30 May 2024
EMA/291571/2024
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Kinpeygo

International non-proprietary name: Budesonide

Procedure No. EMEA/H/C/005653/II/008

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

ACEI	Angiotensin converting enzyme inhibitor
ADA	American Diabetes Association
AE	Adverse event
AESI	Adverse event of special interest
API	Active pharmaceutical ingredient
ARB	Angiotensin II type I receptor blockers
ATC	Anatomical Therapeutic Chemical (classification)
AUC	Area under the curve
AUC (0-24)	Area under the plasma concentration-time curve from time 0 to 24 hours
BA	Bioavailability
BAFF	B-cell activating factor of the tumour necrotizing factor (TNF) family
BCMA	B-cell maturation antigen
BCRP	Breast cancer resistance protein
BE	Bioequivalence
BMI	Body mass index
CI	Confidence interval
CKD	Chronic kidney disease
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CMA	Conditional Marketing Authorisation
Cmax	Maximum plasma concentration
CSR	Clinical Study Report
CV	Coefficient of variation
CYP	Cytochrome P450
DCO	Data Cut-Off
DSMB	Data and Safety Monitoring Board
DVT	Deep vein thrombosis
eGFR	Estimated glomerular filtration rate
EMA	European Medicines Agency
EOP2	End of Phase 2
ESRD	End-stage renal disease
EU	European Union
FAS	Full Analysis Set
FBG	Fasting blood glucose
FDA	Food and Drug Administration
FDCA	Federal Food, Drug, and Cosmetic Act
GALT	Gut-associated lymphoid system
GCP	Good clinical practice
GCS	Glucocorticosteroid
Gd-IgA1	Galactose-deficient IgA1
GFR	Glomerular filtration rate
GI	Gastrointestinal
HbA1c	Haemoglobin A1c
HMG-CoA	3-hydroxy-3-methylglutaryl-coenzyme A
HPA	Hypothalamic-pituitary-adrenal
HR	Hazard ratio
IC50	Half maximal inhibitory concentration
ICH	International Council for Harmonisation

IEC	Independent ethics committee
I-FABP	Intestinal-type fatty acid-binding protein
IgA	Immunoglobulin A
IgAN	Immunoglobulin A nephropathy
IGANF	IgAN Foundation of America
IPCW	Inverse Probability of Censoring Weights
IRB	Institutional review boards
IVIVC	*In vitro–in vivo* Correlation
KDIGO	Kidney Disease Improving Global Outcomes
LGH	Leicester General Hospital
LSmean(s)	Least squares mean(s)
MAA	Marketing Authorisation Application
MAH	Marketing Authorisation Holder
MMRM	Mixed model repeated measures
MRD	Maximum Recommended Dose
MTD	Maximum Tolerated Dose
NKF	National Kidney Foundation
NORD	National Organization for Rare Disorders
OAT	Organic anion transporter
OATP	Organic anion transporter polypeptide
OCT	Organic cation transporter
ODD	Orphan Drug Designation
PD	Pharmacodynamic(s)
P-gp	P-glycoprotein
PK	Pharmacokinetic(s)
PPI	Proton pump inhibitor
PREA	Pediatric Research Equity Act
PT	MedDRA Preferred Term
RAS	Renin-angiotensin system
REMS	Risk Evaluation and Mitigation Strategy
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SAWP	Scientific Advice Working Party
SCE	Summary of Clinical Efficacy
SCS	Summary of Clinical Safety
SGLT2	Sodium-glucose co-transporter-2
SPC	Summary of Product Characteristics
TACI	T cell activator and calcium modulating ligand interactor
TEAE	Treatment-emergent adverse event
TESAE	Treatment-emergent serious adverse event
Tlag	Time prior to first measurable (non-zero) plasma concentration
Tmax	Time to maximum plasma concentration
T1/2	Elimination half-life
UACR	Urine albumin creatinine ratio
UPCR	Urine protein creatinine ratio
US	United States of America
USPI	US Prescribing Information
UK	United Kingdom
VTE	Venous thromboembolism

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, STADA Arzneimittel AG submitted to the European Medicines Agency on 28 September 2023 an application for a variation.

The following variation was requested:

Variation requested		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of indication to slow kidney function decline in adults with primary immunoglobulin A (IgA) nephropathy (IgAN) for KINPEYGO, based on Part B of study NefIgArd (Nef-301), listed as the final specific obligation in the Annex II; this is a Phase 3, randomised, double-blind, placebo-controlled, multicenter study to evaluate the efficacy, safety, and tolerability of oral Nefecon (the product name for Kinpeygo) compared to matching placebo in patients with primary IgAN on a background of optimised RAS inhibitor therapy. As a consequence, sections 4.1, 4.2, 4.8 and 5.1 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 1.1 of the RMP has also been submitted.

The variation requested amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

This application was submitted as a fulfilment of the final condition imposed by the CHMP in frame of a conditional marketing authorisation at the time of the initial approval:

In order to confirm the efficacy and safety of budesonide for the treatment of primary immunoglobulin A nephropathy (IgAN) and more particularly to assess the clinical consequences of proteinuria reduction, as measured by eGFR, the MAH will submit the results (including also a composite clinical outcome and sensitivity analysis according to background therapy) of Part B of study Nef-301, a Phase 3, randomised, double-blind, multicentre study comparing budesonide to placebo in patients with primary IgAN on a background of optimised RAS inhibitor therapy.

Information relating to orphan designation

Kinpeygo, was designated as an orphan medicinal product EU/3/16/1778 on 18 November 2016. Kinpeygo was designated as an orphan medicinal product in the following indication: Treatment of primary IgA nephropathy.

Following the CHMP positive opinion on this marketing authorisation, the Committee for Orphan Medicinal Products (COMP) will review the designation of Kinpeygo as an orphan medicinal product in the approved indication.

Information on paediatric requirements

At the time of submission of the application, the PIP P/0049/2020 covering the extension of indication was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the application included a critical report addressing the possible similarity with authorised orphan medicinal products.

Protocol assistance

The MAH did not seek Protocol Assistance at the CHMP for this extension of indication application.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Christian Gartner

Timetable	Actual dates
Submission date	28 September 2023
Start of procedure:	28 October 2023
CHMP Rapporteur Assessment Report	21 December 2023
PRAC Rapporteur Assessment Report	3 January 2024
PRAC members comments	4 January 2024
Updated PRAC Rapporteur Assessment Report	5 January 2024
PRAC Outcome	11 January 2024
CHMP members comments	15 January 2024
Updated CHMP Rapporteur(s) (Joint) Assessment Report	18 January 2024
Request for supplementary information (RSI)	25 January 2024
CHMP Rapporteur Assessment Report	20 March 2024
PRAC Rapporteur Assessment Report	2 April 2024
PRAC members comments	3 April 2024
PRAC Outcome	11 April 2024
CHMP members comments	15 April 2024
Updated CHMP Rapporteur Assessment Report	18 April 2024
Request for supplementary information (RSI)	25 April 2024
CHMP Rapporteur Assessment Report	15 May 2024
PRAC Rapporteur Assessment Report	15 May 2024
PRAC members comments	21 May 2024
CHMP members comments	21 May 2024
Updated CHMP Rapporteur(s) (Joint) Assessment Report	23 May 2024
Opinion	30 May 2024

2. Scientific discussion

2.1. Introduction

Kinpeygo was developed under the project name Nefecon by Calliditas Therapeutics AB for the treatment of primary immunoglobulin A (IgA) nephropathy (IgAN). Thus, "Nefecon" is used synonymously in the report for the current name "Kinpeygo".

IgAN is rare, and Kinpeygo was designated as an 'orphan medicine' on 18 November 2016. Kinpeygo received a Conditional Marketing Authorisation (CMA) valid throughout the European Union (EU) on 15 July 2022 (EMEA/H/C/005653) for the treatment of primary IgAN in adults at risk of rapid disease progression with a urine protein-to creatinine ratio (UPCR) ≥1.5 g/gram. In September 2022, the CMA of Kinpeygo was transferred from the Marketing Authorisation Holder (MAH) Calliditas Therapeutics AB to the new MAH STADA Arzneimittel AG.

Kinpeygo is considered a hybrid medicinal product as defined in Article 10(3) of Directive 2001/83/EC; the reference medicine is Entocort which has been authorised in the EU since 2 April 1992.

The CMA of Kinpeygo was based on the Part A analysis of the pivotal Phase 3 study Nef-301, a randomised, double-blind, placebo-controlled study to evaluate the efficacy, safety and tolerability of Kinpeygo (16 mg) compared to matching placebo in patients with primary IgAN on a background of optimised renin-angiotensin system (RAS) inhibitor therapy. Nef-301 Part A provided evidence of effectiveness in reducing proteinuria in patients with IgAN who are at high risk of disease progression.

Given the limited Part A data on the efficacy and safety of the product, the CHMP suggested that the indicated population should be restricted to patients with UPCR ≥ 1.5 g/gram until further data are available for a broader patient population. Hence, the approved indication in the initial CMA was:

> *"Kinpeygo is indicated for the treatment of primary immunoglobulin A (IgA) nephropathy (IgAN) in adults at risk of rapid disease progression with a urine protein-to-creatinine ratio (UPCR) ≥1.5 g/gram."*

The CMA of Kinpeygo included a specific obligation to complete post-authorisation measures pursuant to Article 14a of Regulation (EC) No 726/2004: *In order to confirm the efficacy and safety of budesonide for the treatment of IgAN and more particularly to assess the clinical consequences of proteinuria reduction, as measured by estimated glomerular filtration rate (eGFR), the MAH shall submit the results (including also a composite clinical outcome and sensitivity analysis according to background dual RAS inhibitor therapy) of Part B of study Nef-301, which consists of a 15-month observational follow-up period after the 9-month treatment period had ended.*

In Part B of the pivotal trial, the area under the curve (AUC)-based evaluation (calculated as a time-weighted average) of eGFR over 2 years has been selected as a primary efficacy endpoint supplemented by a 2-year eGFR slope analysis. The imposed post-authorisation measures for verifying the clinical benefit of Kinpeygo for a full approval have since been completed and pertinent data is included in this application. Based on the final analysis of the Phase 3 Nef-301 trial, the MAH initially proposed the following revised indication in the first assessment round:

> "*Kinpeygo is indicated to slow kidney function decline in adults with primary immunoglobulin A nephropathy (IgAN)*."

No change was proposed to the approved dosage form, route of administration, or dosing regimen.

Following the assessment, the indication proposed by the MAH was deemed unacceptable. Extending the indication to the entire IgAN population was not supported by the available data, and references to study endpoints such as "slow kidney function decline" should generally not be included in section 4.1.

Following CHMP's assessment and consideration of the data from the Nef-301 study, the indication approvable is:

> *"Kinpeygo is indicated for the treatment of adults with primary immunoglobulin A nephropathy (IgAN) with a urine protein excretion ≥1.0 g/day (or urine protein-to-creatinine ratio ≥0.8 g/g)."*

2.1.1. Problem statement

Disease or condition

IgAN, sometimes referred to as Berger's disease, is a serious, immune complex-mediated autoimmune kidney disease. It is a form of glomerulonephritis, an inflammatory condition affecting the glomeruli. Primary IgA nephropathy is characterised by deposition of the IgA antibody in the glomerulus.

Epidemiology

IgA nephropathy is the most prevalent primary chronic glomerulonephritis worldwide (KDIGO 2021[1]).

IgAN is an orphan disease that is estimated to affect approximately 200,000 people in the EU and in the United Kingdom. There are geographical differences in the disease prevalence, with a higher prevalence in individuals of East Asian origin compared with Caucasians and an even lower prevalence in individuals of African origin. There are also notable differences in sex distribution, with a markedly higher male predominance in Caucasian populations compared to an equal prevalence in males and females in Asia (Feehally and Cameron 2011[2], Schena and Nistor 2018[3], Wyatt and Julian 2013[4]). Primary IgAN can occur at any age, but the clinical onset is common during the second or third decades of life (Donadio and Grande 2002[5]). Patients with IgAN are therefore younger and often have a lower comorbid condition burden than most other patients with chronic kidney disease (Knoop et al 2013[6]).

It is a life-threatening condition that is chronically debilitating due to progressive loss of kidney function that results in reduced quality of life and shortened life expectancy (Glassock et al 2019[7], Jarrick et al 2019[8], Knoop et al 2013[6]). Up to 50% of patients with IgAN develop End Stage Renal Disease (ESRD), requiring haemodialysis and kidney transplantation, within 20 years of diagnosis (Lai

[1] Kidney Disease: Improving Global Outcomes (KDIGO) Clinical practice guideline for the management of glomerular diseases.
[2] Feehally J and Cameron JS. IgA Nephropathy: Progress Before and Since Berger. Am J Kidney Dis. 2011 Aug;58(2):310-9
[3] Schena FP and Nistor I. Epidemiology of IgA Nephropathy: a Global Perspective. Semin Nephrol. 2018;38:435-42.
[4] Wyatt RJ and Julian BA. IgA nephropathy. N Engl J Med. 2013;368(25):2402-14.
[5] Donadio JV and Grande JP. IgA nephropathy. N Engl J Med. 2002;347(10):738-748.
[6] Knoop T, Vikse BE, Svarstad E, Leh S, Reisæter AV, Bjørneklett R. Mortality in patients with IgA nephropathy. Am J Kidney Dis. 2013;62:883–90.
[7] Glassock RJ. Mortality Risk in IgA Nephropathy. JASN 2019;30(5):720-22.
[8] Jarrick S, Lundberg S, Welander A, Carrero J-J, Höijer J, Bottai M, et al. Mortality in IgA Nephropathy: A Nationwide Population-Based Cohort Study. JASN 2019;30(5):866-76.

et al 2016[9], Moriyama et al 2014[10], Schena 1990[11], Vecchio et al 2015[12], Wyatt and Julian 2013[13]).

Aetiology and pathogenesis

IgA nephropathy is a disease characterised by the deposition of mucosal galactose-deficient IgA1 (Gd-IgA1) antibodies, either alone or in complex with immunoglobulin G (IgG) and/or IgA auto-antibodies, in the glomerular mesangium, where they initiate a cascade of inflammatory events, eventually causing irreversible glomerulosclerosis and loss of filtration capability. Although IgAN manifests in the kidney, there is data supporting a pivotal role of the mucosal immune system in the pathogenesis of the condition (Barratt 2020[14], Boyd et al 2012[15], Kiryluk et al 2014[16], Lai 2012[17], McCarthy et al 2011[18], Wyatt and Julian 2013[13]). It is thought that the origins of the disease reside in the mucosal tissue of the gastrointestinal (GI) tract (Barratt 2020[14], Selvaskandan et al 2019[19]). Peyer's patches are aggregations of lymphoid follicles, located in the mucosal layer of the intestine, and concentrated in the ileum, where they produce mucosal IgA antibodies, which play a key role in the gut immune system's first-line defence. They are part of the gut-associated lymphoid system (GALT) and serve as antigen sampling and inductive sites. Peyer's patches are the main source of primed, Gd-IgA1-expressing mucosal B-cells (Boyd et al 2012[15]). In IgAN patients, mucosal B-cells located in Peyer's patches are primed to produce Gd-IgA1, which in circulation can form immune complexes with IgG or IgA auto-antibodies (Wyatt and Julian 2013[13], Smith et al 2006, Suzuki et al 2011[20], Tomana et al 1999[21]). These complexes bind to mesangial cells in the glomeruli, the kidney's filtration apparatus, and initiate an inflammatory cascade that damages the membranes, resulting in renal injury (Wyatt and Julian 2013[13], Suzuki et al 2011[22], Novak et al 2013[23], Novak et al 2015[24]). As the disease progresses, the glomeruli are destroyed, leading to deterioration of renal function which ultimately may result in ESRD and the need for either dialysis or kidney transplantation. This pathogenesis suggests the local mucosa of the ileum to be the origin of IgAN, and thereby a relevant drug target for a potential disease-modifying treatment to delay or prevent ESRD.

This pathogenesis suggests the local mucosa of the ileum to be the origin of IgAN, and thereby a relevant drug target for a potential disease-modifying treatment to delay or prevent ESRD.

[9] Lai KN, Leung JC, Tang SC. Recent advances in the understanding and management of IgA nephropathy. F1000Res. 2016; 5:161.
[10] Moriyama T, Tanaka K, Iwasaki C, et al. Prognosis in IgA nephropathy: 30-year analysis of 1,012 patients at a single center in Japan. PLoS One. 2014;9(3):e91756.
[11] Schena FP. A Retrospective Analysis of the Natural History of Primary IgA Nephropathy Worldwide. Am J Med. 1990;89(2):209-15.
[12] Vecchio M, Bonerba B, Palmer SC, et al. Immunosuppressive agents for treating IgA nephropathy. Cochrane Database Syst Rev. 2015;(8):CD003965.
[13] Wyatt RJ and Julian BA. IgA nephropathy. N Engl J Med. 2013;368(25):2402-14.
[14] Barratt J, Rovin BH, Cattran D, Floege J, Lafayette R, Tesar V, et al. Why target the gut to treat IgA nephropathy. Kidney Int Rep. 2020;5:1620-24.
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[16] Kiryluk K, Li Y, Scolari F, et al. Discovery of new risk loci for IgA nephropathy implicates genes involved in immunity against intestinal pathogens. Nat Genet. 2014;46(11):1187-1196.
[17] Lai KN. Pathogenesis of IgA nephropathy. Nat Rev Nephrol. 2012;8(5):275-283.
[18] McCarthy DD, Kujawa J, Wilson C, et al. Mice overexpressing BAFF develop a commensal flora-dependent, IgA-associated nephropathy. J Clin Invest. 2011;121(10):3991-4002.
[19] Selvaskandan H, Cheung CK, Muto M, Barratt J. New strategies and perspectives on managing IgA nephropathy. Clin Exp Nephrol. 2019;23:577-88.
[20] Suzuki H, Kiryluk K, Novak J, Moldoveanu Z, Herr AB, Renfrow MB, et al. The pathophysiology of IgA nephropathy. JASN 2011;22(10):1795-1803.
[21] Tomana M, Novak J, Julian BA, Matousovic K, Konecny K, Mestecky J. Circulating immune complexes in IgA nephropathy consist of IgA1 with galactose-deficient hinge region and antiglycan antibodies. J Clin Invest. 1999;104(1):73-81.
[22] Smith AC, Molyneux K, Feehally J, Barratt J. O-glycosylation of serum IgA1 antibodies against mucosal and systemic antigens in IgA nephropathy. JASN 2006;17(12):3520-3528.
[23] Novak J, Renfrow MB, Gharavi AG, Julian BA. Pathogenesis of immunoglobulin A nephropathy. Curr Opin Nephrol Hypertens. 2013;22:287-94.
[24] Novak J, Rizk D, Takahashi K, Zhang X, Bian Q, Ueda H, et al. New insights into the pathogenesis of IgA nephropathy. Kidney Dis. 2015;1:8-18

Clinical presentation, diagnosis

The disease can be classified into primary or secondary forms. In the primary form, there are no relevant associated co-morbidities, whereas in the secondary form, the condition may be diagnosed in patients with non-renal diseases, ranging from chronic liver disease and inflammatory states to chronic infections and neoplasms. In the Kinpeygo clinical development programme, patients with primary IgAN only were studied.

Primary IgAN can occur at any age, but the clinical onset is common during the second or third decades of life. Children and adolescents with IgAN typically present with painless macroscopic haematuria during an acute upper respiratory tract or GI illness, whereas adults usually present with proteinuria, microscopic haematuria, or hypertension. The first indication of IgAN, that may be detected incidentally through dipstick or laboratory testing of a urine sample, is usually the appearance of protein and/or blood in the urine (proteinuria and haematuria, respectively), indicating leakage through the damaged glomeruli in the kidney. IgAN can only be diagnosed with a kidney biopsy. There are no validated diagnostic serum or urine biomarkers for IgAN.

Most commonly, IgAN is asymptomatic and follows a slowly progressive course with approximately 25% to 30% of any cohort developing kidney failure within 20 to 25 years of presentation. There is good evidence that the epidemiology, clinical presentation, disease progression, and long-term outcome of IgAN differ across ethnic populations around the world. IgAN is most prevalent and more likely to cause kidney failure in people of East Asian ancestry, followed by Caucasians, and is relatively rare in individuals of African descent. It is currently unclear if these observations are due to differences in pathogenesis and/or the contribution of varying genetic and environmental influences.

Clinical predictors of progression of IgA nephropathy include a reduction in GFR (manifested by elevated serum creatinine), hypertension (>140/90 mmHg), and persistent protein excretion above 1g/day. Patients who have recurrent episodes of gross haematuria without proteinuria are at low risk for progressive kidney disease. Other potentially modifiable risk factors for progressive disease include obesity, hypertriglyceridemia and hyperuricemia and smoking.

Management

Prior to the approval of Kinpeygo, there were no treatments approved for the management of patients with primary IgAN. The latest KDIGO 2021 Clinical Practice Guideline continues to recommend optimised supportive therapy, which focuses on reducing proteinuria and optimizing blood pressure control by maximum tolerated inhibition of the RAS, together with a low sodium diet. For patients with persistent proteinuria >1 g/day, rigorous blood pressure control with RAS inhibitor therapy to achieve blood pressure targets of <130/80 mm Hg remains the cornerstone of therapy. When proteinuria >1 g/day persists despite optimal RAS inhibition with angiotensin converting enzyme inhibitors (ACEIs)/angiotensin II type I receptor blockers (ARBs), patients are at risk of progression to ESRD. The KDIGO 2021 guideline recommends such patients should be considered for enrolment in a clinical trial. Although the clinical benefit of systemic glucocorticosteroid (GCS) therapy has not been established, KDIGO 2021 also suggests patients who remain at a high risk of progressive disease can be considered for a 6-month course of systemic GCS therapy. However, it is noted that the evidence for efficacy is uncertain, and it is emphasised that when systemic corticosteroids are being considered, the important risk of treatment-emergent toxicity must be discussed with patients.
Additional immunosuppressants beyond GCSs, such as cyclophosphamide, azathioprine, mycophenolate mofetil and rituximab are suggested for specific situations only, for example, in cases of crescentic IgAN where renal function is rapidly deteriorating.

Kinpeygo is currently indicated to reduce proteinuria in adults with primary IgAN at risk of rapid disease progression, generally a UPCR≥1.5 g/gram, and is used in addition to RAS inhibitor therapy.
On 22 February 2024, the Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion recommending the granting of a conditional marketing authorisation for the medicinal product Filspari, intended for the treatment of adults with IgAN. The active substance of Filspari is sparsentan, a dual endothelin angiotensin receptor antagonist benefit of Filspari is its ability to reduce proteinuria and slow down the progression of kidney disease. Filspari is indicated for the treatment of adults with primary immunoglobulin A nephropathy (IgAN) with a urine protein excretion ≥1.0 g/day (or urine protein-to-creatinine ratio ≥0.75 g/g).
Sodium-glucose co-transporter-2 (SGLT2) inhibitors, for example dapagliflozin, approved to reduce the risk of adverse kidney and cardiac outcomes in patients with chronic kidney disease are also likely to be increasingly used as an additional supportive care measure in patients with IgAN.

2.1.2. About the product

Kinpeygo is an oral, 4 mg modified-release hard capsule containing budesonide as active substance, a well-known corticosteroid that is used in a number of inflammatory diseases. The recommended dose is 16 mg once daily in the morning, at least one hour before a meal, for 9 months. The modified-release capsule formulation provides a two-step release by combining a delayed capsule disintegration with a sustained/prolonged release of the active substance budesonide in the ileum.

2.1.3. General comments on compliance with GCP

Clinical studies were approved by institutional review boards (IRB) or independent ethics committees (IEC), and studies were only conducted at sites where IRB/IEC approval was obtained. All studies followed International Council for Harmonization (ICH) good clinical practice (GCP) guidelines, consistent with the principles that have their origin in the Declaration of Helsinki, and informed, written consent was obtained from all patients as per GCP requirement.

Following the Part A analysis, the pivotal Nef-301 study remained 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 of the study.

The MAH has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

2.2. Non-clinical aspects

No new clinical data have been submitted, which was considered acceptable by the CHMP. There was no need to update the ERA.

2.3. Clinical aspects

GCP

The Clinical trials were performed in accordance with GCP as claimed by the MAH. The MAH has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies

Summary of clinical efficacy and safety studies for Nefecon in the treatment of adult patients with primary IgAN

Study identifier	**Study design and type of control Dates: FPFV to LPLV**	**Number of study sites location(s)**	**Diagnosis of patients[a] and key inclusion criteria**	**Primary efficacy endpoint(s)**	**Number of patients dosed**	**Duration of treatment**	**Gender (% male) Median age (range) Race**
Nef-301 (Part A CSR and Part B CSR included in Module 5.3.5.1)	Randomised, double-blind, placebo-controlled FPFV 5 Sep 2018 Part A DCO 5 Oct 2020 Part B DCO[b] LPLV for the global study 6 Feb 2023	131 sites 20 countries across Europe, North America, South America, and Asia-Pacific including China	Patients on optimised RAS inhibitor therapy with: Proteinuria based on 2 consecutive measurements separated by at least 2 weeks and calculated by the central laboratory showing either ≥1 g per day (≥1000 mg per day) in 2 consecutive measurements or UPCR≥0.8 g/gram (≥90 mg/mmol) in 2 consecutive measurements, and eGFR ≥35 mL/min per 1.73 m^2 and ≤90 mL/min per 1.73 m^2 using the CKD-EPI formula	**Part A:** Ratio of UPCR (based on 24-hour urine collections) at 9 months following the first dose of study drug compared to baseline **Part B:** Time-weighted average of eGFR over 2 years, supported by 2-year eGFR total slope	Safety Analysis Set: Nefecon[c] 16 mg: 195 Placebo: 194 Part B FAS: Nefecon[c] 16 mg: 182 Placebo: 182 [The Part B FAS for the primary evaluation of efficacy included 2 patients in the Nefecon group and 3 patients in the placebo group who were not dosed]	9 months	In the Part B FAS: 65.9% male Median 43 years (20 to 73) 75.5% Caucasian 22.8% Asian 20.1% patients from United States or Canada

Study identifier	Study design and type of control Dates: FPFV to LPLV	Number of study sites location(s)	Diagnosis of patients[a] and key inclusion criteria	Primary efficacy endpoint(s)	Number of patients dosed	Duration of treatment	Gender (% male) Median age (range) Race
Nef-202 (Module 5.3.5.1)	Randomised, double-blind, placebo-controlled 11 Dec 2012 to 25 June 2015	61 sites 10 European countries	Patients on optimised RAS inhibitor therapy with: UPCR≥0.5 g/gram (≥56.5 mg/mmol) or urine protein ≥0.75 g/24 hours; and estimated GFR (using CKD-EPI formula) or measured GFR≥45 mL/min per 1.73 m^2	Ratio of UPCR (based on 24-hour urine collections) at 9 months following the first dose of study drug compared to baseline **Primary treatment comparison:** Nefecon (16 mg/day + 8 mg/day combined) versus placebo	Nefecon[c] 16 mg: 49 Nefecon[c] 8 mg: 51 Placebo: 50	9 months	70.5% male Median 38 years (18 to 82) 96.6% Caucasian

[a] Patients with a diagnosis of primary IgAN and were treated on a background of RAS inhibitor therapy.
[b] The Part B DCO corresponds to the LPLV date for the last patient enrolled in the global study. An additional 29 patients were enrolled for regulatory requirements in China after global recruitment was complete. These patients are not included in the Part B Full Analysis Set that was planned to include 360 patients for the primary evaluation of efficacy; they are however included in the Safety Analysis Set. At the time of the Part B DCO, all of these patients had completed the 9-month treatment period and 28 were ongoing in follow-up.
[c] The Nefecon formulation used in Nef-301 is the to-be-marketed formulation with hypromellose capsule shell (Nefecon-F). The Nefecon-A (starch capsule) was used in study Nef-202. Nefecon-F and Nefecon-A were shown to be bioequivalent in Study Nef-105 Each Nefecon modified release capsule contains 4 mg budesonide.
CKD-EPI: Chronic Kidney Disease Epidemiology Collaboration; DCO: Data Cut-Off; eGFR: estimated glomerular filtration rate; FAS: Full Analysis Set; FPFV: First Patient First Visit; LPLV: Last Patient Last Visit; RAS: renin-angiotensin system; UPCR: urine protein creatinine ratio.

2.3.1. Pharmacokinetics

There is no new clinical pharmacology information relevant to this application; clinical pharmacology information is unchanged and is adequately described in the SmPC for Kinpeygo.

Overall, the PK of Nefecon have not been studied in patients with IgAN. Nefecon PK has been studied only in 6 healthy volunteer studies following single oral doses to support the biopharmaceutics and clinical pharmacology of Nefecon. The active substance (AS) was extensively characterised during the development programmes for other marketed products containing this drug substance and are described in detail for the oral budesonide product and reference medicine Entocort which has been authorised in the EU since 1992.

2.3.2. Pharmacodynamics

Budesonide has a potent glucocorticoid effect and a weak mineralocorticoid effect, exhibiting potent immunosuppressive and anti-inflammatory properties *in vivo*. Systemic bioavailability of budesonide is low (approximately 10%) due to high first-pass metabolism. Kinpeygo is formulated for local treatment of the gut mucosa in the ileum.
There is no new clinical pharmacology information relevant to this application and this is acceptable.

2.3.3. Conclusions on clinical pharmacology

Since the submission of the Nef-301 Part B data, several additional analyses of biomarkers from Nef-301 have been presented at scientific conferences. These analyses further support the previous findings from Nef-202. To date, no new pharmacology date are available for budesonide.

2.4. Clinical efficacy

This section presents the efficacy data from the final confirmatory analysis of the pivotal Phase 3 Nef-301 study in patients with primary IgAN.

2.4.1. Main study

Title of Study

Nef-301: Phase 3, randomised, double-blind, placebo-controlled, multicentre study

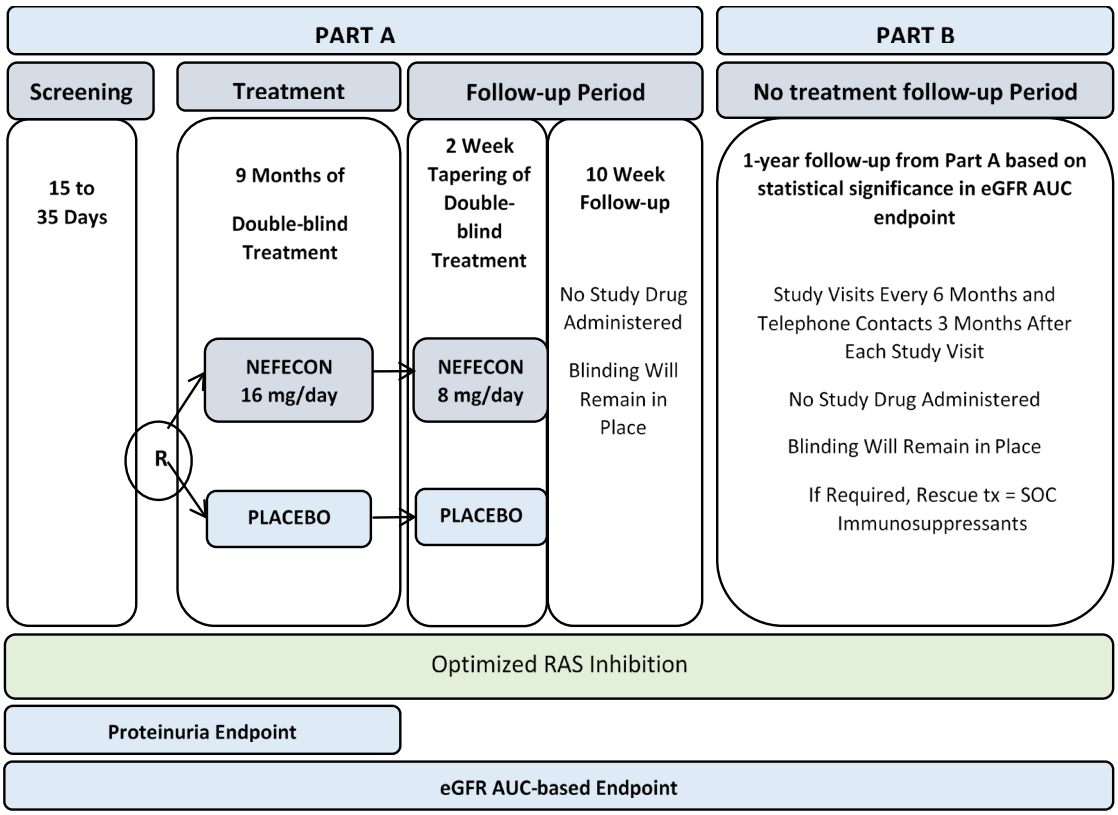
The Nef-301 study was designed to assess the efficacy and safety of Nefecon in patients with primary IgAN. It was a global, randomised, double-blind, placebo-controlled study, and therefore met the standard ICH criteria for robust design of a therapeutic confirmatory trial. The design consists of 2 parts:

- Part A included a screening period, followed by a 9-month blinded treatment period in which eligible patients were randomised in a 1:1 ratio to Nefecon 16 mg/day or placebo, and a 3-month follow-up period.
- Part B consisted of a further 12-month observational follow-up period. Therefore, the overall 2-year study comprised a 9-month treatment period and 15 months of observational follow-up.

Methods

Nef-301 is a Phase 3, randomised, double-blind, placebo-controlled, multicentre study to evaluate the efficacy, safety, and tolerability of oral Nefecon 16 mg once daily compared to placebo in patients with primary IgAN on a background of optimised RAS inhibitor therapy. Approximately 360 patients were required to be randomised across sites in Europe, North America, South America, and Asia Pacific, including China. The 2-year study consists of 2 parts, Part A and Part B, as illustrated in Figure 1.

Figure 1. Nef-301 Study Design



AUC area under the curve (referred to in this Summary of Clinical Efficacy as the time-weighted average of eGFR over 2 years); eGFR estimated glomerular filtration rate; R randomisation; RAS renin angiotensin system; SOC standard of care; tx treatment.

Part A included a screening period (up to 35 days), followed by a 9-month blinded treatment period in which eligible patients were randomised in a 1:1 ratio to Nefecon 16 mg/day or placebo, and a 3-month follow-up period (including a 2-week tapering period during which the study drug dose was reduced from 4 capsules once daily [Nefecon 16 mg or placebo] to 2 capsules once daily [Nefecon 8 mg or placebo]). The randomisation was stratified according to baseline proteinuria (<2 g/24 hours or ≥2 g/24 hours); baseline eGFR (<60 mL/min/1.73 m^2 or ≥60 mL/min/1.73 m^2); and geographic region (Europe, North America, South America, or Asia Pacific).

Following informed consent, patients were required to have proteinuria and serum creatinine for calculation of eGFR based on 2 consecutive measurements (from 24-hour urine sampling and blood), separated by at least 2 weeks, and calculated by the central laboratory (baseline is calculated as the geometric mean of these 2 measurements). Patients were also required to have 2 consecutive measurements for the calculation of eGFR at 24 months, obtained at Visits 17a and 17b.

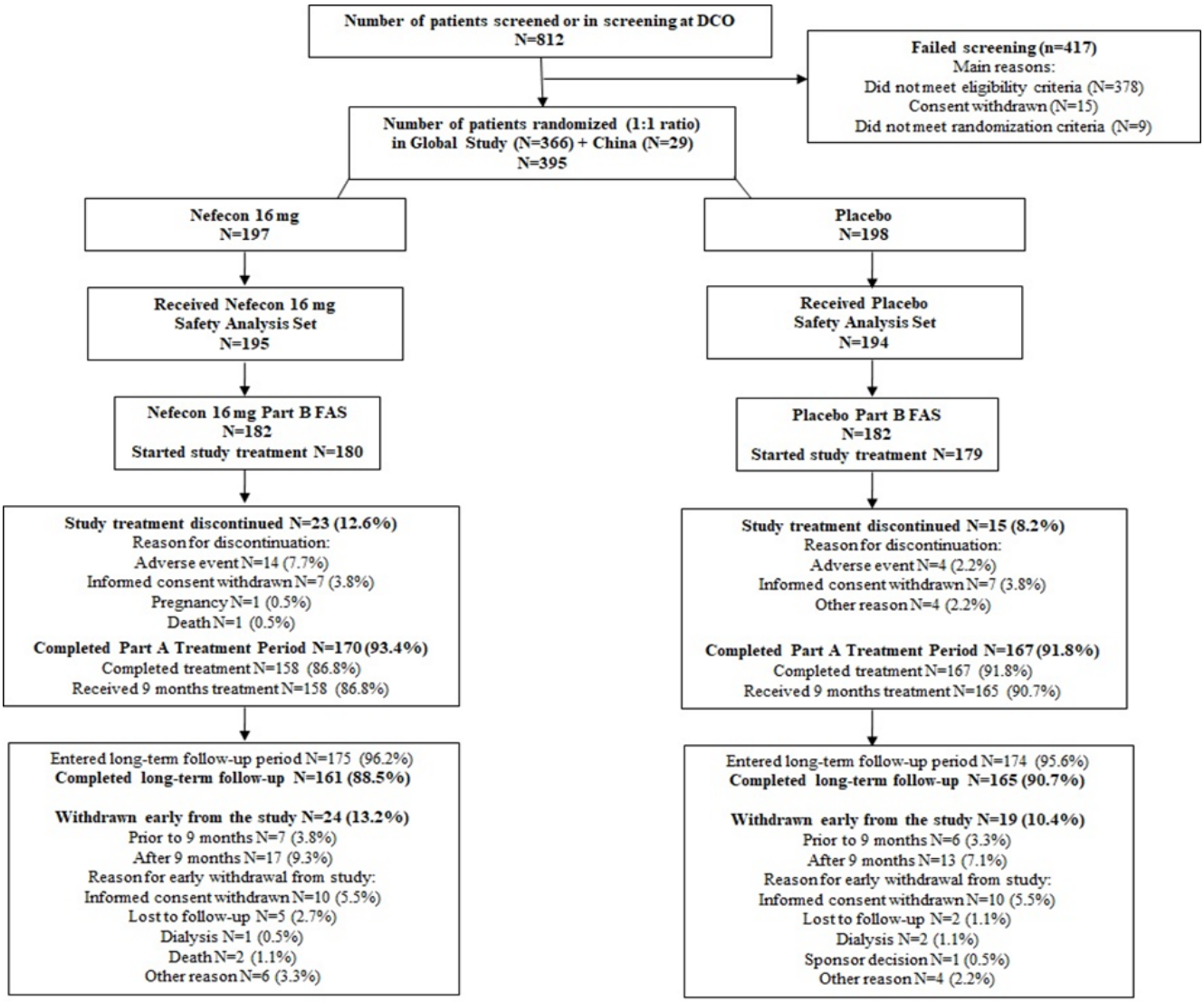
In April 2020, a protocol amendment was incorporated to allow patients to receive treatment for up to 10 months in the event they were unable to attend a visit due to the disruption caused by the COVID-19 pandemic; this was to ensure patients could receive tapering medication. The 9-month analysis time-window extended to 10.5 months after the first dose of therapy; therefore, any assessments performed at 10 months were included with other 9-month data in the analysis.

Part B consisted of a 12-month (+14 to 35 days) observational follow-up period that immediately followed Part A. Therefore, patients were followed for a total of 15 months after completion of the 9-month Treatment Period. The study blinding remained in place throughout Part B, during which no further study drug was administered.

All patients who prematurely discontinued study drug were to continue in the study and have eGFR, proteinuria, and serum creatinine measured at each scheduled visit through to completion of the 2-year study, unless they withdrew their consent to any kind of follow-up. The primary Part A efficacy analysis that formed the basis of the initial MAA, was performed once the first 201 patients randomised had had the opportunity to complete their 9-month visit. The Nef-301 Part B analysis that forms the basis of this supplementary application is the final analysis of the overall 2-year global study and was scheduled to be performed when all 366 patients randomised to the global study had had the opportunity to complete their final 2-year visit (Visit 17b). An additional 29 patients recruited for regulatory requirements in China after recruitment to the global part of the study was completed are not included in the primary Part B Full Analysis Set (FAS), that was planned to include 360 patients for the primary evaluation of efficacy. At the time of the Part B data cut-off (DCO), these patients were ongoing in observational follow-up.

Study participants

Figure 2. Participants flow in Nef-301 B trial



Definitions: Completed Part A Treatment Period defined as the patient has at least one valid UPCR value available in the 9-month visit window

Completed treatment is the number recorded by the investigator. The patient is considered to have received 9 months of treatment if the date of last dose (excluding doses received in the tapering period) – date of first dose + 1 ≥255.
The patient is defined as entered the long-term follow up period if they attended at least one study visit or had any AE recorded that is more than 14 days after the last dose of study treatment (including tapering).
Completion of Part B long-term follow-up is defined as the patient has at least one valid eGFR value within the 24-month visit window
In addition to the main reasons for withdrawal recorded on the eCRF, the COVID-19 situation also contributed to the discontinuation of study treatment in 3 Nefecon-treated patients (2 patient decision and 1 death from COVID-19). All 3 of these patients also discontinued the study, (1 due to other reasons with the COVID-19 situation also a contributing factor, 1 due to subject decision not COVID-related, and the other was the patient who died of COVID-19).

The Nef-301 study entry criteria were designed to enrol a clinically representative population of patients with primary IgAN at risk of progressing to ESRD, as described in the KDIGO 2012 guideline, due to persistent proteinuria despite optimised RAS blockade, whilst also ensuring the safety of study participants. Eligible patients were required to be on a background of optimised RAS inhibitor therapy, which was maintained throughout the study.

Part A: As of the DCO for the Part A analysis of 5 October 2020, 306 patients with primary IgAN had been randomised and 294 patients dosed at 112 sites in 20 countries. The Part A FAS included 199 of the first 201 patients randomised, aged 23 to 73 years (median 44 years). The majority were male (67.8%) and Caucasian (85.9%), with 12.1% Asian. Disease characteristics were reflective of a clinically relevant high-risk IgAN population. For the Part A FAS, median UPCR was 1.26 g/gram (inter-quartile range 0.92 to 1.79), median eGFR CKD-EPI (creatinine) was 55.3 mL/min/1.73 m^2 (inter-quartile range 45.5 to 68.1), and 62.3% of patients had eGFR<60 mL/min/1.73 m^2, which is generally indicative of chronic kidney disease if at this level for 3 months or more.

Overall, 366 patients with primary IgAN were randomised to the global study. A further 29 patients were enrolled in China after global recruitment was complete. These patients are not included in the Part B Full Analysis Set (FAS) for the evaluation of efficacy, that was planned to include approximately 360 patients. Two patients randomised in error were excluded from the Part B FAS. Therefore, the Part B FAS included 364 patients, aged 20 to 73 years (median 43 years). The majority were male (65.9%) and Caucasian (75.5%), with 22.5% Asian. Disease characteristics were reflective of a clinically relevant high-risk IgAN population. The Part B Full Analysis Set included 364 patients, regardless of whether the patient received study drug, and comprised 182 patients randomised to Nefecon 16 mg and 182 patients randomised to placebo (Figure 2). Five patients in the Part B Full Analysis Set were randomised but did not receive any blinded study treatment and discontinued from the study; only 1 of these patients provided post-baseline efficacy data (at Month 3).

In the Part B Full Analysis Set, 170 (93.4%) and 167 (91.8%) patients completed the treatment period and had at least 1 valid UPCR value available in the 9-month visit window (Day 229 to Day 319). For the Part B FAS median UPCR was 1.26 g/gram (inter-quartile range 0.89 to 1.75), median eGFR CKD-EPI (creatinine) was 55.5 mL/min/1.73 m^2 (inter-quartile range 45.9 to 69.8), and 59.9% of patients had eGFR<60 mL/min/1.73 m^2, which is generally indicative of chronic kidney disease if at this level for 3 months or more.

A total of 23 patients (12.6%) from the Nefecon 16 mg group and 15 patients (8.2%) from the placebo group discontinued study treatment early. Adverse events were the most common reason for discontinuation of study treatment in the Nefecon 16 mg group (14 patients [7.7%]) compared with 4 patients (2.2%) discontinued due to an adverse event in the placebo group (Figure 2 above).

Treatments

Part A: Kinpeygo 16 mg (four 4 mg budesonide modified release capsules QD) or placebo (4 matching capsules QD) was administered orally for 9 months during the Treatment Period. After completing 9 months of study treatment, the daily dose of study drug was reduced from 4 capsules QD (Kinpeygo 16 mg or placebo) to 2 capsules QD (Kinpeygo 8 mg or placebo) for 2 weeks to prevent insufficiency of the adrenal glands (Tapering Period in Part A).

Part B: consisted of a further 12-month observational follow-up period. Therefore, the overall 2-year study comprised a 9-month treatment period and 15 months of observational follow-up. In keeping with the KDIGO guideline, patients were to be on a stable dose of RAS inhibitor therapy at the

maximum allowed or maximum tolerated dose for at least 3 months prior to randomisation. Patients were then required to remain on stable RAS inhibitor therapy throughout the study (Part A and Part B), to avoid changes in RAS inhibitor treatment potentially confounding the comparison of Nefecon treatment with placebo.

Rescue medication was defined as any immunosuppressive medication that would be expected to materially impact efficacy, regardless of whether the medication was used for IgAN. Systemic immunosuppressive drugs (including glucocorticosteroids) were prohibited during the study. However, over the entirety of the study (Parts A and B), patients were allowed up to 3 courses of glucocorticosteroid [GCS] treatment in any 2-year period for non-IgAN indications, provided no treatment course was greater than 2 weeks and the GCS dose did not exceed the equivalent of 0.5 mg/kg/day prednisolone.

Objectives

Primary Objective

- The primary objective of Part A is to assess the effect of Nefecon 16 mg treatment on UPCR over 9 months compared to placebo.
- The primary objective of Part B is to assess the effect of the Nefecon 16 mg treatment given in Part A on clinical consequences of any proteinuria reduction as measured by eGFR recorded over 2 years compared to placebo.

Secondary Objectives

Part A:

- To assess the effect of Nefecon 16 mg treatment on eGFR at 9 and 12 months compared to placebo.
- To evaluate additional aspects of renal function, and safety and tolerability of Nefecon 16 mg treatment over 9 months compared to placebo.

Part B:

- to assess the effects of the Nefecon 16 mg treatment given in Part A on different aspects of renal function and safety compared to placebo over 2 years.

Outcomes/endpoints

Part A: The primary efficacy endpoint for the Part A analysis is defined as the ratio of UPCR (based on 24-hour urine collections) at 9 months following the first dose of study drug compared to baseline.

The secondary efficacy endpoints for the Part A analysis are:

- Ratio of eGFR at 9 and 12 months compared to baseline calculated using the CKD EPI formula;
- Ratio of urine albumin to creatinine ratio (UACR) at 9 months compared to baseline.

Supportive analyses of these endpoints were also performed at all time points up to 12 months to describe the time course of the treatment effect. In addition, a supportive analysis of 1-year eGFR total slope was performed.

Part B: The primary efficacy endpoint for the Part B analysis is a time-weighted average of eGFR over 2 years, described as an area under the curve (AUC)-based endpoint in the protocol and Statistical Analysis Plan (SAP), but hereafter referred to as a time-weighted average.

A supportive analysis of the 2-year eGFR slope was also performed and included in the hierarchical testing strategy.

Secondary efficacy endpoints for the Part B analysis:

- Time to 30% reduction from baseline in eGFR confirmed by a second value, with ≥4 weeks of separation between the 2 sampling time points;
- Time from the first dose of study drug until receiving rescue medication;
- Ratio of UPCR, UACR, and eGFR compared to baseline averaged over time points between 12 and 24 months, inclusive, following the first dose of study drug;
- Proportion of patients without microhaematuria in at least 2 of the following time points: 12, 18, and 24 months following the first dose of study drug;
- Proportion of patients receiving rescue treatment; and
- SF-36 quality of life assessment at 9 and 24 months.

Sample size

If 360 patients are recruited and followed for 2 years, and replicate values of eGFR are recorded both at baseline and at 2 years, Part B was supposed to have 90% power to detect a statistically significant difference in eGFR at 2 years, using a 2-sided alpha of 5% if the true effect of Nefecon is 2.24 mL/min/1.73 m^2. This calculation was based on the following set of assumptions:

- The mean eGFR at 2 years in the placebo group is 60 mL/min/1.73 m^2 so that the treatment effect corresponds to a difference of 0.03665 on the log-scale.
- The between-patient standard deviation of eGFR at baseline and 2 years is 0.32 and 0.35, respectively, on the log-scale as observed at baseline and 1 year in the Phase 2b study.
- The correlation between repeat log-transformed values at baseline and 2 years is 0.946 and 0.939, respectively, and the correlation between baseline and 2-year eGFR values is 0.935. These values were based on data observed in the Phase 2b study.
- Combining the between-patient variability and correlation coefficients leads to an expected standard deviation for a log-transformed analysis of covariance of the mean of replicate eGFR values of 0.093.
- A 1-sided significance level of 2.5%; and
- A worst-case assumption for dropout rate by 2 years of 25%.

The power for the primary efficacy endpoint for Part B, 2-year eGFR AUC, is >90% for the expected mean eGFR profiles for Nefecon and placebo over 2 years. A worst-case analysis of eGFR data from Nef-202 demonstrated a 3.7 mL/min/1.73 m^2 improvement in eGFR at 12 months. In this case, the power for 2-year eGFR AUC was computed to be >99%, assuming efficacy reduces linearly after 12 months to a mean difference of a 2.24 mL/min/1.73 m^2 at 2 years. Simulations demonstrated that Part B remains fully powered for 2-year eGFR AUC, using the primary analysis method of robust regression with imputation, even if the rate of outlying data more than doubles compared to Nef-202.

A total of 360 randomised patients were planned to be evaluable for the final primary efficacy analysis for the study and this was acceptable to the CHMP.

Randomisation and Blinding

These aspects of the trial were already addressed during the initial assessment and no issues were identified.

Statistical methods

The Safety Analysis Set was to include all patients who receive at least 1 dose of study drug. All safety analyses were to be conducted on the Safety Analysis Set. The primary safety analyses in the trial were to be based on the on-treatment period defined from the first dose of therapy until 14 days after completion of the tapering period. The primary aim of the safety analyses was to describe the safety and tolerability of Nefecon, for the intended 9-month regimen, whilst patients were still receiving therapy.

For Part B, the primary FAS was to include all patients randomised at the completion of recruitment to the global part of the study (with the exception of the three subjects excluded from the Part A FAS), including any patient already recruited in China. The data cut-off for Part B was planned to occur once all patients, randomised into the global part of the study, have had the opportunity to complete Visit 17b, which can occur up to 35 days after the 2-year visit. Any patient recruited in China after recruitment to the global part of the study was complete were not to be included in the primary Part B FAS. The planned number of patients in the Part B FAS was 360.

In all efficacy analyses, in Part A and Part B, any data impacted by rescue medication were to be excluded. The primary aim of the efficacy analyses was to describe the 9-month regimen of Nefecon irrespective of any early discontinuation and in the absence of rescue medication.

The Per Protocol (PP) Set was to include all patients in the FAS for whom no major protocol deviations (which may interfere with efficacy evaluation) occurred during the study period. Per Protocol Set - Part B was to be determined prior to unblinding for the final analysis.

Major protocol deviations were to be pre-specified prior to unblinding the study. The following criteria were planned to be evaluated for major deviations: Eligibility criteria violations, early discontinuation of study drug, study medication compliance outside of 80-120%, use of prohibited concomitant medication that could have impacted the efficacy of study treatment, unblinding of the patient during Part A and Part B periods, respectively, other substantial protocol violations. The Per Protocol Set was planned to be used to assess robustness of the primary analysis results to assess what the efficacy results might have been had all patients followed the protocol as intended.

Analysis methods for primary efficacy: The primary efficacy endpoint for the Part B analysis was an AUC-based endpoint calculated as a time-weighted average of eGFR (CKD-EPI) measurements recorded over 2 years, where each time point was given a weight in proportion to the time elapsing from the previous recording. Therefore, recordings made at 18 and 24 months received twice as much weight as those made at 3, 6, 9, and 12 months. Any data impacted by rescue medication (including dialysis or renal transplantation) was to be excluded from the primary efficacy analyses in Part B so that the underlying effect of Nefecon could be estimated free from the confounding effects of rescue medication.

Part B Primary Efficacy Endpoint Analysis: 2-year eGFR AUC: eGFR data were to be log-transformed prior to analysis. Data included at baseline and 24 months were to be the log of the geometric mean of the 2 replicate values recorded at each time point, respectively. Previous eGFR data from Nefecon trials suggest it is possible there will be a small sub-population of patients with extreme outlying data resulting from very rapid progression of disease. Therefore, the primary analysis was planned to be

based on a Robust Regression approach with independent variables of treatment and log-transformed baseline eGFR. transformed baseline eGFR. M-estimation was to be used with Huber weights and a cut-off value of 2 with the median method used to estimate the scale parameter. This approach means that standardised residuals with an absolute value of smaller or equal 2, corresponding to the central 95% of the data if normally distributed, have equal weight and outlying data are weighted according to a pre-specified function, W (x), which gives lower weights to the most outlying data.

To handle missing data, the analysis was to be performed over 3 phases: an imputation, analysis, and pooling phase, as detailed in the SAP. Missing data may result from the exclusion of data due to rescue medication, the patient having discontinued from the study or, in rare cases, because the patient has died, as well as the lack of recording of data. In all such cases, missing data will be imputed conditional on previous outcomes observed within the same patient.

Three sensitivity analyses were preplanned in the SAP: One analysis under an assumption of "absence of outliers", one analysis under alternative missing data assumptions, and a Tipping Point analysis. In a supplementary analysis, the Part B primary analysis was planned to be repeated with all observed eGFR data included regardless of the use of rescue medication. With this analysis it was planned to apply a treatment policy estimand and estimate the effect of Nefecon regardless of any other intervention that might impact efficacy.

The primary endpoint for Part B, as well as eGFR at 9 months, was planned to be summarised according to important subgroups as detailed in the SAP. If a subgroup level had fewer than 20 patients exposed to Nefecon 16mg, data in that subgroup level were not to be assessed. A global interaction test amongst all subgroups was to be performed for eGFR AUC at 2 years to assess whether any heterogeneity in the treatment effect between subgroups is consistent with a constant treatment effect across all subgroups.

On request of the CHMP, the MAH provided a mixed model repeated measurements (MMRM) analysis of the mean change of eGFR from baseline using different techniques to handle missing data under different missingness assumptions. The MAH provided analyses of all observed eGFR data regardless of the use of prohibited medication, start of dialysis or renal transplant, without explicit missingness assumption (treatment policy estimand). The MAH further provided two analyses with copy reference (CR) and jump to reference (J2R) imputation for the excluded measurements, corresponding to a missing not at random (MNAR) assumption. All three analyses were performed in the FAS and in the subgroups in the FAS with baseline UPCR < 1.5 g/gram and baseline UPCR ≥ 1.5 g/gram.

Analysis methods for secondary efficacy: The time to a 30% reduction in eGFR (CKD-EPT) was to be measured from the time of the first dose of study drug or the time of the randomisation (if the patient randomised does not receive any study drug) and was to include all data prior to the use of rescue medication. The aim of the analysis was to estimate the effect of Nefecon in the absence of rescue medication, irrespective of the actual duration of treatment each patient receives.

To prevent informative censoring, if a patient dies from a renal-related event, as determined by a blinded medical review, or has dialysis for at least 1 month, kidney transplantation, or kidney failure defined as a sustained eGFR <15 mL/min/1.73 m^2 prior to a 30% reduction, they were to be included in the analysis as having had a clinical event occur at that time. Patients were defined as having a renal-related death if the investigator provides 'Death due to kidney failure' as being the reason for early termination from study and was confirmed on blinded medical review.

To estimate the effect of Nefecon in the absence of the use of rescue medication, an Inverse Probability of Censoring Weights (TPCW) model was planned to be used. This approach censors patients who take rescue medication and matches them with those that did not based on their clinical status at the time, such as their change in eGFR and UPCR from baseline and reweighting based on the

outcome of matched patients. A weighted Cox model was planned to be fitted. The SAP contains further details.

A supplementary analysis was planned which considered receiving rescue medication as a clinical event. A Cox model was to be applied to analyse the earliest of the time to 30% reduction in eGFR or use of rescue medication; covariates were to include treatment, log-baseline UPCR, log-baseline eGFR and geographic region. Patients without an event were be censored at the time of their latest eGFR measurement.

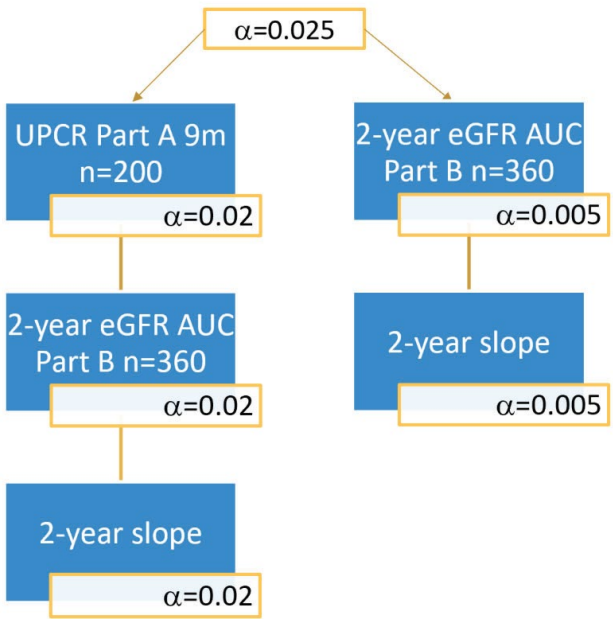
The secondary endpoints that assess time-averaged parameters (UPCR and UACR) between 12 and 24 months were to be log-transformed prior to analysis and were to be analysed using a MMRM model with separate visit terms for 3, 6, 9, 12, 18, and 24 months.

Any binary endpoints that compare the proportion of patients with an outcome were to be analysed using a logistic regression model and were to include terms for treatment, log-baseline UPCR, log-baseline eGFR, and geographic region as defined in the stratification variable. The odds ratio was to be estimated together with the associated 95% CI and p-value, with the CI estimated using a profile-likelihood approach and the p-values from a likelihood-ratio test.

Al 36 questions in the SF-36 v2 survey were grouped into one of 8 subscales: physical functioning, role limitations due to physical health, bodily pain, general health perceptions, vitality, social functioning, role limitations due to emotional problems and mental health. 8 subscale scores, overall physical and mental health scores were to be obtained by using Optum PRO CoRE software version 1.4. The mean recoded score for each of the 8 subscales, overall physical and mental health scores were to be summarised by treatment arm at baseline, 9, 18 and 24 months.

Standard statistical analysis methodology was foreseen in the SAP to analyse patient safety data, demographic and baseline characteristics and concomitant medication.

Hypothesis Testing Strategy: In order to provide strong control of the type I error rate of 2.5% 1-sided across both Parts A and B of the study, the endpoints of UPCR at 9 months from Part A, 2-year eGFR AUC and 2-year eGFR slope from Part B were to be tested in an endpoint hierarchy as described below:



The CHMP acknowledged that the analyses set for the Part B analyses were predefined in the SAP. Description of the full analysis set included a specification concerning exclusion of any data impacted by rescue medication (hypothetical strategy in estimand framework). No methodological concerns arise in relation to type-1-error control over part's A and part's B hypotheses testing as an appropriate testing strategy was foreseen and consequently the 2-year eGFR endpoint can be tested at the alpha level of 0.025 (one-sided).

Concerning the preplanned statistical analysis strategy for the primary efficacy outcome in Part B, three methodological issues were raised:

First, the AUC-analysis approach for eGFR 2-year outcome is not considered appropriate to directly address the outstanding question to describe/estimate the effect size remaining at the time point of 24 months, i.e. 15 months after treatment cessation, in order to be able "to assess the clinical consequences of proteinuria reduction, as measured by eGFR" (see wording SOB). Via the AUC-analysis approach the whole-time course (starting from baseline) is included in the analysis and therefore influences estimates and p-values. This definition of the endpoint does not represent the effect size remaining at month 24 and therefore cannot be interpreted as the 24-months eGFR-outcome. However, many additional analyses are provided and among those also analyses that refer to the 24-months eGFR-outcome are available. Most of these analyses carried out are supportive of a clinically relevant remaining group-difference in eGFR at the end of a two-year time course. However, the actual choice of the primary endpoint as well as the two additional methodological issues presented below (hypothetical estimand strategy and use of robust regression) contribute to the fact that there was no methodologically appropriate estimate for the eGFR effect size remaining at the 24-month time point. Such an estimate is not only relevant for the assessment, but also for subsequent communication in the SmPC.

Data collected in part B of the trial stem from a 15 months-long `off-Nefecon-treatment´ observation period. In such a setting of a long period of post-treatment observation without (pre-planned) active treatment, it is generally not straight forward to regard alternative treatment against the targeted disease as `rescue medication´. The understanding is rather that the alternative treatment is given/initiated at the HCP/investigators discretion based on the actual patient status resulting from the natural course of the disease. It is not considered reasonable to base the decisions in this setting on estimates retrieved following a hypothetical strategy of no alternative ('rescue') treatment given after cessation of Nefecon. This is not considered a scenario of interest. The most meaningful strategy is considered to carry out primary eGFR analyses under the treatment policy assumption. The study design including the observation period does represent clinical practice exactly in this sense. One of the pre-planned supplementary analyses would cover that aspect, i.e. by repeating the primary analysis with all observed eGFR data included regardless of the use of rescue medication. However, for this analysis only results from the robust regression analysis were available. As the application of a robust regression model is not endorsed (see further discussion), the results presented from this supplementary analysis are - while indicative of a remaining treatment effect at month 24 - not considered fully adequate to estimate the treatment benefit remaining at 24-months following a treatment policy strategy.

The reasoning behind the choice of `Robust regression´-modelling for primary eGFR analysis is not understood. Following a fundamental methodological principle, all observations for the primary variable eGFR should enter the analysis with the same (full) weight, regardless of their location on the scale. Any analysis approach with down-weighing of "outliers" solely based on fulfilment of arbitrary mathematical distance criteria is not accepted as the primary analysis.

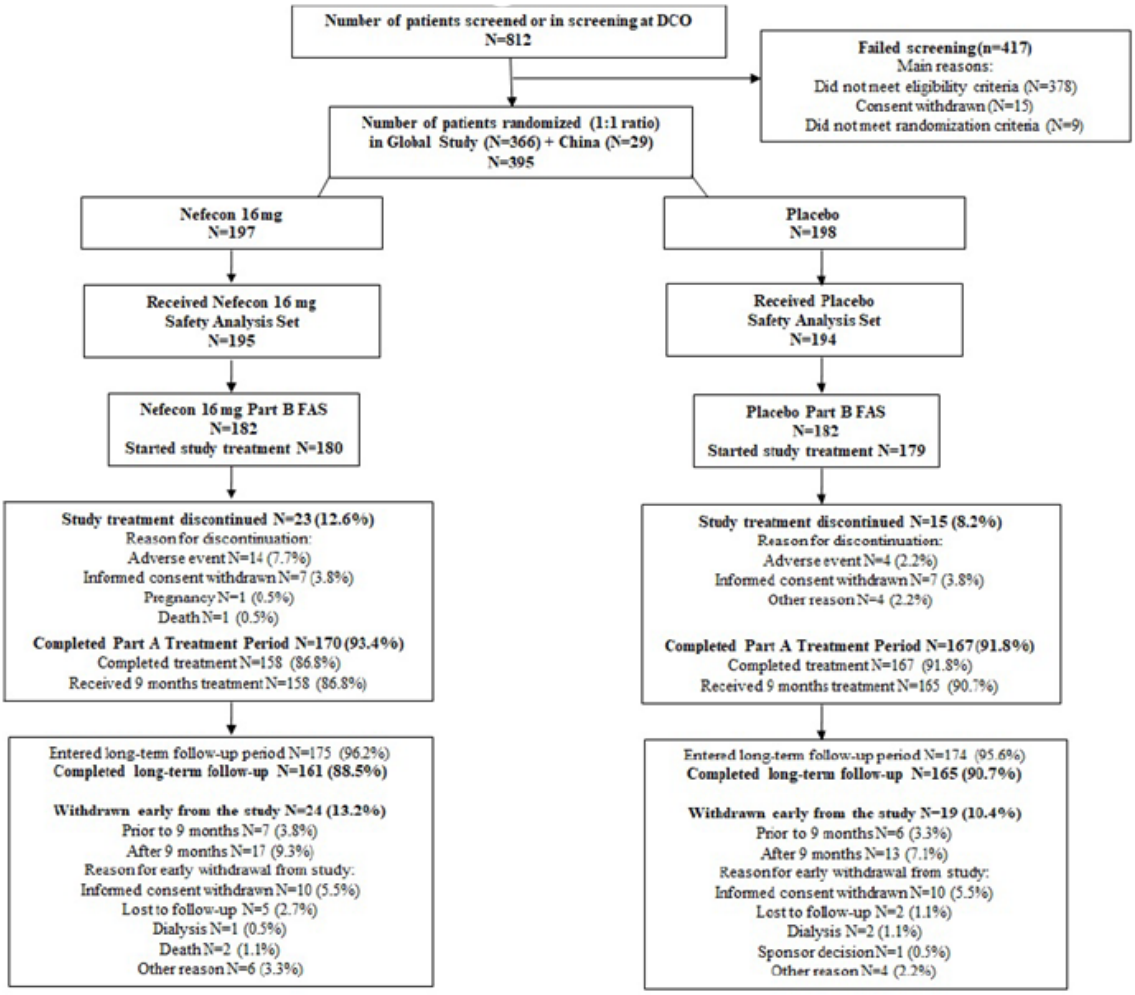
On request of the CHMP, the MAH provided mixed model repeated measurement (MMRM) analyses using all available data irrespective of the use of rescue medication (treatment policy strategy in estimand framework) and MMRM analyses using imputation techniques to address data missing not at random. The endpoint of eGFR change from baseline at 24 months used in the ancillary analyses can be considered

adequate to estimate the treatment benefit remaining at 24 months. In the ancillary analyses all observations enter the model with the same full weight without down-weighing of outliers.

The MMRM analysis using the treatment policy intercurrent event strategy is considered the most relevant to assess the treatment benefit in terms of population, endpoint and intercurrent event strategy. No further issues arise in relation to the analysis methods applied for safety data analyses.

Results

Participant flow



Recruitment

Planned: 360 patients. Screened: 812 patients. Randomised: 395 patients (366 patients in the global study plus an additional 29 patients enrolled in China for regulatory requirements after global recruitment had ended). Dosed (Safety Analysis Set): 389 patients.

Conduct of the study

Protocol Version 1.0 (16 January 2018) was the first version used to recruit patients in the study and was amended 8 times during the study, including trial amendment due to COVID-19 pandemic.

Baseline data

Descriptive statistics and frequency tabulations were presented by treatment group. Baseline characteristics were balanced across randomised treatment groups and any minor imbalances between treatment groups were not expected to have impacted the overall efficacy conclusions. Median age was 43 years, with just over half of all patients aged <45 years. The ratio of males to females (approximately 2:1) was consistent with that expected for a predominantly Caucasian IgAN patient population. Patients were recruited from 131 sites in 20 countries across Europe, North America, South America, and Asia-Pacific including China; 22% of patients in the Part B Full Analysis Set were of Asian racial origin, with no black or African American patients enrolled.

Patients were on optimised RAS inhibitor therapy with: proteinuria based on 2 consecutive measurements separated by at least 2 weeks and calculated by the central laboratory showing either ≥1 g per day (≥1000 mg per day) in 2 consecutive measurements or UPCR≥0.8 g/gram (≥90 mg/mmol) in 2 consecutive measurements, and eGFR ≥35 mL/min per 1.73 m^2 and ≤90 mL/min per 1.73 m^2 using the CKD-EPI formula.

Most patients were receiving at least 50% of the maximum allowed dose of RAS inhibitor therapy, with the majority of patients on either an ACEI or an ARB; a small number of patients (<5% in the Part B FAS) were on combined ACEI and ARB therapy.

Prior to enrolment, it was recommended that patients achieve a target systolic blood pressure <125 mm Hg and target diastolic blood pressure <75 mm Hg in accordance with the 2012 KDIGO guideline. Patients with unacceptable blood pressure defined as systolic blood pressure ≥140 mm Hg or diastolic blood pressure ≥90 mm Hg were excluded from the study. Overall, blood pressure was well controlled at study entry.

Numbers analysed

The Safety Analysis Set included all patients who received at least 1 dose of study drug: 195 patients in the Nefecon 16 mg group and 194 patients in the placebo group. It comprises of 389 patients in total.

The Part B FAS included all patients randomised at the completion of recruitment to the global part of the study (with the exception of the 2 incorrectly enrolled patients who were also excluded from the Part A FAS): 182 patients in the Nefecon 16 mg group and 182 patients in the placebo group.

Twenty-nine patients recruited in China after recruitment to the global part of the study was completed are not included in the Part B FAS but are included in the Safety Analysis Set. Five patients (2 in the Nefecon 16 mg group and 3 in the placebo group) were randomised and included in the Part B FAS but did not receive any blinded study treatment. Thus, 359 patients were dosed in the Part B FAS. The Part B Full Analysis Set comprised 364 patients.

The primary efficacy analyses are based on the Part B Full Analysis, which included all patients in the Part B FAS for whom no protocol deviations occurred during the study that were considered to have the potential to impact the efficacy evaluation: 161 patients in the Nefecon 16 mg group and 164 patients in the placebo group. A total of 39 patients in the Part B FAS had 1 or more protocol

deviations leading to exclusion from the Part B Per Protocol Set. In addition to excluding all data from 39 patients, individual data points were excluded from the Part B Per Protocol Set, such as those recorded after early discontinuation from study treatment or after rescue medication; this resulted in 2-year eGFR data from 161 patients in the Nefecon 16 mg group and 164 patients in the placebo group being included in the Per Protocol Set. The Part B Per Protocol Set comprised 325 patients. Table 1 summarises analysis sets for all randomised patients.

Table 1. Analysis sets – all randomised patients

	Nefecon 16 mg (N=197) n (%)	Placebo (N=198) n (%)	Total (N=395) n (%)
Safety Analysis Set [1]	195 (99.0)	194 (98.0)	389 (98.5)
Excluded from the Safety Analysis Set	2 (1.0)	4 (2.0)	6 (1.5)
Part B FAS [2]	182 (92.4)	182 (91.9)	364 (92.2)
Excluded from the Part B FAS	15 (7.6)	16 (8.1)	31 (7.8)
Part B FAS patients dosed [3]	180 (91.4)	179 (90.4)	359 (90.9)
Part B Per Protocol Set [4]	161 (81.7)	164 (82.8)	325 (82.3)
Excluded from the Part B Per Protocol Set	21 (10.7)	18 (9.1)	39 (9.9)
Study treatment compliance during Treatment Period <80% or >120%	10 (5.1)	9 (4.5)	19 (4.8)
Change in RAS treatment more than 25%	4 (2.0)	5 (2.5)	9 (2.3)
No study treatment was received	2 (1.0)	3 (1.5)	5 (1.3)
Major deviation from eligibility criteria	2 (1.0)	1 (0.5)	3 (0.8)
Change in RAS treatment more than 25% with also unblinding during Part A or Part B	2 (1.0)	0 (0.0)	2 (0.5)
Unblinding during Part A or Part B	1 (0.5)	0 (0.0)	1 (0.3)

Note: % = 100 × n/N.

1. The Safety Analysis Set included all patients who received at least 1 dose of study drug. The 6 patients excluded from the Safety Analysis Set were randomized but not dosed.
2. The Part B FAS included all patients randomized at the completion of recruitment to the global part of the study (with the exception of the 2 incorrectly enrolled patients who were also excluded from the Part A FAS). The 29 patients recruited in China after recruitment to the global part of the study was completed were not included in the Part B FAS. The planned number of patients in the Part B FAS was 360.
3. This is the number of patients in the Part B FAS who received at least 1 dose of study treatment.
4. The Part B Per Protocol Set included all patients in the Part B FAS for whom no protocol deviations occurred during the study that were considered to have the potential to impact the efficacy evaluation.

FAS = Full Analysis Set; RAS = renin-angiotensin system.

Sources: Post-text Tables 14.1.1.3 and 14.1.1.4

Outcomes and estimation

The results are for the pre-planned Part B analysis, which is the final analysis of the overall 2-year global study. The DCO date of 06 February 2023 was scheduled to occur once the last patient randomised in the global study had the opportunity to complete Visit 17b, which could occur up to 35 days after Visit 17a (the 24-month visit). The Part A analysis results were presented within the initial MAA.

Primary Efficacy Evaluation

The primary efficacy endpoint for the Part B analysis was a time-weighted average of eGFR observed at each time point over 2 years, with the treatment effect interpreted as the average effect of Nefecon compared to placebo over 2 years. Data impacted by rescue medication were excluded from the

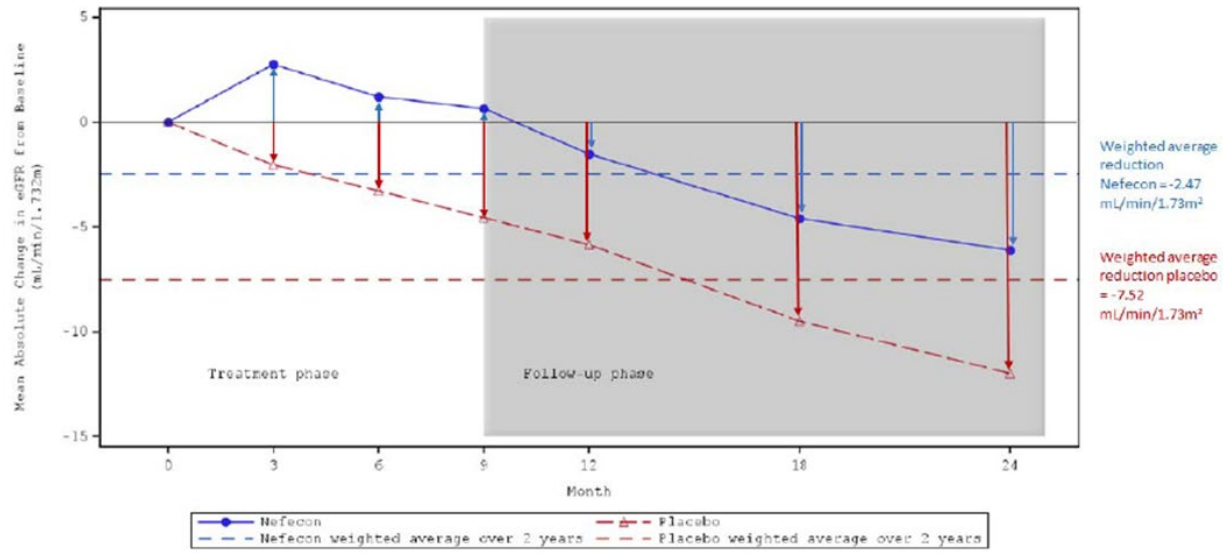
primary analysis of eGFR over 2 years. Averaged over the 2-year study period (9 months of treatment + 15 months of observational follow-up), the primary endpoint of time-weighted average of eGFR over 2 years showed a 5.05 mL/min/1.73 m^2 eGFR treatment benefit in favour of Nefecon 16 mg compared to placebo (p<0.0001), see Table 2 and Figure 3.

Table 2. Primary analysis of the time-weighted average of eGFR over 2 years (ml/min/1.73m^2) using robust regression – part B FAS

	Nefecon 16 mg (N=182)	Placebo (N=182)
Number of patients included in the analysis	182	182
Ratio of geometric LS mean time-weighted average of eGFR over 2 years (95% CI)	0.96 (0.93 to 0.98)	0.87 (0.84 to 0.89)
Mean change from baseline in eGFR averaged over 2 years (mL/min/1.73 m^2) (95% CI)	-2.47 (-3.88 to -1.02)	-7.52 (-8.83 to -6.18)
Nefecon 16 mg versus placebo treatment effect		
Ratio of geometric LS means (95% CI)	1.10 (1.06 to 1.15)	
1-sided p-value	<0.0001	
Average difference in eGFR over 2 years (mL/min/1.73 m^2) (95% CI)	5.05 (3.24 to 7.38)	

Note: The primary endpoint was calculated as a time-weighted average of log-eGFR baseline ratio of measurements at each post-baseline visit compared to baseline for Month 3, 6, 9, 12, 18, and 24, respectively, where recordings made at 18 and 24 months received twice as much weight as those made at 3, 6, 9, and 12 months. For more information, see Section 3.3.2.1 of the SAP (Appendix 16.1.9).
Data included at baseline and 24 months are the log of the geometric mean of the 2 replicate values recorded at each time point, respectively. All patients in the Part B FAS are included in the robust regression analysis, with data multiply imputed, either implicitly or explicitly, prior to analysis.
Mean changes in eGFR averaged over the 2-year period of treatment and observation were derived directly from the robust regression analysis performed on the log scale. Mean change from baseline = baseline geometric mean for the total across both treatment arms × (geometric LS mean of ratio of time-weighted average over 2 years compared to baseline for each treatment arm – 1).
eGFR was calculated by the central laboratory using the CKD-EPI formula.
CI = confidence interval; CKD-EPI = Chronic Kidney Disease Epidemiology Collaboration; eGFR = estimated glomerular filtration rate; FAS = Full Analysis Set; LS = least squares; SAP = Statistical Analysis Plan.
Source: Post-text Table 14.2.1.2.1

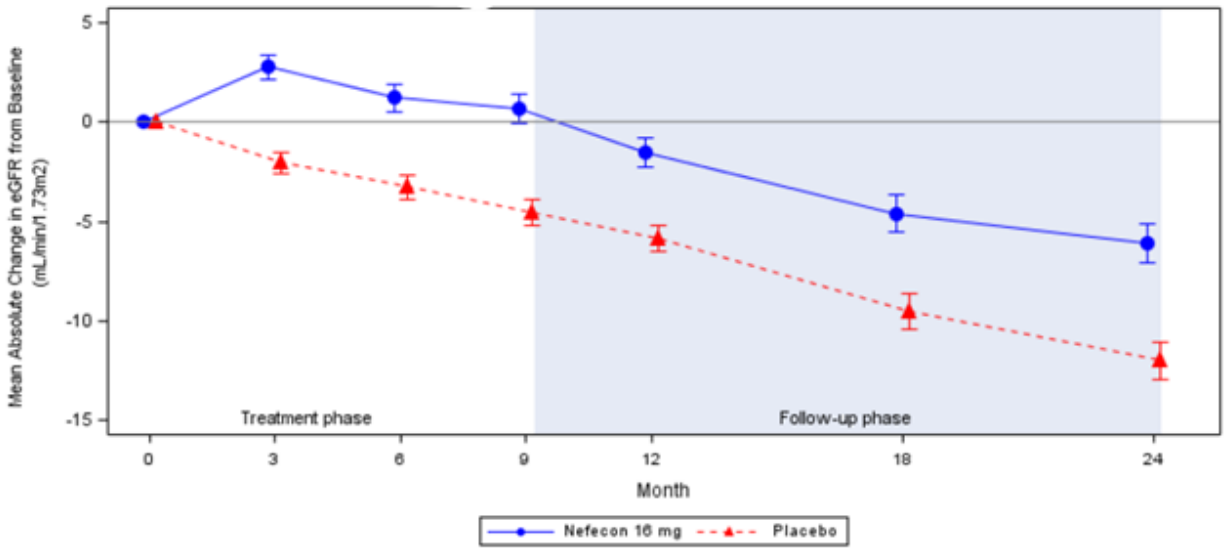
Figure 3. Illustration of time-weighted average of eGFR over 2 years



All post-baseline measurements contribute to give a time-weighted average reduction during 2 years of treatment and observation.
eGFR = estimated glomerular filtration rate.

The eGFR trajectories observed in each treatment group show that a 9-month treatment course of Nefecon 16 mg/day reduced the rate of eGFR decline over 2 years (Figure 3). After 9 months of treatment, the change from baseline in eGFR was 0.66 mL/min/1.73 m^2 in Nefecon-treated patients, compared to -4.56 mL/min/1.73 m^2 in placebo-treated patients. The eGFR benefit accrued by the end of 9 months of treatment was maintained during 15 months of observational follow-up.

Figure 4. Mean absolute change in eGFR from baseline – part B FAS



Sensitivity and supplementary analyses of the time-weighted average of eGFR over 2 years

Results from all sensitivity and supplementary analyses were consistent with the primary analysis, suggesting results were not unduly affected by missing data, protocol deviations, or the use of rescue medication.

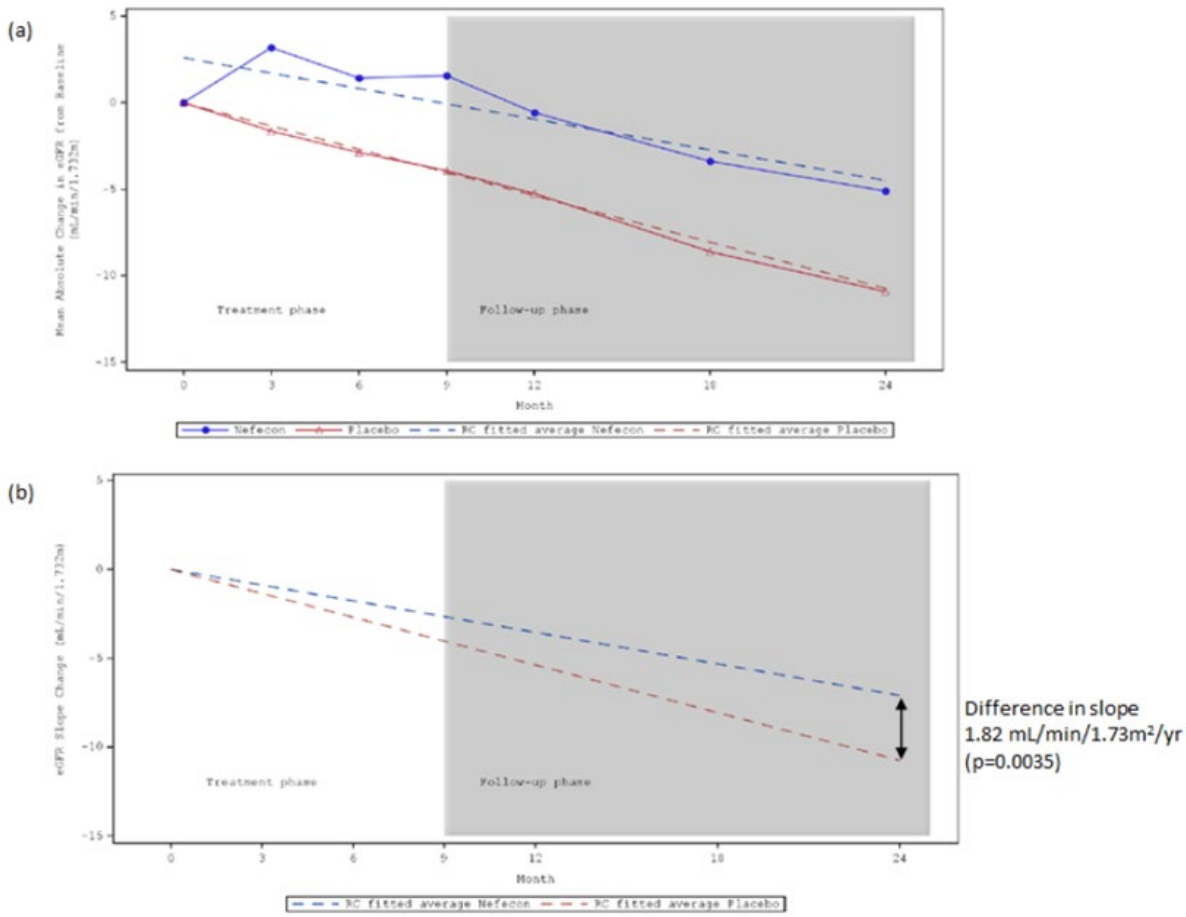
In the primary supportive analysis of 2-year eGFR total slope, Nefecon 16 mg once daily provided a statistically significant and clinically relevant 1.82 mL/min/1.73 m^2 per year improvement in 2-year eGFR total slope compared to placebo (p=0.0035), see Table 3.

Table 3. Primary supportive analysis of 2-year eGFR total slope (mL/min/1.73m^2 er year) using random coefficient regression – part B FAS

Analysis	Difference Between Nefecon 16 mg and Placebo in 2-year eGFR Total Slope (95% CI) (mL/min/1.73 m^2 per year); 1-sided p-value	eGFR 2-year Total Slope (95% CI) (mL/min/1.73 m^2 per year)	
		Nefecon 16 mg (N=182)	Placebo (N=182)
Primary supportive random coefficients analysis excluding data observed after receiving rescue medication	1.82 (0.50 to 3.13); p=0.0035	-3.55 (-4.48 to -2.62)	-5.37 (-6.30 to -4.43)

Note: In all analyses, missing data were multiply imputed, either implicitly or explicitly, prior to analysis. "N" represents the total number of patients included who either had data observed or imputed.
eGFR was calculated by the central laboratory using the CKD-EPI formula.
CI = confidence interval; CKD-EPI = Chronic Kidney Disease Epidemiology Collaboration; eGFR = estimated glomerular filtration rate; FAS = Full Analysis Set.
Source: Post-text Table 14.2.1.2.7

Figure 5. Illustration of primary random coefficients analysis of 2-year eGFR total slope



Analysis pre-specified prior to Part A results when no acute increase in eGFR was expected.
Figure 10a illustrates the random coefficients analysis, which fits a regression line to the data that is not forced through baseline.
Figure 10b illustrates that, when the slope in Nefecon patients is compared with the slope in placebo patients, there is divergence of the slopes but an under-estimation of the relative treatment effect.
Mean of imputed, non-transformed eGFR values per time point are displayed, reflecting that data were not log-transformed in this analysis.
eGFR = estimated glomerular filtration rate; RC = random coefficients; yr = year.

The primary supportive analysis of 2-year eGFR total slope using random coefficient regression was planned prior to unblinding Part A, when no acute increase in eGFR was expected (see Figure 5). In light of the acute eGFR effect observed in the Part A analysis, and prior to unblinding Part B, 2 supplementary analysis methods for 2-year eGFR slope were defined in the SAP Addendum Version 2.0:

Analysis of the change from baseline at 2 years, and a linear spline mixed-effects model.

Supplementary Efficacy Evaluation Based on SAP Addendum

- *Analyses of the change in eGFR from baseline to 2 years* – please see Table 4.

Table 4. Analyses of eGFR change from baseline to 2 years presented as the change per year (mL/min/1.73m²) using robust regression – part B FAS

Robust Regression Analysis of Multiply Imputed 2-year eGFR values	Difference Between Nefecon 16 mg and Placebo		Annualized eGFR Change From Baseline at 2 Years (mL/min/1.73 m² per year)	
	eGFR Change From Baseline at 2 Years (mL/min/1.73 m²) (95% CI); 1-sided p-value	Estimated eGFR 2-year slope (mL/min/1.73 m² per year)	Nefecon 16 mg (N=182)	Placebo (N=182)
Excluding data observed after receiving rescue medication	5.89 (3.35 to 9.15); p<0.0001	2.95	-3.06	-6.00
Including data observed after receiving rescue medication	5.56 (2.92 to 8.89); p<0.0001	2.78	-3.18	-5.96

- *Analyses of 2-year eGFR slope using a linear spline mixed-effects model*

In this analysis, eGFR was modelled simultaneously and separately over the acute (baseline to 3 months) and chronic (from 3 months onward) phases and then combined to give an estimate of the overall total slope. The "knot," i.e., the point at which the slope changes from the acute to chronic phase, was set to 3 months to coincide with the first assessment visit, and the point at which the direction of the slope had been observed to change in the Part A analysis.

The difference in acute slope between Nefecon and placebo was nominally significant, the chronic slope was not significant. Once the Nefecon acute effect had stabilised, the eGFR treatment benefit relative to placebo was maintained through to 2 years. An analysis using the linear spline mixed-effects model and including data observed after the use of rescue medication provided similar results. The sensitivity analysis using GEE to assess any sensitivity to the use of robust standard errors in this modelling approach also provided consistent results. Please refer to Table 5.

Table 5. Analyses of eGFR change from baseline to 2 years presented as the change per year (mL/min/1.73m²) using robust regression – part B FAS

Linear Spline Mixed-Effects Model	Difference Between Nefecon 16 mg and Placebo (mL/min/1.73 m² per year) (95% CI); 1-sided p-value			eGFR 2-year total slope (95% CI) (mL/min/1.73 m² per year)	
	Acute Slope	Chronic Slope	Total 2-Year Slope	Nefecon 16 mg (N=182)	Placebo (N=182)
Excluding data observed after rescue medication	17.05 (10.35 to 23.75); p<0.0001	0.74 (-0.84 to 2.33); p=0.1790	2.78 (1.39 to 4.17); p<0.0001	-2.65 (-3.59 to -1.72)	-5.44 (-6.50 to -4.37)
Including data observed after rescue medication	16.93 (10.39 to 23.47); p<0.0001	0.57 (-1.00 to 2.14); p=0.2374	2.62 (1.23 to 4.00); p=0.0001	-2.89 (-3.86 to -1.93)	-5.51 (-6.53 to -4.49)
Generalized estimating equations approach to assess any sensitivity to the use of robust standard errors, excluding data observed after rescue medication	19.60 (12.99 to 26.21); p<0.0001	0.52 (-1.05 to 2.09); 0.2591	2.90 (1.42 to 4.38); p<0.0001	-2.37 (-3.45 to -1.29)	-5.27 (-6.29 to -4.26)

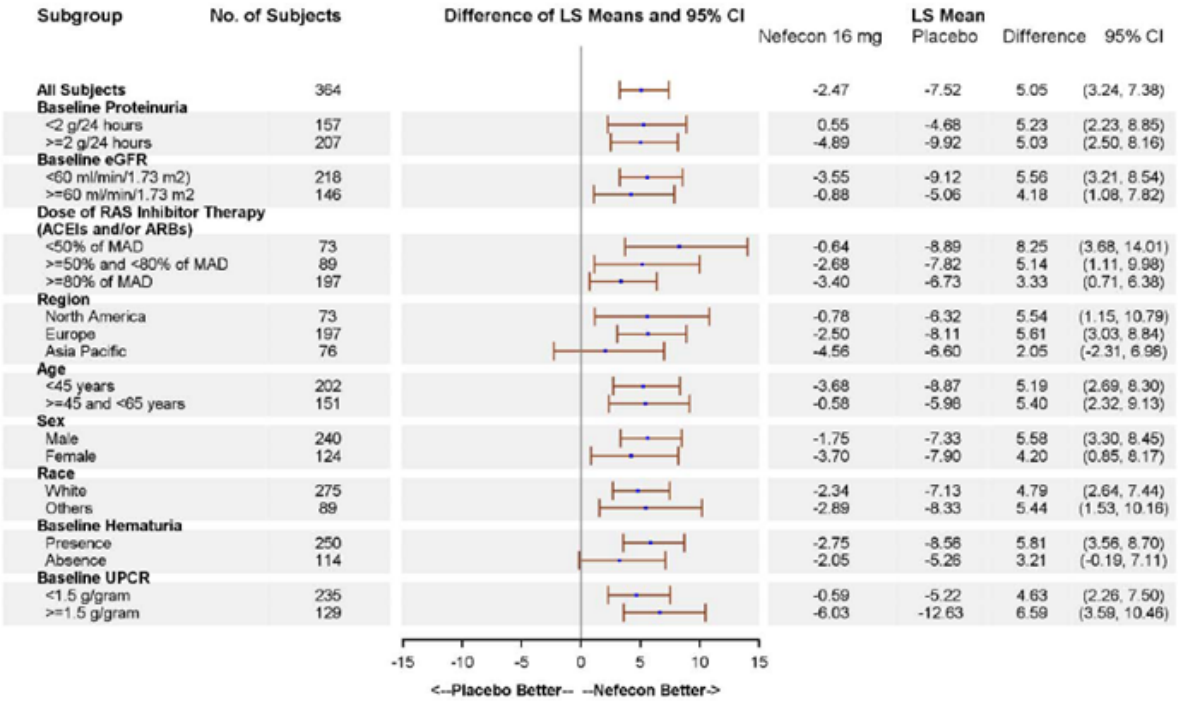
Note: In all analyses, missing data were multiply imputed, either implicitly or explicitly, prior to analysis. "N" represents the total number of patients included who either had data observed or imputed.
eGFR was calculated by the central laboratory using the CKD-EPI formula.
CI = confidence interval; CKD-EPI = Chronic Kidney Disease Epidemiology Collaboration; eGFR = estimated glomerular filtration rate; FAS = Full Analysis Set.
Sources: Post-text Tables 14.2.5.1.1, 14.2.5.1.3, and 14.2.5.1.4

Subgroup analyses

Analyses of the time-weighted average of eGFR over 2 years using robust regression were performed for subgroups of patients in the Part B FAS based on age (<45 years or ≥45 and <65 years); gender (male or female); race (White or others); region (Europe, North America, or Asia Pacific); baseline eGFR (<60 mL/min/1.73 m² or ≥60 mL/min/1.73 m²); baseline proteinuria (<2 g/24 hours or ≥2 g/24

hours); and dose of RAS inhibitor therapy (ACEIs and/or ARBs). Baseline UPCR subgroups (<1.5 g/gram or ≥1.5 g/gram) were added to the SAP Addendum. Please refer to the Figure 6.

Figure 6. Subgroup analysis: time-weighted average of eGFR over 2 years (mL/min/1.73m^2) using robust regression – Part B FAS



Note: Subgroup levels with fewer than 20 patients exposed to Nefecon 16 mg were not assessed.
Continuous factors categorized for the forest plots were analyzed as continuous variables when performing the interaction tests, with baseline proteinuria and baseline eGFR log transformed prior to analysis.
eGFR was calculated by the central laboratory using the CKD-EPI formula.
ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin II type I receptor blocker; CI = confidence interval; CKD-EPI = Chronic Kidney Disease Epidemiology Collaboration; eGFR = estimated glomerular filtration rate; FAS = Full Analysis Set; LS = least squares; MAD = maximum allowable dose; RAS = renin-angiotensin system; UPCR = urine protein to creatinine ratio.

A supplementary analysis excluding data of patients who were receiving dual RAS inhibitor therapy with an ACEI and an ARB (Part B FAS: 8 patients randomised to Nefecon 16 mg and 8 patients randomised to placebo) was also performed. Results were consistent with the primary analysis (Nefecon *vs* placebo treatment effect: 5.29 (95% CI 3.38 to 7.74) mL/min/1.73 m^2)

Ancillary analyses

As requested by the CHMP during the first assessment round, the MAH provided additional analyses for estimating the effect size remaining at the 24 months' time point. A mixed model for repeated measurements was used to assess the difference in mean change in eGFR from baseline between study drug and placebo in the full analysis set. Estimation was done using different strategies to handle intercurrent events including use of rescue medication. The first strategy used was a treatment policy strategy using all observed data irrespective of intercurrent events. The second strategy was to use imputation methods to impute the values missing due to intercurrent events (hypothetical strategy). Imputation methods used were copy reference (CR) and jump to reference (J2R) which don't rely on any assumptions on the missingness patterns. The analyses were repeated in the subgroups of baseline UPCR < 1.5 g/gram and baseline UPCR ≥ 1.5 g/gram. Please refer to Table 6 and Table 7.

Table 6. Nef-301 part B MMRM analyses of the change from baseline in eGFR at 24 months regardless of the use of prohibited medications, dialysis or transplant (mL/min/1.73m^2) (part B full analysis set)

Analysis	Nefecon 16 mg versus Placebo Treatment Effect eGFR difference at 24 months (95% CI) (mL/min/1.73 m^2); 1-sided p-value	Mean change from baseline in eGFR at 24 months (95% CI); (mL/min/1.73 m^2)	
		Nefecon 16 mg (N=182)	Placebo (N=182)
MMRM analysis without explicit missing data assumptions (MAR assumption)	6.00 (2.76 to 10.08); p=0.0002	-7.50 (-9.91 to -4.97) [n=161]	-13.50 (-15.60 to -11.29) [n=165]
MMRM analysis with reference-based imputation for missing data (CR imputation)[a]	5.91 (2.58 to 10.10); p=0.0003	-7.73 (-10.19 to -5.13) [n=182]	-13.63 (-15.78 to -11.37) [n=182]
MMRM analysis with reference-based imputation for missing data (J2R imputation)[a]	5.71 (2.42 to 9.86); p=0.0004	-8.03 (-10.51 to -5.41) [n=182]	-13.74 (-15.92 to -11.45) [n=182]

Table 7. Nef-301 part B MMRM analyses of the change from baseline in eGFR at 24 months regardless of the use of prohibited medications, dialysis or transplant according to baseline UPCR <1.5 g/gram and ≥1.5/gram (mL/min/1.73m^2) (part B full analysis set)

Analysis	Nefecon 16 mg versus Placebo Treatment Effect eGFR difference at 24 months (95% CI) (mL/min/1.73 m^2); 1-sided p-value	Mean change from baseline in eGFR at 24 months (95% CI); (mL/min/1.73 m^2)	
		Nefecon 16 mg (N=182)	Placebo (N=182)
Baseline UPCR<1.5 g/gram			
MMRM analysis without explicit missing data assumptions (MAR assumption)	6.34 (2.13 to 11.53); p=0.0016	-4.55 (-7.73 to -1.16) [n=104]	-10.89 (-13.62 to -7.98) [n=113]
MMRM analysis with reference-based imputation for missing data (CR imputation)[a]	6.44 (2.19 to 11.67); p=0.0015	-4.45 (-7.60 to -1.09) [n=117]	-10.88 (-13.61 to -7.99) [n=118]
MMRM analysis with reference-based imputation for missing data (J2R imputation)[a]	5.76 (1.50 to 10.96); p=0.0040	-5.14 (-8.40 to -1.67) [n=117]	-10.91 (-13.64 to -8.00) [n=118]
Baseline UPCR≥1.5 g/gram			
MMRM analysis without explicit missing data assumptions (MAR assumption)	6.04 (1.34 to 12.09); p=0.0059	-12.19 (-15.70 to -8.37) [n=57]	-18.23 (-21.35 to -14.82) [n=52]
MMRM analysis with reference-based imputation for missing data (CR imputation)[a]	5.13 (0.57 to 10.88); p=0.0137	-12.81 (-16.25 to -9.04) [n=65]	-17.93 (-21.14 to -14.42) [n=64]
MMRM analysis with reference-based imputation for missing data (J2R imputation)[a]	5.12 (0.24 to 11.28); p=0.0198	-13.10 (-16.67 to -9.19) [n=65]	-18.22 (-21.60 to -14.48) [n=64]

Summary of main study

The following table summarises the efficacy results from the main study supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Summary of efficacy for study Nef-301

Title: A Randomised, Double-Blind, Placebo Controlled Study to Evaluate Efficacy and Safety of Kinpeygo in Patients With Primary IgA Nephropathy at Risk of Progressing to End-Stage Renal Disease (NefIgArd)			
Study identifier	Nef-301		
Design	Phase 3, randomised, double-blind, placebo-controlled, multicenter study to evaluate the efficacy, safety, and tolerability of oral Kinpeygo compared to matching placebo in patients with primary IgAN on a background of optimised RAS inhibitor therapy		
	Duration of Part A: Duration of Part B:		9 months 12-month (+14 to 35 days) observational Follow-up Period
Hypothesis	Part A: The primary objective of Part A is to assess the effect of Kinpeygo 16 mg treatment on UPCR over 9 months compared to placebo. Part B: The primary objective of Part B is to assess the effect of the Kinpeygo 16 mg treatment given in Part A on clinical consequences of any proteinuria reduction as measured by eGFR recorded over 2 years compared to placebo		
Treatments groups	Part A		Kinpeygo 16 mg/day. 9 months, Completed: 158 Nefecon; 167 Placebo; Randomised: 366 (29 from China not included in Part B FAS; minus 2 patients randomised in error: Total 364
	Part B		observational follow-up 12 months: The primary Part B analysis was conducted based on the Part B FAS, which included all 364 patients (Nef:182; Placebo:182) randomised at the completion of recruitment to the global part of the study
Endpoints and definitions	Part A Primary efficacy endpoint	UPCR	The primary efficacy endpoint for the Part A analysis was defined as the ratio of UPCR (based on 24-hour urine collections) at 9 months following the first dose of study drug compared to baseline.
	Secondary endpoints	eGFR	Ratio of eGFR at 9 and 12 months compared to baseline calculated using the CKD-EPI formula, Ratio of urine albumin to creatinine ratio (UACR) at 9 months compared to baseline. In addition, a supportive analysis of 1-year eGFR total slope was performed.

Endpoints and definitions	Part B	eGFR	**predefined primary efficacy endpoint** for the Part B analysis was a time-weighted average of eGFR over 2 years ***post-hoc* request- most relevant analysis** eGFR change from baseline at 24 months Supportive analysis of 2-year eGFR slope was also performed and included in the hierarchical testing strategy **secondary efficacy endpoints** Time to 30% reduction from baseline in eGFR Time from the first dose of study drug until receiving rescue medication Ratio of UPCR, UACR, and eGFR Other (see study report): Proportions of patients without microhaematuria and patients receiving rescue treatment, SF-36 quality of life
Database lock	Data Cutoff Date (Part B): 06 February 2023		

Results and Analysis

Analysis description	**Primary Analysis**		
Analysis population and time point description	Primary IgAN patients randomised to Kinpeygo or Placebo (1:1) both on a stable RAS inhibitor therapy; The primary analysis in Part B was to occur 25 months after the last patient was dosed (or, if the last patient randomised did not receive any study drug, 25 months after the last patient was randomised).		
Descriptive statistics and estimate variability	Treatment group	Kinpeygo	Placebo
	Number of subjects	182	182
	Mean change from baseline in eGFR averaged over 2 years (mL/min/1.73 m^2) (supportive analysis of the 2-year eGFR slope)	**-**2.47	**-**7.52
	(95% CI)	-3.88 to -1.02	-8.83 to -6.18

Effect estimate per comparison	Average difference in eGFR over 2 years (95% CI) (mL/min/1.73 m^2)	**Nefecon 16 mg *vs* Placebo Treatment Effect**	
		difference between groups	5.05
		95%-CI	3.24 to 7.38
		P-value (1-sided)	<0.0001

	Mean change from baseline in eGFR at 24 months (mL/min/1.73 m^2) (95% CI) difference between groups (mL/min/1.73 m^2 (95% CI) 1-sided p-value **(MMRM analysis without explicit missing data assumptions (MAR assumption))**	Nefecon -7.50 (-9.91 to -4.97) 6.00 (2.76 to 10.08) p=0.0002	Placebo -13.50 (-15.60 to -11.29)
	Primary Supportive Analysis of 2-Year eGFR **Total Slope** (mL/min/1.73 m^2 per year) Using Random Coefficient Regression Part B FAS	Primary supportive random coefficients analysis excluding data observed after receiving rescue medication	
	Difference Between Nefecon16 mg and Placebo in 2-year eGFR **Total Slope** (95% CI) (mL/min/1.73 m^2 per year)	difference between groups 95%-CI P-value (1-sided)	1.82 0.50 to 3.13 0.0035
	Analyses of eGFR 2-Year Slope Using Linear Spline Mixed-Effects Model (mL/min/1.73 m^2 per year) Part B FAS Difference in **acute slope** between groups	difference between groups 95%-CI P-value (1-sided)	17.05 10.35 – 23.75 <0.0001
	Difference in **chronic slope** between groups	difference between groups 95%-CI P-value (1-sided)	0.74 0.84 – 2.33 0.1790
Notes	In the linear spline mixed-effects model, an additional 2-year eGFR slope analysis, the difference in acute slope between Nefecon and placebo was nominally significant (17.05 (95% CI 10.35; 23.75); p<0.0001, whereas chronic slopes were not significantly different (0.74 (95% CI -0.84 - 2.33); p=0.1790 (analyses excluded data observed after rescue medication)		
Analysis description	**Secondary analysis (most important endpoints)**		

Time to 30% reduction from baseline in eGFR confirmed by a second value, with ⩾4 weeks of separation between the 2 sampling time points	**Comparison Nefecon 16 mg *vs* Placebo**	
	Hazard ratio (95% CI)	0.45 (0.26 to 0.75)
	1-sided p-value	0.0014

UPCR (g/gram) at 9, 12 and 24 months compared to baseline

Time point (n, n)	Comparison Nefecon 16 mg *vs* Placebo		Percentage change from baseline	
	Ratio of geometric LSmeans (95% CI); 1-sided p-value	Corresponding percentage reduction (95% CI)	Nefecon 16 mg (N=182)	Placebo (N=182)
9 months (n=166, 164)	0.70 (0.61 to 0.80); p<0.0001	30% (20% to 39%)	-34%	-5%
12 months (n=157, 160)	0.50 (0.43 to 0.58); p<0.0001	50% (42% to 57%)	-51%	-3%
24 months (n=145, 142)	0.70 (0.59 to 0.84); p<0.0001	30% (16% to 41%)	-31%	-1%

UACR (g/gram) at 9, 12and 24 months compared to baseline

Time point (n, n)	Comparison Nefecon 16 mg *vs* Placebo		Percentage change from baseline	
	Ratio of geometric LSmeans (95% CI); 1-sided p-value	Corresponding percentage reduction (95% CI)	Nefecon 16 mg (N=182)	Placebo (N=182)
9 months (n=167, 165)	0.66 (0.56 to 0.77); p<0.0001	34% (23% to 44%)	-38%	-6%
12 months (n=158, 159)	0.44 (0.37 to 0.53); p<0.0001	56% (47% to 63%)	-57%	-4%
24 months (n=145, 142)	0.65 (0.53 to 0.80); p<0.0001	35% (20% to 47%)	-37%	-3%

2.4.2. Discussion on clinical efficacy

Design and conduct of clinical study

The study design of the pivotal study Nef-301, a randomised, double-blind, placebo-controlled study to evaluate the efficacy, safety and tolerability of Kinpeygo (16 mg) compared to matching placebo in patients with primary IgAN on a background of optimised RAS inhibitor therapy, has already been discussed during the initial MAA. The study included female and male patients ≥18 years of age with biopsy-verified primary IgAN, persistent proteinuria of ≥1 g/d or UPCR ≥0.8 g/g and an eGFR of ≥35 mL/min per 1.73m^2 and ≤90 ml/min per 1.73m^2 using the CKD-EPI formula. Patients with insufficiently controlled type 1 or type 2 diabetes (HbA1c >8%), any secondary form of IgA nephropathy or non-IgA nephropathy glomerulonephritis, poorly controlled blood pressure (≥140/90 mmHg), or who had undergone a kidney transplant were excluded. The recruited population for the phase 3 trial Nef-301 was generally deemed acceptable. Patient demographics and baseline characteristics were balanced across the treatment groups and considered representative of the intended primary IgA nephropathy population.

Kinpeygo was approved in the indication "*Kinpeygo is indicated for the treatment of primary immunoglobulin A (IgA) nephropathy (IgAN) in adults at risk of rapid disease progression with a urine protein-to-creatinine ratio (UPCR) ≥1.5 g/gram*". This was based on the Part A analysis of the pivotal Phase 3 study Nef-301.

The primary efficacy endpoint for the Part A analysis was defined as the ratio of UPCR (based on 24 hours urine collections) at 9 months following the first dose of study drug compared to baseline.

The secondary efficacy endpoints for the Part A analysis were ratio of eGFR at 9 and 12 months compared to baseline calculated using the CKD-EPI formula and ratio of UACR at 9 months compared to baseline. There was intensive discussion about considering proteinuria as a robust primary surrogate endpoint as part of several CHMP Scientific Advices, therefore, the MAH followed the recommendation and additionally provided also a 1-year eGFR slope analysis from Part A as secondary endpoint.

The primary efficacy endpoint for the Part B analysis was an AUC-based endpoint calculated as a time-weighted average of eGFR (CKD-EPI) measurements recorded over 2 years, where each time point was given a weight in proportion to the time elapsing from the previous recording. Therefore, recordings made at 18 and 24 months received twice as much weight as those made at 3, 6, 9, and 12 months. The weights were to sum to one so that the treatment effect could be interpreted as the average effect of Nefecon over 2 years.

The presented AUC-analysis approach for eGFR 2-year outcome was, however, not considered appropriate to directly address the outstanding question to estimate the effect size remaining at the time point of 24 months in order to be able to "assess the clinical consequences of proteinuria reduction, as measured by eGFR" (see wording SOB). Via the AUC-analysis approach the whole time course (starting from baseline) is included in the analysis and therefore influences estimates and p-values. This definition of the endpoint was considered to not represent the effect size remaining at month 24 and therefore was seen not eligible to be interpreted as the 24-months eGFR-outcome. As the actual choice of the primary endpoint was not considered a methodologically appropriate estimate for the eGFR effect size remaining at the 24-month time point targeted, the MAH was asked to provide additional analyses.

As requested during the first assessment round, the MAH provided an MMRM analysis using a treatment policy intercurrent event strategy, which was considered most appropriate for estimating the effect size remaining at the 24-month time point and giving all eGFR observations the same weight in the regression modelling.

The primary efficacy endpoint for the Part B analysis was supplemented by a 2-year eGFR total slope analysis. Generally, the rate of eGFR decline, or eGFR slope, can be regarded as a valid endpoint and two- and three-year eGFR-based endpoints are now being used in all currently recruiting phase 3 studies of immunotherapies in IgAN to confirm response to treatment as also described in the literature. Because the total slope includes both the acute and chronic GFR slope, total slope is generally considered the superior performance. However, in cases where a positive acute effect is observed, as seen in the Nef-301 trial, the total slope may overestimate the treatment benefit and the chronic slope may represent the more conservative endpoint.

Of note, the analyses of 2-year eGFR total slope were planned prior to unblinding Part A (SAP Version 5.0), based on eGFR results observed in Study Nef-202, which did not show an acute effect. In light of the acute eGFR effect observed in the Part A analysis of study Nef-301, and prior to unblinding Part B, 2 supplementary analysis methods for 2-year eGFR slope were defined in the SAP Addendum v.2.0 analysis of the change from baseline at 2 years, and a linear spline mixed-effects model, which fits a separate acute and chronic phase to estimate the total rate of change over 2 years.

Secondary efficacy endpoints included the composite endpoint of time from randomisation to confirmed 30% reduction in eGFR or confirmed kidney failure, the ratios of UPCR and urine albumin– creatinine ratio (UACR) compared with baseline, averaged over timepoints between 12 and 24 months and the proportion of patients without microhaematuria during observational follow-up. Other secondary endpoints were the ratio of eGFR compared with baseline averaged over timepoints between 12 and 24 months, time from first dose of study drug to receiving rescue medication, the proportion of patients receiving rescue treatment, and Short Form 36 quality of life assessment at 9 and 24 months. Overall, the secondary endpoints are considered informative and further support the primary findings.

Efficacy data and additional analyses

The primary endpoint of the pivotal study Part A, reduction of proteinuria (UPCR) at 9 months compared to baseline, was met. The efficacy data from Part A showed that the ratio of UPCR at 9 months to baseline was 0.69 (CI 95% 0.61 to 0.79) in the Kinpeygo treatment arm and 0.95 (CI 95% 0.83 to 1.08) in the placebo arm. This means a reduction of proteinuria (UPCR) of 31 % for Kinpeygo and 5 % for placebo during a treatment course of 9 months and was even more pronounced at 12 months showing a ratio of 0.52 (CI 95% 0.42 to 0.64). Reliability of these data derived from the primary MMRM analysis (Part A FAS) was strongly supported by supplementary and sensitivity analysis, indicating the robustness of the 9-month treatment effect on UPCR. The key secondary endpoint analyses of renal function based on eGFR at 9 months showed a statistically significant and clinically relevant 7 % (CI 95% 3% to 13%) treatment benefit compared to placebo. In contrast to proteinuria (primary endpoint), this effect was not pronounced after 12 months. Additional analyses indicated that the difference in 1-year eGFR chronic slope between Kinpeygo and placebo became statistically significant in patients with higher levels of baseline proteinuria. Therefore, a restriction of the target population was recommended in section 4.1 to patients with higher levels of baseline proteinuria (cut-off value UPCR $\geq$1.5 g/gram at baseline) which was a pre-specified subgroup.

This subgroup was also noted to be at particular risk of rapid disease progression over a relatively short time-period and had a considerable unmet medical need. However, there was no significant difference in eGFR chronic slope in the overall study population. Therefore, the indication was

restricted to patients with higher levels of baseline proteinuria (cut-off value of ≥ 1.5 g/gram). In order to fulfil the SOBs for the CMA (i.e. confirmation of efficacy (and safety) of Kinpeygo for the treatment of primary IgAN and assessment of the clinical consequences of proteinuria reduction), the MAH provided the results of Part B of study Nef-301.

As of the Part B data cut-off date (06 February 2023), patients had been dosed at 131 clinical sites in Europe, North America, South America and Asia Pacific.

Efficacy data were analysed in the full analysis set (FAS), which included all randomly assigned patients (apart from two patients who were prospectively excluded due to being incorrectly randomised, and patients recruited for regulatory requirements in China after enrolment of the planned 360 patients was complete). The FAS comprised 364 patients (182 per treatment group). 359 patients in the full analysis set (180 assigned to Nefecon and 179 to placebo) received at least one dose of the assigned study treatment. Five patients (two assigned to Nefecon and three to placebo) did not start study treatment. 158 (87%) of 182 patients in the Nefecon group and 165 (91%) of 182 in the placebo group received 9 months of randomised treatment. Compliance with study treatment was high (171 [94%] patients in each treatment group took at least 80% of the total capsules). The overall rate of study completion was high and similar in both treatment groups; 161 (88%) patients in the Nefecon arm and 165 (91%) in the placebo arm completed the study (patients who had at least one eGFR value within the visit window at 24 months).

Th Part B primary endpoint, the time-weighted average of eGFR over 2 years (9 months of treatment + 15 months of observational follow-up), showed a 5.05 (95% CI 3.24 to 7.38) mL/min/1.73 m^2 eGFR treatment benefit in favour of Nefecon 16 mg compared to placebo ($p<0.0001$) with an average change of −2.47 mL/min per 1·73 m² (95% CI −3·88 to −1·02) reported with Nefecon and −7.52 (95% CI −8·83 to −6·18) mL/min per 1.73 m² reported with placebo. This assessment of Part B focusses on analyses representing mean (absolute) differences from baseline results. The further provided "ratio of geometric mean time-weighted averages" analyses refer to an average ratio over time and this parametrisation is difficult to interpret with regards to their meaning and do therefore not further contribute to this assessment.

After 9 months of treatment, the mean change from baseline in eGFR was 0.66 mL/min per 1.73 m² (95% CI −0.80 to 2.15) in the Nefecon treated patients, compared to −4.56 mL/min per 1.73 m² (95% CI −5.86 to −3.22) in the placebo group. The eGFR benefit accrued by the end of 9 months of treatment with Nefecon was maintained during the 15 months of observational follow-up. After 24 months, there was a decline in eGFR from baseline of 6.11 mL/min per 1.73 m² (95% CI −8.04 to −4.11) compared with 12.0 mL/min/1.73 m^2 (95% CI −13.76 to −10.15) decline in the placebo group.

Results of supplementary analyses that included all data recorded after the use of rescue medication or prohibited immunosuppressive medications (eGFR treatment benefit at 2 years *vs* placebo was 5.56 (95% CI 2.92 to 8.89) mL/min/1.73 m^2) as well as other sensitivity analyses such as an analysis excluding data from patients who were receiving dual RAS inhibitor therapy with an ACEI and an ARB (Nefecon *vs* placebo treatment effect: 5.29 (95% CI 3.38 to 7.74) mL/min/1.73 m^2) were consistent with the primary analysis.

Of note, the 2-year eGFR treatment effect was also consistent across sub-groups, including the baseline proteinuria (2g/24 hours < baseline proteinuria ≥ 2g/24 hours) and UPCR subgroups (1.5 g/gram <UPCR ≥1.5 g/gram). For example, mean treatment difference Nefecon *vs* placebo in subjects with baseline UPCR<1.5 g/gram was 4.63 (95% CI 2.26 to 7.50) compared to 6.59 (95% CI 3.59 *vs* 10.46) in subjects with baseline UPCR ≥1.5 g/gram.

However, as already mentioned above, there were several methodological issues identified limiting the interpretability of the results presented. First of all, the definition of the primary endpoint does not

represent the effect size remaining at month 24 and therefore cannot be interpreted as the 24-months eGFR-outcome.

Furthermore, the description of the full analysis set excluded any data impacted by rescue medication. This was not considered acceptable. Data collected in part B of the trial stem from a 15 months-long `off-Nefecon-treatment´ observation period. In such a setting of a long period of post-treatment observation without (pre-planned) active treatment, it is generally not seen straight forward to regard alternative treatment against the targeted disease as `rescue medication´. The most meaningful and also conservative strategy, representing clinical praxis, is considered to carry out primary eGFR analyses under a treatment policy assumption. One of the pre-planned supplementary analyses covered that aspect, i.e. by repeating the primary analysis with all observed eGFR data included regardless of the use of rescue medication. However, for this analysis only results from robust regression analysis were available. As the application of a robust regression model is not endorsed, the results presented from this supplementary analysis were - while indicative of a remaining treatment effect at month 24 - not considered adequate to reveal a reasonable estimate for the treatment benefit remaining at 24-months following a treatment policy strategy.

Thus, against the background of the three methodological issues raised (endpoint definition, treatment policy estimand, choice of `Robust regression´-analyses), the MAH was asked to perform an analysis for eGFR primary efficacy evaluation which adequately estimates and tests the effect size at the 24 month time point, delivers an effect estimate based on a treatment policy estimand strategy (i.e. making use of all observed eGFR data included regardless of the use of rescue medication) and gives all eGFR observations the same weight in the regression modelling. In the analyses performed on request in the first round of assessment, the main endpoint was eGFR change from baseline after 2 years in the full analysis set regardless of the use of prohibited medications or starting dialysis or having a renal transplant (treatment policy estimand). The endpoint showed a 6.00 (95% CI 2.76 to 10.08) mL/min/1.73 m^2 eGFR treatment benefit in favour of Nefecon (mean change from baseline -7.50 (95% CI -9.91 to -4.97) mL/min/1.73 m^2 for Nefecon and -13.05 (95% CI -15.60 to -11.29) mL/min/1.73 m^2 for placebo) and these are reflected in the PI. In the subgroup of patients with a baseline UPCR < 1.5 g/gram the mean difference was 6.34 (95% CI 2.13 to 11.53) mL/min/1.73 m^2 and in the subgroup of patients with UPCR ≥ 1.5 g/gram the mean difference was 6.04 (95% CI 1.34 to 12.09) mL/min/1.73 m^2.

In additional analyses, all missing data resulting from the exclusion of data due to rescue medication or starting dialysis or having a renal transplant, or if the patient discontinued the study or, in rare cases, because the patient died, as well as a lack of recording of data, were imputed using reference based imputation techniques (hypothetical estimand). The mean differences were 5.91 (95% CI 2.58 to 10.10) mL/min/1.73 m^2 for the copy reference imputation and 5.71 (95% CI 2.42 to 9.86) mL/min/1.73 m^2 for jump to reference imputation.

In the primary supportive random coefficients analysis of 2-year eGFR total slope, Nefecon 16 mg once daily provided a statistically significant and clinically relevant 1.82 (95% CI 0.50 to 3.13) mL/min/1.73 m^2 per year improvement in 2-year eGFR total slope compared to placebo (p=0.0035). This corresponded to a 2-year eGFR slope of -3.55 (95% CI -4.48 to -2.62) mL/min/1.73 m^2 per year in the Nefecon 16 mg group, and -5.37 (95% CI -6.30 to -4.43) mL/min/1.73 m^2 per year in the placebo group.

Based data in literature, for modest-sized trials, a study would be required to have observed treatment effects of 0.72 or 0.74 ml/min per 1.73 m^2/yr mean difference in total GFR slope over either 2 or 3 years, respectively, and 0.85 ml/min per 1.73 m^2/yr mean difference for chronic GFR slope, to confer 97.5% probability of clinical benefit. Since the thresholds described in the publication were expected to apply to a trial approximately twice the size of Nef-301, a revised threshold has been calculated by the

MAH for a trial similar in size to Nef-301. It has been estimated that an observed treatment effect of 1.23 mL/min/1.73 m^2 per year mean difference in total eGFR slope over 2 years would be likely to confer >97.5% probability of clinical benefit.

However, as already mentioned in the "study conduct" part, the analyses of 2-year eGFR total slope were planned prior to unblinding Part A, based on eGFR results observed in Study Nef-202, which did not show an acute effect. Given the positive acute effect and observed eGFR profile over 2 years in the Nef-301 trial, the between-group comparison of total slopes does not account for the obvious slope change in the verum group. Hence, the estimated advantage in total slope presented above is not considered an adequate interpretation of eGFR outcome data. This phenomenon is also mentioned in the literature, i.e., a group comparison *via* total slope of eGFR may overestimate the treatment benefit. Also, the EMA's *Draft Qualification opinion for GFR slope as a Surrogate Endpoint in RCT for CKD (04 September 2023, EMA/SA/00000104642)* repeatedly refers to the importance to differentiate between acute and chronic phases when investigating a potential treatment benefit.

The additional 2-year eGFR slope analyses (an analysis of the change from baseline at 2 years, and a linear spline mixed-effects model) described in the SAP Addendum provide a more accurate assessment of total eGFR slope over 2 years in the presence of an acute effect. In particular, the applied linear spline mixed-effects model is of special interest.

As expected, given the acute increase in eGFR observed between baseline and 3 months in Nefecon-treated patients compared with the deterioration in eGFR observed in placebo-treated patients, the difference in acute slope between Nefecon and placebo was nominally significant. In contrary, chronic slopes were not significantly different. Once the Nefecon acute effect had stabilised, the eGFR treatment benefit relative to placebo was however maintained through to 2 years. The analysis using a linear spline mixed-effects model estimated the improvement in 2-year eGFR total slope, in the absence of rescue medication, to be 2.78 (95% CI 1.39 to 4.17) mL/min/1.73 m^2 per year with Nefecon 16 mg once daily compared to placebo ($p<0.0001$). This corresponds to a 2-year eGFR total slope of -2.65 (95% CI -3.59 to -1.72) mL/min/1.73 m^2 per year in the Nefecon 16 mg group, and -5.44 (95% CI -6.50 to -4.37) mL/min/1.73 m^2 in the placebo group. An analysis using the linear spline mixed-effects model and including data observed after the use of rescue medication provided similar results with a 2-year eGFR total slope of -2.89 (95% CI -3.86 to -1.93) mL/min/1.73 m^2 per year in the Nefecon 16 mg group, and -5.51 (95% CI -6.53 to -4.49) mL/min/1.73 m^2 in the placebo group.

The time to a confirmed 30% reduction in eGFR was significantly delayed in patients who received Nefecon treatment compared with those who received placebo (HR 0.45; 95% CI 0.26 to 0.75; 1-sided p=0.0014; 11.5% *vs* 21.4% with a confirmed 30% eGFR reduction in the Nefecon and placebo groups, respectively). A supplementary analysis with the use of rescue medication included as an event provided similar results (HR 0.51; 95% CI 0.33, 0.79). A *post-hoc* analysis using a standard Cox model, in which the time to a confirmed 30% eGFR reduction was estimated regardless of rescue medication, provided similar results (HR 0.44, 95% CI 0.27 to 0.71). In a *post-hoc* analysis, similar results were also observed in patients with baseline UPCR <1.5 g/gram (HR 0.51; 95% CI 0.21, 1.12) and in patients with baseline UPCR ≥1.5 g/gram (HR 0.42; 95% CI 0.21, 0.83).

The maximum effect of Kinpeygo *vs* placebo in proteinuria reduction (50%; 95% CI 42% to 57%) was observed at 12 months but proteinuria in the Kinpeygo arm is increasing again since that point in time. The percentage reduction in UPCR in the Kinpeygo group *vs* placebo group at 24 months (30%; 95% CI 16% to 41%) is similar to that observed at the end of the 9-month treatment period (30%; 95% CI 20% to 39%). When looking at the data it seems that proteinuria increases in a linear manner again after month 12 in the Nefecon arm, which does not support the MAH's statement about the durability of the proteinuria reduction observed with Nefecon treatment.

Re-treatment might be needed at least for some patients, and assessment to determine a most appropriate re-treatment strategy is warranted. An ongoing open-label extension study for patients who have completed Nef-301 and have proteinuria levels that meet the same inclusion criteria as Nef-301 will provide valuable additional information on a repeated treatment cycle. Upon availability section 4.2. of the SmPC might need to be updated.

In order to gain clarity and to further assess the efficacy in the patients at the lower end of the inclusion criterion of UPCR ≥ 0.8g, the MAH was asked to provide additional analyses for all non-intersecting subgroups ranging from UPCR 0.8 g/gram to 1.5 g/gram in steps of 0.1 g/gram. The MAH provided the requested analyses of change from baseline in eGFR in the non-intersecting subgroups of baseline UPCR. Patients were grouped by baseline UPCR from 0.4 g/g to 0.6 g/g, 0.6 g/g to 0.8 g/g, … and from 0.5 g/g to 0.6 g/g, 0.6 g/g to 0.7 g/g, … respectively, see Table 8 and 9.

The groups of UPCR 0.4 g/g to 0.6 g/g, UPCR 0.6 g/g to 0.8 g/g and the groups of UPCR 0.5 g/g to 0.6 g/g, UPCR 0.6 g/g to 0.7 g/g and UPCR 0.7 g/g to 0.8 g/g consisted entirely of subjects included in the study due to presenting with proteinuria ≥ 1g/day at baseline. Of the groups with UPCR < 0.8 g/g all point estimates for the difference between treatments were positive favouring Kinpeygo. With respect to the subgroups covering the revised label all confidence intervals for the difference in eGFR change from baseline of all groups covered zero or lie even entirely above zero. Only the subgroups of baseline UPCR from 0.8 g/g to 0.9 g/g and baseline UPCR from 1.3 g/g to 1.4 g/g had negative point estimates. However, these estimates are highly variable due to the small group sizes and may represent random observations.

With respect to the groups at the lower end of the inclusion criterium of UPCR ≥ 0.8 g/g, it is noted that this subgroup nearest to the cutoff point (baseline UPCR of 0.8 g/g to 0.9 g/g) had a negative point estimate for the difference in eGFR change from baseline at 2 years. However, this group consists of only 19 patients and is accompanied by high variability. No pattern of reduced efficacy for patients with UPCR below this cut-off (though included based on proteinuria) is observed, supporting a conclusion of a random observation. Moreover, also the subgroups with larger width of 0.2 g/g (Table 8), including relevantly the subgroup with baseline UPCR of 0.8 g/g to 1 g/g, had a positive point estimate for the difference in eGFR change from baseline well above 0. Therefore, it is concluded, that not only was no detrimental effect observed, but all subgroups contained by the inclusion criteria do rather suggest a positive effect. As a consequence, the subgroup analyses support the wider indication based on the study inclusion criteria of UPCR ≥ 0.8 g/g or proteinuria ≥ 1 g/day. This is reflected in the updated PI.

Table 8. Nef-301 Part B analysis of the eGFR change from baseline at 2 years in baseline UPCR increments of 0.2 g/gram using MMRM analysis without explicit missing data assumptions and including all data regardless of the use of prohibited medications, dialysis or transplant (Part B Full Analysis Set)

Baseline UPCR cut-off (g/gram)	Difference between Nefecon 16 mg and placebo in eGFR change from baseline at 2 years (95% CI); 1-sided p-value (mL/min/1.73 m^2 per year)	eGFR change from baseline at 2 years (mL/min/1.73 m^2 per year) [n]	
		Nefecon 16 mg N=182	Placebo N=182
All UPCR	6.00 (2.76 to 10.08); p=0.0002	-7.50 [n=161]	-13.50 [n=165]
UPCR≥0.4 to <0.6	7.19 (-4.77 to 23.65); p=0.1190	-1.29 [n=6]	-8.48 [n=14]

UPCR≥0.6 to <0.8	4.07 (-0.70 to 9.56); p=0.0465	-1.00 [n=26]	-5.07 [n=21]
UPCR≥0.8 to <1.0	3.63 (-2.15 to 10.35); p=0.1073	-1.69 [n=21]	-5.31 [n=27]
UPCR≥1.0 to <1.2	7.71 (-4.01 to 23.59); p=0.1015	-8.08 [n=16]	-15.80 [n=22]
UPCR≥1.2 to <1.4	4.75 (-3.01 to 14.41); p=0.1167	-6.45 [n=28]	-11.20 [n=20]
UPCR≥1.4 to <1.6	10.79 (2.46 to 22.25); p=0.0059	-3.74 [n=17]	-14.54 [n=16]

Log-transformed eGFR post-baseline to baseline ratios at each timepoint analyzed using MMRM with treatment, visit, treatment-by-visit interaction as fixed factors, with log-baseline eGFR and log-baseline UPCR as covariates, and patient as a random effect. All observed eGFR data included, regardless of the use of prohibited medications, or starting dialysis, or having a renal transplant. Each MMRM subgroup analysis was run under the MAR assumption, without explicit missing data imputation. N represents the total number of patients in the Part B Full Analysis Set; n represents the number of patients included in each MMRM subgroup analysis. CI confidence interval; eGFR CKD-EPI estimated glomerular filtration rate based on Chronic Kidney Disease Epidemiology Collaboration calculation; MAR missing at random; MMRM mixed model repeated measures.

Table 9. : Nef-301 Part B analysis of the eGFR change from baseline at 2 years in baseline UPCR increments of 0.1 g/gram using MMRM analysis without explicit missing data assumptions and including all data regardless of the use of prohibited medications, dialysis or transplant (Part B Full Analysis Set)

Baseline UPCR cut-off (g/gram)	**Difference between Nefecon 16 mg and placebo in eGFR change from baseline at 2 years (95% CI); 1-sided p-value (mL/min/1.73 m^2 per year)**	**eGFR change from baseline at 2 years (mL/min/1.73 m^2 per year) [n]**	
		Nefecon 16 mg N=182	**Placebo N=182**
All UPCR	6.00 (2.76 to 10.08); p=0.0002	-7.50 [n=161]	-13.50 [n=165]
UPCR≥0.5 to <0.6	8.34 (-3.44 to 24.45); p=0.0796	1.07 [n=5]	-7.28 [n=11]
UPCR≥0.6 to <0.7	5.04 (-3.80 to 15.76); p=0.1302	0.31 [n=12]	-4.73 [n=8]
UPCR≥0.7 to <0.8	3.41 (-2.78 to 10.65); p=0.1351	-2.20 [n=14]	-5.61 [n=13]
UPCR≥0.8 to <0.9	-2.46 (-10.78 to 7.03); p=0.2779	-4.72 [n=8]	-2.26 [n=11]
UPCR≥0.9 to <1.0	7.50 (-1.12 to 18.29); p=0.0434	0.44 [n=13]	-7.06 [n=16]
UPCR≥1.0 to <1.1	6.92 (-13.72 to 39.85); p=0.2714	-6.96 [n=7]	-13.88 [n=13]
UPCR≥1.1 to <1.2	5.82 (-6.91 to 23.85); p=0.1846	-11.07 [n=9]	-16.90 [n=9]
UPCR≥1.2 to <1.3	9.29 (1.14 to 19.99); p=0.0132	-4.05 [n=14]	-13.34 [n=12]
UPCR≥1.3 to <1.4	-0.96 (-15.53 to 19.66); p=0.4534	-8.91 [n=14]	-7.95 [n=8]
UPCR≥1.4 to <1.5	17.92 (1.26 to 44.58); p=0.0176	1.11 [n=7]	-16.81 [n=9]
UPCR≥1.5 to <1.6	3.03 (-5.88 to 14.29); p=0.2476	-7.10 [n=10]	-10.13 [n=7]

Log-transformed eGFR post-baseline to baseline ratios at each timepoint analyzed using MMRM with treatment, visit, treatment-by-visit interaction as fixed factors, with log-baseline eGFR and log-baseline UPCR as covariates, and patient as a random effect. All

observed eGFR data included, regardless of the use of prohibited medications, or starting dialysis, or having a renal transplant. Each MMRM subgroup analysis was run under the MAR assumption, without explicit missing data imputation. N represents the total number of patients in the Part B Full Analysis Set; n represents the number of patients included in each MMRM subgroup analysis. CI confidence interval; eGFR CKD-EPI estimated glomerular filtration rate based on Chronic Kidney Disease Epidemiology Collaboration calculation; MAR missing at random; MMRM mixed model repeated measures.

Of note, the analyses of the secondary endpoints are similarly affected by the choice of the hypothetical strategy to handle the intercurrent event of `rescue medication´ as criticised for the primary endpoint analyses. However, the applied statistical models and tests are considered sufficient for these being secondary endpoints and therefore repeated analyses following a treatment policy strategy were not requested. Based on the above, the CHMP considered that the MAH fulfilled the specific obligation imposed by the Committee at the time of granting of the initial MA.

2.4.3. Conclusions on the clinical efficacy

The Part B trail's primary endpoint, time-weighted average of eGFR over 2 years showed a statistically significant treatment benefit with Nefecon *vs* placebo (5.05 (95% CI 3.24 to 7.38) mL/min/1.73 m^2 eGFR). Results of sensitivity analyses were consistent with the primary analysis. The treatment effect was also consistent across sub-groups, including the baseline proteinuria (2g/24 hours < baseline proteinuria ≥ 2g/24 hours) and UPCR subgroups (1.5 g/gram <UPCR ≥1.5 g/gram), e.g. mean treatment difference Nefecon *vs* placebo in subjects with baseline UPCR<1.5 g/gram was 4.63 (95% CI 2.26 to 7.50) compared to 6.59 (95% CI 3.59 *vs* 10.46) in subjects with baseline UPCR ≥1.5 g/gram.

However, because several methodological issues have been identified currently limiting the interpretability of the results presented, the MAH was asked to conduct additional analyses for the eGFR primary efficacy evaluation. This involved estimating the effect size at the 24-month time point, delivering an effect estimate based on a treatment policy estimand strategy (making use of all observed eGFR data included regardless of the use of rescue medication) and assigning equal weight to all eGFR observations in the regression modelling. The additional ancillary analyses requested by the CHMP and provided by the MAH showed a consistent benefit of the investigated drug compared to placebo in the clinically relevant endpoint of eGFR change from baseline at 24 months. The effect was consistent between different strategies to handle intercurrent events and across subgroups of baseline UPCR<1.5 g/gram and baseline UPCR ≥1.5 g/gram. For MMRM using the treatment policy intercurrent event strategy, the mean change from baseline eGFR was 6.0 (2.76 – 11.53) mL/min/1.73m² in the FAS, 6.34 (2.13 – 11.53) mL/min/1.73m² in the subgroup of baseline UPCR<1.5 g/gram and 6.04 (1.34 – 12.09) mL/min/1.73m² in the subgroup of baseline UPCR ≥1.5 g/gram.

As the lower baseline proteinuria level from which the eligible patients upwards would benefit from the Kinpeygo therapy was not entirely clear from the presented data, the MAH was asked to provide additional subgroup analyses starting from UPCR 0.8g/gram to 1.5 g/gram in steps of 0.1 g/gram or 0.2 g/gram if sample sizes were limited.

Overall, the provided subgroup analysis supports the indication based on the study inclusion criteria of UPCR ≥ 0.8 g/g or proteinuria ≥ 1 g/day, whereof it should be mentioned, that the group nearest to the cut-off point (baseline UPCR of 0.8 g/g to 0.9 g/g) had a negative point estimate for the difference in eGFR change from baseline at 2 years. However, the group consisted of only 19 subjects and the estimate was highly variable. Importantly, the larger subgroups of width 0.2 g/g and especially the subgroup with baseline UPCR of 0.8 g/g to 1 g/g had positive estimates, suggesting a benefit of Kinpeygo. Also, there were no groups with lower baseline UPCR (included based on the proteinuria inclusion criterion) that had a negative point estimate for difference in eGFR change from baseline.

Therefore, despite random variation in small subgroups, a positive treatment benefit is seen in all patient groups in the study inclusion criteria.

The additional 2-year eGFR slope analyses using a linear spline mixed-effects model in which eGFR is modelled simultaneously over an acute and chronic phase and then combined to give an estimate of total slope, could also demonstrate that the eGFR treatment benefit relative to placebo maintained through to 2 years.

Therefore, based on the data provided:

- The newly proposed indication "*Kinpeygo is indicated for the treatment of adults with primary immunoglobulin A nephropathy (IgAN) with a urine protein excretion ≥1 g per day (or urine protein-to- creatinine ratio ≥0.8 g/gram).*" is considered acceptable.

Furthermore, it is also considered that the long-term results of the Nef-301 part B trial are in support of the findings of the part A (basis for the Kinpeygo CMA) and the study report can consequently be considered as a fulfilment of the imposed obligation. Hence, the MAH is in the position to provide the comprehensive clinical data necessary within the current variation which support the conversion of the originally granted conditional marketing authorisation into a full one.

2.5. Clinical safety

Introduction

This Summary of Clinical Safety (SCS) includes data from the pivotal Phase 3 Nef-301 study, pooled data from Nef-301 and the Phase 2b Nef-202 study in a similar population of IgAN patients. The Nef-202 study design was comparable to Part A of Nef-301. Narratives for treatment-emergent serious adverse events (TESAEs), adverse events of special interest (AESI), and discontinuations due to TEAEs, that have been reported in the open-label extension study by the time of the Nef-301 Part B DCO are also provided: Between February 1, 2021, and May 3, 2023, a total of 119 patients have been enrolled and dosed in the Phase 3b Nef-301 open-label extension study.

The primary objective of the safety evaluation is to describe the safety and tolerability of Kinpeygo 16 mg once daily, when administered for 9 months. Therefore, the appropriate common placebo-controlled duration of 9 months is presented for the pooled summaries. Additional safety information reported during 15 months of observational follow-up is provided by Nef-301.

Patient exposure

The overall extent of exposure in Nef-301 and Nef-202 comprises a total of 488 IgAN patients dosed with Nefecon 16 mg once daily or placebo (173.8 patient years exposure to the Nefecon 16 mg dose). As of the Nef-301 Part B data cut-off (DCO; 06 Feb 2023):

- 389 patients had received at least one dose of study treatment in the Nef-301 Safety Analysis Set
- and the Nef-301 Part B analysis that forms the basis of this SCS, was performed when all 366 patients randomised to the global study had had the opportunity to complete their final 2-year visit (Visit 17b).
- An additional 29 patients recruited for regulatory requirements in China are included in the Safety Analysis Set and

- 488 patients had received at least one dose of Nefecon 16 mg or placebo in the pooled Safety Analysis Set. All pooled analyses with Nef-202 include all dosed patients in the Nef-301 Part B Safety Analysis Set.

The Safety Analysis Set, which includes all patients who received at least 1 dose of study treatment, comprises 389 patients in total. Of the 195 patients who received Nefecon 16 mg in the Safety Analysis Set, 172 (88.2%) received at least 9 months of study treatment. Of the 194 patients who received placebo in the Safety Analysis Set, 180 (92.8%) received at least 9 months of study treatment.

Adverse events

Treatment-emergent adverse events
Nef-301 Safety Analysis Set:

173 (88.7%) patients treated with Nefecon 16 mg once daily reported 895 TEAEs, and

140 (72.2%) placebo-treated patients reported 534 TEAEs.

The frequencies of TEAEs considered to be possibly drug-related by the Investigator were higher with Nefecon 16 mg/day compared to placebo. The majority of TEAEs were graded mild or moderate in severity. Nine (4.6%) Nefecon treated patients and 4 (2.1%) placebo-treated patients reported TEAEs graded severe, with a very low proportion of all events graded severe (1.3% of all TEAEs reported in the Nefecon group compared with 0.9% of all TEAEs reported in the placebo group).

TESAEs (treatment-emergent serious adverse events)
The number of TESAEs was low in both treatment groups (18 [9.2%] with Nefecon 16 mg *vs* 9 [4.6%] with placebo). The number and percentage of patients reporting TESAEs considered to be possibly drug-related by the investigator was very low in both treatment groups (4 [2.1%] with Nefecon 16 mg *vs* 4 [2.1%] with placebo).

Discontinuation
In Nef-301, the frequency of treatment-emergent adverse events (TEAEs) leading to discontinuation of study drug was <10% in Nefecon-treated patients, with only 11 (5.6%) Nefecon-treated patients undergoing dose reduction because of clinically relevant adverse events.

Dose reduction
11 (5.6%) Nefecon-treated patients in the Safety Analysis Set underwent dose reduction, compared to 3 (1.5%) placebo-treated patients who also had their blinded treatment reduced. In accordance with the protocol, the daily dose of double-blinded study drug could be reduced from 4 capsules once daily (QD) (Nefecon 16 mg or placebo) to 2 capsules QD (Nefecon 8 mg or placebo) if clinically relevant AEs developed that the Investigator considered related to the study drug and which mandated dose reduction.

Serious adverse event/deaths/other significant events

There was 1 death reported during Nefecon treatment due to a fatal coronavirus infection and was considered unrelated to study treatment. Another death was reported with cerebral haemorrhage that occurred during follow-up (321 days after the last dose of study). This case occurred 321 days after the last dose of study NEF-301. Neither was it considered by the investigator to be potentially related to study treatment. There was no deaths reported in the Nef-301 OLE study.

Laboratory findings

Clinical safety laboratory assessments included haematology, serum chemistry, and urine analysis parameters from collection of blood and urine samples in accordance with each study protocol. Clinically significant abnormal laboratory findings, as assessed by the Investigator, that were detected during the study or were present when the first dose of study drug was administered and significantly worsened during the study were reported as AEs.

There were no other clinically relevant findings from clinical chemistry or haematology laboratory assessments, nor were there clinically relevant effects on blood pressure or body weight. As expected for an oral budesonide product on repeat dosing, reversible suppression of cortisol was observed.

Any minor changes in laboratory parameters, blood pressure, or weight observed during treatment were generally reversible within 3 months of treatment cessation.

Liver enzymes and related parameters

There were no clinically relevant changes from baseline levels in liver enzymes ALT or GGT; median levels remained stable during treatment and follow-up. Numerical increases from baseline in bilirubin, together with modest decreases in ALP, AST, albumin and total protein observed with Nefecon treatment were not considered clinically relevant and resolved after the end of the treatment period.

Other clinical chemistry parameters

Numerical increases in median LDH, calcium, sodium, and phosphate levels and a small decline in median creatine kinase observed during Nefecon treatment were not considered clinically relevant and returned to baseline levels after the end of the treatment period. A small number of Nefecon treated patients had transient decreases in potassium to below the lower limit of the normal range (<3.5 mmol/L) during the treatment period, with all patients returning above the lower limit of the normal range by 3 months post-treatment.

Small, predictable increases in white cell counts, haemoglobin, and haematocrit, and a small, expected decrease in eosinophils were observed during Nefecon treatment, which returned to baseline levels after the end of treatment.

The Nef-301 study allowed patients with type 1 or type 2 diabetes mellitus to be included if the condition was adequately controlled (defined as HbA1c ≤8% [64 mmol/mol]), whereas patients with type 1 or type 2 diabetes mellitus were excluded from Nef-202 study. A higher percentage of patients in the Nefecon 16 mg group had a medical history of diabetes mellitus compared to the placebo group (16 [8.2%] Nefecon-treated patients *vs* 8 [4.1%] placebo-treated patients. In addition, more Nefecon-treated patients had pre-diabetic levels of HbA1c ≥5.7% or FBG≥100 mg/dL at baseline, as compared to placebo-treated patients (37.9% and 28.4% respectively). At a group level, a small numerical increase in median HbA1c levels was observed during Nefecon treatment (0.2% median change from baseline at month 9), with some outliers also evident in the Nefecon treatment group.

Of those patients treated with Nefecon 16 mg/day who were either diabetic at baseline or defined as pre-diabetic, 67 (77.9%) had no change in HbA1c ≥1% during treatment. There were 19 (22.1%) patients treated with Nefecon, all with pre-diabetes or diabetes at baseline, who had an increase in HbA1c ≥1% during treatment; 11 (12.8%) had increases in HbA1c ≥1% to <2.0%, 5 of whom already had diabetes mellitus listed in their medical history, and 8 (9.3%) had an increase in HbA1c ≥2%, 6 of whom already had diabetes mellitus listed in their medical history. The highest increase in HbA1c seen during Nefecon treatment was 5.2%. Three placebo-treated patients (4.8%) who all had diabetes mellitus listed in their medical history also had an increase in HbA1c ≥1% to <2%.

In the Nef-301 Safety Analysis Set, 24-hour urine cortisol excretion was suppressed at 9 months by approximately 68% with Nefecon 16 mg compared to placebo with reversibility to baseline levels when measured after 3 months of follow-up. Urine cortisol levels have remained stable with further follow-up.

Safety in special populations

As for other oral budesonide products, Kinpeygo should be used with caution in patients with infections, hypertension, diabetes mellitus, osteoporosis, peptic ulcer, glaucoma, or cataracts; or with a family history of diabetes or glaucoma; or with any other condition where the use of GCSs may have unwanted effects. Impaired liver function may reduce the rate of elimination of GCSs, resulting in higher systemic exposure. The Nefecon patient studies excluded patients with hepatic cirrhosis because of the risk of increased systemic exposure to budesonide. The pooled SAS was used for this evaluation of subgroups to maximize the number of events for analysis. A threshold incidence ≥10% in the Kinpeygo 16 mg treatment group with a 2-fold increase in rate over placebo was applied, which resulted in an evaluation of subgroups for the TEAEs of peripheral oedema, acne, hypertension, and muscle spasms. Subgroup summaries were produced where there were at least 20 patients exposed to Kinpeygo 16 mg. No safety concerns have been identified within any particular subgroups of intrinsic or extrinsic factors.

Safety related to drug-drug interactions and other interactions

No clinically relevant effect of food on the overall systemic exposure of budesonide was observed when either a moderate or high fat meal was consumed 1 hour after a single Kinpeygo 16 mg dose, or when a moderate fat meal was consumed 2 hours prior to dosing. No clinical drug-drug interaction studies have been performed with Kinpeygo. Budesonide, the active pharmacological ingredient of Kinpeygo, is metabolised by cytochrome P450 3A4 (CYP3A4). Drugs that induce CYP3A4 such as carbamazepine may lower plasma budesonide concentrations. Potent inhibitors of CYP3A4, including grapefruit juice, can increase plasma levels of budesonide. Thus, clinically relevant drug interactions with potent CYP3A inhibitors, such as ketoconazole, itraconazole, ritonavir, indinavir, saquinavir, erythromycin, and cyclosporine are to be expected, and may increase systemic budesonide concentrations. The use of potent CYP3A4 inhibitors was prohibited in the Kinpeygo phase 2 and 3 patient studies, and patients were also instructed to avoid grapefruit and grapefruit juice. Given its low affinity for CYP3A4 and low systemic exposure, budesonide is unlikely to inhibit the metabolism of other drugs after oral administration.

Discontinuation due to adverse events

The proportion of patients with TEAEs that led to discontinuation of Nefecon 16 mg per day was considerably lower in the Nef-301 study than in the Nef-202 study. TEAEs led to discontinuation of study treatment in 17 (8.7%) Nefecon-treated patients and 3 (1.5%) placebo-treated patients. A lower proportion of patients were withdrawn from the Nef-301 study due to a TEAE in the Nefecon 16 mg/day group compared with Nef-202. It should be noted that there was no distinction made between TEAEs that led to withdrawal from the study and TEAEs that led to discontinuation of study treatment in Nef-202. In both studies, there were also several patients who reported >1 TEAE preferred terms at the time of discontinuation, with no specific TEAE highlighted as the key reason for discontinuation.

In summary, TEAEs in the main safety summaries have been included from the start of dosing up to 14 days after the last dose of study treatment (including tapering). This approach has been

retrospectively applied to Nef-202 for on-treatment summaries that are pooled with Nef-301. When considering the pooled Nef-301 and Nef-202 Safety Analysis Set evaluating the 9-month treatment period, and with specific reference to treatment with Nefecon:

• The overall number of serious or severe adverse events was low. One patient died as a result of a coronavirus infection, considered unrelated to study treatment.

• New onset diabetes mellitus was reported in 4 patients who all met the American Diabetes Association (ADA) criteria for pre-diabetes at baseline; all 4 patients continued treatment and haemoglobin A1c (HbA1c) levels declined after completion of treatment.

• HbA1c levels were generally unchanged, except for minor, reversible changes observed in a small number of patients with pre-enrolment diabetes mellitus or who fulfilled the criteria for pre-diabetes at baseline.

• There was no increase in the risk of infection. Two severe coronavirus infections that required hospitalisation were reported, one of which was fatal. One other SAE of community-acquired pneumonia also required hospitalisation. None of these severe infections was considered by the investigator to be related to study treatment.

• There was no increase in the risk of fractures or osteonecrosis.

• Venous thromboembolic events were reported in 5 patients, all of whom had confounding risk factors, and therefore no causal relationship is concluded.

• There were no other clinically relevant findings from clinical chemistry or haematology laboratory assessments, nor were there clinically relevant effects on blood pressure or body weight. As expected for an oral budesonide product on repeat dosing, reversible suppression of cortisol was observed.

During observational follow-up in Nef-301:

• Frequencies of the most commonly reported AEs (including coronavirus infection that was the most frequently reported event), were similar in both treatment groups.

• One patient previously treated with Nefecon died due to a cerebral haemorrhage (almost 1 year after their last dose of study treatment; considered unrelated to study treatment).

• New onset diabetes mellitus and fractures were reported at similar frequencies in both treatment groups. One patient experienced an event of osteonecrosis, with a clear temporal relationship to the administration of oral prednisolone for a 258-day period after study treatment was discontinued. Two severe infections requiring hospitalisation (bacterial arthritis and respiratory tract infection) in patients previously treated with Nefecon were not considered by the investigator or sponsor to be related to study treatment.

• Any minor changes in laboratory parameters, blood pressure, or weight observed during treatment were generally reversible within 3 months of treatment cessation.

Overall, these updated safety data based on the final Phase 3 analysis have confirmed Kinpeygo 16 mg once daily is generally well tolerated with an acceptable Any minor changes in laboratory parameters, blood pressure, or weight observed during treatment were generally reversible within 3 months of treatment cessation safety profile.

Post marketing experience

During the period of post-marketing safety review from January 28, 2022 to March 31, 2023, worldwide post-marketing cumulative exposure was 409.58 patient-years (401.25 patient years in the

US based on prescription sales and 8.33 in the EU estimated from cumulative patient exposure), based on 1,131 patients exposed to the marketed product. As of March 31, 2023, no post-marketing safety data have been received from the EU for the marketed product.

Among 1131 patients who have received the marketed product during the reporting period, a total of 947 unique individual case safety reports (ICSRs) with 2910 adverse events in 649 patients were received from post-marketing surveillance (PMS) sources, including 139 serious ICSRs (202 SAEs, 376 AEs) in 122 patients, and 808 non-serious ICSRs (2332 AEs) in 576 patients. ICSRs were most frequently reported in the general disorders and administration site conditions SOC (n=575 events), gastrointestinal disorders SOC (n=357 events) and nervous system disorders SOC (n=302 events). The most frequently reported non-serious PMS events, were hypertension (n=99 events), peripheral swelling (n=92 events), fatigue (n=90 events), and blood pressure increased (n=84 events). These events, that are known side effects of budesonide, were commonly reported (reporting rate >1/100 to <1/10 of patients exposed) and are and are consistent with the clinical trial data summarised in Kinpeygo SmPC.

The most frequently reported SAEs during post-marketed use were ESRD, hypertensive urgency, and renal impairment. ESRD was often associated with the need for dialysis or renal transplant. The post-marketing experience is consistent with the clinical trial data and no new safety concerns have been identified. Potential risks included in product information are hypercorticism, adrenal suppression, immunosuppression and other corticosteroid-associated effects. Not all the potential risks listed in labelling have been observed with the use of Kinpeygo to date. Some of these risks, e.g., hypertension and pre-diabetes, are consistent with comorbidities seen in IgAN or in the general population. In summary, there have been no changes to the established safety profile of Kinpeygo and no new safety concerns have been identified in the post-marketing period, to date.

2.5.1. Discussion on clinical safety

The MAH provided a summary of clinical safety, which included data from the entire pivotal Nef-301 study and pooled data from Nef-301 and Nef-202 study in a similar population of IgAN patients. The primary objective of the safety evaluation was the safety and tolerability of Kinpeygo 16 mg once daily, when administered for 9 months. Therefore, the appropriate common placebo-controlled duration of 9 months was presented for the pooled summaries. The overall extent of exposure in Nef-301 and Nef-202 comprises a total of 488 IgAN patients dosed with Nefecon 16 mg once daily or placebo (173.8 patient years exposure to the Nefecon 16 mg dose).

Safety data from Nef-301 study continue to show that Nefecon 16 mg once daily over a treatment duration of 9 months is generally well tolerated and has an acceptable safety profile for the intended patient population. In Nef-301, the frequency of treatment-emergent adverse events leading to discontinuation of study drug was <10% in Nefecon-treated patients, with only 11 (5.6%) Nefecon-treated patients undergoing dose reduction as a result of clinically relevant AEs.

The most commonly reported AEs observed with an increased frequency compared to placebo were peripheral oedema, hypertension, white blood cell count increased, neutrophil count increased, face oedema, muscle spasms, and acne. These non-serious adverse events, together with other low-grade GCS-related adverse events, are generally of mild severity and reversible.

Typical corticosteroid-like side effects, including increased blood pressure, oedema, cushingoid features and indigestion. Any minor changes in laboratory parameters, blood pressure, or weight observed during treatment were generally reversible within 3 months of treatment cessation. Nefecon 16 mg/day over a 9-month treatment period does not appear to increase the risk of GI adverse effects over what would be expected for an oral budesonide product. Peripheral oedema, acne, dyspepsia,

insomnia, Cushingoid, and abdominal pain were reported more frequently among Nefecon-treated patients in the Nef-202 study compared with Nef-301. These are all TEAEs that were more likely to be reported at a higher rate in the Nef-202 study due to the GCS-related and GI-related adverse effects that were solicited *via* questionnaire at all visits.

New onset diabetes mellitus was reported in 4 patients who continued treatment; the haemoglobin A1c levels declined after completion of treatment. The HbA1c levels were generally unchanged, except for minor, reversible changes observed in a small number of patients with pre-enrolment diabetes mellitus or who fulfilled the criteria for pre-diabetes at baseline.

From a total of 114 patients exposed to Nefecon 16 mg/day in the open-label extension study, 7 SAEs have been reported in 7 patients as of February 6, 2023. Six of these patients were receiving Nefecon treatment at the time of event onset. No SAEs were reported in more than 1 Nefecon-treated patient.

The SAEs reported during treatment were CNS vasculitis, headache, and vomiting (in the same patient), femorotibial gonarthrosis, serous chorioretinopathy (2 events of right and left eye in one patient), carcinoma of the breast, and monoclonal B-cell lymphocytosis. For 2 patients, the SAE led to discontinuation of treatment, one due to the event of serous chorioretinopathy and one due to the need for treatment with systemic corticosteroids (CNS vasculitis). One other patient reported an SAE of right neck lymphadenopathy during the follow-up period. No new safety signals were identified from the SAEs reported in the Nef-301 OLE study.

The post-marketing experience is consistent with the clinical trial data and no new safety concerns have been identified. The frequently reported SAEs of hypertensive urgency, ESRD, and renal impairment are consistent with the underlying chronic kidney disease. The combination of all SAEs and AEs consistent with hypertension was very commonly reported (reporting rate >1/10). This reporting rate for hypertension is consistent with the general population. Potential risks referred to in the SmPC include hypercorticism, adrenal suppression, immunosuppression, and other corticosteroid-associated effects. Not all the potential risks listed in labelling have been observed with the use of Kinpeygo to date. Some of these risks, e.g., hypertension and pre-diabetes, are consistent with comorbidities seen in IgAN or in the general population.

Concomitant medication is very common in patients with IgA nephropathy. Other than ARBs and ACEIs, part of the background RAS inhibitor therapy for both studies, the overall most common classes of concomitant medications were HMG-CoA reductase inhibitors, dihydropyridine derivatives, and preparations inhibiting uric acid production. Since the start of Nef-301, SGLT2 inhibitors have been approved for use in chronic kidney disease and were used by some patients in the study.

None of the concomitant medications were found to be associated with any of the observed TEAE. The median blood pressure was only transiently increased by budesonide. No drug-drug interaction studies have been performed with Kinpeygo. Considering that budesonide is a well-known substance and the respective section in the Kinpeygo SmPC is aligned with the SmPC for the oral budesonide product Entocort, this is considered acceptable. There are no new drug interaction data since the granting of the initial CMA of Kinpeygo.

2.5.2. Conclusions on clinical safety

In summary, there have been no changes to the established safety profile of Kinpeygo and no new safety concerns have been identified in the post-marketing period, to date.

Routine pharmacovigilance activities will include collection, assessment and processing of individual case safety reports (ICSRs) and ongoing safety surveillance and periodic signal detection. In order to gain further post-authorisation exposure data on use of budesonide during pregnancy and/or lactation,

a targeted specific adverse reactions questionnaire is included in the RMP for the risk "use in pregnancy and lactation". In addition, pregnancy cases occurring in the post marketing setting should be collected and presented in the PSUSRs accordingly. From the safety database all the adverse reactions reported in clinical trials have been included in the SmPC.

Overall, the safety profile of Kinpeygo has been well characterised in the clinical development programme and is in line with the known safety profile of already approved budesonide medicinal products. The most common adverse drug reactions were mainly of mild or moderate severity and reversible, reflecting the low systemic exposure to budesonide after oral administration.

2.5.3. PSUR cycle

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.6. Risk management plan

The MAH submitted/was requested to submit an updated RMP version with this application. The CHMP received the following PRAC Advice on the submitted Risk Management Plan: The PRAC considered that the risk management plan version 1.3 is acceptable.

Safety concerns

Summary of safety concerns
Important identified risks · None
Important potential risks · None
Missing information · Use in pregnancy and lactation

The MAH proposed the above summary of safety concerns in the RMP Version 1.3. Having considered the data in the safety specification, the summary of safety concerns in the RMP is acceptable.

Pharmacovigilance plan

The pharmacovigilance plan is unchanged. This is agreed by PRAC and CHMP.

Risk minimisation measures

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Missing Information		
Use in pregnancy and lactation	Routine risk minimisation measures: • SmPC section 4.6, 5.3 • Legal status: Prescription only medicinal product Additional risk minimisation measures: • None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • Targeted Pregnancy/ Breast-feeding follow-up Questionnaire • Cumulative review of case reports on the use of Kinpeygo in pregnancy and lactation will be included in the PSUR. Additional pharmacovigilance activities: • None

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.8 and 5.1 of the SmPC are updated. The package leaflet is also updated accordingly. Please refer to the attached PI.

In addition, Annex II has been updated to remove the final condition as this is being fulfilled with the submission of the results of study Nef-301.

2.7.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH and has been found acceptable.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

Kinpeygo (budesonide) was intended for the treatment of primary IgAN in adults at risk of rapid disease progression with a UPCR ≥1.5 g/gram, based on the CHMP' positive opinion granted for the CMA in 2022.

IgAN, sometimes referred to as Berger's disease, is a serious, immune complex-mediated autoimmune kidney disease, that is the most prevalent primary chronic glomerulonephritis worldwide. Glomerulonephritis is an inflammatory condition affecting the glomeruli, characterised by intraglomerular inflammation and cellular proliferation associated with haematuria, the hallmark of which is the predominance of galactose-deficient IgA1 (Gd-IgA1) deposits, either alone or with IgG, IgA, or both, in the glomerular mesangium. The disease can be classified into primary or secondary forms. In the primary form, there are no relevant associated co-morbidities, whereas in the secondary form, the condition may be diagnosed in patients with non-renal diseases, ranging from chronic liver disease and inflammatory states to chronic infections and neoplasms.

It is a life-threatening condition that is chronically debilitating due to progressive loss of kidney function that results in reduced quality of life and shortened life expectancy. IgAN is a serious, progressive, autoimmune kidney disease. Most patients are expected to progress to ESRD, requiring haemodialysis and kidney transplantation, within their lifetime. Furthermore, even patients traditionally regarded as "low-risk" based on proteinuria levels have high rates of kidney failure within 10 years, emphasizing the importance of intervention with effective treatments. Specifically, a recent analysis of a UK cohort of patients with IgAN showed that 30% of patients with proteinuria in the range 0.44 to 0.88 g/gram on average, progressed to kidney failure within 10 years of diagnosis.

IgA nephropathy is an orphan disease that is estimated to affect approximately 200,000 people in the EU (including the United Kingdom), and approximately 130,000 people in the United States.

3.1.2. Available therapies and unmet medical need

Prior to the approval of Kinpeygo, there were no treatments approved for the management of patients with primary IgAN. However, on 22 February 2024, the CHMP adopted a positive opinion recommending the granting of a conditional marketing authorisation for the medicinal product Filspari, intended for the treatment of adults with IgAN. The active substance of Filspari is sparsentan, a dual endothelin angiotensin receptor antagonist. The benefit of Filspari is its ability to reduce proteinuria and slow down the progression of kidney disease, as seen in a phase 3, randomised, active-control (irbesartan) study in adults with IgAN.

Nevertheless, the initial management of patients with primary IgAN continues to focus on proteinuria reduction and optimal blood pressure control by maximum tolerated inhibition of the RAS with ACEIs/ARBs, together with a low sodium diet (KDIGO 2021).

Whilst not specifically approved for the condition, SGLT2 inhibitors may also be used as an additional supportive care measure in some patients with IgAN. In patients with CKD, including a subset of patients with primary IgAN, a reduced incidence of the composite endpoint of ≥50% sustained decline of eGFR, progression to ESRD, cardiovascular or renal death has been shown with dapagliflozin *vs* placebo.

Under the circumstances where significant proteinuria persists despite maximal supportive care, a 6-month course of high dose systemic GCS may also be used in some patients, despite concerns regarding the benefit-risk balance of this approach (KDIGO 2021). The published randomised controlled trials of systemic GCS administration have shown conflicting evidence of efficacy, with serious infections (leading to death in 5 patients in the 2 studies), metabolic complications, and serious adverse bone effects considered a barrier to treatment for many patients and treating nephrologists. Although the risk of severe infection may have been somewhat mitigated by reducing the dose of GCS and by administering prophylactic antimicrobial treatment, 5 of these severe infections occurred in the low-dose group. It needs to be emphasised that when systemic corticosteroids are being considered, the important risk of treatment-emergent toxicity must be discussed with patients; furthermore, if a

course of systemic corticosteroids is used, the treatment regimen should incorporate prophylaxis against Pneumocystis pneumonia along with gastroprotection and bone protection.

3.1.3. Main clinical studies

The Nef-301 study was designed to assess the efficacy and safety of Nefecon in patients with primary IgAN. It was a global, randomised, double-blind, placebo-controlled study, and therefore met the standard ICH criteria for robust design of a therapeutic confirmatory trial. The design consists of 2 parts, Part A and Part B:

Part A included a screening period, followed by a 9-month blinded treatment period in which eligible patients were randomised in a 1:1 ratio to Nefecon 16 mg/day or placebo, and a 3-month follow-up period.

Part B consisted of a further 12-month observational follow-up period. Therefore, the overall 2-year study comprised a 9-month treatment period and 15 months of observational follow-up.

3.2. Favourable effects

Efficacy results in the pivotal phase 3 study (Part A) (Nef-301)

- After 9 months of treatment, patients treated with Kinpeygo 16 mg once daily showed a 27% reduction in UPCR (primary endpoint) compared to placebo (96% CI 12% to 39%; p=0.0003).
- After 12 months (after 3 months of treatment withdrawal and observational follow up) patients treated with Kinpeygo 16 mg once daily showed a 48% reduction in UPCR compared to placebo (p<0.0001).
- The ratio of UPCR at 9 months was 0.69 in the Kinpeygo treatment arm and 0.95 in the placebo arm (CI 95%). This means a reduction of proteinuria (UPCR) from baseline by 31% in patients treated with Kinpeygo 16 mg once daily compared with 5% in placebo-treated patients. The ratio of geometric LS means comparing Kinpeygo/placebo was 0.73 (27%, p 0.0003), showing that the primary endpoint in Part A was met.
- The reduction of proteinuria could be observed already at earlier stages after starting the treatment (ratio geometric means comparing Kinpeygo/placebo 0.99 at 3 months and 0.86 at 6 months) but was more pronounced at 12 months showing a ratio of 0.52 (p < 0.0001). Reliability of these data derived from the primary MMRM analysis (Part A FAS) was strongly supported by supplementary and sensitivity analysis, indicating the robustness of the 9-month treatment effect on UPCR.
- Improvements in UPCR due to Kinpeygo treatment were found to occur earlier in patients with higher levels of UPCR at baseline (≥1.5 g/gram; significant already after 6 months), compared to patients with lower levels of UPCR at baseline (<1.5 g/gram; significant reduction of UPCR evident only after 9 months).
- After 9 months of treatment, Kinpeygo 16 mg once daily provided a 7% treatment benefit on eGFR (secondary endpoint) compared to placebo (p=0.0014). This 3.87 mL/min/1.73 m^2 treatment benefit at 9 months corresponded to a reduction from baseline of 0.17 mL/min/1.73 m^2 in patients who received Kinpeygo 16 mg once daily and a deterioration from baseline of 4.04 mL/min/1.73 m^2 in patients who received placebo.

- In the subgroup of patients with baseline UPCR ≥1.5 g/g, eGFR declined by 10.1 mL/min/1.73 m^2 over 12 months in the placebo group of Nef-301. In comparison, eGFR declined by only 1.1 mL/min/1.73 m^2 in the Kinpeygo treatment group, resulting in a difference of 8.98 mL/min/1.73 m^2 at 12 months.
- Additional eGFR slope data were evaluated from 3 months onwards up to the currently available 12-month time-point and analysed according to different baseline UPCR cut-offs from 1.0 to 2.0 g/gram. The Kinpeygo treatment effect, in comparison to placebo, on the rate of loss of renal function (eGFR chronic slope) gradually increases and becomes statistically significant at a baseline UPCR cut-off of 1.3 g/gram, and then appears to plateau at an average of 6 to 6.5 mL/min/1.73 m^2 per year from UPCR≥1.4 g/gram, suggesting a relevant clinical benefit for Kinpeygo in terms of slowing the chronic rate of loss of renal function in patients with a UPCR ≥1.5 g/g at baseline. This subgroup was also noted to be at particular risk of rapid disease progression over a relatively short time-period and had a considerable unmet medical need.

Efficacy results in the pivotal phase 3 study (Part B) (Nef-301)

- Average difference in eGFR over the 2-year study period (9 months of treatment + 15 months of observational follow-up) was 5.05 (95% CI 3.24 to 7.38) mL/min/1.73 m^2 in favour of Nefecon 16 mg compared to placebo (p<0.0001) with an average change of –2.47 mL/min per 1·73 m² (95% CI –3·88 to –1·02) reported with Nefecon and –7.52 (–8·83 to –6·18) mL/min per 1.73 m² reported with placebo.
- Results of requested ancillary analyses that describe the effect remaining after 24 months for the treatment policy estimand, with each observation entering with the same weight, were consistent with the results of the pre-specified analyses. Difference in mean change from baseline of eGFR after 24 months was 6.0 (2.76 – 11.53) mL/min/1.73m² in the FAS, 6.34 (2.13 – 11.53) mL/min/1.73m² in the subgroup of baseline UPCR<1.5 g/gram and 6.04 (1.34 – 12.09) mL/min/1.73m² in the subgroup of baseline UPCR ≥1.5 g/gram in favour of Nefecon compared to placebo.

Results from all sensitivity and supplementary analyses were consistent with the primary analysis.

- The 2-year eGFR treatment effect was consistent across sub-groups, including the UPCR subgroups (1.5 g/gram <UPCR≥1.5 g/gram). The mean difference in eGFR over the 2-year study period for the <1.5 g/gram UPCR subgroup was 4.63 (95% CI 2.26 to 7.50) and for the subgroup with UPCR≥1.5 g/gram, 6.59 (95% CI 3.59 *vs* 10.46), respectively.
- Primary supportive random coefficients analysis of 2-year eGFR total slope: Nefecon 16 mg once daily provided a statistically significant and clinically relevant 1.82 (95% CI 0.50 to 3.13) mL/min/1.73 m^2 per year improvement in 2-year eGFR total slope compared to placebo (p=0.0035). This corresponded to a 2-year eGFR slope of -3.55 (95% CI -4.48 to -2.62) mL/min/1.73 m^2 per year in the Nefecon 16 mg group, and -5.37 (95% CI -6.30 to -4.43) mL/min/1.73 m^2 per year in the placebo group.
- The linear spline mixed-effects model estimated the improvement in 2-year eGFR total slope, in the absence of rescue medication, to be 2.78 (95% CI 1.39 to 4.17) mL/min/1.73 m^2 per year with Nefecon 16 mg once daily compared to placebo (p<0.0001). This corresponds to a 2-year eGFR total slope of -2.65 (95% CI -3.59 to -1.72) mL/min/1.73 m^2 per year in the Nefecon 16 mg group, and -5.44 (95% CI -6.50 to -4.37) mL/min/1.73 m^2 in the placebo group.

- The percent reduction in UPCR at 2 years, in the Nefecon group compared to placebo was similar to that seen at the end of the 9-month Treatment Period (9 month: Nef: -33.6% , Placebo: 5.2%; 24 month: Nef: -30.7%, Placebo: -1.0%). Comparison of Nefecon 16 mg *vs* placebo: Ratio of Geometric LS Means (95% CI) was 0.70 (0.61 to 0.80) at 9-month with a corresponding Percentage Reduction of 30% (20% to 39%) and 0.70 (0.59 to 0.84) at the 24-month time point with a corresponding Percentage Reduction of also 30% (16% to 41%).
- Results from the UACR analysis were consistent with those for UPCR. At 2 years, the percent reduction in UACR in the Nefecon group compared to placebo was similar to that seen at the end of the 9-month Treatment Period: Percentage Reduction Nefecon *vs* Placebo was 34% (95% CI 23% to 44%) at 9 month and 35% (95% CI 20% to 47%) at 24 months.
- The time to a confirmed 30% reduction in eGFR was significantly delayed in patients who received Nefecon treatment compared with those who received placebo (HR 0.45, 95% CI 0.26-0.75).
- The proportion of patients without microhaematuria during the observational follow-up period was significantly higher in the Nefecon group than in the placebo group .

3.3. Uncertainties and limitations about favourable effects

- Ancillary analyses that describe the effect remaining after 24 months for the treatment policy estimand, with each observation entering with the same weight, were statistically significant but were only conducted *post-hoc*. The results were however consistent with the results of the pre-specified analyses.
- In the linear spline mixed-effects model, an additional 2-year eGFR slope analysis, the difference in acute slope between Nefecon and placebo was nominally significant (17.05 (95% CI 10.35; 23.75); p<0.0001, whereas chronic slopes were not significantly different (0.74 (95% CI -0.84 - 2.33); p=0.1790).
- The eGFR trajectories observed in each treatment group show that once the Nefecon acute effect had stabilised, the eGFR treatment benefit relative to placebo was maintained through to 2 years, as evidenced by eGFR curves decreasing in parallel from month 3 through to the end of observational follow-up (parallel chronic slopes). Therefore, while the data support a conversion to a full MA, these do not support a change in the label regarding slowing kidney function decline.
- Durability of proteinuria: The maximum effect of Kinpeygo *vs* placebo in proteinuria reduction was observed at 12 months (50% (95% CI 42% to 57%), but proteinuria in the Kinpeygo arm is increasing since that point in time. The percentage reduction in UPCR in the Kinpeygo group *vs* placebo group at 24 months is similar to that observed at the end of the 9-month treatment period 30% (95% CI 16% to 41%). This observation speaks against slowing of the slope.
- With respect to the non-intersecting subgroups of baseline UPCR, the group nearest to the cut-off point (baseline UPCR of 0.8 g/g to 0.9 g/g) had a negative point estimate for the difference in eGFR change from baseline at 2 years. However, the group consisted of only 19 subjects and is associated with high variability. Neither the broader subgroup of baseline UPCR of 0.8 g/g to 1 g/g nor any groups with lower baseline UPCR had a negative point estimate for difference in eGFR change from baseline, therefore this is considered a random observation.

3.4. Unfavourable effects

Adverse events during treatment

- 11 (5.6%) Nefecon-treated patients underwent dose reduction, compared to 3 (1.5%) placebo-treated patients who also had their blinded study treatment reduced.
- In the Safety Analysis Set, 173 (88.7%) patients in the Nefecon 16 mg group reported 895 TEAEs, and 140 (72.2%) patients in the placebo group reported 534 TEAEs.
- Nine (4.6%) patients in the Nefecon 16 mg group experienced 12 severe TEAEs, and 4 (2.1%) patients in the placebo group experienced 5 severe TEAEs. Of all TEAEs reported, 1.3% in the Nefecon 16 mg group and 0.9% in the placebo group were graded severe.
- TEAEs led to discontinuation of study treatment in 17 (8.7%) patients in the Nefecon 16 mg group and 3 (1.5%) patients in the placebo group.
- The frequencies of TEAEs considered to be possibly study treatment-related by the Investigator were higher in the Nefecon 16 mg group compared to the placebo group (109 [55.9%] patients with Nefecon 16 mg and 39 [20.1%] patients with placebo).
- Nine (4.6%) patients in the Nefecon 16 mg group and 2 (1.0%) patients in the placebo group reported an AESI during treatment.

Adverse events during the 15 months of observational follow-up

- In the Safety Analysis Set, 138 (72.6%) patients in the Nefecon 16 mg group reported 453 TEAEs, and 134 (70.9%) patients in the placebo group reported 485 TEAEs.
- Seventeen (8.9%) patients in the Nefecon 16 mg group experienced 21 severe TEAEs, and 9 (4.8%) patients in the placebo group experienced 17 severe TEAEs. Of all TEAEs reported, 4.6% in the Nefecon 16 mg group and 3.5% in the placebo group were graded severe.
- The number of patients reporting TESAEs considered to be possibly study treatment-related by the Investigator was low (1 [0.5%] in each treatment group).
- 8 (4.2%) patients in the Nefecon 16 mg group and 4 (2.1%) patients in the placebo group reported an AESI during follow-up. For further details regarding AESIs.

3.5. Uncertainties and limitations about unfavourable effects

Reliable conclusions on safety with regard to special populations are not possible, since the size of the study population is quite limited, which results in very small subgroups. For example, no meaningful conclusions can be drawn for patients aged >65 (n=11).

3.6. Effects Table

Table 10. Effects Table for Kinpeygo (budesonide) indicated in the IgAN, data cut-off: 06 February 2023, 24-month data.

Favourable Effects				
eGFR	Average difference in eGFR over 2 years (95% CI)	mL/min/1.73 m^2	5.05 (95% CI 3.24 to 7.38) p <0.0001	Nef 301
eGFR	Mean difference in eGFR at 2 years (95% CI)	mL/min/1.73 m^2	6.0 (95% CI 2.76 to 10.08) p = 0.0002 (one sided, nominal)	Nef 301

eGFR	2-Year eGFR Total Slope (95% CI)	mL/min/1.73 m^2 per year	1.82 (95% CI 0.50 to 3.13) p= 0.0035	Nef 301
eGFR	Time to Confirmed 30% Reduction in eGFR (95% CI)	Hazard ratio	0.45 (95% CI 0.26 to 0.75) p= 0.0014	Nef 301
UPCR	Percentage reduction in UPCR at 24 months compared to baseline (95% CI)	%	30% (95% CI 16% to 41%) p<0.0001	Nef 301
UPCR	Percentage reduction in UPCR at 12 months compared to baseline (95% CI)	%	50% (95% CI 42% to 57%) p<0.0001	Nef 301
UPCR	Percentage reduction in UPCR at 9 months compared to baseline (95% CI)	%	30% (95% CI 20% to 39%) p<0.0001	Nef 301
Unfavourable Effects during the 15 months of observational follow-up, Safety Set				
TEAE	Reported TEAS, numbers (%)	Nef: 138 (72.6) Plac: 134 (70.9)		
AESI	Patients with AESI, numbers (%)	Nef: 8 (4.2) Plac: 4 (2.1)		

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Importance of favourable effects

The primary endpoint of Part B of the pivotal study Nef-301, time-weighted average of eGFR over 2 years, showed a statistically significant treatment benefit with Nefecon *vs* placebo. Results of sensitivity analyses were consistent with the primary analysis. The treatment effect was also consistent across sub-groups, including the baseline proteinuria and UPCR subgroups (1.5 g/gram<UPCR ≥1.5 g/gram). Importantly, requested additional analyses further supported the efficacy of Kinpeygo in patients at the lower end of the inclusion criterion, i.e. UPCR ≥ 0.8g or proteinuria ≥ 1 g/day. Therefore, it is agreed that the currently approved indication, can be extended to patients with lower baseline proteinuria, in line with the inclusion criteria of study Nef-301.

As discussed in the efficacy section, several methodological issues were identified, which to some degree limited the interpretability of the results. The MAH was asked to conduct additional analyses for the eGFR primary efficacy evaluation. These weighted all observations uniformly and showed a statistically significant treatment benefit of Nefecon *vs* placebo in an endpoint that can be interpreted as the benefit remaining after 24 months. Moreover, the ancillary analysis contained analyses using an intercurrent event strategy corresponding to the treatment policy estimand. The methodological concerns with respect to the primary analysis (endpoint definition, treatment policy estimand and weighting of the observations) were therefore addressed in the ancillary analyses.

While the presented advantage in 2-year total slope using the random coefficients analysis is not considered an adequate interpretation of eGFR outcome data and may overestimate the treatment benefit, results of a supplementary analysis indicate that once the Nefecon acute effect had stabilised, the eGFR treatment benefit relative to placebo was maintained through to 2 years, reflected in a statistically difference in the 2-year eGFR total slope. This analysis used a linear spline mixed-effects model, in which eGFR is modelled simultaneously over an acute and chronic phase and then combined to give an estimate of total slope.

Among the secondary endpoints of Part B, the time to a confirmed 30% reduction in eGFR was significantly delayed in patients who received Nefecon treatment compared with those who received placebo. In a *post-hoc* analysis, similar results were also observed in patients with baseline UPCR <1.5 g/gram and in patients with baseline UPCR ≥1.5 g/gram.

The maximum effect of Kinpeygo *vs* placebo in proteinuria reduction (50%) was observed at 12 months. The percentage reduction in UPCR in the Kinpeygo group *vs* placebo group at 24 months is similar to that observed at the end of the 9-month treatment period (30%).

Importance of unfavourable effects

The safety profile of Kinpeygo was well characterised in the clinical development programme and is in line with the known safety profile of already approved budesonide medicinal products. The most commonly reported adverse drug reactions were acne, hypertension, peripheral oedema, face oedema, and dyspepsia; these were mainly of mild or moderate severity and reversible, reflecting the low systemic exposure to budesonide after oral administration.

During the observational follow-up, frequencies of the most commonly reported treatment-emergent AEs were similar in both treatment groups, including of SARS-CoV-2 infection, which was the most frequently reported event (Nefecon 15% *vs* placebo 17%).

One death due to SARS-CoV-2 infection was reported during Nefecon treatment and another patient treated with Nefecon died from a cerebral haemorrhage 10.5 months after the last dose. Neither death was related to study drug. No treatment emergent AE leading to death was reported with placebo. The incidence of infections during treatment was similar between treatment groups.

HbA1c concentrations were generally unaffected by Nefecon treatment; minor and reversible changes in HbA1c were observed in a small number of patients who were diabetic or pre-diabetic at baseline.

AEs reported as new-onset diabetes occurred in seven patients during the 2-year study, all of whom met the definition of pre-diabetes at baseline. Four of these patients (all treated with Nefecon) had events of diabetes reported during the 9-month treatment period; three patients (one Nefecon-treated patient and two placebo-treated patients) had diabetes events reported during the 15-month follow-up.

No increased risk of fractures associated with Nefecon treatment was seen, nor clinically relevant differences in bodyweight or blood pressure measurements between the treatment groups.

Nefecon treatment did not change the amount of creatinine excreted in the urine compared with placebo, indicating no evidence of a sarcopenic effect.

3.7.2. Balance of benefits and risks

The selected GFR based primary efficacy endpoints, AUC-based evaluation of eGFR over 2 years supplemented by a 2-year eGFR slope, are considered acceptable to serve as surrogate for CKD progression, especially as IgAN commonly follows a slowly progressive course with approximately 25% to 30% of any cohort developing kidney failure within 20 to 25 years of presentation.

The originally identified methodological concerns with respect to the primary analysis (endpoint definition, treatment policy estimand and weighting of the observations) were adequately addressed in the ancillary analyses of the MAH, submitted upon CHMP's request.

Results of sensitivity analyses were consistent with the primary analysis. The treatment effect was also consistent across sub-groups, including the baseline proteinuria and UPCR subgroups (1.5 g/gram <UPCR ≥1.5 g/gram). The lower baseline proteinuria level from which onwards patients benefit from therapy with Kinpeygo was established based on analyses for all non-intersecting subgroups ranging from UPCR 0.8 g/gram to 1.5 g/gram in steps of 0.1 g/gram and 0.2 g/gram. These supported an extension of indication to patients in line with the inclusion criteria (UPCR ≥ 0.8 g/g or proteinuria ≥ 1 g/day).

Results of other secondary efficacy analyses were generally supportive of the overall beneficial effect of Nefecon treatment. The 2-year analysis also found that the Nefecon safety profile (as expected for a locally acting budesonide product), showed adverse events that were generally mild to moderate in severity and reversible, and not resulting in substantial numbers of patients discontinuing treatment.

In summary, there have been no changes to the established safety profile of Kinpeygo and no new safety concerns have been identified in the post-marketing period, to date.

3.7.3. Additional considerations on the benefit-risk balance

Conditional marketing authorisation (CMA)

In order to fulfil the specific obligations and convert the CMA into a ful marketing authorisation, the MAH submitted the results of Part B of study Nef-301 to confirm the efficacy and safety of budesonide for the treatment of IgAN, and more particularly to assess the clinical consequences of proteinuria reduction, as measured by eGFR.

Based on the comprehensive clinical data provided by the MAH, conversion of the CMA to a full MA is considered acceptable by the CHMP.

3.8. Conclusions

The overall B/R of Kinpeygo is positive.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the marketing authorisation, concerning the following change:

Variation accepted		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I, II and IIIB

Extension of indication to slow kidney function decline in adults with primary immunoglobulin A (IgA) nephropathy (IgAN) for KINPEYGO, based on Part B of study NefIgArd (NEF-301), listed as the final specific obligation in the Annex II in the initial MA; this is a Phase 3, randomised, double-blind, placebo-controlled, multicenter study to evaluate the efficacy, safety, and tolerability of oral Nefecon compared to matching placebo in patients with primary IgAN on a background of optimized RAS

inhibitor therapy. As a consequence, sections 4.1, 4.2, 4.8 and 5.1 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 1.3 of the RMP has been agreed. In addition, the CHMP, having considered the application and having reviewed the data submitted by the marketing authorisation holder including the evidence concerning compliance with specific obligations, is of the opinion that the risk-benefit balance of the above mentioned medicinal product remains favourable, that all specific obligations laid down in Annex II have been fulfilled and that comprehensive data supports a favourable benefit-risk balance of the above mentioned medicinal product. Therefore, pursuant to Article 14-a(8) of Regulation (EC) No 726/2004, the CHMP recommends by consensus the granting of a marketing authorisation in accordance with Article 14(1) of Regulation (EC) No 726/2004 for the above mentioned medicinal product for which the draft Summary of Product Characteristics is set out in Annex I.

The variation assessment leads to amendments to the Summary of Product Characteristics, Annex II and Package Leaflet and to the RMP.

Amendments to the marketing authorisation

In view of the data submitted with the variation, amendments to Annexes I, II and IIIB and to the Risk Management Plan are recommended. The following obligation has been fulfilled, and therefore it is recommended it be deleted from the Annex II:

> *to assess the clinical consequences of proteinuria reduction, as measured by estimated glomerular filtration rate (eGFR), the MAH shall submit the results (including also a composite clinical outcome and sensitivity analysis according to background dual RAS inhibitor therapy) of Part B of study Nef-301, which consists of a 15-month observational follow-up period after the 9-month treatment period had ended.In order to confirm the efficacy and safety of budesonide for the treatment of IgAN and more particularly*

Similarity with authorised orphan medicinal products

The CHMP by consensus is of the opinion that Kinpeygo is not similar to Filspari within the meaning of Article 3 of Commission Regulation (EC) No. 847/200. See appendix 1.

5. EPAR changes

The EPAR will be updated following Commission Decision for this variation. In particular, the EPAR module 8 "*steps after the authorisation*" will be updated as follows:

Scope

Please refer to the Recommendations section above.

Summary

Please refer to Scientific Discussion 'Kinpeygo-H-C-5653 -II-Var.0008'

Attachments

1. SmPC, Annex II, Labelling, Package Leaflet of Kinpeygo, 4 mg modified-release hard capsules, as a relevant example with changes highlighted as adopted by the CHMP on 30 May 2024.

Appendix

1. CHMP AR on similarity dated 30 May 2024