009605	response to external stimulus	0.38349	0.015653
GO:0033554	cellular response to stress	0.42383	0.015653
GO:0002263	cell activation involved in immune response	0.40543	0.019023
GO:0009967	positive regulation of signal transduction	0.43257	0.020140
GO:0002366	leukocyte activation involved in immune response	0.40197	0.020140
GO:0080134	regulation of response to stress	0.42627	0.020417
GO:0002274	myeloid leukocyte activation	0.40534	0.021614
GO:0009986	cell surface	0.45022	0.021865
GO:0002443	leukocyte-mediated immunity	0.40019	0.021946
GO:0010647	positive regulation of cell communication	0.42567	0.022175
GO:0023056	positive regulation of signaling	0.42699	0.023965
GO:0002444	myeloid leukocyte-mediated immunity	0.40808	0.023965
GO:0043299	leukocyte degranulation	0.40453	0.028193
GO:0002252	immune effector process	0.37813	0.034174
GO:0045637	regulation of myeloid cell differentiation	0.54056	0.037771
GO:0023051	regulation of signaling	0.38341	0.038167
GO:0048584	positive regulation of response to stimulus	0.38498	0.038876
GO:0006935	chemotaxis	0.48048	0.039247
GO:0042330	taxis	0.48048	0.039247
GO:0009966	regulation of signal transduction	0.38914	0.039247
GO:0002275	myeloid cell activation involved in immune response	0.40185	0.040444

CONCLUSIONS

These urine proteomic data support the positive impact of Nefecon on downstream proinflammatory and profibrotic pathways within the kidneys. These data will be validated in biomarker analyses currently underway as part of the NefIgArd study.

REFERENCES

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

2. 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* 2023;103:391-402

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Hematuria reduction in patients with IgAN following Nefecon treatment: A secondary analysis of the full 2-year NeflgArd Phase 3 trial results

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INTRODUCTION

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

Hematuria is a common clinical manifestation of IgAN, and changes in hematuria can be measured to determine the efficacy of IgAN treatments.[2]

Nefecon 16 mg/day was associated with, among other benefits, a reduction in microhematuria after a 9-month course of treatment and 3-month follow-up in the Phase 2b NEFIGAN trial.[3]

In the interim analysis of the Phase 3 NeflgArd 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.[4] These findings led to the Food and Drug Administration and European Medicines Agency approval of Nefecon in patients with primary IgAN.[4,5]

Here, we present results from the entire 2-year NeflgArd study consisting of the full dataset of 364 patients.

AIM

To assess the effect of 9 months of Nefecon 16 mg/day treatment on microhematuria in patients with IgAN during the subsequent 15-month, off-drug, observational follow-up period of the Phase 3 NeflgArd trial.

METHODS

NeflgArd 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 (Figure 1).

Key inclusion criteria:

- Patients ≥18 years with biopsy-confirmed primary IgAN
- Urine protein-to-creatinine ratio (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

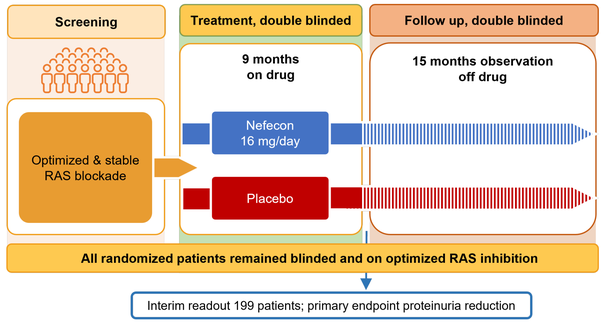
Key exclusion criteria:

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

METHODS (CONT.)

Presence of microhematuria (a secondary efficacy endpoint for this trial) was defined as presenting a positive urine dipstick result in at least 2 of the follow-up visits assessed at 12, 18, and 24 months after the first dose of Nefecon or placebo.

Figure 1: Study design for the full Phase 3 NeflgArd trial.



eGFR, estimated glomerular filtration rate; RAS, renin–angiotensin system.

- Odds ratio was estimated using logistic regression model with treatment, log-baseline UPCR, log-baseline eGFR, and geographic region as covariates; confidence interval (CI) was estimated using a profile likelihood approach and the p-value was from a likelihood-ratio test.

RESULTS

- Baseline characteristics were **well balanced** for the Nefecon 16 mg and placebo groups (Table 1)
- Of the 364 patients in the full analysis set, **158/182 patients in the Nefecon group and 152/182 patients in the placebo group had ≥2 valid urine dipstick results** during the observational follow-up period
- At randomization, **the proportion of patients with microhematuria was similar in the Nefecon (68%) and placebo (70%) groups** (Table 1)
- **The proportion of patients with microhematuria in the Nefecon group decreased from 66.5% at baseline to 40.5% during follow-up,** compared with a decrease from 67.8% to 61.2% in the placebo group at the same time points (Figure 2)

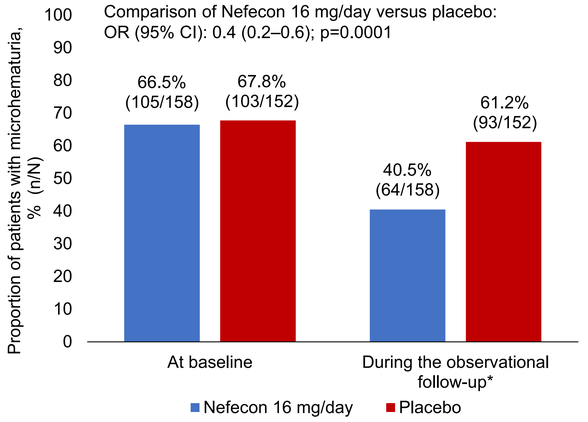
RESULTS (CONT.)

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

	Nefecon 16 mg (n=182)	Placebo (n=182)
Age, years, median (range)	43 (21-69)	42 (20-73)
Sex, male, n (%)	117 (64)	123 (68)
Race, White, n (%)	138 (76)	137 (75)
Race, Asian, n (%)	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)
eGFR CKD-EPI, mL/min/1.73 m^2, median (IQR)	56.1 (46-71)	55.1 (46-68)
Patients with microhematuria at randomization, n (%)	123 (68)	127 (70)

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

Figure 2: Proportion of patients with microhematuria at different time points during the observational follow-up.



**Patients with a positive urine dipstick result in at least 2 of the following time points: 12, 18, and 24 months following the first dose of study drug.*

CI, confidence interval; OR, odds ratio.

CONCLUSIONS

This secondary analysis shows that after 9 months of Nefecon 16 mg/day treatment, a clinically relevant and durable reduction in microhematuria was seen in patients with primary IgAN. These results provide further evidence for the disease-modifying effect of Nefecon.

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

calliditas THERAPEUTICS

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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.

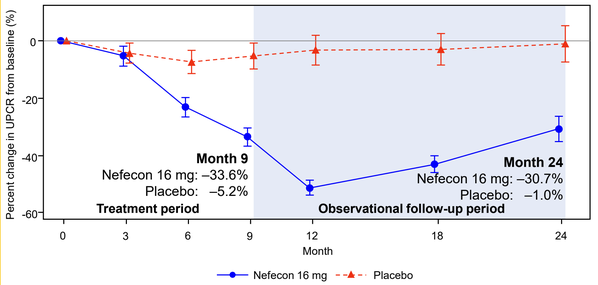
	Nefecon 16 mg (n=182)	Placebo (n=182)
Age (years), median (range)	43 (21–69)	42 (20–73)
Sex (n, % male)	117 (64)	123 (68)
Race (n, % White)	138 (76)	137 (75)
Race (n, % Asian)	43 (24)	40 (22)
Systolic BP, median (range)	126 (121, 132)	124 (117, 130)
Diastolic BP, median (range)	79 (76, 84)	79 (74, 84)
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.

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