Results from part A of the multi-center, double-blind, randomized, placebo-controlled NeflgArd trial, which evaluated targeted-release formulation of budesonide for the treatment of primary immunoglobulin A nephropathy

see commentary on page 258

Jonathan Barratt[1], Richard Lafayette[2], Jens Kristensen[3], Andrew Stone[4], Daniel Cattran[5], Jürgen Floege[6], Vladimir Tesar[7], Hernán Trimarchi[8], Hong Zhang[9], Necmi Eren[10], Alexander Paliege[11] and Brad H. Rovin[12]; for the NeflgArd Trial Investigators[13]

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

The therapeutic potential of a novel, targeted-release formulation of oral budesonide (Nefecon) for the treatment of IgA nephropathy (IgAN) was first demonstrated by the phase 2b NEFIGAN trial. To verify these findings, the phase 3 NefigArd trial tested the efficacy and safety of nine months of treatment with Nefecon (16 mg/d) versus placebo in adult patients with primary IgAN at risk of progressing to kidney failure (ClinicalTrials.gov: NCT03643965). NeflgArd was a multicenter, randomized, double-blind, placebo-controlled two-part trial. In Part A, 199 patients with IgAN were treated with Nefecon or placebo for nine months and observed for an additional three months. The primary endpoint for Part A was 24-hour urine protein-to-creatinine ratio (UPCR) after nine months. Secondary efficacy outcomes evaluated included estimated glomerular filtration rate (eGFR) at nine and 12 months and the UPCR at 12 months. At nine months, UPCR was 27% lower in the Nefecon group compared with placebo, along with a benefit in eGFR preservation corresponding to a 3.87 ml/min/1.73 m^2 difference versus placebo (both significant). Nefecon was well-tolerated, and treatment-emergent adverse events were mostly mild to moderate in severity and reversible. Part B is ongoing and will be reported on later. Thus, NeflgArd is the first phase 3 IgA nephropathy trial to show clinically important improvements in UPCR and eGFR and confirms the findings from the phase 2b NEFIGAN study.

Correspondence: *Brad H. Rovin, Division of Nephrology, the Ohio State University Wexner Medical Center, 410 W 10th Avenue, Columbus, Ohio 43210, USA. E-mail: Brad.Rovin@osumc.edu*

[13]The NeflgArd Trial Investigators are listed in the Appendix.

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IgA nephropathy (IgAN) is a mesangioproliferative glomerulonephritis, characterized by the deposition of galactose-deficient IgA1 (Gd-IgA1)–containing immune complexes in the glomerular mesangium.[1] These immune complexes initiate a cascade of inflammatory events, eventually causing irreversible glomerulosclerosis and tubulointerstitial inflammation and fibrosis with loss of kidney function; in patients with progressive disease (i.e., proteinuria >1 g/24 h), the risk of kidney failure may be up to 50% within 20 years.[2–5] At the time the present study was initiated, no IgAN-specific treatments were available, and guidelines recommended goal-directed supportive care comprising lifestyle change, optimal blood pressure control, and renin-angiotensin system (RAS) blockade to reduce proteinuria.[6–8]

There is accumulating evidence for the gut mucosal immune system and mucosal-derived Gd-IgA1 in the pathogenesis of primary IgAN. Peyer's patches are aggregations of lymphoid follicles, located in the mucosal layer of the intestine, and concentrated in the ileum. They are part of the gut-associated lymphoid system and serve as antigen sampling

and inductive sites and appear to be an important source of primed, Gd-IgA1-expressing mucosal B cells.[9] In patients with IgAN, the levels of Gd-IgA1 in the circulation are increased and can form immune complexes with IgG or IgA autoantibodies.[1,10–12] The mesangial accumulation of these immune complexes initiates inflammatory and fibrotic cascades, resulting in progressive kidney injury.[1,11,13,14] Given the role of Gd-IgA1 in the pathogenesis of IgAN, we postulated that a drug targeting the gut-associated lymphoid system could attenuate Gd-IgA1 production and effectively treat IgAN.

With this in mind, a new formulation of the oral glucocorticoid budesonide was specifically designed to deploy in the ileum (Nefecon; Calliditas Therapeutics AB) and deliver the glucocorticoid locally, with limited systemic exposure, to the ileal gut-associated lymphoid system.[15] Although this location and mechanism of action of Nefecon remain to be proven, the therapeutic potential of Nefecon was first demonstrated in the phase 2b study "The Effect of Nefecon in Patients With Primary IgA Nephropathy at Risk of Developing End-stage Renal Disease (NEFIGAN)" (NCT01738035).[16] In this randomized controlled trial, 9 months of treatment with Nefecon 8 mg or 16 mg once daily was compared with placebo in patients with IgAN at risk of progression to kidney failure defined by persistent proteinuria despite optimized RAS inhibition. Patients treated with Nefecon 16 mg achieved a significantly greater reduction in urine protein-to-creatinine ratio (UPCR) and experienced a smaller decline in estimated glomerular filtration rate (eGFR) than those treated with placebo. In particular, the mean percentage change from baseline in eGFR at 9 months was −9.8% for placebo versus 0.6% for Nefecon 16 mg, resulting in a statistically significant between-groups difference of 12% ($P = 0.0026$). eGFR benefits remained sustained for the duration of the study, with a mean percentage change from baseline at 12 months of 0.7% with Nefecon 16 mg versus −10.9% for placebo (difference: 11%; $P = 0.0134$).[16]

The positive impact of Nefecon treatment on established surrogate endpoints for predicting long-term kidney outcomes in patients with IgAN[16–19] led to the unique 2-part design of the phase 3 Efficacy and Safety of Nefecon in Patients With Primary IgA Nephropathy (NefIgArd) randomized controlled trial (NCT03643965), which aims to confirm the efficacy, safety, and tolerability of Nefecon 16 mg/d in adult patients with primary IgAN at risk of progression to kidney failure despite optimized and stable RAS blockade.[2] Herein, we report results for the part A analysis, which evaluated the effect of 9 months of treatment with Nefecon 16 mg on the relative reduction of UPCR from baseline and eGFR compared with placebo in addition to optimized and stable RAS blockade in 199 patients, and which has led to the accelerated approval of Nefecon by the US Food and Drug Administration as the first approved treatment for patients with IgAN at high risk of progression to kidney failure.[20]

This phase 3 study will continue blinded into an observational, follow-up phase (part B) to verify the clinical benefit of Nefecon on long-term kidney function by assessing an eGFR-based endpoint calculated over 2 years. It remains blinded to patients, the clinical study team, and all personnel directly involved with patients and the ongoing conduct of the study, thus providing reassurance of the integrity of part B. All 360 patients required for the part B analysis have now been enrolled, with final results expected in 2023.[2,21]

METHODS

Trial design and oversight

NefIgArd part A consisted of a 15- to 35-day screening period, 9-month treatment period, and a 3-month follow-up period (including a 2-week tapering period). Part B is a further 12-month observational follow-up period, during which the study blinding will remain in place, to assess the effect of treatment on eGFR. Maintaining study integrity and the blind in part B is being done through intense interaction with site investigators and staff to encourage working directly with patients on retention issues. Study integrity during part B is also facilitated by limited regulatory approval of Nefecon (United States only) that occurred well after the start of part B. This global trial is being conducted at 112 clinical sites in 20 countries, across Europe, North America, South America, and Asia Pacific (Supplementary Table S1). The protocol and informed consent form were submitted to and approved by the duly constituted institutional review board or independent ethics committee for each center before the initiation of the study. An independent Data and Safety Monitoring Board is in place to monitor the overall conduct of the study and safety data. The study was conducted in accordance with the Declaration of Helsinki and with all applicable laws and regulations of the locale and country where the study was conducted, and in compliance with International Council for Harmonisation Good Clinical Practice E6 (R2) guidelines. The design and methods of the NefIgArd trial have been described previously.[2]

Patient population

All patients provided written informed consent before enrolment. Adult patients with biopsy-confirmed primary IgAN, persistent proteinuria (UPCR ≥0.8 g/g or proteinuria ≥1 g/24 h) despite optimized supportive care, and an eGFR of ≥35 to ≤90 ml/min per 1.73 m^2 using the Chronic Kidney Disease Epidemiology Collaboration formula[22] were eligible for NefIgArd. Optimized supportive care required that patients receive the maximum tolerated or maximum allowed (country-specific) dose of an angiotensin-converting enzyme inhibitor and/or an angiotensin II type I receptor blocker for at least 3 months before randomization. This dose remained stable throughout the duration of the trial. Patients with type 1 or type 2 diabetes were eligible provided their diabetes was adequately controlled, defined as glycated hemoglobin ≤8% (64 mmol/mol). Main exclusion criteria included all secondary forms of IgAN or any non-IgAN glomerulonephritis, inadequately controlled blood pressure (i.e., systolic blood pressure/diastolic blood pressure ≥140/90 mm Hg), kidney transplant, or treatment with systemic glucocorticoids or immunosuppressants in the 12 months before enrolment. Full eligibility criteria are available in the Supplementary Methods.

Randomization and blinding

Participants were randomized 1:1, using an Interactive Response Technology system, to Nefecon or matching placebo capsules within

35 days of study visit 1 (screening). Patients were stratified according to baseline proteinuria (<2 g/24 h or ≥2 g/24 h), baseline eGFR (<60 ml/min per 1.73 m^2 or ≥60 ml/min per 1.73 m^2), and geographic region (Europe, North America, South America, or Asia Pacific).

Several measures were taken to ensure blinding. Both Nefecon and placebo were provided as modified release capsules, carefully matched in appearance, smell, and taste to ensure maintenance of treatment masking. No cortisol listings were made available because this would have led to unblinding based on expected cortisol reduction with Nefecon treatment.

After 9 months of treatment and after a 2-week tapering period, during which patients had their blinded treatment reduced from 4 to 2 capsules, patients entered the observational follow-up period (part B), during which no study drug was administered, but patients continued on optimized supportive care. The allocation to treatment groups will remain blinded to investigators, patients, and all personnel directly involved with patients and the ongoing conduct of the study until completion of part B. During part B no further blinded treatment (placebo or Nefecon) is given, but the blind is maintained.

Clinical outcomes

All proteinuria data (UPCR and urine albumin-to-creatinine ratio [UACR]) are based on 24-hour urine collection. The primary efficacy outcome for part A was the effect of Nefecon on UPCR at 9 months. Secondary efficacy outcomes were eGFR (Chronic Kidney Disease Epidemiology Collaboration) and UACR at 9 months and eGFR (Chronic Kidney Disease Epidemiology Collaboration) at 12 months. The statistical analysis plan specified analysis of the 1-year eGFR slope using a random coefficients model with random intercept and slope. eGFR was analyzed on a linear scale. Data impacted by rescue medication were excluded.

Safety outcomes included treatment-emergent adverse events (TEAEs), defined as adverse events (AEs) that occurred for the first time after dosing with study drug up until 14 days after the last dose, or existed before but worsened in severity or relationship to study drug after dosing, serious TEAEs, TEAEs leading to discontinuation of study drug, and TEAEs of special interest. Other safety assessments comprised clinical laboratory measurements (chemistry, hematology, and urinalysis), vital signs (heart rate and blood pressure), and physical examinations.

Statistical analysis

Based on the phase 2b NEFIGAN study, 200 patients in part A were required to provide >90% power to demonstrate statistical significance using a 1-sided alpha level of 0.025, assuming a 25% relative reduction in UPCR with Nefecon treatment compared with placebo and a standard deviation of 0.59 for the change in log(UPCR). Type 1 error is controlled across parts A and B using a predefined testing hierarchy in which the part A primary endpoint was tested at a 1-sided significance level of 0.02. All *P* values are 1-sided. The rationale for using 1-sided *P* values is that this was a superiority study, so testing was only performed in the direction favoring Nefecon. As such the level of significance was 2.5%.

The primary efficacy analyses were conducted in the part A Full Analysis Set (FAS), including 199 of the first 201 patients randomized (2 patients were prospectively excluded because of being incorrectly randomized). Patients were included in the FAS if they had the opportunity to receive the intended 9 months of therapy, regardless of whether they actually received the study drug. Data were recorded throughout, irrespective of early discontinuation, unless the patient withdrew their consent.

The primary aim of the efficacy analyses was to estimate the effect of Nefecon even if patients discontinued treatment early, but in the absence of rescue medication.

All efficacy endpoints, apart from eGFR 1-year slope, were log-transformed before analysis. UPCR and UACR were analyzed using a mixed-effect model for repeated measures, including baseline, 3-, 6-, 9-, and 12-month data. eGFR analyses at 9 and 12 months were performed using robust regression with Huber weights and a cutoff value of 2 with sequentially multiply imputed missing data. The imputation model for eGFR included treatment, baseline eGFR, and the 3, 6, 9, and 12 months of eGFR values. Sensitivity analyses assessed the robustness of the primary analysis and are listed in the Supplementary Methods. The analysis of total eGFR 1-year slope was performed using a random coefficients model, which included all available data recorded at baseline up to 12 months (Supplementary Methods). As a supportive analysis, the 1-year eGFR slope was estimated using a random coefficients model with random intercept and slope, using observed data only. In addition, eGFR at each time point was analyzed using a linear regression with actual time. These analyses were supportive of the individual 1-year slopes analyzed using robust regression with independent treatment and baseline.

The part A FAS was used to assess safety in the 197 dosed patients who had been followed for 9 months by the data cutoff. Two patients from the FAS were excluded from the safety analysis because they were randomized to placebo but did not receive any study treatment, discontinued from the study, and did not provide any follow-up data. Safety was also assessed in the Safety Analysis Set, which included 294 patients dosed by the time of the data cutoff (Supplementary Methods).

Predefined subgroup analyses were performed to assess the effect of Nefecon on UPCR and eGFR outcomes as described in the Supplementary Methods.

RESULTS

Study participants

Up to October 5, 2020, 657 patients had been screened, 306 of the planned 360 patients had been randomized, and 294 patients had received at least 1 dose of study drug (Figure 1). The FAS for the part A efficacy analyses included patients followed for at least 9 months by data cutoff (October 5, 2020) and comprised 97 patients randomized to Nefecon and 102 to placebo.

Demographic and disease characteristics were balanced between treatment groups (Table 1). The proportion of men (67.8%) and women (32.2%) was consistent with that expected for a predominately White (85.9%) IgAN patient population,[23,24] with approximately half of all patients aged <45 years. Median UPCR at baseline was 1.26 g/g; approximately 60% of patients had baseline proteinuria of ≥2 g/24 h, and kidney function was mildly to moderately impaired overall (median eGFR of 55 ml/min per 1.73 m^2). In addition, most patients (65.3%) had microhematuria at baseline, detected by dipstick. By chance, a higher percentage of patients in the Nefecon group had a medical history of diabetes or were identified as prediabetic compared with the placebo group (Table 1).

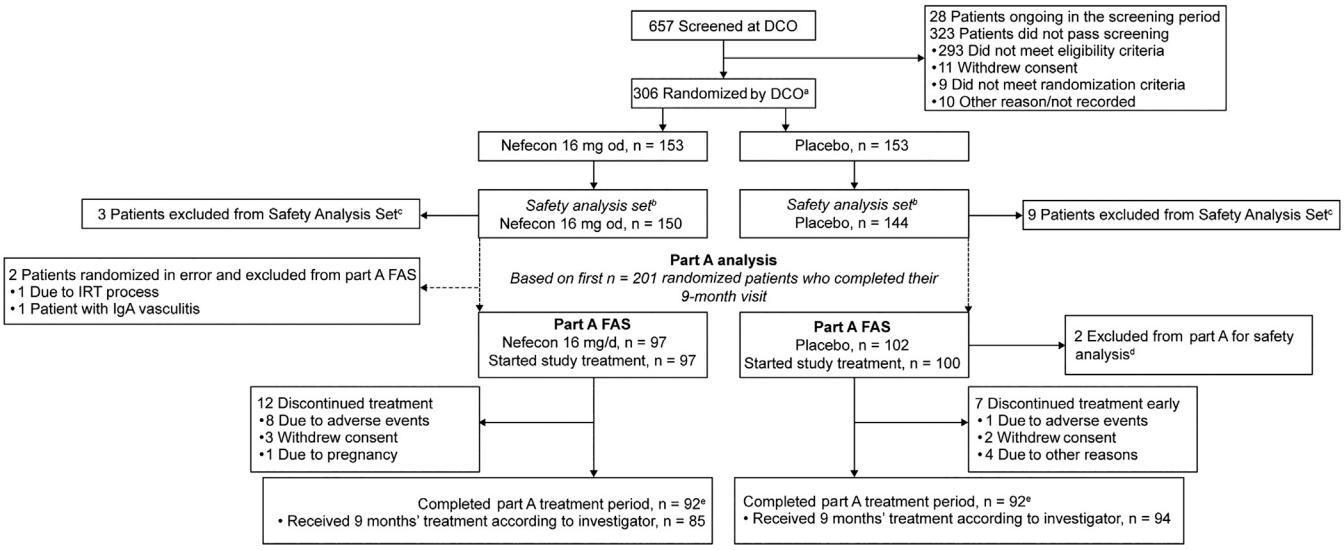

Figure 1 | Patient disposition as of part A data cutoff (DCO). [a]The DCO for the part A analysis was scheduled to occur once the first 201 patients randomized had the opportunity to complete their 9-month visit. The dataset extracted from the database and cleaned for analysis included all safety data from 294 patients dosed by the time of the DCO date of October 5, 2020, and all efficacy data up to and including the 12-month visit from all patients randomized at the DCO date. Part A database lock occurred on October 28, 2020. Part A Full Analysis Set (FAS) included data from 199 patients among the first 201 patients randomized, regardless of whether the patient received study drug (2 patients incorrectly randomized were excluded). The data cutoff was predefined to be based on the first 201 patients because the 200th and 201st patient were randomized on the same day. [b]Safety analysis set included all patients who had received at least 1 dose of study drug as of the DCO (n = 294) and, therefore, includes data from patients who have not yet completed the 9-month treatment phase. [c]The number of patients randomized before the DCO but who had not yet started treatment at the time of DCO. Five patients (2 of whom were included in the part A FAS) are not expected to be dosed because of withdrawal of consent. The remaining 7 patients were randomized close to the DCO and had not yet been dosed by the time of the DCO. [d]Two patients were excluded from the part A FAS for safety analyses as they were randomized to placebo but did not receive any study treatment, discontinued from the study, and did not provide any follow-up data. [e]Completed part A treatment period was defined as the patient has at least 1 valid urine protein-to-creatinine ratio value available in the 9-month visit window (days 229–319). IRT, Interactive Response Technology; od, once daily.

Three-quarters of patients received at least 92% of the maximum intended dose over the 9-month period, and almost all patients in the Nefecon (92 [94.8%]) and placebo (92 [90.2%]) groups completed the 9-month treatment period and had UPCR data at 9 months. Three patients in the Nefecon group and 2 in the placebo group had data excluded after rescue treatment at 9 months. Of the 199 patients in the part A FAS, 89 (91.8%) of those in the Nefecon 16 mg group and 90 (88.2%) of those in the placebo group provided UPCR data at 9 months in the absence of rescue treatment. A total of 144 patients had been on study for ≥12 months by the data cutoff; of these, 125 (87%) provided UPCR data at 12 months in the absence of rescue treatment.

Efficacy

After 9 months, with all patients being maintained on optimized and stable RAS blockade, those who received Nefecon achieved a 27% reduction in UPCR compared with placebo ($P = 0.0003$, Table 2); reductions from baseline values were 31% and 5% in the Nefecon and placebo groups, respectively (Figure 2a). Results were highly consistent among all prespecified groups, including analyses stratified by baseline UPCR, eGFR, and 24-hour proteinuria (Figure 3). Sensitivity analyses (Supplementary Table S2) also confirmed the results observed. UPCR continued to improve in Nefecon-treated patients; at 12 months, 3 months after treatment discontinuation, there was a 48% reduction in UPCR with Nefecon compared with placebo ($P < 0.0001$, Table 2). The absolute changes in proteinuria of the Nefecon and placebo-treated patients at 9 and 12 months are given in the legend for Table 2. Results for UACR paralleled UPCR, showing a 31% reduction with Nefecon compared with placebo at 9 months ($P = 0.0005$) and a 54% reduction at 12 months ($P < 0.0001$; Figure 2b, Table 2).

Because of the apparent skewing at baseline in the number of patients with diabetes or with glycated hemoglobin or fasting blood glucose levels indicative of prediabetes, we performed additional *post hoc* interaction tests and found that baseline glycated hemoglobin had no impact on the primary endpoint.

After 9 months of treatment, eGFR in Nefecon-treated patients decreased from baseline by 0.17 ml/min per 1.73 m^2 compared with a decrease of 4.04 ml/min per 1.73 m^2 in the placebo group (Figure 2c, Table 2). This translates to a statistically significant 3.87 ml/min per 1.73 m^2 eGFR treatment benefit ($P = 0.0014$) for Nefecon, which was maintained at 12 months. The improvement in 1-year eGFR slope was 3.37 ml/min per 1.73 m^2/yr ($P = 0.0111$) with Nefecon compared with placebo. As part of the prespecified analyses, it was observed that in the subgroup of patients who entered the trial with

Table 1 | Patient demographics and baseline characteristics (part A FAS)

Patient descriptors	Placebo (n = 102)	Nefecon 16 mg once daily (n = 97)
Age, yr	43 (23–73)	44 (25–69)
<45	56 (54.9)	52 (53.6)
Sex		
Male	67 (65.7)	68 (70.1)
Female	35 (34.3)	29 (29.9)
Baseline BMI, kg/m^2	28 (24–31)	29 (26–32)
Race		
White	86 (84.3)	85 (87.6)
Asian	13 (12.7)	11 (11.3)
Other	3 (2.9)	1 (1.0)
Ethnicity		
Hispanic or Latino	7 (6.9)	9 (9.3)
Not Hispanic or Latino	94 (92.2)	88 (90.7)
Not reported/unknown	1 (1.0)	0
Baseline blood pressure, mm Hg		
Systolic	124 (117–131)	128 (122–134)
Diastolic	78 (73–83)	79 (76–84)
Baseline UPCR, g/g	1.21 (0.87–1.79)	1.27 (0.95–1.75)
Baseline proteinuria, g/24 h	2.25 (1.51–3.57)	2.33 (1.71–3.25)
<2 g/24 h	43 (42.2)	39 (40.2)
≥2 to ≤3.5 g/24 h	31 (30.4)	36 (37.1)
>3.5 g/24 h	28 (27.5)	22 (22.7)
Baseline UACR, g/g	0.98 (0.66–1.55)	0.98 (0.75–1.35)
eGFR CKD-EPI, ml/min per 1.73 m^2	55.5 (45.5–67.7)	54.9 (46.4–68.9)
<60 ml/min per 1.73 m^2	61 (59.8)	63 (64.9)
Patients with microhematuria	70 (68.6)	60 (61.9)
Time from diagnosis to start of treatment, yr (range)	2.8 (0.5–7.1)	2.0 (0.8–6.1)
Patients previously treated with glucocorticosteroids or immunosuppressants	7 (6.9)	9 (9.3)
Use of any RAS inhibitor therapy		
Patients on ACEi alone	44 (43.1)	54 (55.7)
Patients on ARB alone	48 (47.1)	38 (39.2)
Patients on ACEi and ARB	7 (6.9)	3 (3.1)
Level of RAS blockade[a]	Placebo (n = 101)	Nefecon 16 mg od (n = 95)
<50% of maximum allowed dose	20 (19.8)	22 (23.2)
≥50 to <80% of maximum allowed dose	33 (32.7)	22 (23.2)
≥80% of maximum allowed dose	48 (47.5)	51 (53.7)
Diabetes at baseline[b]	1 (1.0)	9 (9.3)
Prediabetic[c]	30 (29.4)	44 (45.4)

ACEi, angiotensin-converting enzyme inhibitor; ADA, American Diabetes Association; ARB, angiotensin II type I receptor blocker; BMI, body mass index; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; eGFR, estimated glomerular filtration rate; FAS, Full Analysis Set; FBG, fasting blood glucose; HbA1c, glycated hemoglobin; RAS, renin-angiotensin system; UACR, urine albumin-to-creatinine ratio; UPCR, urine protein-to-creatinine ratio.
[a]Sum of the % of maximum allowable dose for patients taking both ACEi and ARBs was summarized.
[b]Diabetes reported as either type 2 diabetes mellitus, type 1 diabetes mellitus, diabetes mellitus, or steroid diabetes.
[c]These patients had levels of FBG or HbA1c before the start of treatment that indicated a prediabetic condition, defined as an FBG ≥100 mg/dl or HbA1c ≥5.7%, according to the ADA 2020 guidelines.
Data are expressed as n (%) or median (interquartile range) unless otherwise stated.

Table 2 | Change in UPCR (g/g), UACR (g/g), and eGFR (CKD-EPI) (ml/min per 1.73 m^2) at 9 and 12 months compared with placebo (part A FAS)

Timepoints	UPCR (g/g), percentage reduction (95% CI); *P* value	UACR (g/g), percentage reduction (95% CI); *P* value	eGFR percentage change (95% CI) [corresponding difference in absolute change (ml/min per 1.73 m^2)]; *P* value
9 mo[a]	27% (13%–39%); $P = 0.0003$	31% (14%–45%); $P = 0.0005$	7% (3%–13%) [3.87]; $P = 0.0014$
12 mo[a]	48% (36%–58%); $P < 0.0001$	54% (40%–64%); $P < 0.0001$	7% (1%–13%) [3.56]; $P = 0.0106$

CI, confidence interval; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; eGFR, estimated glomerular filtration rate; FAS, Full Analysis Set; LS, least-squares; MMRM, mixed-effects model for repeated measures; UACR, urine albumin-to-creatinine ratio; UPCR, urine protein-to-creatinine ratio.
[a]Data recorded at 9 and 12 months respectively after the first dose of study treatment regardless of duration of treatment; 12-month data are prespecified but exploratory.
Treatment effects are expressed as percent change for Nefecon compared with placebo, derived from the ratio of geometric LS means at the respective timepoint. The number of patients with a valid UPCR result at 9 and 12 months in the placebo group was n = 90 and n = 66, respectively, and n = 89 and n = 59 in the Nefecon group, respectively. The 31% reduction from baseline in the Nefecon arm corresponds to a ratio of 0.69 (=1 – 31/100); likewise, the 5% reduction for placebo corresponds to a ratio of 0.95. The analysis of UPCR was performed on the log-scale; therefore, the treatment effect equals the ratio of 0.69 to 0.95 = 0.73, which corresponds to a 27% reduction in UPCR for Nefecon compared with placebo at 9 months. eGFR was compared with baseline using robust regression. The number of patients with a valid eGFR result at 9 and 12 months in the placebo group was n = 91 and n = 67, respectively, and n = 91 and n = 58 in the Nefecon group, respectively. The results from this MMRM analysis are provided as geometric mean ratios and percentage reduction from baseline. From the primary analysis on the Full Analysis Set, the estimated mean change in UPCR was −0.41 g/g and −0.07 g/g at 9 months, and from the exploratory analysis −0.68 g/g and −0.09 g/g at 12 months, for the Nefecon and placebo groups, respectively. For eGFR, results have additionally been presented in terms of the mean difference in absolute change from baseline, which were derived from the geometric LS means. The number of patients with a valid UACR result at 9 and 12 months in the placebo group was n = 91 and n = 65, respectively, and n = 90 and n = 60 in the Nefecon group, respectively.

baseline UPCR ≥1.5 g/g, the eGFR benefit was greater in the Nefecon-treated patients compared with the overall population (Figure 4); however, this benefit was not observed for patients with baseline UPCR <1.5 g/g (Supplementary Figure S1). Otherwise, eGFR results were largely consistent across predefined subgroups (Supplementary Figure S2).

Safety

Overall, the 9-month treatment regimen of Nefecon was well tolerated. Discontinuations from treatment due to TEAEs were low (9.3% and 1.0% in the Nefecon and placebo groups, respectively; Table 3). Most TEAEs were reversible and categorized as mild or moderate in severity, with 1% of events classified as severe in intensity. The most common TEAEs reported with increased frequency in the Nefecon group compared with placebo were hypertension, peripheral oedema, muscle spasms, and acne (Supplementary Table S3). The overall number of serious AEs reported with Nefecon treatment was low. Of the total of 21 reported serious AEs, 4 were judged as related to study treatment: 2 in Nefecon-treated patients and 2 in placebo recipients. Similar proportions of patients had AEs related to infection in the Nefecon and placebo groups (39.2% and 41.0%, respectively), with no severe infections leading to hospitalization in either treatment group. There were no fractures or osteonecrosis

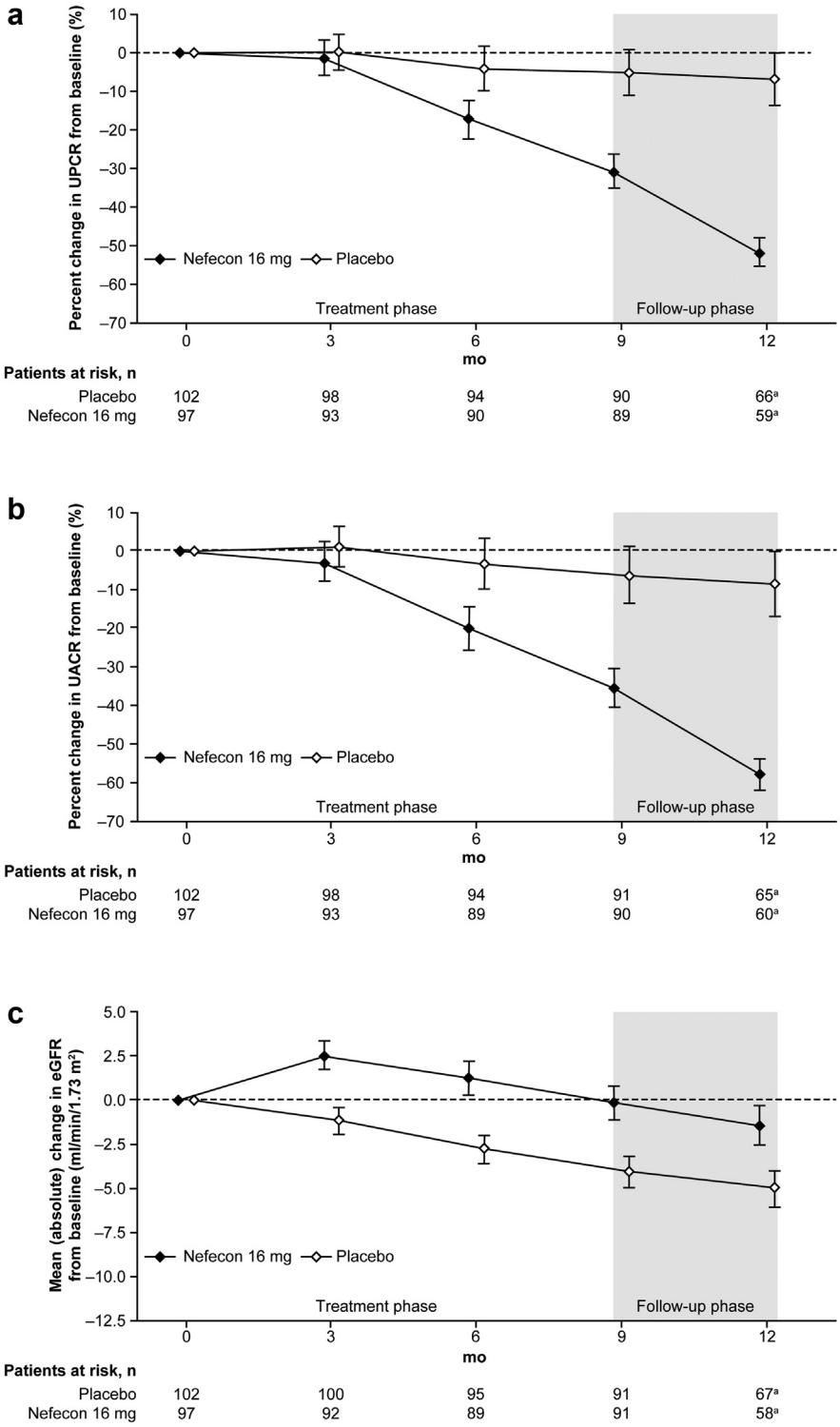

Figure 2| Percent change in (a) Urine protein-to-creatinine ratio (UPCR) (g/g), (b) urine albumin-to-creatinine ratio (UACR) (g/g), and (c) estimated glomerular filtration rate (eGFR) (Chronic Kidney Disease Epidemiology Collaboration [CKD-EPI]) (ml/min per 1.73 m^2) from baseline to 12 months (part A FAS). Baseline was defined as the geometric mean of the 2 consecutive measurements before randomization. All UPCR and UACR measurements were obtained from a 24-hour urine collection. Mean percent changes of UPCR and UACR for each visit were calculated using the ratio of geometric LS means from the model; both ratio of LS means and least-squares means ± SE were transformed back into the original scale from mixed-effects model for repeated measures estimates. Mean changes ± SE of eGFR (CKD-EPI) were estimated from robust regression analysis back-transforming log-transformed postbaseline to baseline ratios at 3, 6, 9, and 12 months. [a]Only 69 Nefecon-treated patients and 75 placebo recipients had the chance to provide 12-month data before the data cutoff.

Subgroup	n	Ratio of geometric LS means (95% CI)	Geometric LS mean			
			Nefecon 16 mg	Placebo	Ratio	(95% CI)
All patients	199		0.69	0.95	0.73	(0.61–0.87)
Age						
<45 yr	108		0.70	0.96	0.72	(0.57–0.92)
≥45–<65 yr	83		0.73	0.94	0.78	(0.59–1.02)
Sex						
Male	135		0.73	1.01	0.72	(0.58–0.90)
Female	64		0.61	0.85	0.72	(0.53–0.98)
Region						
North America	42		0.76	0.92	0.82	(0.55–1.21)
Europe	122		0.65	0.97	0.67	(0.54–0.84)
Baseline UPCR						
<1.5 g/g	126		0.72	0.93	0.78	(0.62–0.97)
≥1.5 g/g	73		0.64	0.98	0.65	(0.49–0.88)
Baseline proteinuria						
<2 g/24 h	82		0.62	0.90	0.69	(0.53–0.91)
≥2 g/24 h	117		0.74	0.98	0.76	(0.60–0.95)
Baseline eGFR						
<60 ml/min per 1.73 m²	124		0.72	1.00	0.72	(0.58–0.90)
≥60 ml/min per 1.73 m²	75		0.64	0.89	0.72	(0.54–0.96)
Dose of RASi (ACEi and/or ARB)						
<50% of MAD	42		0.57	0.91	0.62	(0.42–0.93)
≥50–<80% of MAD	55		0.70	0.99	0.71	(0.50–1.00)
≥80% of MAD	99		0.74	0.94	0.78	(0.61–1.01)

Figure 3 | Ratio of urine protein-to-creatinine ratio (UPCR) (g/g) at 9 months compared with baseline across predefined subgroups. For patients who took both an angiotensin-converting enzyme inhibitor (ACEi) and angiotensin II type I receptor blocker (ARB), the categorization was applied to the sum of the percentage of the maximum allowed dose of each renin-angiotensin system inhibitor (RASi) therapy. Patients who were not recorded as having received either an ACEi or an ARB were included in the <50% category. It was not possible to assign a category to some patients where the dose was not recorded. CI, confidence interval; LS, least-squares; MAD, maximum allowable dose.

events observed in the Nefecon group (Table 1). Glycated hemoglobin levels were generally unchanged throughout treatment (Supplementary Figure S3). The exceptions were 2 Nefecon-treated patients who fulfilled criteria for prediabetes at baseline and were later diagnosed with type 2 diabetes during the study, 1 of whom resolved after the end of treatment and 1 initiated antidiabetic treatment. No change in urine creatinine excretion was observed during the 9-month treatment period (Supplementary Figure S4), suggesting that systemic glucocorticoid exposure was limited in patients who

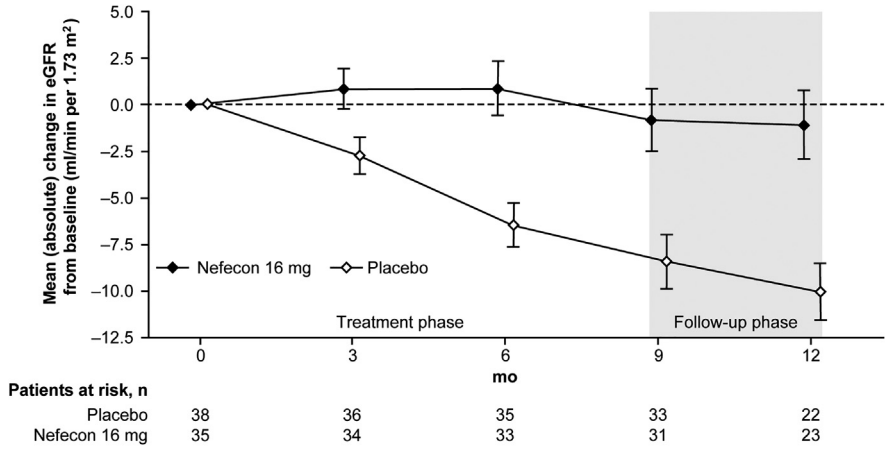

Figure 4 | Prespecified subgroup analysis: change in estimate glomerular filtration rate (eGFR) (Chronic Kidney Disease Epidemiology Collaboration [CKD-EPI]) (ml/min per 1.73 m²) from baseline in patients with baseline urine protein-to-creatinine ratio ≥1.5 g/g. Baseline was defined as the geometric mean of the 2 consecutive measurements before randomization. Mean changes ± SE of eGFR (CKD-EPI) were estimated from robust regression analysis back-transforming log-transformed postbaseline to baseline ratios at 3, 6, 9, and 12 months.

Table 3 | Overall safety data (part A, FAS)

Adverse event descriptors	Placebo (n = 100) n (%)	Events	Nefecon 16 mg/d (n = 97) n (%)	Events
All TEAEs	73 (73.0)	300	84 (86.6)	429
Maximum severity of TEAEs				
Mild	46 (46.0)	243	49 (50.5)	330
Moderate	26 (26.0)	56	31 (32.0)	95
Severe	1 (1.0)	1	4 (4.1)	4
AE of infection	41 (41.0)	–	38 (39.2)	–
Any AESI	0 (0.0)	–	2 (2.1)	–
Severe infection that required hospitalization	0 (0.0)	–	0 (0.0)	–
New onset of diabetes mellitus[a]	0 (0.0)	–	2 (2.1)	–
Confirmed fracture	0 (0.0)	–	0 (0.0)	–
New osteonecrosis	0 (0.0)	–	0 (0.0)	–
GI bleeding requiring hospitalization	0 (0.0)	–	0 (0.0)	–
Reported occurrence of cataract formation	0 (0.0)	–	0 (0.0)	–
Reported onset of glaucoma	0 (0.0)	–	0 (0.0)	–
Any treatment-emergent SAE	5 (5.0)	5	11 (11.3)	16
Any study treatment related treatment-emergent SAE	2 (2.0)	2	2 (2.1)	2
Any AE leading to death	0 (0.0)	0	0 (0.0)	0
Any TEAE leading to discontinuation of study treatment[b]	1 (1.0)	5	9 (9.3)	27

ADA, American Diabetes Association; AE, adverse event; AESI, adverse event of special interest; CRF, case report form; FAS, Full Analysis Set; FBG, fasting blood glucose; GI, gastrointestinal; HbA1c, glycated hemoglobin; IQR, interquartile range; SAE, serious adverse event; TEAE, treatment-emergent adverse event.

[a]These patients had levels of FBG or HbA1c before the start of treatment that indicated a prediabetic condition, defined as an FBG ≥100 mg/dl or HbA1c ≥5.7%, according to the ADA 2020 guidelines.

[b]Note that for 1 Nefecon-treated patient with a TEAE leading to discontinuation of study treatment, this was not their primary reason for withdrawal recorded on the withdrawal CRF that is described in Figure 1.

AEs were coded using the Medical Dictionary for Regulatory Activities (Version 22.0). AEs were considered to have been reported during the "on-treatment" period if the start date was after the first dose of study treatment until 14 days after completion of the tapering period. AEs that started >14 days after the last dose of study treatment were attributed to follow-up (not reported herein). TEAEs were defined as AEs that occurred for the first time after dosing with study drug or existed before but worsened in severity or relationship to study drug after dosing. AESIs were defined as severe infections requiring hospitalization, new onset of diabetes mellitus, confirmed fracture, new osteonecrosis, gastrointestinal bleeding requiring hospitalization, reported occurrence of cataract formation, and reported onset of glaucoma.

received Nefecon. There were no other clinically relevant findings from clinical chemistry or hematology laboratory assessments (Supplementary Table S4).

DISCUSSION

NefIgArd is the first pivotal phase 3 randomized controlled trial to confirm the efficacy of an immunomodulatory medication in significantly reducing proteinuria and slowing the decline in eGFR in patients with primary IgAN already receiving optimized and stable RAS blockade. Patients treated with Nefecon experienced a significant 27% reduction in UPCR levels compared with placebo, with results highly consistent among prespecified subgroups including patients stratified by baseline UPCR, 24-hour proteinuria, and eGFR. For IgAN, reducing the risk of GFR loss has been tied to the relative (as opposed to the absolute) reduction of UPCR.[8,16–19] Consistently, this 9-month Nefecon treatment regimen also attenuated the decline in eGFR, which for the placebo group was on average 4.04 ml/min per 1.73 m^2 after 9 months and consistent with previous reports.[4,19,25] Treatment with Nefecon led to a virtually unchanged eGFR and a treatment benefit (eGFR difference between Nefecon and placebo) of 3.87 ml/min per 1.73 m^2 at 9 months ($P = 0.0014$). The treatment effect replicated results observed in the phase 2b NEFIGAN trial, which showed a 29% ($P = 0.0092$) UPCR reduction compared with placebo and a similar eGFR benefit ($P = 0.0064$) after 9 months of treatment with Nefecon 16 mg daily; UPCR results become more pronounced, and eGFR results were maintained, during follow-up at 12 months.[16]

The design of the NefIgArd trial represents a novel approach to study new treatments for IgAN that originated from a collaboration between the US Food and Drug Administration and the American Society of Nephrology's Kidney Health Initiative. The primary endpoint of part A, proteinuria reduction, is an accepted reasonably likely surrogate for long-term clinical outcomes in IgAN and is the basis of the US Food and Drug Administration approval, granted to Nefecon under an accelerated pathway.[20] This regulatory pathway is based on the expectation that early benefits in UPCR levels are likely to translate into a slower eGFR decline over time, and this will be fully assessed in part B of NefIgArd for full US Food and Drug Administration approval of Nefecon. Indeed, published evidence in IgAN has shown that there is a strong association between treatment effects on UPCR and subsequent changes in the rate of eGFR decline and the risk of development of kidney failure.[8,17,19,25,26] Based on 2 meta-analyses,[17,19] the magnitude of the treatment effects observed on UPCR and eGFR at 1 year in part A of the NefIgArd trial is highly likely to predict, with >97.5% confidence, clinical benefit on long-term preservation of kidney function. Supporting this prediction, a separate meta-analysis[18] suggested that the magnitude of proteinuria reduction observed in NefIgArd part A should, with high confidence, lead to a clinically meaningful eGFR benefit in part B.

Importantly, the clinical benefits of Nefecon were achieved safely. The 9-month treatment regimen of Nefecon was well tolerated, with low rates of AEs that were generally of mild or moderate severity and reversible. Glucocorticoid-related AEs were as expected for an oral budesonide treatment and without the serious side effects associated with systemic glucocorticoids, which can be long-lasting and life-altering.[27,28] Prolonged administration of Nefecon (beyond 9 months) was not tested here. Should longer exposures be considered in the future, continued vigilance for glucocorticoid side effects should be maintained. In addition, Nefecon over a 9-month treatment period did not increase the risk of infection, and there were no severe infections leading to hospitalization. This is in marked contrast to results of recent studies using systemic glucocorticoids (STOP-IgAN and TESTING) for IgAN.[27,29,30] Hospitalizations and mortality due to severe infections were still seen in the reduced dose arm of the TESTING study, although less commonly with the reduced dose of 0.4 mg/kg per day methylprednisolone and use of

prophylactic antibiotics compared with the full dose.[30] This lower dose of systemic glucocorticoid (equivalent to prednisone 35–40 mg/d for a 70 kg patient) has, however, still been associated with significant long-term safety concerns.[31–33]

Consistent with this good safety profile, the NefIgArd trial had low rates of missing data and few discontinuations. The number of patients with data recorded at 12 months was lower than at 9 months because not all patients in the part A FAS had reached the 12-month time point by the data cutoff, not due to study discontinuations. Sensitivity analyses to assess the impact of missing data, rescue medication, and outliers on the primary efficacy results were highly consistent with the primary analysis.

The acute increase in eGFR seen in the Nefecon-treated patients at 3 months was unexpected. This observation remains to be explained. Often such acute eGFR changes are attributed to hemodynamic effects of a medication. We suggest that this is unlikely because a purely hemodynamic effect may be expected to also increase proteinuria acutely, which was not seen. In addition, a sarcopenic effect is unlikely because no change in urine creatinine excretion was observed during the 9-month treatment period (Supplementary Figure S3).

The acute effect on eGFR and the small eGFR decline in the placebo group limited the opportunity to demonstrate a treatment effect on eGFR change at 9 months in patients with low baseline UPCR (<1.5 g/g). However, given the pronounced UPCR reduction in all patients, highly consistent in all subgroups and independent of baseline UPCR and baseline eGFR, we speculate that those with low baseline UPCR may also experience a treatment benefit on eGFR with longer follow-up. This will be evaluated at 2 years in part B.

By chance, more patients with diabetes and prediabetes were randomized to treatment with Nefecon. In addition, several patients in both treatment arms were overweight or obese. A contribution of diabetic or obesity-related kidney damage to the proteinuria of these patients cannot be absolutely excluded without concurrent biopsies. However, as there is no expectation that Nefecon can impact diabetic or obesity-related kidney disease, the finding that Nefecon reduced proteinuria despite these potentially confounding factors suggests that the effects of Nefecon on controlling proteinuria are robust.

A limitation of NefIgArd is that it includes mainly Caucasian patients and, although the disease mechanism and Nefecon efficacy are expected to be similar across different ethnic origins, these positive results will need to be confirmed in diverse patient populations. Contemporaneous biopsies were not required for entry into the study, preventing association of histologic features with indications for and/or response to treatment. Another limitation of this study is that the postulated location of, and mechanism of action of Nefecon, which distinguishes it from other formulations of budesonide, albeit appealing, is still speculative at this time.[2] Understanding how Nefecon, once deployed at the gut-associated lymphoid system level, modulates the different components of the pathogenic cascade in IgAN may allow identification of novel biomarkers to better inform the future use of Nefecon in clinical practice. Such mechanistic studies are currently ongoing, and we look forward to communicating their results in the near future.

In conclusion, the NefIgArd trial has shown that 9 months of treatment with Nefecon, in addition to optimized and stable RAS blockade, was well tolerated and resulted in clinically important improvements in UPCR, UACR, and eGFR compared with optimized supportive care alone. This is the first phase 3 randomized controlled trial to show treatment benefits of this magnitude with a drug that we postulate may target the underlying pathophysiology of IgAN. NefIgArd is the largest commercially sponsored study ever completed in IgAN and supports Nefecon as the first disease-modifying therapy approved for patients with primary IgAN at risk of kidney failure.

APPENDIX

The authors would like to thank all the investigators, trial teams, and patients for their participation in the trial. Participating Investigators are listed below.

Members of the NefIgArd Trial Investigators

Argentina. Guillermo Fragale, Hospital Universitario Austral, Pilar; Alejandra Karl, Hospital Universitario Austral, Pilar; Patricia Losisolo, Hospital Universitario Austral, Pilar; Hernán Trimarchi, Hospital Britanico de Buenos Aires, Capital Federal; Ivan Gonzalez Hoyos, Hospital Britanico de Buenos Aires, Capital Federal; Mauro Guillermo Lampo, Hospital Britanico de Buenos Aires, Capital Federal; Matias Monkowski, Hospital Britanico de Buenos Aires, Capital Federal; Jorge De La Fuente, Hospital Privado - Centro Medico de Cordoba, Cordoba; Magdalena Alvarez, Hospital Privado - Centro Medico de Cordoba, Cordoba; Daniela Stoppa, Hospital Privado - Centro Medico de Cordoba, Cordoba; Carlos Chiurchiu, Hospital Privado - Centro Medico de Cordoba, Cordoba; Pablo Antonio Novoa, Sanatorio Allende, Cordoba; Marcelo Orias, Sanatorio Allende, Cordoba; Maria Belen Barron, Sanatorio Allende, Cordoba; Ana Giotto, Sanatorio Allende, Cordoba; Mariano Arriola, Clinica de Nephrologia Urology, Sante Fe; Evelin Cassini, Enfermedades Cardiovasculares, Santa Fe; Rafael Maldonado, Clinica Priv Velez Sarsfield, Cordoba; and Maria Paula Dionisi, Clinica Priv Velez Sarsfield, Cordoba.

Australia. Jessica Ryan, Monash Medical Centre, Clayton Victoria; Nigel Toussaint, Melbourne Health – Royal Melbourne Hospital, Parkville Victoria; Grant Luxton, Prince of Wales Hospital, Randwick NSW; Chen Au Peh, Royal Adelaide Hospital, Adelaide SA; Vicki Levidiotis, Western Health, St. Albans Victoria; Ross Francis, Princess Alexandra Hospital, Wooloongabba QLD; and Richard Phoon, Westmead Hospital, Westmead NSW.

Belarus. Elena Fedosiuk, Brest Regional Clinical Hospital, Brest; Dmitry Toropilov, 4-th N.E. Savchenko City Clinical Hospital, Minsk; Ruslan Yakubtsevich, Grodno University Hospital, Grodno; and Elena Mikhailova, Gomel Regional Clinical Hospital, Gomel.

Belgium. Christophe Bovy, Centre Hospitalier Universitaire (CHU) de Liege, Liege; Nathalie Demoulin, Cliniques Universitaires Saint-Luc, Brussels; Jean-Michel Hougardy, Universite Libre de Bruxelles (ULB) - Hopital Erasme, Bruxelles; Bart Maes, AZ Delta, Roeselare; and Marijn Speeckaert, University Hospital Gent, Gent.

Canada. Louis-Philippe Laurin, Hospital Maisonneuve-Rosemont, Montreal; Sean Barbour, Vancouver Coastal Health Authority - Diamond Health Centre, Vancouver; David Philibert, CHUQ - L'Hotel Dieu de Québec, Quebec City; Melanie Masse, Centre Hospitalier Universitaire de Sherbrooke (CHUS), Sherbrooke; Michelle Hladunewich, Sunnybrook Health Sciences Centre (Odette Cancer Center), Toronto; Heather Reich, Toronto General Hospital, Toronto; Serge Cournoyer, CISSS de la Monteregie-Centre – Hopital Charles LeMoyne, Greenfield Park; Karthik Tennankore, Queen Elizabeth II Health Science Center, Haliafax; and Sean Barbour, Vancouver General Hospital - Kidney Clinic, Vancouver.

China. Jicheng Lv, Peking University First Hospital, Beijing; Zhangsuo Liu, The First Affiliated Hospital of Zhengzhou University, Zhengzhou; Caili Wang,

The First Affiliated Hospital of Baotou Medical College, Baotou; Shaomei Li, The Second Hospital of Hebei Medical University, Shijiazhuang; Qun Luo, Hwa Mei Hospital, University of Chinese Academy of Science, Ningbo; Zhaohui Ni, Renji Hospital, Shanghai Jiaotong University School of Medicine, Shanghai; Tiekun Yan, General Hospital of Tianjin Medical University, Tianjin; Ping Fu, West China Hospital, Sichuan University, Chengdu, Sichuan Province; Hong Cheng, Beijing Anzhen Hospital, Capital Medical University, Beijing; Bicheng Liu, Zhongda Hospital Southeast University, Jiangsu Province; Wanhong Lu, First Affiliated Hospital of Medical college of Xi'an Jiaotong University, Xian; Jianqin Wang, Lan Zhou University Second Hospital, Gansu Province; Qinkai Chen, The First Affiliated Hospital of Nanchang University, Nanchang; DeGuang Wang, The Second Hospital of Anhui Medical University, Hefei; Zuying Xiong, Peking University Shenzhen Hospital, Guangdong; Menghua Chen, General Hospital of Ningxia Medical University, Ningxia; Yan Xu, The Affiliated Hospital of Qingdao University, Qingdao; Jiali Wei, Hainan General Hospital, Haikou; Pearl Pai, The University of Hong Kong-Shenzhen Hospital, Guangdong Province; and Lianhua Chen, The Affiliated Huaian No.1 People's Hospital of Nanjing Medical University, Huaian.

Czech Republic. Jitka Rehorova, Fakultni nemocnice Brno, Brno; Dita Maixnerova, Vseobecna fakultni nemocnice v Praze, Praha 2; Roman Safranek, Fakultni nemocnice Hradec Kralove, Hradec Kralove; Ivan Rychlik, Fakultni nemocnice Kralovske Vinohrady, Praha 10; and Miroslav Hruby, Fakultni nemocnice Olomouc, Olomouc.

Finland. Satu Makela, Tampere University Hospital, Tampere; Kati Vaaraniemi, StudyCor Oy, Jyväskylä; and Fernanda Ortiz, Helsinki University Central Hospital, Helsinki.

France. Eric Alamartine, CHU St Etienne - Hopital Nord, Saint-Priest-En-Jarez; Maite Daroux, Centre Hospitalier Boulogne sur Mer, Boulogne sur Mer Cedex (France); Claire Cartery, Centre Hospitalier de Valenciennes, Valenciennes Cedex; Francois Vrtovsnik, Hopital Bichat - Claude Bernard - AP-HP, Paris Cedex 18; and Jean-Emmanuel Serre, CHU de Montpellier – Hôpital Lapeyronie, Montpellier Cedex 5.

Germany. Eleni Stamellou, Universitaetsklinikum Aachen, AoeR, Aachen; Volker Vielhauer, University Clinic Munich, LMU - Inner City Medical Polyclinic, Munich; Claudia Sommerer, Universitaetsklinikum Heidelberg, Heidelberg; Christian Hugo, Universitaetsklinikum Carl Gustav Carus Dresden, Dresden; Klemens Budde, Charite - Universitaetsmedizin Berlin, Berlin; Britta Otte, Universitatsklinikum Munster Med.Klinik u.Poliklinik D, Münster; and Martin Nitschke, Universitatklinik Schleswig-Holstein – Campus Lubek, Lubeck.

Greece. Evangelia Ntounousi, University General Hospital of Ioannina, Ioannina; Ioannis Boletis, General Hospital of Athens – Laiko, Athens; Aikaterini Papagianni, Hippokration General Hospital of Thessaloniki, Thessaloniki; Dimitrios Goumenos, University General Hospital of Patras, Patras; Konstantinos Stylianou, University General Hospital of Heraklion, Heraklion; and Synodi Zermpala, General Hospital of Nikaia Ag. Panteleimon, Nikaia.

Italy. Ciro Esposito, Istituti Clinici Scientifici Maugeri-IRCCS Pavia, Pavia; Mario Gennaro Cozzolino, ASST Santi Paolo e Carlo-Presidio Ospedale San Carlo, Milano; Sara Maria Viganò, ASST di Lecco-Presidio Ospedaliero "Alessandro Manzoni", Lecco; and Loreto Gesualdo, Azienda Ospedaliera Universitaria Consorziale - Policlinico Bari, Bari.

Poland. Michal Nowicki, Samodzielny Publiczny Zaklad Opieki Zdrowotnej Centralny Szpital Kliniczny, Uniwersytetu Medycznego w Lodzi, Lodz; Tomasz Stompor, Wojewodzki Szpital Specjalistyczny w Olsztynie, Oddzial Kliniczny Nefrologiczny, Hipertensjologii i Chorob Wewnetrznych, Olsztyn; Karolina Kedzierska-Kapuza, SONOMED Sp. z o.o., Szczecin; and Ilona Kurnatowska, Samodzielny Publiczny ZOZ Uniwersytecki Szpital Kliniczny Nr 1 im. Norberta Barlickiego Uniwersytetu Medycznego w Lodzi, Oddzial Nefrologii, Lodz.

South Korea. Sung Gyun Kim, Hallym University Sacred Heart Hospital, Gyeonggi- do; Yong-Lim Kim, Kyungpook National University Hospital, Daegu; Ki-Ryang Na, Chungnam National University Hospital, Daejeon; Dong Ki Kim, Seoul National University Hospital, Seoul; and Su-Hyun Kim, Chung-Ang University Hospital, Seoul.

Spain. Luis Quintana Porras, Hospital Clinic Barcelona, Barcelona; Eva Rodriguez Garcia, Hospital del Mar, Barcelona; Irene Agraz Pamplona, Hospital Universitario Vall d'Hebron, Barcelona; Alfons Segarra, Hospital Universitari Arnau de Vilanova, Lleida; and Marian Goicoechea, Hospital General Universitario Gregorio Maranon, Madrid.

Sweden. Bengt Fellstrom, Uppsala University Hospital, Uppsala; Sigrid Lundberg, Danderyd Hospital, Stockholm; Peter Hemmingsson, Karolinska University Hospital Huddinge, Stockholm; Gregor Guron, Sahlgrenska University Hospital, Goteborg; and Anna Sandell, Linköping University Hospital, Linköping.

Taiwan. Cheng-Hsu Chen, Taichung Veterans General Hospital, Taichung.

Turkey. Bulent Tokgoz, Erciyes University Faculty of Medicine, Kayseri; Soner Duman, Ege University Medical Faculty Department of Internal Disease, Division of Nephorology, Izmir; Mehmet Riza Altiparmak, Istanbul University Cerrahpasa Medical Faculty, Istanbul; and Metin Ergul, Kocaeli University Medical School - Internal Medicine – Nephrology, Kocaeli.

United Kingdom. Peter Maxwell, Belfast Health and Social Care Trust, Belfast; Patrick Mark, Queen Elizabeth University Hospital – Glasgow, Glasgow; Kieran McCafferty, The Royal London Hospital, London; Arif Khwaja, Northern General Hospital, Sheffield; Chee Kay Cheung, Leicester General Hospital, Leicester; Matthew Hall, Nottingham City Hospital, Nottingham; Albert Power, Southmead Hospital, Bristol; Durga Kanigicherla, University of Manchester, Manchester Royal Infirmary, Manchester; Richard Baker, Leeds Teaching Hospitals NHS Trust, Leeds; and Jim Moriarty, Gloucestershire Royal Hospital, Gloucester.

United States. Amr Mohamed, University of Kentucky Medical Center, Lexington; Joseph Aiello, Mountain Kidney & Hypertension Associates, P.A., Asheville; Pietro Canetta, Columbia University Medical Center - Division of Nephrology, New York; Isabelle Ayoub, The Ohio State University (OSU) Wexner Medical Center, Columbus; Derrick Robinson, Eastern Nephrology Associates, Wilmington; Surabhi Thakar, University of Minnesota, Minneapolis; Amy Mottl, University of North Carolina (UNC), Chapel Hill; Isaac Sachmechi, Queens Hospital Center, Jamaica; Bernard Fischbach, Renal Disease Research Institute, Forth Worth; Harmeet Singh, Western Nephrology and Metabolic Bone Disease, PC – Westminster, Arvada; Jeffrey Mulhern, Kidney Care and Transplant Services of New England, PC, Springfield; Fahmeedah Kamal, Stanford University Medical Center, Palo Alto; Douglas Linfert, Nephrology Associates, P.C., Nashville; Dana Rizk, University of Alabama at Birmingham, Birmingham; Shikha Wadhwani, Northwestern University The Feinberg School of Medicine, Chicago; Menaka Sarav, NorthShore University Health System, Evanston; Kirk Campbell, Icahn School of Medicine at Mount Sinai, New York; Gaia Coppock, University of Pennsylvania, Philadelphia; Randy Luciano, Yale University School of Medicine, New Haven; John Sedor, Cleveland Clinic, Cleveland; Rupali Avasare, Oregon Health & Science University (OHSU), Portland; Richard Solomon, University of Vermont, Burlington; and Wai Lang Lau, University of Florida (UF) – Gainesville, Gainesville.

DISCLOSURE

JB is a consultant to Calliditas and Chair of the NefIgArd Study Steering Committee, and reports grants and personal fees from Calliditas, outside the submitted work. RL reports receiving personal fees and grants from Alexion, Aurinia, Calliditas, Omeros, Pfizer, Roche, Travere, and Vera, and being an advisory board member for Akahest and Equillium. JK served as Chief Medical Officer for Calliditas until November 30, 2019. AS reports personal fees from Calliditas and has acted as a consultant for Athenex, Biosight, Carrick, Cogent, Cullinan, Deciphera, Dizal, GSK, Guard, Intellia, IO Biotech, Iteos, Jazz, Jounce, Keros, Mina, PsiOxus, Repare, RhoVac, and Urogen in therapeutic areas other than kidney disease. DC reports grants from Alnylam Pharmaceuticals and personal fees from Alexion, outside the submitted work; he is also data monitoring committee chair/member for ChemoCentryx, Novartis, and Vera Therapeutics, as well as a member for the clinical endpoint committee of Aurinia. JF reports personal fees from Calliditas, Chinook, Idorsia, Novartis, Omeros, Travere, and Visterra during the conduct of the study, as well as from Amgen, AstraZeneca, Astellas, Boehringer Ingelheim, Fresenius, and Vifor, outside the submitted work. VT reports personal fees from Calliditas during the conduct of the study, as well as personal fees from Novartis, Omeros, and Travere, outside the submitted work. HT reports personal fees from Calliditas during the conduct of this study, as well as Chinook, Novartis, and Omeros, outside the submitted work. AP reports grants from Calliditas during the conduct of the study, and personal fees from Alexion, AstraZeneca, and Vifor Pharma, outside the submitted work. BHR reports personal fees from AstraZeneca, Aurinia, Bristol Myers Squibb, Calliditas, ChemoCentryx, EMD Serono, Janssen, Novartis, Morphosys, Omeros, and Retrophin; nonfinancial support from Lupus Foundation of America; and grants from the National Institutes of Health (NIH), outside the submitted work. HZ reports personal fees from Calliditas during the conduct of the study, as well as personal fees from Chinook, Novartis, and Omeros, outside the submitted work. The other author declared no competing interests.

DATA STATEMENT

The data underlying this article, the study protocol, and statistical analysis plan will be shared with researchers on reasonable request to

the corresponding author. Data will be shared through a secure online platform after signing a data access agreement. Data will be available at the time of publication and for a minimum of 5 years from the end of the trial.

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This trial was sponsored and funded by Calliditas Therapeutics AB. A trial steering committee including participating international investigators and representatives of the sponsor oversaw the conduct of the trial in conformation with the approval protocol. All participants provided written informed consent before enrolment. An independent Data and Safety Monitoring Board is in place to monitor the overall conduct of the study and safety data and reviewed the part A analysis. All authors were involved in the development and approval of the manuscript, assume responsibility for the completeness and accuracy of the data, and vouch for the fidelity of the trial to the study protocol. The first author drafted the first version of the manuscript with assistance from 2 medical writers, Fiona Wilson and Chiara Triulzi, funded by the sponsor. All authors submitted revisions and jointly made the decision to submit the manuscript for publication. The sponsor oversaw all study processes. JK is an employee of the sponsor, who contributed to the study design, provided study oversight, participated in data analysis, data interpretation, and writing of the report. Both placebo and Nefecon treatments were provided by the sponsor. Following database lock and unblinding, the sponsor and all investigators had access to analyses performed on trial data. BHR had final responsibility for the decision to submit for publication.

AUTHOR CONTRIBUTIONS

JB, RL, BHR, VT, HT, JF, DC, JK, and AS conceived and designed the trial and protocol. JB, RL, VT, HT, JF, HZ, and NE were the principal investigators. JB, RL, BHR, VT, HT, JF, DC, JK, and AS contributed to the trial design and protocol. JB, RL, BHR, VT, HT, JF, HZ, NE, and AP were study site investigators and contributed to implementation of the study and data collection. JK was responsible for execution of the study. AS was responsible for statistical analyses, performed by MedPace (Cincinnati, Ohio, USA). JB, BHR, JK, and AS prepared the first draft of the manuscript. All authors had access to all of the data from the study, and AS and JK verified the raw data. All authors contributed to data analysis, interpretation of study results, and preparation of the report, critically reviewed and edited the manuscript, and approved the final version for submission.

SUPPLEMENTARY MATERIAL

Supplementary File (Word)

Supplementary Methods.

Figure S1. Change in estimated glomerular filtration rate (eGFR) (Chronic Kidney Disease Epidemiology Collaboration [CKD-EPI]) (ml/min per 1.73 m^2) from baseline in patients with baseline urine protein-to-creatinine ratio (UPCR) <1.5 g/g.

Figure S2. Ratio of estimated glomerular filtration rate (eGFR) (Chronic Kidney Disease Epidemiology Collaboration [CKD-EPI]) (ml/min per 1.73 m^2) at 9 months compared with baseline using robust regression across predefined subgroups.

Figure S3. Glycated hemoglobin (HbA1c) shift plots at 3, 6, 9, and 12 months compared with baseline (Safety Analysis Set).

Figure S4. Urine creatinine excretion (mmol/24 h) (part A Full Analysis Set [FAS]).

Table S1. Participating countries (part A Full Analysis Set [FAS]).

Table S2. Sensitivity analyses for the ratio of urine protein-to-creatinine ratio (UPCR) (g/g) at 9 months compared with baseline.

Table S3. Most common adverse events (AEs) from first day of study treatment until 14 days after completion of the tapering period (part A Full Analysis Set [FAS] and Safety Analysis Set).

Table S4. Other clinically relevant findings (Safety Analysis Set).

Supplementary References.

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