19 May 2022
EMA/570757/2022
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Kinpeygo

International non-proprietary name: budesonide

Procedure No. EMEA/H/C/005653/0000

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
AE	Adverse Event
AESI	Adverse Event of Special Interest
ARB	Angiotensin II type I Receptor Blocker
AS	Active Substance
AUC	Area Under the Curve
$AUC_{(0-2)}$	Area Under the Curve from time 0 to 2 years
$AUC_{(0-24)}$	Area Under the plasma oncentration-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
BCS	Biopharmaceutics Classification System
BE	BioEquivalence
BMI	Body Mass Index
CEP	Certificate of Suitability to the monographs of the Ph. Eur.
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
CKD	Chronic Kidney Disease
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CMA	Critical Material Attribute
C_{max}	Maximum plasma concentration
CPP	Critical Process Parameter
CQA	Critical Quality Attribute
CYP	Cytochrome P450
DCO	Data Cut-Off
EC	European Commission
EDQM	European Directorate for the Quality of Medicines
eGFR	Estimated Glomerular Filtration Rate
EMA	European Medicines Agency
ESRD	End-Stage Renal Disease

FAS	Full Analysis Set
FCP	Final Commercial Product
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
HDPE	High Density Polyethylene
HS-GC	Headspace Gas Chromatography
HMG-CoA	3-Hydroxy-3-Methylglutaryl-Coenzyme A
HPA	Hypothalamic-Pituitary-Adrenal
HR	Hazard Ratio
ICH	International Council for Harmonisation
ICSR	Individual Case Safety Report
I-FABP	Intestinal-type Fatty Acid-Binding Protein
IgA	Immunoglobulin A
IgAN	Immunoglobulin A Nephropathy
ICP-MS	Inductively Coupled Plasma Mass Spectrometry
IPC	In-Process Control
KDIGO	Kidney Disease Improving Global Outcomes
LSmean(s)	Least squares mean(s)
MAH	Marketing Authorisation Holder
MMRM	Mixed model repeated measures
NLT	Not Less Than
NMT	Not More Than
NOR	Normal Operating Tange
NORD	National Organization for Rare Disorders
ODD	Orphan Drug Designation
PAPP	Polyester-Aluminium-Polyester-Polypropylene
PAR	Proven Acceptable Range
PD	Pharmacodynamic(s)

PDE	Permitted Daily Exposure
PE	Polyethylene
P-gp	P-glycoprotein
Ph. Eur	European Pharmacopoeia
PIP	Paediatric Investigation Plan
PK	Pharmacokinetic(s)
PP	Polypropylene
PT	MedDRA Preferred Term
QC	Quality Control
QTPP	Quality Target Product Profile
RAS	Renin-Angiotensin System
REC	RECommendation
RH	Relative Humidity
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAWP	Scientific Advice Working Party
SmPC	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
UPCL	Ultra Performance Liquid Chromatography
UPCR	Urine Protein Creatinine Ratio
UV	UltraViolet
XRPD	X-ray powder diffraction

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Calliditas Therapeutics AB submitted on 28 May 2021 an application for marketing authorisation to the European Medicines Agency (EMA) for Kinpeygo, through the centralised procedure under Article 3(1) and point 4 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 28 May 2020.

The application concerns a hybrid medicinal product as defined in Article 10(3) of Directive 2001/83/EC and refers to a reference product, as defined in Article 10 (2)(a) of Directive 2001/83/EC, for which a marketing authorisation is, or has been granted in the Union on the basis of a complete dossier in accordance with Article 8(3) of Directive 2001/83/EC.

The applicant applied for the following indication:

Kinpeygo is indicated for the treatment of primary immunoglobulin A (IgA) nephropathy (IgAN) in adults.

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

Following the CHMP positive opinion on this marketing authorisation, the Committee for Orphan Medicinal Products (COMP) reviewed the designation of Kinpeygo as an orphan medicinal product in the approved indication. More information on the COMP's review can be found in the Orphan maintenance assessment report published under the 'Assessment history' tab on the Agency's website:

https://www.ema.europa.eu/en/medicines/human/EPAR/Kinpeygo

1.2. Legal basis, dossier content

The legal basis for this application refers to:

Hybrid application (Article 10(3) of Directive No 2001/83/EC).

The dossier is composed of a full quality module, a non-clinical dossier relying on data from a reference medicinal product in combination with bibliographic data, and the applicant's own clinical data to support the new indication.

The chosen reference product is:

Medicinal product which is or has been authorised in accordance with Union provisions in force for not less than 6/8/10 years in the EEA:

- Product name, strength, pharmaceutical form: Entocort, 3 mg, modified-release capsule
- Marketing authorisation holder: Tillotts Pharma GmbH
- Date of authorisation: 02-04-1992
- Marketing authorisation granted by:
  - Member State (EEA): Denmark
    - National procedure
- Marketing authorisation number: 17169

Medicinal product authorised in the Union/Members State where the application is made or European

reference medicinal product:

- Product name, strength, pharmaceutical form: Entocort, 3 mg, modified-release capsule
- Marketing authorisation holder: Tillotts Pharma GmbH
- Date of authorisation: 02-04-1992
- Marketing authorisation granted by:
  - Member State (EEA): Denmark
    - National procedure
- Marketing authorisation number: 17169

1.3. Information on paediatric requirements

This application included, an EMA Decision (P/0049/2020) on the agreement of a paediatric investigation plan (PIP) and on the granting of a deferral and a waiver for budesonide (EMEA-002500-PIP01-18). However, Article 7 or 8 was not applied for, in accordance with Article 9 of the Regulation (EC) No 1901/2006.

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

1.4. Information relating to orphan market exclusivity

1.4.1. Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

1.5. Applicant's request(s) for consideration

1.5.1. Conditional marketing authorisation and Accelerated assessment

The applicant requested consideration of its application for a conditional marketing authorisation in accordance with Article 14-a of the above-mentioned Regulation.

The applicant requested accelerated assessment in accordance to Article 14 (9) of Regulation (EC) No 726/2004.

1.6. Protocol assistance

The applicant received the following Protocol assistance on the development relevant for the indication subject to the present application:

Date	Reference	SAWP co-ordinators
25 January 2012	EMEA/H/SA/2293/1/2012/SME/III	Peter Kiely and Brigitte Blöchl-Daum
18 May 2017	EMEA/H/SA/2293/2/2017/PA/SME/III	Christian Gartner and Kolbeinn

		Gudmundsson
12 October 2017	EMEA/H/SA/2293/2/FU/1/2017/SME/II	Hrefna Gudmundsdottir and Karin Janssen van Doorn
12 December 2019	EMEA/H/SA/2293/2/FU/2/2019/PA/SME/II CORRIGENDUM	Hrefna Gudmundsdottir and Karin Janssen van Doorn

The applicant received Scientific Advice and Protocol Assistance on four occasions as mentioned in the table above for the development of Kinpeygo (budesonide) for treatment of IgA Nephropathy. The advice pertained to the following Quality, Pre-Clinical and Clinical aspects:

- API specifications including particle size limits;
- Finished product specifications and testing;
- Dissolution testing;
- Overall non-clinical strategy;
- Evidence to support phase 2b study;
- General considerations for planning of pivotal clinical studies: validation proposal for proteinuria as surrogate endpoint, eGFR slope as efficacy endpoint, choice comparator, standard of care, safety database requirements;
- Phase 2b study design: general design features, efficacy endpoints, safety monitoring, study population, trial duration, run-in phase, follow-up phase, sample size, management of concomitant medications, central and local measurements for efficacy vs. safety analysis;
- Pharmacokinetics (PK) study plans;
- Phase 3 study design: general study design, primary and secondary efficacy endpoints, study population, dose regimen, study duration, study periods, interim analysis plan, statistical analysis plan, blinded re-treatment option, safety assessments and safety database;
- Justification for eligibility for conditional marketing authorisation and envisaged type of supportive evidence including evidence requirements to achieve full marketing authorisation post-approval for efficacy and safety.

1.7. Steps taken for the assessment of the product

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

Rapporteur: Andrea Laslop

Co-Rapporteur: Martina Weise

The application was received by the EMA on	28 May 2021
The procedure started on	17 June 2021
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	17 August 2021
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	24 August 2021

The CHMP Co-Rapporteur's first critique was circulated to all CHMP and PRAC members on	27 August 2021
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	14 September 2021
The applicant submitted the responses to the CHMP consolidated List of Questions on	25 November 2021
The CHMP Rapporteur circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on	05 January 2022
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	13 January 2022
The CHMP agreed on a list of outstanding issues to be sent to the applicant on	27 January 2022
The applicant submitted the responses to the CHMP consolidated List of Outstanding Issues on	21 February 2022
The CHMP Rapporteur circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	10 and 18 March 2022
The CHMP agreed on a 2nd list of outstanding issues to be sent to the applicant on	24 March 2022
The applicant submitted the responses to the 2nd CHMP consolidated List of Outstanding Issues on	14 April 2022
The CHMP Rapporteur circulated the updated CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the 2nd List of Outstanding Issues to all CHMP and PRAC members on	04 and 12 May 2022
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Kinpeygo on	19 May 2022

2. Scientific discussion

2.1. Introduction

2.1.1. Disease or condition

Kinpeygo was originally developed for the indication: treatment of primary immunoglobulin A (IgA) nephropathy (IgAN) in adults at high risk of disease progression. The indication was, however, restricted during the CHMP assessment to the treatment of primary IgAN in adults at risk of rapid disease progression with a urine protein-to-creatinine ratio (UPCR) ≥1.5 g/g (see further details in section 2.4.).

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.

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

2.1.3. 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

[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.
[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.

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 201313). It is thought that the origins of the disease reside in the mucosal tissue of the gastrointestinal (GI) tract (Barratt 202014, 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 201215).

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 201313, 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 201313, 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.

2.1.4. Clinical presentation, diagnosis and stage/prognosis

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 (Donadio and Grande 2002[5]). 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),

[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.
[15] Boyd JK, Cheung CK, Molyneux K, Feehally J, Barratt J. An update on the pathogenesis and treatment of IgA nephropathy. Kidney Int. 2012;81(9):833–43.
[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

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.

Certain findings on renal biopsy (Histologic predictors of progression) in patients with IgA nephropathy have also been associated with an increased risk of progressive disease. These include markers of more severe inflammatory disease, such as crescent formation and immune deposits in the capillary loops in addition to the mesangial deposits that are present in all patients, and markers of chronic fibrotic disease such as glomerulosclerosis, tubular atrophy, interstitial fibrosis, and vascular disease.

2.1.5. Management

There are currently no treatments approved for the management of patients with primary IgAN in the European Union. Standard of care comprises supportive therapy, which focuses on lowering of proteinuria and optimising blood pressure control by maximum tolerated inhibition of the renin angiotensin system (RAS), together with a low sodium diet (KDIGO 2021 guideline). When proteinuria persists despite optimal RAS inhibition with angiotensin converting enzyme inhibitors (ACEIs) and/or angiotensin II type I receptor blockers (ARBs), patients are at risk of progression to ESRD. There are no further recommended treatments, and therapeutic options are generally limited to consideration of a 6-month treatment course of high-dose systemic glucocorticosteroids (GCS). However, the benefit-risk balance for the use of GCS over optimised supportive care in IgAN has been questioned, based on the increased risk of serious steroid-related adverse effects, in particular life-threatening serious infections reported in two recent randomised controlled trials in IgAN patients (STOP-IgAN and TESTING, Lv et al 2017[25], Rauen et al 2015[26], Rauen et al 2020[27]). Additional immunosuppressants beyond GCS, such as cyclophosphamide, are suggested for specific situations only, for example in cases of crescentic IgAN where renal function is rapidly deteriorating. Therefore, there is a high unmet medical need for a targeted treatment with a favourable benefit-risk profile for patients with primary IgAN at risk of progressing to ESRD.

[25] Lv J, Zhang H, Wong MG, Jardine MJ, Hladunewich M, Jha V, et al. Effect of oral methylprednisolone on clinical outcomes in patients with IgA nephropathy: The TESTING randomised clinical trial. JAMA 2017;318:432–442.
[26] Rauen T, Eitner F, Fitzner C, Sommerer C, Zeier M, Otte B, et al. Intensive Supportive Care plus Immunosuppression in IgA Nephropathy. N Engl J Med. 2015;373:2225-36.
[27] Rauen T, Wied S, Fitzner C, Eitner F, Sommerer C, Zeier M, et al. After ten years of follow-up, no difference between supportive care plus immunosuppression and supportive care alone in IgA nephropathy. Kidney Int. 2020;98(4):1044-52.

2.1.6. 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 proposed 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.

2.1.7. Type of Application and aspects on development

The CHMP agreed to the applicant's request for an accelerated assessment as the product was considered to be of major public health interest. This was based on:

- IgAN is the most common form of primary glomerulonephritis worldwide.
- Progression to ESRD occurs in up to 50% of affected patients, often over 20-25 years of observation.
- There are currently no treatments approved for the management of patients with primary IgAN. Current standards of care focus on optimisation of antihypertensive and antiproteinuric therapies (typically renin-angiotensin system blockade) to reduce disease progression (KDIGO 2021).
- The main evidence for safety and efficacy of Kinpeygo (budesonide) is derived from a randomised double-blind, placebo-controlled phase 3 study in a high-risk primary IgAN population of patients with significant proteinuria and mild to moderate loss of kidney function on a background of optimised RAS inhibitor therapy (Nef-301). Additionally, there are supportive data from a placebo-controlled phase 2b clinical trial (Nef-202). The strength of evidence was considered sufficient to support an accelerated assessment.

However, during assessment the CHMP concluded that it was no longer appropriate to pursue accelerated assessment, as there were major objections in quality and clinical and a number of other concerns which precluded an assessment under accelerated timelines.

The applicant requested consideration of its application for a conditional marketing authorisation in accordance with Article 14-a of the above-mentioned Regulation, based on the following criteria:

- The benefit-risk balance is positive.
- It is likely that the applicant will be able to provide comprehensive data.

Based on the observed difference in eGFR slope over 1 year, it is highly likely that the primary eGFR $AUC_{(0-2)}$ endpoint and eGFR 2-year slope will be statistically significant in this patient population after 2 years of follow-up at the time of the Part B analysis of the phase 3 trial, which is fully recruited and ongoing. There is $\geqslant$90% power for the Part B analysis of 2-year chronic slope in this patient population. A difference in chronic slope of 4.79 mL/min/1.73 m^2 per year in the subgroup of patients with UPCR $\geqslant$1.3 g/gram is well in excess of the 0.85 mL/min/1.73 m^2 per year threshold given for the 1-year eGFR chronic slope to predict longer term clinical benefit on the composite clinical endpoint in Table 3 of Inker et al 2019[28]. Therefore, longer term clinical benefit in this patient population is highly

[28] Inker LA et al. GFR Slope as a Surrogate End Point for Kidney Disease Progression in Clinical Trials: A Meta-Analysis of Treatment Effects of Randomized Controlled Trials. J Am Soc Nephrol. 2019 Sep;30(9):1735-1745

likely to be confirmed at the time of the final analysis of the phase 3 study.

- Unmet medical needs will be addressed.

Patients with baseline UPCR ⩾1.3 g/gram are at risk of rapid disease progression to ESRD over a short period of time, and represent a group of patients for whom the unmet medical need is considerable. Without treatment, an eGFR deterioration of 9.36 mL/min/1.73 m2 per year would be expected (1-year eGFR slope in the placebo group of the Phase 3 trial), and as a result these patients are at significant risk of requiring dialysis or kidney transplantation in the near term.

- The benefits to public health of the immediate availability outweigh the risks inherent in the fact that additional data are still required.

The benefits to public health of the immediate availability of Kinpeygo for this restricted patient population are considered to outweigh the potential risks, including any uncertainties regarding the interpretability and durability of the benefits shown for UPCR. In these patients with higher levels of baseline proteinuria, the applicant believes a positive benefit-risk profile has already been demonstrated during the first year of follow-up, including substantial eGFR benefit over 1 year.

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as modified release hard capsules containing 4 mg budesonide as active substance.

Other ingredients are:

Capsule content: Sugar spheres (sucrose and corn starch), hypromellose, macrogol, citric acid monohydrate, ethylcellulose, medium chain triglycerides and oleic acid;

Capsule shell: hypromellose, macrogol, titanium dioxide (E171), methacrylic acid and methyl methacrylate copolymers, talc and dibutylsebacate;

Printing ink: shellac and iron oxide black (E172).

The product is packaged in white high density polyethylene (HDPE) bottles with white polypropylene (PP) child-resistant closures with induction seals as described in section 6.5 of the SmPC.

2.2.2. Active substance

General information

The chemical name of budesonide is 6α, 17α -[(1*RS*)-butylidenebis(oxy)]-11β, 21-dihydroxypregna-1,4-diene-3,20-dione corresponding to the molecular formula $C_{25}H_{34}O_6$. It has a relative molecular mass of 430.5 g/mol and the following structure:

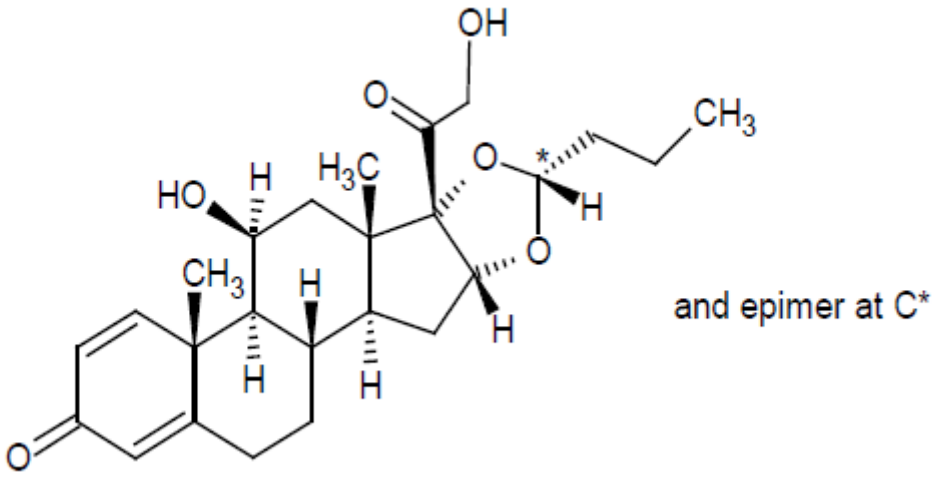


Figure 1: active substance structure

The active substance (AS) is a slightly hygroscopic white to off-white crystalline solid, practically insoluble in water.

Budesonide exhibits stereoisomerism due to the presence of nine chiral centres. Eight stereocentres are defined whereas the other is a mixture of epimers at C* (Figure 1). Polymorphism has not been observed for budesonide.

As there is a monograph of budesonide in the European Pharmacopoeia, the manufacturers of the active substance has been granted a Certificate of Suitability of the European Pharmacopoeia (CEP) which has been provided within the current Marketing Authorisation Application.

Manufacture, characterisation and process controls

The relevant information for both manufacturers has been assessed by the EDQM before issuing the Certificates of Suitability (CEP 2010-190 and CEP 1997 067).

For CEP 2010 190, the container closure system is stated in the CEP. For CEP 1997-067, the active substance is packaged in the PE bags are placed inside thermally welded polyester-aluminium- polyester polypropylene (PAPP). Between the double PE bag and PAPP, oxygen scavengers are placed. The bag is then placed alternatively into a fibre carton drum or Moplen® containers. The container closure system complies with the EC directive 2002/72/EC and EC 10/2011 as amended.

Specification

The consolidated active substance specification covering both sources of AS includes tests for identity, assay, impurities, loss on drying, microbiological quality and residual solvents (all Ph. Eur.).

The control tests were carried out to comply with the specifications and test methods of the Ph. Eur. monograph. Additional specifications have been set for particle size distribution (laser diffraction). All additional methods have been adequately validated and described according to ICH Q2.

Satisfactory information regarding the reference standards has been presented.

Batch analysis data on 3 production scale batches of active substance from each manufacturer were provided. The results are within the specifications and consistent from batch to batch.

Stability

Stability is covered in CEP 2010-190 which indicates a re-test period of 24 months for both micronized and non-micronized material, without any special storage conditions. Only micronized AS is used to manufacture finished product.

For CEP 1997-067, which does not include a re-test period, stability data for up to 5 years under long-term conditions (25 °C/60% RH) and 6 months under accelerated conditions (40 °C/75% RH) were submitted. These studies used an earlier packaging format without the oxygen scavenger. Further data was provided up to 12 months under long term conditions with the scavenger which does not impact the stability profile.

The stability results indicate that the active substance in CEP 1997-067 is sufficiently stable. The stability results justify the proposed retest period of 60 months protected from light in the proposed container.

2.2.3. Finished medicinal product

Description of the product and Pharmaceutical development

The finished product is presented as white, modified release, size 1, hard capsules containing 4 mg budesonide as active substance. The capsules are enterically coated and contain beads with additional modified release properties.

The proposed finished product is designed to pass through the stomach intact and then provide a delayed and somewhat prolonged release of budesonide in the ileum, for local pharmacological effect.

The active substance budesonide is practically insoluble in water and belongs to Biopharmaceutical Classification System (BCS) Class II (low solubility, high permeability) and so is micronized. It is ensured by each of the active substance manufacturer that the same crystalline polymorph is routinely formed as demonstrated comparative XRPD profiles.

Formulation development was based on analysis of the Quality Target Product Profile (QTPP) and risk assessment of critical quality attributes (CQAs) of coated beads and enteric coated capsules. The QTPP was defined as a modified release oral capsule containing 4 mg budesonide which meets compendial and other quality standards, and which is delivered intact to the ileum. After capsule disintegration, a prolonged release of the complete dose of budesonide is intended. Assay, content uniformity, impurities and dissolution have been identified as CQAs. The effect of most of the critical material attributes (CMAs) on CQAs has been rated by the applicant as "no impact" or "low" due to prior knowledge and initial experimental data.

Several formulations were used during the product development, denoted by letters A- F. Formulation F (Nefecon-F) was used for phase 3 clinical study and is the intended final commercial product. The development through all formulations (A, B, C-D-E to F) has been described. A detailed overview of development and clinical batches was presented (from 2004 – 2020). Pharmacokinetic studies have been performed (PK study Nef-103, Nef-104 and Nef-105) to assess the improved formulations including selection of Nefecon-F. Based on the results of these studies using Nefecon-A as reference, formulation improvements have been made to obtain a robust phase 3 and final commercial product with the desired release profile. Sufficient information has been given on changes in formulation, batch size and manufacturing size as well as corresponding dissolution data for batches used in bioequivalence and clinical studies.

All excipients are well known pharmaceutical ingredients and their quality is compliant with compendial standards. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC and in paragraph 2.2.1 of this report.

The release profile of the active substance in the target region, the ileum, has been demonstrated *in vivo*.

Dose dumping was investigated during development in the range of 0 – 40% ethanol. The results indicate that the release profile is not significantly altered in the presence of alcohol and no dose dumping occurs.

The development of the manufacturing process included the identification of critical process parameters (CPPs). CPPs and their impact on CQAs were discussed for manufacturing of the beads and for manufacturing of the capsules. Risk assessments were carried out with follow up experimentation (including design of experiments) that lead to the risk of all but 1 CPPs being defined as low, which was not considered acceptable by CHMP. Definition of CPPs was subsequently amended to include additional parameters.

It was unclear in the original dossier whether or not design spaces were claimed for certain steps as the process had not been clearly defined, resulting in a major objection. In response, the applicant explained that it was not the intention to claim design spaces and revised the process description to include set-points and associated normal operating ranges (NORs). A PAR is proposed for 1 step and the applied range ensures that the beads exhibit the desired release profile without re-processing. All other process parameters are defined by setpoints with associated NORs based on equipment capability. The process as defined is considered suitably robust.

Development of the dissolution methods has been extensively discussed. The dissolution methods are deemed critical by the CHMP since they ensure the desired release profile. The initially proposed method for both the IPC and the finished product release test was not considered sufficiently discriminatory by CHMP thus resulting in a major objection. In response, the applicant submitted a new release method which was more discriminatory and after tightening the specifications, was considered acceptable by CHMP.

The revised specifications have been set based on batches used in relevant clinical studies including PK studies and are now considered acceptable. Discriminatory power was investigated for capsules by varying critical material attributes (CMAs) and critical process parameters (CPPs). The method was able to discriminate bad batches from those manufactured according to the agreed process description and is considered adequate.

The applicant currently applies a different dissolution method for IPC of beads compared to the QC method for finished product The applicant wasn’t able to demonstrate that the revised IPC method was suitable for the bead curing IPC within the frame of this procedure. Therefore, the existing method will still be used for now. At the request of CHMP, specification limits have been tightened in line with relevant clinical batches. The CHMP recommended the applicant to re-develop the dissolution IPC method for beads and to implement a more discriminatory dissolution method post-approval. The applicant has committed to doing so (**REC**).

The primary packaging is white HDPE bottles with white PP child-resistant closures with induction seals. The materials comply with Ph. Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

Manufacture of the product and process controls

The manufacturing process consists of coating of sugar spheres to produce beads with modified release properties that are filled into capsules that are enterically coated. The process is considered to be a non-standard manufacturing process due to the modified release properties and low active substance content.

The updated IPCs as well as targets and ranges for process parameters are considered justified and adequate. No intermediates are defined in the current process.

The information provided on the holding time for bulk product (enteric coated capsules) and the bulk product packaging material is satisfactory. Confirmation of compliance with requirements of NfG on Start of Shelf Life of the Finished Dosage Form (CPMP/QWP/072/96) was provided.

In the initial submission, no process validation data was submitted which is not acceptable for a non-standard process resulting in a 3rd major objection. In response, the applicant submitted a validation report covering four commercial scale batches. With subsequent revisions and further tightening of process parameters, the CHMP considers that it has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner.

Product specification

The finished product release specifications include appropriate tests for this kind of dosage form including description, identification (UPLC, UV), assay (UPLC), impurities (UPLC), uniformity of dosage units (Ph. Eur.), dissolution (UPLC) microbial limits (Ph. Eur.) and residual solvents (HS-GC).

The finished product specification contains all parameters relevant for this dosage form and is acceptable. The proposed limits for residual solvents and impurities have been satisfactorily discussed and justified during the procedure considering a maximum daily dose (MDD) of 16 mg (4 capsule with 4 mg budesonide), the relevant guidelines and the presented data. The final assay range limits (release and shelf life) are also acceptable. The limits for dissolution are acceptable as discussed above. Omission of testing for water content and disintegration have been justified and can be accepted.

The potential presence of elemental impurities in the finished product has been assessed following a risk-based approach in line with the ICH Q3D Guideline for Elemental Impurities. Batch analysis data on 3 batches using a validated ICP-MS method was provided, demonstrating that each relevant elemental impurity was not detected above 30% of the respective PDE. Based on the risk assessment and the presented batch data, it can be concluded that it is not necessary to include any elemental impurity controls in the finished product specification.

A risk assessment concerning the potential presence of nitrosamine impurities in the finished product has been performed considering all suspected and actual root causes in line with the "Questions and answers for marketing authorisation holders/applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products" (EMA/409815/2020) and the "Assessment report- Procedure under Article 5(3) of Regulation EC (No) 726/2004- Nitrosamine impurities in human medicinal products" (EMA/369136/2020). Based on the information provided, it is accepted that there is no risk of nitrosamine impurities in the active substance or the related finished product.

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis results are provided for 13 production scale batches of the commercial formulation confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

The finished product is released on the market based on the above release specifications, through traditional final product release testing.

Stability of the product

Stability data from 3 production scale batches of finished product stored for up to 24 months under long term conditions (25ºC / 60%RH) and for up to 6 months under accelerated conditions (40ºC / 75% RH) according to the ICH guidelines were provided. The batches of medicinal product were identical to those proposed for marketing and were packed in the primary packaging proposed for marketing. Samples were tested for appearance, assay, impurities, dissolution and water content. Under long term conditions, no significant changes were observed to any of the measured parameters. Under accelerated conditions, there was a slight increase in impurity content but within the specification limits.

In addition, 1 batch was exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. Kinpeygo is photostable, either in- or outside of the bottle.

The results from two in-use studies were provided. The studies mimic the use of the bottles for a duration of 60 days. The amount of water did not change significantly, and no effect of the slight water increase was observed on the measured parameters. In-use stability of the final finished product if stored below 25°C is defined as one month, which is acceptable as it covers the intended dosage regimen.

Based on available stability data, the proposed shelf-life of 3 years without specific storage conditions as stated in the SmPC (sections 6.3 and 6.4) is acceptable.

Adventitious agents

No excipients derived from animal or human origin have been used.

2.2.4. Discussion on chemical, and pharmaceutical aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use. The 3 interlinked major objections covering the description of the manufacturing process (ranges and design spaces), validation of the manufacturing process, and the development and discriminatory nature of the dissolution methods used for release to confirm the desired modified release properties have been adequately addressed. Process validation data has been submitted confirming the robustness of the process and the process description was amended by defining set-points and tightening associated NORs to ensure that the product meets its quality requirements without further processing. The QC dissolution method was replaced and suitable limits were established, whereas the applicant committed to further developing the IPC method post-approval.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

2.2.6. Recommendation for future quality development

In the context of the obligation of the MAH to take due account of technical and scientific progress, the CHMP recommends the following points for investigation:

- the applicant is recommended to re-develop the dissolution IPC method for cured beads and to implement a more discriminatory dissolution method

2.3. Non-clinical aspects

2.3.1. Introduction

A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is based on up-to-date and adequate scientific literature and data from a reference medicinal product. The overview justifies why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data. The non-clinical aspects of the SmPC are in line with the SmPC of the reference product. The impurity profile has been discussed and was considered acceptable.

Therefore, the CHMP agreed that no further non-clinical studies are required.

2.3.2. Ecotoxicity/environmental risk assessment

A comprehensive environmental risk assessment (ERA) has been provided by the applicant.

The PEC/PNEC ratio for microorganisms is below 0.1, and the PEC/PNEC ratio for surface water and ground water are <1. The PEC value is below 0.01 µg/L, which is below the trigger for a Phase II environmental fate and effects analysis, unless other environmental concerns are apparent. However, budesonide is a*n endocrine active substance*, which can be regarded as an environmental concern, and a tailored Phase II environmental fate and effects analysis, addressing its specific mechanism of action, was performed by the applicant.

The potential endocrine disrupting properties were addressed in a zebrafish full lifecycle test and the most sensitive endpoint (early life stage survival of F1 generation, which was the most sensitive endpoint of all aquatic long-term studies) was used in the Predicted Environmental Concentration (PEC)/Predicted No Effect Concentration (PNEC) assessment. In addition, budesonide is not persistent, and it is not likely to bioaccumulate in aquatic organisms, which means it is not a PBT or a vPvB substance.

Budesonide showed no toxicity to the sediment dwelling organism Chironomus riparius.

The provided extensive ERA has not identified any potential risk or significant risk to the environment as a consequence of the use of budesonide (Kinpeygo).

Table 1 Summary of main study results

Substance (INN/Invented Name): Budesonide

CAS-number (if available): 51333-22-3					
PBT screening		Result			**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD107	3.45			N, but B triggered
PBT-assessment					
Parameter	**Result relevant for conclusion**				**Conclusion**
Bioaccumulation	log K_{ow}	3.45			Potentially B
	BCF	9			not B
Persistence	$DT_{50,\ 12\ °C,\ Sediment}$	62.6 d			not P
Toxicity	NOEC, Fish-FLC (*Danio rerio*)	0.032 µg/L			T
PBT-statement :	The compound is not considered as PBT nor vPvB				
Phase I					
Calculation	**Value**	**Unit**			**Conclusion**
$PEC_{surfacewater}$, refined (prevalence)	0.0016	µg/L			< 0.01 µg/L threshold (N)
Other concerns (e.g. chemical class)	*Potential Endocrine Disruptor*				(Y)
Phase II Physical-chemical properties and fate					
Study type	**Test protocol**	**Results**			**Remarks**
Adsorption-Desorption	OECD 106	K_{FSOIL}: 26 (mean of 5 soils) Soil type / $K_{F,\ Ads.}$ Clay 41 Silt Loam 22 Loam 19 Silt 17 Loamy Sand 31			No correlation with OC
Ready Biodegradability Test	OECD 301	Not Readily Biodegradable			
Aerobic and Anaerobic Transformation in Aquatic Sediment systems	OECD 308 (River/Pond system; all SFO)	$DT_{50,\ 12\ °C\ water}$ = 13.7/14.7 d $DT_{50,\ 12\ °C\ sediment}$ = 48.4/62.6 d $DT_{50,\ 12\ °C\ whole\ system}$ = 26.6/37.1 d % shifting to sediment = 49.0/68.6 % (both @ 30 d) Mineralisation: 86.2/68.6 %			No sediment dwelling organism test required due to specific work mechanism of Budesonide
Phase IIa Effect studies					
Study type	**Test protocol**	**Endpoint**	**value**	**Unit**	**Remarks**
Algae, Growth Inhibition Test (*Pseudokirchneriella subcapitata*)	OECD 201OECD 201	NOEC	≥ 7900	µg/L	Limit test
Daphnia sp. Reproduction Test (*Daphnia magna*)	OECD 211	NOEC LOEC EC_{10} EC_{50}	3360 6950 3990 5300	µg/L	Most sensitive endpoint: mortality of offspring
Fish, Full Life Cycle Test (*Danio rerio)*		NOEC LOEC	0.032 0.1	µg/L	Most sensitive endpoint: 28 d survival of F1 generation
Activated Sludge, Respiration Inhibition Test	OECD 209	EC	10^6	µg/L	
Phase IIb Studies					

Bioconcentration in fish, aqueous exposure (*Cyprinus carpio*)	OECD 305	BCF_{ss} BCF_L	5-6 8-9	L/kg	Measured BCF at steady state. No depurination stage included in test due to low BCF value. 5% lipid normalization of BCF.

2.3.3. Conclusion on the non-clinical aspects

The non-clinical sections of the SmPC are acceptable and in line with the reference product. The grounds for not providing new non-clinical data are adequately justified. The non-clinical overview on pharmacology, pharmacokinetics and toxicology submitted by the applicant for Kinpeygo is considered sufficient and the ERA is acceptable.

2.4. Clinical aspects

2.4.1. Introduction

This is an application for a modified-release hard capsule containing budesonide. To support the marketing authorisation application the applicant conducted 6 phase 1 studies in healthy volunteers, 2 randomised double-blind placebo-controlled studies and 1 open-label uncontrolled study in adult patient with primary IgAN. Study Nef-301 was the pivotal study for the assessment.

CHMP scientific advice pertinent to the clinical development was given for this medicinal product.

In the clinical development program, another name for the intended product was used "Nefecon" and is used synonymously in the report for the current name "Kinpeygo" in particular when referring to the different formulations (Nefecon A to F).

GCP aspect

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant 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

Table 2 Summary of Phase 1 studies conducted in healthy volunteers that have provided relevant PK data for Kinpeygo

Study identifier and location in Module 5	Type of study	Relevant PK data
Nef-101 Module 5.3.4.1	Healthy Subject PD and PK/PD	This study provides PK and PD data for 2 doses (8 mg and 16 mg) of the Nefecon-A formulation that was used in the Phase 2 patient studies. The primary objective was to compare the individual changes from untreated conditions in serum cortisol levels over 24 hours after a single 8 mg dose of Nefecon, a single 16 mg dose of Nefecon and a single 9 mg dose of Entocort. The aim of the primary objective was to compare the 3 treatments with regard to change in $AUC_{(0-24)}$ for serum cortisol, and to find the dose of Nefecon that corresponded to a single 9 mg dose of Entocort with regard to serum cortisol $AUC_{(0-24)}$ Secondary objectives were to compare cortisol excretion in urine over 24 hours; to compare PK parameters based on plasma concentrations of budesonide; and to find the dose of Nefecon that corresponded to a single 9 mg dose of Entocort with regard to plasma budesonide $AUC_{(0-24)}$.
Nef-103 Module 5.3.1.2	Comparative BA/BE	This study provides PK data including $AUC_{(0-24)}$, C_{max}, T_{max}, T_{lag}, and $T_{1/2}$ for the 16 mg dose of Nefecon-A that was used in the Phase 2 patient studies.
Nef-104 Module 5.3.1.2	Comparative BA/BE	This study provides PK data including $AUC_{(0-24)}$, C_{max}, T_{max}, T_{lag}, and $T_{1/2}$ for the 16 mg dose of Nefecon-A that was used in the Phase 2 patient studies.
Nef-105 Module 5.3.1.2	Comparative BA/BE	This study provides PK data for the 16 mg dose of Nefecon-A that was used in the Phase 2 patient studies, as well as the 16 mg dose of Nefecon-F (the intended FCP) that was used in Phase 3. The primary objectives were to assess budesonide PK variables of Nefecon-A (reference), Nefecon-F (test), and Entocort EC (test) capsules after administration in healthy volunteers by comparison of $AUC_{(0-24)}$, $AUC_{(0-inf)}$, C_{max}, T_{max}, T_{lag}, and $T_{1/2}$, and to assess the intra-individual variability in PK parameters for Nefecon-A and Nefecon--F after repeat single dose administration of each formulation.
Nef-106 Module 5.3.1.1	BA food effect	This study provides PK data including $AUC_{(0-24)}$, C_{max}, T_{max}, T_{lag} and $T_{1/2}$ under fasted and fed conditions for the 16 mg dose of Nefecon-F (the intended FCP) that was used in Phase 3.
Nef-107 Module 5.3.1.1	BA food effect	This study provides PK data including $AUC_{(0-48)}$, C_{max}, T_{max}, T_{lag} and $T_{1/2}$ under fasted and fed conditions for the 16 mg dose of Nefecon-F (the intended FCP) that was used in Phase 3.

Note that Nefecon-A was used in studies Nef-101, Nef-103 (referred to simply as Nefecon in these Clinical Study Reports), Nef-104, Nef-105, Nef-201 and Nef-202; Nefecon-F (also the intended FCP) is the formulation used in Nef-301, Nef-106, and Nef-107, and assessed versus Nefecon-A in Nef-105. Each modified release capsule contains 4 mg budesonide.

$AUC_{(0-24)}$ area under the plasma concentration-time curve from time 0 to 24 hours; BA bioavailability; $AUC_{(0-inf)}$ area under the plasma concentration-time curve from time zero to infinity; BE bioequivalence; C_{max} maximum plasma concentration; FCP Final Commercial Product; PD pharmacodynamic(s); PK pharmacokinetic(s); $T_{1/2}$ elimination half-life; T_{lag} time prior to first measurable (non-zero) plasma concentration; T_{max} time to maximum plasma concentration.

Table 3 Summary of clinical efficacy and safety studies for Kinpeygo 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	Randomized, double-blind, placebo-controlled Ongoing study FPFV 5 Sep 2018 DCO 5 Oct 2020	112 sites 20 countries across Europe, North America, South America, and Asia-Pacific including China	Patients on optimized 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:** AUC-based endpoint of eGFR calculated as a time-weighted average of eGFR recordings observed at each time point over 2 years	**Part A DCO:** Nefecon[b] 16 mg: 150 Placebo: 144 **Part A FAS:** Nefecon[b] 16 mg: 97 Placebo: 100 [an additional 2 patients randomized to placebo in the Part A FAS were not dosed but included in the analysis population for efficacy]	9 months	**In the Part A FAS:** 67.8% male Median 44 (23 to 73) years 85.9% Caucasian 12.1% Asian
Nef-202[c]	Randomized, double-blind, placebo-controlled 11 Dec 2012 to 25 June 2015	61 sites 10 European countries	Patients on optimized 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[b] 16 mg: 49 Nefecon[b] 8 mg: 51 Placebo: 50	9 months	70.5% male Median 38 (18 to 82) years 96.6% Caucasian
Nef-201 [PL-56]	Open-label uncontrolled 09 Jan 2006 to 24 Oct 2008	3 sites Sweden	Patients on current RAS inhibitor therapy with: Proteinuria based on 24-hour urine albumin of >0.5 g and serum creatinine of <200 µmol/L	Change from baseline in 24-hour urine albumin excretion	Nefecon[b] 8 mg: 16	6 months	62.5% male Median 40 (29 to 46) years Race data not available

[a] Patients with a diagnosis of primary IgAN and were treated on a background of RAS inhibitor therapy.
[b] The Nefecon formulation used in Nef-301 is the intended Final Commercial Product with hypromellose capsule shell (Nefecon-F). The Nefecon-A (starch capsule) was used in studies Nef-201 [PL-56] and Nef-202. Nefecon-F and Nefecon-A were shown to be bioequivalent in Study Nef-105 (Section 2). Each Nefecon modified release capsule contains 4 mg budesonide.
[c] Results of this study are provided in the Nef-202 CSR and were published in Fellström et al 2017.
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.

2.4.2. Clinical pharmacology

2.4.2.1. Pharmacokinetics

Data from 6 healthy volunteer studies are included with this application to support the biopharmaceutics and clinical pharmacology of Kinpeygo. This includes studies that were conducted as part of the formulation development (Nef-103, Nef-104, Nef-105), a pharmacodynamic (PD) and pharmacokinetic (PK) study that assessed the effect of single doses of Kinpeygo on serum cortisol, with the oral budesonide product Entocort included as comparator (Nef-101), and 2 studies that have assessed the impact of food on the bioavailability of Kinpeygo (Nef-106, Nef-107).

The Nefecon-F formulation used in the phase 3 Nef-301 study is the intended Final Commercial Product (FCP). Following demonstration of efficacy in the phase 2b Nef-202 study using the initial Nefecon-A formulation, subsequent formulations were developed (Nefecon A, B, C, D, E and F) for pharmaceutical reasons to improve patient compliance (by using a smaller capsule) and to gain a robust formulation and manufacturing process suited for commercial production. In terms of PK, the aim was for subsequent formulations and the FCP to mimic the PK properties of Nefecon-A.

Table 4 Overview of PK parameters for a single 16 mg dose of the Nefecon-A and Nefecon-F formulations (healthy volunteer studies)

Formulation	Study	N	Median (range)		Mean (SD)	Geometric mean (CV%)	
			T_{lag} (h)	T_{max} (h)	$T_{1/2}$ (h)	C_{max} (ng/mL)	$AUC_{(0-24)}$ (ng/mL×h)
Nefecon-A [Formulation used in Phase 2 IgAN patient studies]	Nef-101[a]	24	2.0 (1.0-12.0)	4.0 (2.0-24.0)	4.4 (1.80)	4.49	23.17
	Nef-103	22	2.0 (1.5-4.0)	5.0 (3.0-10.0)	4.2 (0.99)	4.33 (62.8)	21.73 (58.2)
	Nef-104	16	2.5 (1.5-4.3)	5.3 (3.3-16.0)	4.6 (0.97)	5.52 (104.2)	28.05 (79.1)
	Nef-105[b]	25	2.5 (2.0-4.5) 2.5 (1.0-3.5)	4.5 (3.0-10.0) 4.5 (4.0-10.0)	4.9 (0.87)	4.61 (48.2)	22.79 (43.8)
Nefecon-F [Intended FCP used in Phase 3 IgAN patient study]	Nef-105[b]	24	3.3 (0-6.0) 3.0 (0-4.5)	5.3 (4.5-10.0) 5.0 (4.5-10.0)	5.0 (0.82)	4.41 (58.3)	24.13 (49.7)
	Nef-106[c]	26	3.0 (2.3-6.0)	5.2 (4.3-9.0)	5.1 (1.14)	4.25 (78.7)	24.76 (72.0)
	Nef-107[c]	27	3.0 (2.0-16.0)	5.5 (4.0-30.0)	6.8 (1.95)	3.19 (98.1)	21.36 (84.3)[d]

[a] Nef-101 data is for the 16 mg dose group with conversion of AUC and C_{max} units. CV% not calculated for C_{max} or AUC in this study.
[b] Nef-105 C_{max}, $AUC_{(0-24)}$, and $T_{1/2}$ data based on the average of 2 administrations.
[c] Nef-106 and Nef-107 data is for the fasted period in these 2 studies.
[d] $AUC_{(0-48)}$.
$AUC_{(0-24)}$ area under the plasma concentration-time curve from time 0 to 24 hours; C_{max} maximum plasma concentration; CV coefficient of variation; FCP Final Commercial Product; N number of subjects in PK analysis set; SD standard deviation; $T_{1/2}$ elimination half-life; T_{lag} time prior to first measurable (non-zero) plasma concentration; T_{max} time to maximum plasma concentration.

Absorption

The Kinpeygo formulation is designed to deliver budesonide topically in the ileum.

The extent of oral absorption of budesonide seems to be complete (Edsbäcker and Andersson 2004[29]) and is rapid.

The time to maximum plasma concentration (Tmax) is formulation dependent. For Nefecon-F, median Tmax ranged from 5.0 to 5.5 hours in the fasted state (studies Nef-105, Nef-106, and Nef-107).

Following single oral administration of a 16 mg dose of Nefecon-F to healthy subjects, geometric mean Cmax ranged between 3.2 and 4.4 ng/mL, and AUC (0-24) ranged between 24.1 and 24.8 ng/mL×h.

Bioavailability

Systemic bioavailability of budesonide is low (approximately 10%) due to high first-pass metabolism.

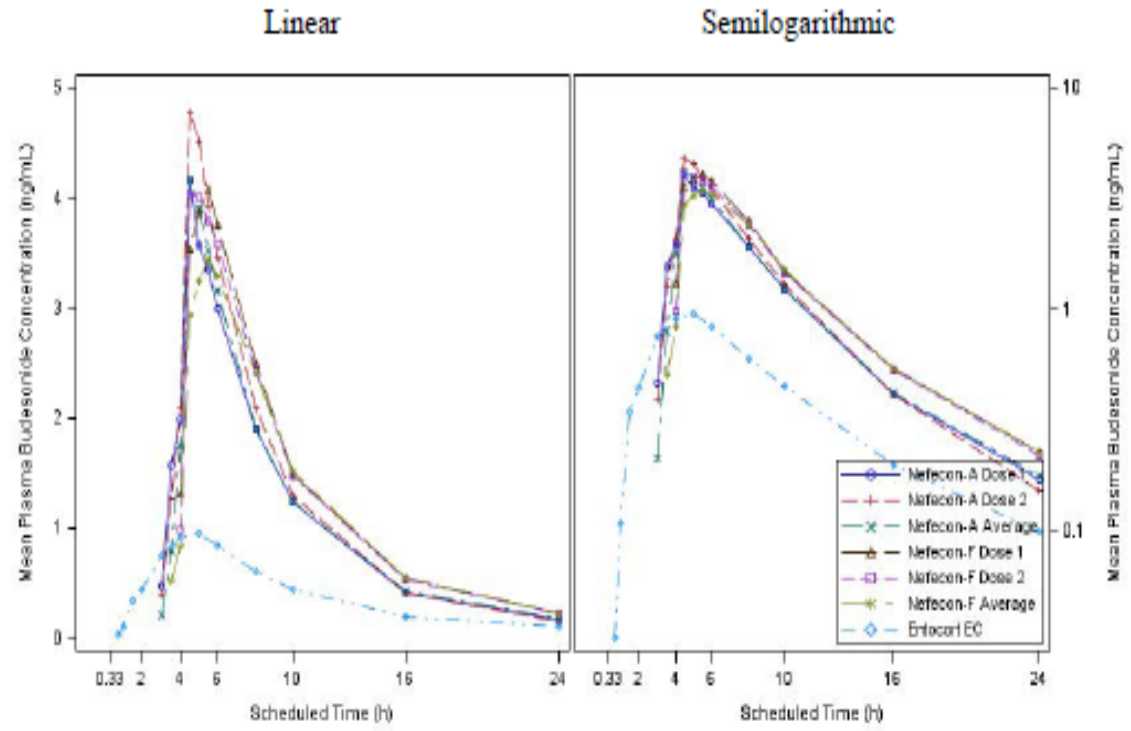
Bioequivalence

Bioequivalence studies (Nef-103, Nef-104, and Nef-105) were carried out to address equivalence for manufacturing changes during the development (Nefecon formulations A, B, C, D, E and F) and to justify changes between clinical trials formulation and finished product intended for marketing.

Nefecon B formulation was compared to Nefecon A in phase 1 healthy volunteer comparative BA/BE study Nef-103. Nefecon C, D and E formulations were compared to Nefecon A in phase 1 healthy volunteer comparative BA/BE study Nef-104. Nefecon F is the formulation used in the pivotal phase 3 study Nef-301 and was assessed versus Nefecon A in phase 1 healthy volunteer comparative BA/BE study Nef-105.

[29] Edsbäcker S and Andersson T. Pharmacokinetics of budesonide (Entocort™ EC) capsules for Crohn's disease. Clin Pharmacokinet. 2004;43(12):803-21.

The results of study Nef-105 (A Five-Period, Open-Label, Randomised, Repeat Design, Cross-Over Study to Assess Budesonide Pharmacokinetic Variables and Intra-Individual Variability of Kinpeygo Formulations A and F, and to Assess Single Dose Administration Entocort Pharmacokinetic-Parameters in 24 Healthy Volunteers) are presented below:



h = hours.
Source: Post-text Figure 14.2.1.1

Figure 2 Plot of mean plasma budesonide concentrations versus time by treatment on linear and semilogarithmic scales – PK analysis set

The plasma concentration-time profile for Entocort EC was different from the plasma concentration-time profile for the Kinpeygo formulations. The onset of absorption for Entocort EC was rapid with a median Tlag of 40 minutes.

The ratio of Cmax to AUC was lower for Entocort EC than for Kinpeygo due to a flatter plasma concentration-time profile, indicating a longer release and absorption phase.

The Entocort EC dose contained 9 mg budesonide, which is the highest clinically approved dose that could be administered during this study. Even when scaled for the differences in budesonide content, the Cmax and AUC obtained from Entocort EC were lower than that seen with the Kinpeygo preparations.

Table 5 Summary of PK variables for budesonide by treatment – PK analysis set

PK Parameter (Unit)	Statistic	Nefecon-A Dose 1	Nefecon-A Dose 2	Nefecon-A Average	Nefecon-F Dose 1	Nefecon-F Dose 2	Nefecon-F Average	Entocort EC
C_{max} (ng/mL)	n	25	22	25	24	23	24	23
	Geo. Mean (CV%)	4.209 (68.7)	4.890 (47.8)	4.611 (48.2)	4.709 (54.0)	4.110 (94.5)	4.407 (58.3)	1.064 (51.0)
$AUC_{(0-24)}$ (h·ng/mL)	n	25	22	25	24	23	24	23
	Geo. Mean (CV%)	21.327 (51.4)	23.241 (44.5)	22.789 (43.8)	25.171 (43.7)	22.492 (68.4)	24.131 (49.7)	8.361 (47.1)
$AUC_{(0-inf)}$ (h·ng/mL)	n	25	22	25	24	23	24	23
	Geo. Mean (CV%)	22.426 (52.2)	24.278 (44.5)	23.943 (44.7)	26.812 (43.3)	24.289 (66.3)	25.929 (49.7)	9.278 (47.5)
T_{max} (h)	n	25	22	NA	24	23	NA	23
	Median (min, max)	4.520 (3.00, 10.00)	4.500 (4.00, 10.00)	NA	5.250 (4.50, 10.05)	5.000 (4.50, 10.00)	NA	4.000 (1.50, 10.02)
T_{lag} (h)	n	25	22	NA	24	23	NA	23
	Median (min, max)	2.500 (2.00, 4.50)	2.500 (1.00, 3.50)	NA	3.250 (0.00, 6.00)	3.000 (0.00, 4.50)	NA	0.670 (0.00, 1.50)
λ_z (1/h)	n	25	22	NA	24	23	NA	23
	Mean (SD)	0.1444 (0.02138)	0.1508 (0.02666)	NA	0.1422 (0.02528)	0.1408 (0.02958)	NA	0.1128 (0.02717)
$T_{½}$ (h)	n	25	22	25	24	23	24	23
	Mean (SD)	4.920 (0.8501)	4.744 (0.8977)	4.903 (0.8743)	5.027 (0.9185)	5.162 (1.2345)	5.043 (0.8198)	6.547 (1.8220)

Note: For AUCs and C_{max}, the "Nefecon-A Average" and "Nefecon-F Average" were the geometric means of the two Nefecon-A and Nefecon-F doses of each subject, respectively (ie. SQRT[$AUC_{nefecon1}$*$AUC_{nefecon2}$], if both were non-missing, otherwise the available AUC was used). For $T_{½}$, the harmonic mean was presented.
λ_z = the first order rate constant associated with the terminal portion of the curve; AUC = area under the plasma concentration-time curve; $AUC_{(0-24)}$ = area under the plasma concentration-time curve from time 0 to 24 hours; $AUC_{(0-inf)}$ = area under the plasma concentration-time curve from time 0 to infinity; C_{max} = peak investigational product concentration; CV = coefficient of variation; Geo. = geometric; max = maximum; min = minimum; NA = not available; PK = pharmacokinetic; SD = standard deviation; $T_{½}$ = terminal elimination half-life; T_{max} = time of peak investigational product concentration; T_{lag} = time prior to the first measurable (non-zero) concentration.
Source: Post-text Table 14.2.5.1

Table 6 Comparison of budesonide PK variables (C_{max} and AUCs) between products – PK analysis set (Nefecon-A Average, Nefecon-F average, and Entocort EC)

Dose-Normalized PK Parameter (Unit)	Test (T)		Reference (R)		Ratio of Mean (T/R) (%)*	90% CI for Ratio**
	n	Mean*	n	Mean*		
Nefecon-F (Test) versus Nefecon-A (Reference)						
C_{max} (ng/[mL·mg])	24	0.30	25	0.30	102.0	(82.81, 125.54)
$AUC_{(0-24)}$ (h·ng/[mL·mg])	24	1.64	25	1.50	109.0	(94.81, 125.40)
$AUC_{(0-inf)}$ (h·ng/[mL·mg])	24	1.75	25	1.58	110.6	(96.81, 126.34)
Entocort EC (Test) versus Nefecon-A (Reference)						
C_{max} (ng/[mL·mg])	23	0.12	25	0.30	39.8	(31.41, 50.48)
$AUC_{(0-24)}$ (h·ng/[mL·mg])	23	0.95	25	1.50	63.0	(53.76, 73.90)
$AUC_{(0-inf)}$ (h·ng/[mL·mg])	23	1.06	25	1.58	66.8	(57.46, 77.77)

Note: An ANOVA model was performed on natural logarithm-transformed dose-normalized PK variables with treatment arm, period, and sequence as fixed-effects and subjects within sequence as a random effect. "Nefecon-A Average" and "Nefecon-F Average" were used for Nefecon-A and Nefecon-F, respectively. The dataset only contains data for Nefecon-A and Nefecon-F.
* Means were the least-square means after back transformation to the original scale.
** The CIs were presented after back transformation to the original scale.
ANOVA = analysis of variance; $AUC_{(0-24)}$ = area under the plasma concentration-time curve from time 0 to 24 hours; $AUC_{(0-inf)}$ = area under the plasma concentration-time curve from time 0 to infinity; CI = confidence interval; C_{max} = peak investigational product concentration; PK = pharmacokinetic.
Source: Post-text Table 14.2.2.1.1

Influence of food

Studies Nef-106 and Nef-107 assessed the effect of food on the bioavailability of Kinpeygo. 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 Kinpeygo dosing. There was a small decrease in Cmax observed under fed conditions compared with the fasted condition that was not considered clinically relevant.

Distribution

Budesonide is rapidly and extensively distributed into tissues and organs. Approximately 85 to 90% of budesonide binds to plasma proteins in blood over the concentration range of 1 to 100 nmol/L. The volume of distribution at steady state is 3 to 4 L/kg (Edsbäcker and Andersson 2004[29]).

Elimination

Budesonide has a high clearance rate of approximately 72 to 80 L/h (Edsbäcker and Andersson 2004[29], Entocort SmPC DK 2020 (EN)), that is close to the estimated liver blood flow, and accordingly suggests that budesonide is a high hepatic clearance drug (Ryrfeldt et al 1984[30]). For Nefecon-F, mean T1/2 ranged from 5.0 to 6.8 hours in healthy volunteer studies.

Excretion

Budesonide is excreted in urine and feces in the form of metabolites. After oral administration, no unchanged budesonide is detected in urine (Edsbäcker and Andersson 2004[29], Ryrfeldt et al 1984[30], Entocort SmPC DK 2020 (EN)).

Metabolism

Budesonide is rapidly metabolised by the liver, primarily by oxidative pathways via the cytochrome CYP3A4 and transported by the multidrug resistance 1 (MDR1) and is also metabolised to a lesser extent locally in the gut (Edsbäcker and Andersson 2004[29]). There is known polymorphisms in CYP3A4 (*22) and MDR1.

The main metabolites of budesonide are 16α-hydroxyprednisolone and 6β-hydroxybudesonide, which have less than 1% of the glucocorticoid receptor affinity and anti-inflammatory activity of budesonide (Edsbäcker and Andersson 2004[29]). After oral administration, it is estimated that approximately 90% of budesonide is cleared by first-pass metabolism through hepatic biotransformation, with the metabolites mainly excreted via the kidneys.

There are no Kinpeygo PK data related to *intrinsic or extrinsic factors* and no *drug-drug interaction* studies have been performed with Kinpeygo. The proposed prescribing information for Kinpeygo includes guidance on the use of budesonide in specific patient populations is aligned with the SmPC for the oral budesonide product Entocort.

The PK of Kinpeygo has not been evaluated in *IgAN patients*.

2.4.2.2. Pharmacodynamics

Mechanism of action

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.

By directing release of budesonide to the ileum where the target immune tissues reside in high density, a local pharmacological effect is anticipated. The intended action of Kinpeygo is the suppression of mucosal B-cells, located in the Peyer's patches in the ileum, and inhibition of their proliferation and differentiation into plasma cells that produce Gd-IgA1. Consequently, it is expected that the occurrence of Gd-IgA1 antibodies and formation of immune complexes in the systemic

[30] Ryrfeldt A, Edsbäcker S, Pauwels R. Kinetics of the epimeric glucocorticoid budesonide. Clin Pharmacol Ther. 1984;35:525-30.

circulation will be suppressed, therefore preventing the downstream effects of glomerular mesangial deposition of immune complexes containing Gd-IgA1, manifesting as glomerulonephritis and loss of renal function.

Primary pharmacology

The mechanism of action of Kinpeygo is supported by exploratory analyses of patient serum samples from the Nef-202 study, where systemic levels of Gd-IgA1 and of IgA-containing immune complexes were significantly reduced by treatment with Kinpeygo in a dose dependent manner (Bhachu et al 2018[31]). It was also shown that IgA antibodies for two common dietary antigens, casein and gliadin, were reduced, as was I-FABP, a marker of gut permeability (Muto et al 2018[32]), in contrast to systemically derived IgA specific for tetanus toxid, which was unchanged. In addition, the cytokine B-cell activating factor of the tumour necrotising factor (TNF) family (BAFF) as well as the soluble forms of the cytokine receptors B-cell maturation antigen (BCMA) and T cell activator and calcium modulating ligand interactor (TACI), all involved in B-cell regulation (Bossen and Schneider 2006[33]), were significantly reduced in response to Kinpeygo treatment (Molyneux et al 2020[34]). BAFF is a cytokine commonly increased in IgAN and its serum levels have been shown to be associated with the clinical and histopathological severity of the disease (Xin et al 2013[35]).

In the original submission, the PD marker results of Study Nef-202 were provided partially only as copies from poster presentations. Upon request, the applicant submitted the totality of the PD data along with a statistical evaluation. The most relevant findings are presented below.

For the IgA-related markers Gd-IgA1 and IgA-IgG complexes, a small and dose-dependent decrease compared to placebo was observed with Kinpeygo after 9 months. This decrease was no longer present after 12 months, i.e. 3 months after cessation of treatment.

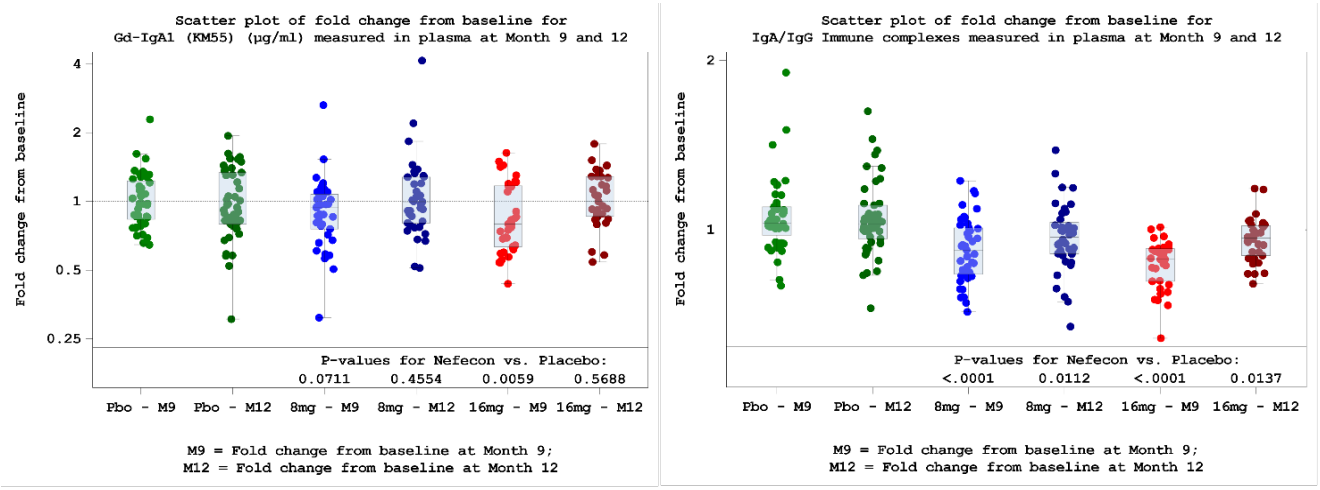


Figure 3 Log-transformed fold change from baseline plots of Gd-IgA1 and IgA-IgG immune complexes (Study Nef-202 Full Analysis Set)

[31] Bhachu JS, Scionti K, Muto M, Molyneux K, Barratt J. Targeted release-budesonide (Nefecon) modifies circulating IgA-IgG immune complex levels and levels of poorly O-galactosylated IgA in IgAN. Kidney Dis. 2018;4:121. Abstract 0038 Poster.
[32] Muto M, Bhachu J, Brown J, Molyneux K, Coppo R, Barratt J. Targeted release-budesonide (Nefecon) modifies mucosal IgA responses and possibly gut permeability in IgA nephropathy. Kidney Dis. 2018;4:138. Abstract 0034 Poster.
[33] Bossen C and Schneider P. BAFF, APRIL and their receptors: Structure, function and signaling. Semin Immunol 2006;18(5):263-75.
[34] Molyneux K, Barratt J, Wimbury DHJ. Nefecon® (Budesonide) Selectively Reduces Circulating Levels of BAFF (BLyS) and Soluble BCMA and TACI in IgA Nephropathy. ASN 2020. Abstract FR-OR37.
[35] Xin G, Shi W, Xu L-X, Su Y, Yan L-J, Li K-S. Serum BAFF is elevated in patients with IgA nephropathy and associated with clinical and histopathological features. J Nephrol. 2013;26(4):683-90.

Table 7 Analysis of relative change from baseline using robust regression for biomarkers (Gd-IgA1 and IgA-IgG immune complexes) measured in plasma

Biomarker	Month	Treatment group	N	Geometric LSmean change from baseline	Ratio of geometric LSmeans (Nefecon:placebo) and 95% CI	Unadjusted p-value	AFDR p-value
Gd-IgA1 (KM55) (µg/ml)	9	Nefecon 16 mg Nefecon 8 mg Placebo	33 38 44	0.829 0.890 1.003	0.827 (0.722 to 0.947) 0.887 (0.779 to 1.010)	0.0059 0.0711	0.0163 0.1107
	12	Nefecon 16 mg Nefecon 8 mg Placebo	33 37 46	1.003 1.014 0.962	1.042 (0.904 to 1.202) 1.054 (0.918 to 1.210)	0.5688 0.4554	0.7791 0.6332
IgA-IgG immune complexes	9	Nefecon 16 mg Nefecon 8 mg Placebo	33 41 44	0.869 0.921 1.043	0.834 (0.789 to 0.881) 0.883 (0.839 to 0.929)	<0.0001 <0.0001	<0.0001 <0.0001
	12	Nefecon 16 mg Nefecon 8 mg Placebo	33 40 46	0.966 0.968 1.035	0.933 (0.883 to 0.986) 0.935 (0.888 to 0.985)	0.0137 0.0112	0.1173 0.0565

The cytokine BAFF was dose-dependently reduced vs. placebo after 9 months' treatment with Kinpeygo. After 12 months (i.e. 3 months after cessation of Kinpeygo), it was markedly increased compared to baseline. In the placebo group the BAFF level also was increased over baseline after 12 months for unknown reasons. Also with the other cytokines tested (BCMA, TACI and APRIL) no consistent changes were observed.

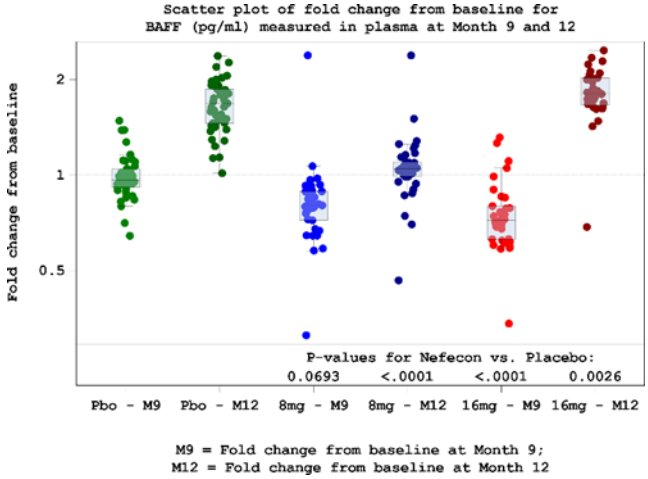


Figure 4 Log-transformed fold change from baseline plots of BAFF (Study Nef-202 Full Analysis Set)

Table 8 Analysis of relative change from baseline using robust regression for biomarker BAFF measured in plasma

Biomarker	Month	Treatment group	N	Geometric LSmean change from baseline	Ratio of geometric LSmeans (Nefecon:placebo) and 95% CI	Unadjusted p-value	AFDR p-value
BAFF (pg/ml)	9	Nefecon 16 mg Nefecon 8 mg Placebo	34 38 44	0.707 0.875 0.959	0.737 (0.683 to 0.795) 0.913 (0.828 to 1.007)	<0.0001 0.0693	<0.0001 0.1107
	12	Nefecon 16 mg Nefecon 8 mg Placebo	34 37 45	1.777 1.183 1.586	1.120 (1.040 to 1.206) 0.746 (0.677 to 0.821)	0.0026 <0.0001	0.0402 <0.0001

The figure and table below show IgA-antibodies against the food proteins casein and gliadin. In case of anti-gliadin, the variability was high so that no conclusions can be drawn. Anti-casein was decreased vs. baseline and compared to placebo after 9 months with Kinpeygo. Dose-dependency can be seen. Three months later (Month 12), there was still a decrease vs. baseline, but at this time point anti-casein was also decreased in the placebo group to virtually the same extent. The meaning of this finding is unclear.

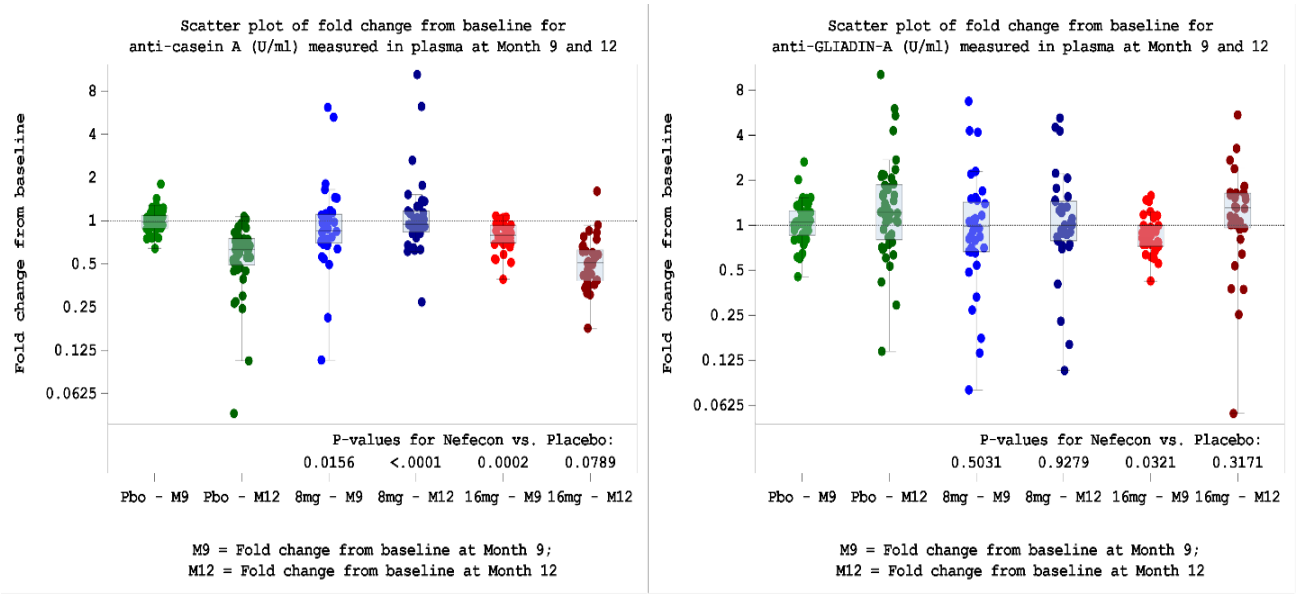


Figure 5 Log-transformed fold change from baseline plots of anti-casein A and anti-gliadin IgA (Study Nef-202 Full Analysis Set)

Table 9 Analysis of relative change from baseline using robust regression for biomarkers (anti-casein A and anti-gliadin IgA) measured in plasma

Biomarker	Month	Treatment group	N	Geometric LSmean change from baseline	Ratio of geometric LSmeans (Nefecon:placebo) and 95% CI	Unadjusted p-value	AFDR p-value
Anti-casein A (U/ml)	9	Nefecon 16 mg Nefecon 8 mg Placebo	33 36 44	0.792 0.858 0.994	0.797 (0.708 to 0.897) 0.864 (0.767 to 0.973)	0.0002 0.0156	0.0008 0.0505
	12	Nefecon 16 mg Nefecon 8 mg Placebo	33 38 46	0.516 0.981 0.605	0.853 (0.715 to 1.018) 1.621 (1.359 to 1.933)	0.0789 <0.0001	0.3947 <0.0001
Anti-gliadin IgA (U/ml)	9	Nefecon 16 mg Nefecon 8 mg Placebo	33 36 43	0.851 0.978 1.040	0.818 (0.681 to 0.983) 0.940 (0.786 to 1.126)	0.0321 0.5031	0.0594 0.5031
	12	Nefecon 16 mg Nefecon 8 mg Placebo	33 35 44	1.093 1.264 1.249	0.875 (0.674 to 1.136) 1.012 (0.780 to 1.313)	0.3171 0.9279	0.6811 0.9279

Intestinal fatty acid binding protein (IFABP or FABP2) showed a dose- and time-dependent decrease from baseline in response to Kinpeygo. The strongest effect was -26.9% compared to placebo and was observed after 12 months with 16 mg Kinpeygo. The variability was rather high so that statistical significance was not always reached.

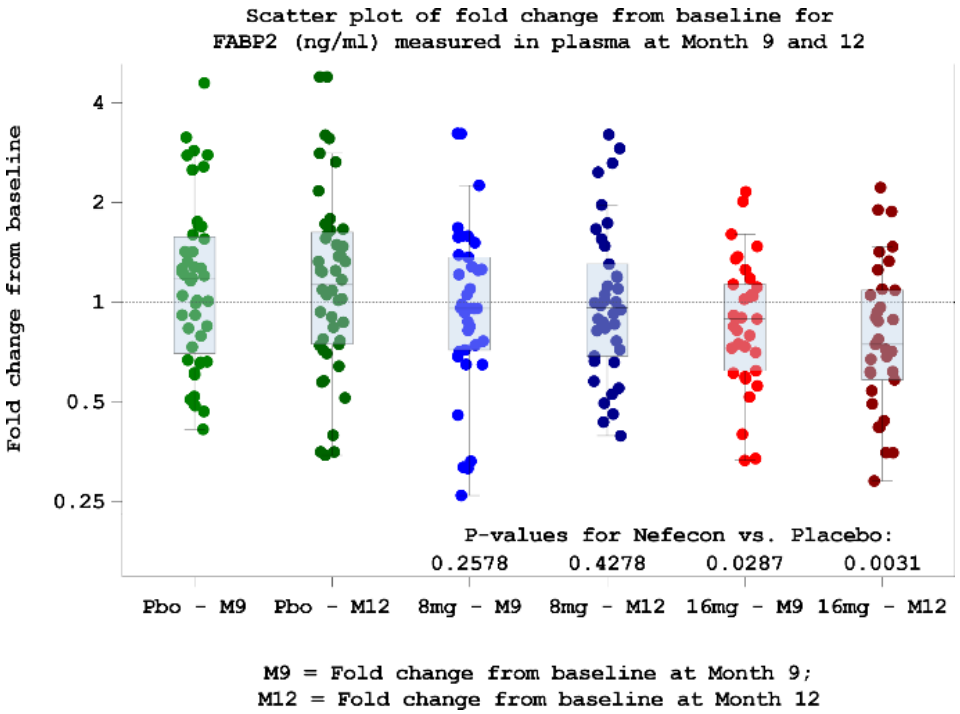


Figure 6 Log-transformed fold change from baseline plots of IFAB-P2 (Study Nef-202 FAS)

Table 10 Analysis of relative change from baseline using robust regression for biomarkers (IFAB-P2) measured in plasma

Biomarker	Month	Treatment group	N	Geometric LSmean change from baseline	Ratio of geometric LSmeans (Nefecon:placebo) and 95% CI	Unadjusted p-value	AFDR p-value
IFAB-P2 (ng/ml)	9	Nefecon 16 mg	33	0.857	0.785 (0.632 to 0.975)	0.0287	0.0560
		Nefecon 8 mg	37	0.967	0.886 (0.718 to 1.093)	0.2578	0.2707
		Placebo	44	1.092			
	12	Nefecon 16 mg	33	0.774	0.731 (0.594 to 0.900)	0.0031	0.0402
		Nefecon 8 mg	38	0.977	0.922 (0.755 to 1.126)	0.4278	0.6332
		Placebo	46	1.059			

Secondary pharmacology

Following single oral doses of Kinpeygo and Entocort to healthy volunteers (study Nef-101) both products suppressed serum cortisol levels compared to baseline.
An evaluation of the extent of cortisol suppression after repeated dosing with Kinpeygo in IgAN patients, based on 24-hour urine cortisol excretion, was studied in Nef-202 and Nef-301.

Table 11 Nef-101 mean (SD) serum cortisol $AUC_{(0-24)}$ and total amount of cortisol excreted in urine per day for Nefecon-A and Entocort formulations of budesonide

	Baseline (N=24)	Nefecon-A 16 mg (N=24)	Nefecon-A 8 mg (N=23)	Entocort 9 mg (N=24)
Serum cortisol				
$AUC_{(0-24)}$ (nmol×h/L)	5372 (1126)	2971 (1153)	3479 (1128)	3034 (706)
Change from baseline[a]		-2401 (895)	-1901 (710)	-2215 (778)
Urine cortisol excretion (0-24 hours)				
Amount excreted (nmol/day)	110 (48.0)	56.1 (32.8)	65.2 (34.8)	55.1 (31.9)
Change from baseline[a]		-53.7 (34.6)	-44.3 (40.5)	-54.8 (35.8)

Table 12 Budesonide PK parameters (PK analysis set)

Variable		NEFECON 8 mg (n=23)	NEFECON 16 mg (n=24)	ENTOCORT 9 mg (n=24)
$AUC_{(0-24)}$ (pg*h/mL)	No. of obs.	23	24	24
	Mean (sd)	13076 (7901)	29493 (21498)	12220 (8944)
	Median	12254	23581	10088
	Q1, Q3	7423, 16455	16788, 36456	7418, 14443
	Min, Max	1200, 28227	1254, 109398	2973, 47563
	Geometric mean (standard error)	10093 (1853)	23168 (3931)	10229 (1260)
C_{max} (pg/mL)	No. of obs.	22	24	24
	Mean (sd)	3154 (2463)	6507 (5920)	1763 (1173)
	Median	2467	4046	1566
	Q1, Q3	1459, 3471	2952, 7783	892, 2177
	Min, Max	198, 8910	209, 25573	371, 4734
	Geometric mean (standard error)	2323 (441)	4494 (905)	1455 (193)
T_{max} (h)	No. of obs.	22	24	24
	Mean (sd)	5.64 (5.99)	5.63 (5.73)	3.38 (1.89)
	Median	4.00	4.00	3.04
	Q1, Q3	3.00, 5.00	3.00, 5.00	2.00, 4.00
	Min, Max	3.00, 24.0	2.00, 24.0	1.50, 10.1
T_{lag} (h)	No. of obs.	22	24	24
	Mean (sd)	3.00 (2.93)	2.75 (2.87)	0.650 (0.524)
	Median	2.00	2.00	1.00
	Q1, Q3	2.00, 2.00	2.00, 2.00	0, 1.00
	Min, Max	2.00, 12.0	1.00, 12.0	0, 1.50
$t_{1/2}$ (h)	No. of obs.	20	21	24
	Mean (sd)	4.27 (1.77)	4.40 (1.80)	4.95 (1.32)
	Median	3.77	4.07	4.70
	Q1, Q3	3.00, 4.91	3.48, 4.41	4.04, 5.87
	Min, Max	2.44, 7.79	1.95, 10.1	2.68, 7.32
	Geometric mean (standard error)	3.97 (0.349)	4.13 (0.325)	4.78 (0.269)

PD in Patients

In the Kinpeygo IgAN patient studies the effect of Kinpeygo on urine cortisol suppression following repeat dosing was assessed. In both Nef-301 and Nef-202, 24-hour urine cortisol collections were analysed by a central laboratory at baseline, after 1 month in Nef-202, and after 3, 6, and 9 months of treatment in both studies, and during follow-up after the last treatment dose had been administered.

In Nef-301, 24-hour urine cortisol excretion was suppressed by approximately 70% with Kinpeygo 16 mg compared to placebo and showed reversibility to baseline levels after 3 months of follow-up.

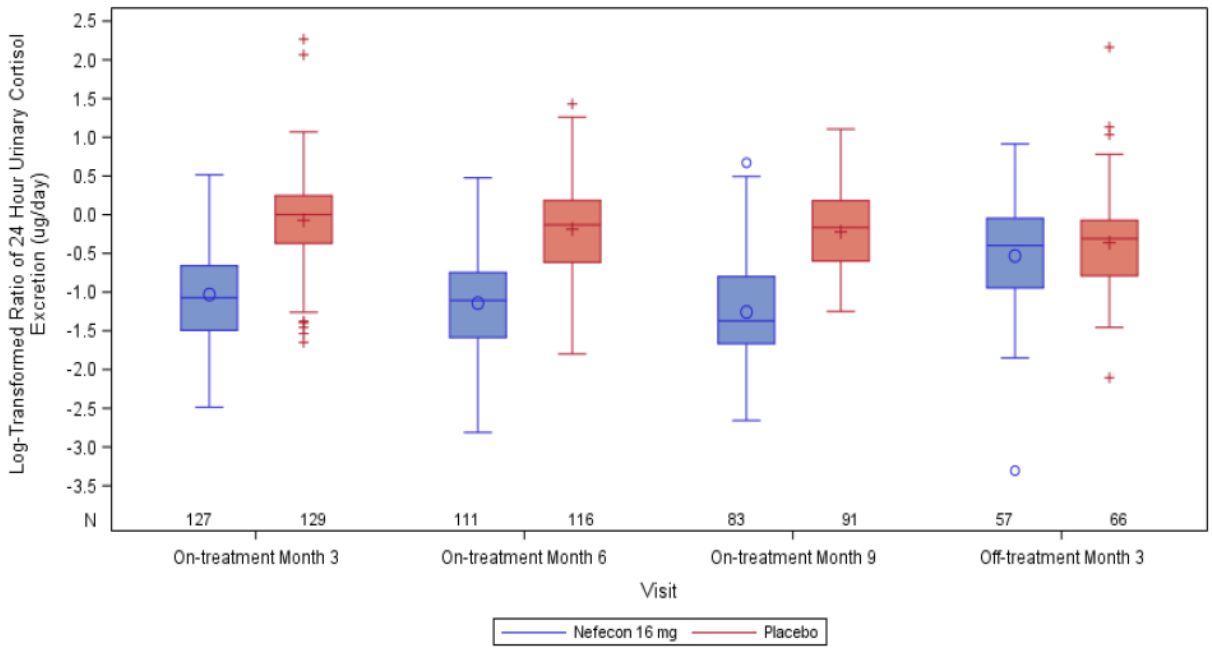
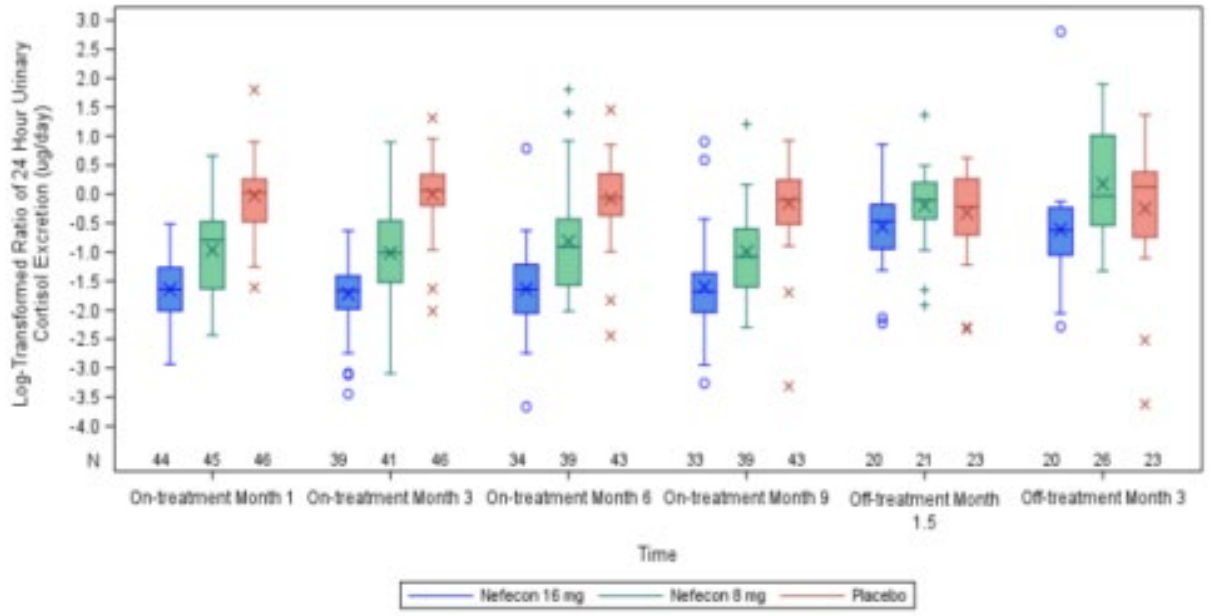


Figure 7 Nef-301 log-transformed ratio of 24 hour urinary cortisol excretion compared to baseline (SAS)

In Nef-202, 24-hour urine cortisol excretion was suppressed by approximately 80% and 60% with Kinpeygo 16 mg and Kinpeygo 8 mg, respectively, compared to placebo, which remained stable from Month 1 throughout treatment. This was followed by a return towards baseline values following discontinuation of treatment, which was somewhat slower for the Kinpeygo 16 mg dose compared with Kinpeygo 8 mg. Therefore, as would be expected for a budesonide product on repeat dosing, and as has also been observed with other oral budesonide products (Entocort SmPC DK 2020 (EN)), there is evidence of cortisol suppression after multiple doses of Kinpeygo in patients.



Source: Supportive Tables and Figures for SCS Figure 2.7.4.5.5.1.2.

Figure 8 Nef-202 Log-transformed ratio of 24 hour urinary cortisol excretion compared to baseline (SAS)

2.4.3. Discussion on clinical pharmacology

Pharmacokinetics

The PK properties of budesonide have extensively been characterised during the development programs for marketed products containing this active substance. The clinical pharmacology programs have included studies on PK properties, metabolism and elimination, drug-drug interactions, and the PK in subjects with hepatic impairment. Apart from the site of release in the GI tract and the concentration-time profile for budesonide in plasma, all other properties for budesonide were expected to be similar to Kinpeygo as for other oral budesonide products.

Kinpeygo PK has only been studied in healthy volunteers following single oral doses. Kinpeygo PK results from the healthy volunteer studies are deemed representative for the target population of patients with IgAN. As systemic exposure to budesonide is not required for a therapeutic effect of Kinpeygo in IgAN, plasma PK parameters are relevant only for assessment of safety related to systemic GCS effects.

Based on Nefecon-F PK data from Study Nef-105, demonstrating a short half-life (~5 hours), it is considered unlikely that the Kinpeygo 16 mg repeated dosing regimen would lead to an accumulation of budesonide when used in IgAN patients. No accumulation of budesonide has been observed on repeated administration of Entocort EC (Edsbäcker and Andersson 2004[29]). The PK of Kinpeygo has not been evaluated in IgAN patients. There is no scientific reason to believe that the GI tract of patients with IgAN is different from healthy volunteers in terms of release characteristics of budesonide from Kinpeygo, rate and extent of absorption, or degree of first-pass metabolism, therefore, Kinpeygo PK results from the healthy volunteer studies are deemed representative for patients with IgAN.

The Kinpeygo formulation is designed to deliver budesonide topically in the ileum. The delayed onset of release of budesonide is achieved by a pH-governed polymer coating of the capsules, intended to prevent capsule disintegration until it reaches the ileum. Assuming a normal GI transit time, onset of

budesonide drug release after 2-3 hours and peak budesonide plasma concentration at around 4-5 hours for Kinpeygo indicate that the major proportion of the active substance is released in the ileum, where Peyer's patches reside, therefore meeting the requirements for a product intended to act locally in this area of the small intestine.

Bioequivalence studies were carried out to address equivalence for manufacturing changes during the development and to justify changes between clinical trials formulation and finished product intended for marketing. Following demonstration of Kinpeygo efficacy in the phase 2b Nef-202 study using the Nefecon-A formulation, the aim was for subsequent formulations to mimic the PK properties of Nefecon-A. Nefecon F (= final commercial product) is the formulation used in the pivotal phase 3 study Nef-301 and was assessed versus Nefecon A in the phase 1 healthy volunteer comparative BA/BE study Nef-105. The applicant claims bioequivalence between both formulations in terms of AUC and Cmax, however, the 90% CIs for Cmax and AUC ranged from 82.8% to 126.3%, overlapping the upper boundary for a conventional BE margin. Accordingly, both Nefecon preparations can at best be assessed as similar with regard to PK, but not as bioequivalent. However, since Nefecon F formulation has been used in the pivotal study, demonstrating efficacy in terms of reduction in proteinuria, with an acceptable safety profile, this concern is considered negligible from a clinical perspective; however might hamper the pooling of data with results derived from the part 2B study Nef 202, where Nefecon A has been used. Another critical point is the observed lower Cmax and AUC obtained from Entocort EC compared to Nefecon preparations, even when scaled for the differences in budesonide content. However, even though the Cmax and AUC of Nefecon are considerably higher than with Entocort, they are still of a similar dimension. Furthermore, safety data did not raise concern for a clinically relevant increase of unwanted systemic glucocorticoid side effects in comparison to Entocort. Therefore, the transfer of the PK-related instructions for use from Entocort is considered acceptable.

Budesonide is metabolised by CYP3A4 and transported by MDR1(ABCB1). There is known polymorphisms in CYP3A4 (*22) and MDR1. Thus, the applicant has provided available literature on possible impact of CYP3A4 and ABCB1 Genotypes on the PKs of budesonide. Data from literature do not suggest a pronounced influence.

No drug-drug interaction studies have been performed with Kinpeygo. The respective section in the proposed SmPC is aligned with the SmPC for the oral budesonide product Entocort. This is acceptable to the CHMP.

Pharmacodynamics

By directing release of budesonide to the ileum where the target immune tissues reside in high density, a local pharmacological effect is anticipated. The intended action of Kinpeygo is the suppression of mucosal B-cells, located in the Peyer's patches in the ileum, and inhibition of their proliferation and differentiation into plasma cells that produce Gd-IgA1. Consequently, it is expected that the occurrence of Gd-IgA1 antibodies and formation of immune complexes in the systemic circulation will be suppressed, therefore preventing the downstream effects of glomerular mesangial deposition of immune complexes containing Gd-IgA1, manifesting as glomerulonephritis and loss of renal function.

The applicant states that the mechanism of action of Nefecon is supported by exploratory analyses of patient serum samples from the phase 2b Nef-202 study, where systemic levels of Gd-IgA1 and of IgA-containing immune complexes were significantly reduced by treatment with Kinpeygo in a dose dependent manner.

The applicant provided the results of all exploratory biomarker measurements that were obtained within the phase 2 trial Nef-202. The selection of biomarkers was appropriate. All were described to be

increased in the serum of IgAN patients, and a causal relationship with IgAN pathogenesis is discussed (reviewed by Selvaskandan et al. 2020[36]).

The most pronounced effect was observed for FABP2 which became significantly reduced with Kinpeygo over time from baseline in a dose-dependent manner and compared to placebo. The magnitude of the effect was comparably high, -21.5% after 9 months and -26.9% after 12 months. Thus, this effect was still detectable 3 months after cessation of Kinpeygo administration.

The IgA-related markers Gd-IgA1 and IgA-IgG complex, revealed a (mostly) statistically significant, dose-dependent decrease from baseline and compared to placebo after 9 months, but the decrease was no longer present after 12 months. Thus, this effect cannot explain the claimed persistent action of Kinpeygo after cessation of treatment.

The IgA-antibodies against the food protein casein were significantly decreased with high-dose (16 mg) Kinpeygo after 9 months but not after 12 months. Intriguingly, the low Kinpeygo dose (8 mg) caused a marked and significant increase in anti-casein IgA vs. placebo after 12 months. This is biologically not plausible.

Overall, the most consistent finding was a long-lasting (12 months) decrease in FABP2. This FABP2 reduction is assumed to correspond to a decreased permeability of the gut mucosa which in turn prevents the organism from (potentially IgA-inducing) antigens.

However, it did not become clear how the decreased permeability of gut mucosa translates to beneficial kidney effects since IgA-related markers were not consistently altered. Thus, at present, the PD findings cannot support the assumption of a prolonged treatment effect of enteral budesonide. This further emphasises the need of obtaining efficacy data on "hard" clinical endpoints (e.g., time to first occurrence of a composite of death, ESKD, or a decline exceeding 40% in eGFR).

The applicant intends to follow the PD markers also in the ongoing phase 3 study (Nef-301). This may provide more robust data due to a higher patient number.

Since dose-related suppressive effects on hypothalamic-pituitary-adrenal axis (HPA) axis function is reported for budesonide in literature, the applicant performed a PD/PK study (Nef-101), that compared the effect of single doses of Kinpeygo (8 mg and 16 mg) and Entocort on serum cortisol. The change in serum cortisol AUC (0-24) was significantly lower for the 8 mg dose of Nefecon-A than for the 16 mg dose (8 mg: -1901 vs, 16 mg: -2401; p=0.003). Of note, adjusted Cmax serum budesonide values in study Nef-101 were found to be twice as high for Kinpeygo compared to Entocort.

In the Kinpeygo IgAN patient studies, the effect of Kinpeygo on urine cortisol suppression following repeat dosing was assessed. In Nef-202, 24-hour urine cortisol excretion was suppressed by approximately 80% and 60% with Kinpeygo 16 mg and Kinpeygo 8 mg, respectively, compared to placebo. Furthermore, recovery from dose-dependent cortisol suppression after the 3-months off-treatment period was not fully obtained in the 16 mg dose group in contrast to the 8 mg group. Based on these results and considering more frequently observed serious adverse events (SAEs) with the 16 mg dose while demonstrating comparable efficacy with the 8 mg and 16 mg dose, the dose selection for the 16 mg daily dose remains unclear. However, it is acknowledged that the 16 mg dose was used in the pivotal phase 3 study and therefore this issue was not further pursued.

Systemic action of budesonide is illustrated by a pronounced suppression of physiological cortisol production, with a clear dose dependency from 16 mg to 8 mg to placebo. The 8 mg dose, which is used during dose tapering, still shows a pronounced cortisol-suppressing effect. The data presented are not considered sufficient to allow abrupt discontinuation of Kinpeygo at the 8 mg dose. Tapering of

[36] Selvaskandan H et al. Monitoring Immune Responses in IgA Nephropathy: Biomarkers to Guide Management. Front Immunol. 2020 Oct 6;11:572754.

glucocorticoids must be done carefully to avoid both recurrent activity of the underlying disease (rebound effect) and possible cortisol deficiency resulting from HPA suppression during the period of steroid therapy. Budesonide plasma levels are disproportionately increased with the proposed 16 mg dose of Kinpeygo as compared to the standard 9 mg dose of Entocort (4-fold for Cmax and 2.5-fold for AUC), and the 8 mg tapering dose of Kinpeygo results in similar systemic budesonide exposure as the 9 mg standard dose of Entocort. Therefore, inclusion of a further tapering step on the 4 mg dose level is required. The product information now reflects that when treatment is to be discontinued, the dose should be reduced to 8 mg once daily for the last 2 weeks of therapy. This may be followed by an additional 2-week period with 4 mg once daily at the discretion of the treating physician.

2.4.4. Conclusions on clinical pharmacology

The applicant has exploratively studied several biomarkers in the phase 2 trial Nef-202, but mechanistic understanding how exactly oral budesonide could affect IgAN, and in particular why the effect of budesonide should persist after cessation of treatment is still incomplete. This is in part due to the high variability of the biomarker data. Data from more subjects will come from the ongoing phase 3 programme.

2.4.5. Clinical efficacy

2.4.5.1. Dose response study

The applicant conducted a supportive, phase 2b, randomised, double-blind, placebo-controlled study to evaluate the efficacy and safety of two different doses of Kinpeygo (8 mg and 16 mg) in primary IgA nephropathy patients at risk of developing ESRD (Nef-202).

The data demonstrated that Kinpeygo 16 mg per day generally provided better efficacy than Kinpeygo 8 mg per day when compared with placebo across all renal function parameters evaluated at both 9 and 12 months, with an acceptable safety profile. Therefore, the Kinpeygo 16 mg per day dose was selected for the following phase 3 study (Nef-301) (see section 2.4.5.5. Supportive study).

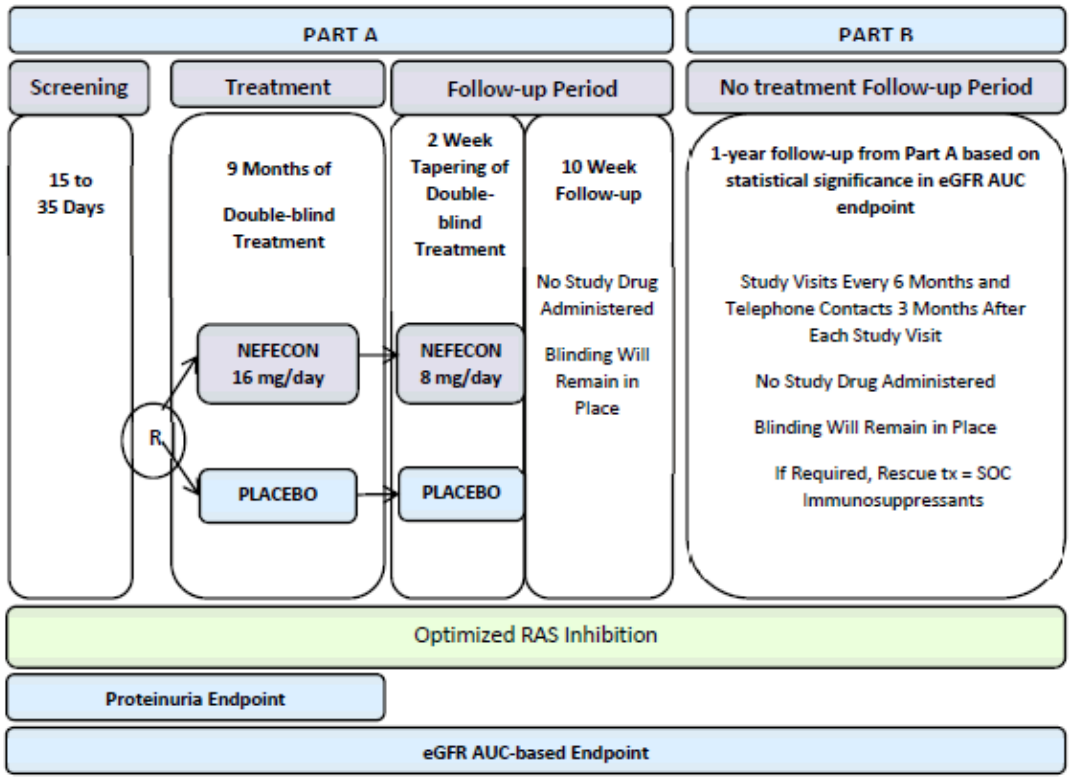
2.4.5.2. Main study

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

Methods

The study consisted of 2 parts, Part A and Part B. The Part A study design includes a Screening Period (up to 35 days) followed by a 9-month blinded Treatment Period, and a 3-month Follow-up Period (including a 2-week Tapering Period).

Part B consists of a 12-month (+14 to 35 days) observational follow-up period after Part A has ended. Each patient randomised will be followed for 25 months after the first dose (or, if the patient randomised does not receive any study drug, 25 months after the patient is randomised). The total duration of the study is up to 26.5 months (including the screening period and a final visit for replicate eGFR sampling at 2 years). The study is blinded throughout. No study drug is administered during Part B.



AUC = area under the curve; eGFR = estimated glomerular filtration rate; R = randomization; RAS = renin-angiotensin system; SOC = standard of care; tx = treatment.
Source: Study Protocol (Appendix 16.1.1)

Figure 9 Summary of study design

Study Participants

- Main inclusion criteria:

  1. Female or male patients ≥18 years of age;

  2. Diagnosed IgAN with biopsy verification within the past 10 years;

  3. On a stable dose of RAS inhibitor therapy (ACEIs and/or ARBs) at the maximum allowed dose or maximum tolerated dose according to the 2012 KDIGO guideline for the 3 months prior to randomisation;

  4. Willing and able to provide written informed consent at screening;

  5. Proteinuria based on 2 consecutive measurements (24-hour urine sampling) after informed consent, separated by at least 2 weeks and calculated by the central laboratory. Both samples of the same parameter must have shown either of the following:

     o Proteinuria ≥1 g per day (≥1000 mg per day) in 2 consecutive measurements, or

     o UPCR ≥0.8 g/gram (≥90 mg/mmol) in 2 consecutive measurements; and

  6. eGFR ≥35 mL/min per 1.73 m2 and ≤90 mL/min per 1.73 m2 using the CKD-EPI formula, confirmed by the central laboratory at Study Visit 1 or Study Visit 3.

- Main exclusion criteria:

  Patients were excluded from the study if they had systemic diseases that may cause mesangial IgA deposition; had undergone a kidney transplant; had presence of other glomerulopathies and with nephrotic syndrome; had acute, chronic, or latent infectious disease; had liver

cirrhosis, as assessed by the Investigator; had poorly controlled type 1 or type 2 diabetes mellitus (defined as haemoglobin A1c [HbA1c] >8% [64 mmol/mol]); had history of unstable angina, class III or IV congestive heart failure, and/or clinically significant arrhythmia, as judged by the Investigator; had unacceptable blood pressure control (patients with ≥140 mmHg systolic blood pressure or ≥90 mmHg diastolic blood pressure were not eligible); had known osteoporosis in medium- or high-risk category according to the 2010 American College of Rheumatology recommendations; had known glaucoma, known cataract(s), and/or history of cataract surgery, unless the surgery was performed on both eyes; had been treated with systemic immunosuppressive medications, other than GCSs, within the 12 months before randomisation; had been treated with any systemic GCSs within the 3 months before randomisation; had been treated with any systemic GCSs within the 12 months before randomisation except for a maximum of 3 periods of 2 weeks with the equivalent of 0.5 mg/kg/day prednisolone or less for non-IgAN indications; or were taking potent inhibitors of cytochrome P450 3A4.

Treatments

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 in Part A. The daily dose of double-blinded study drug may have been reduced from 4 capsules QD (Kinpeygo 16 mg or placebo) to 2 capsules QD (Kinpeygo 8 mg or placebo) if clinically relevant AEs developed that the Investigator considered related to the study drug and that mandated dose reduction. The Medical Monitor was preferably to be consulted prior to reducing the daily dose of study drug. If a dose reduction was made, then the dose was not to be increased back to 4 capsules QD (Kinpeygo 16 mg or placebo).

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). Patients who had their daily dose of study drug reduced to 2 capsules QD (Kinpeygo 8 mg or placebo) due to safety and/or tolerability reasons during the Part A Treatment Period remained on this dose of study drug for an additional 2 weeks after completing 9 months of study treatment (during the Tapering Period in Part A). Patients who prematurely discontinued study treatment while taking 4 capsules QD (Kinpeygo 16 mg or placebo) were to have the daily dose of study drug reduced to 2 capsules QD (Kinpeygo 8 mg or placebo) for 2 weeks, if feasible, to prevent insufficiency of the adrenal glands.

Objectives

Primary Objective:

- The primary objective of Part A was to assess the effect of Kinpeygo 16 mg treatment on UPCR over 9 months compared to placebo.
- 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 estimated glomerular filtration rate (eGFR) recorded over 2 years compared to placebo.

Secondary Objectives:

The secondary objectives of Part A were:

- To assess the effect of Kinpeygo 16 mg treatment on eGFR at 9 and 12 months compared to placebo; and

- To evaluate additional aspects of renal function, and safety and tolerability of Kinpeygo 16 mg treatment over 9 months compared to placebo.

The secondary objectives of Part B are:

- to assess the effects of the Kinpeygo 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 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.

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 urine albumin to creatinine ratio (UACR) at 9 months compared to baseline.

Part B

The primary efficacy endpoint for the Part B analysis is an area under the curve (AUC)-based evaluation of eGFR calculated as a time-weighted average of eGFR recordings observed at each time point over 2 years. The eGFR at 2 years (which must be repeated to provide a second value obtained within 14 to 35 days) will be the geometric mean of the 2 assessments. An analysis of the 2-year eGFR slope will also be performed at this time.

The secondary efficacy endpoints for the Part B analysis are:

- 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 microhematuria in at least 2 of the following time points: 12, 18, and 24 months following the first dose of study drug (patients defined as without microhematuria if the urine dipstick returned a result of negative or trace);
- Proportion of patients receiving rescue treatment; and
- SF-36 quality of life assessment at 9 and 24 months.

Sample size

The phase 2b study (Nef-202) gave an estimated standard deviation of 0.59 for the change in the log of UPCR from baseline after 9 months of treatment. Based on this assumption, 200 patients in Part A of Nef-301 would provide >90% power to demonstrate statistical significance at a 1-sided alpha level of 0.025 given a true 25% relative reduction in UPCR with Kinpeygo treatment compared to placebo.

Randomisation and Blinding (masking)

Patients were randomised in a 1:1 ratio to Kinpeygo 16 mg or placebo within 35 days of Study Visit 1 (screening) using an Interactive Response Technology (IRT) system. The study was double-blinded, and randomisation was stratified according to baseline proteinuria (<2 g/24 hours or ≥2 g/24 hours); baseline eGFR (<60 mL/min/1.73 m2 or ≥60 mL/min/1.73 m2); and geographic region (Europe, North

America, South America, or Asia Pacific). Randomised patients received either Kinpeygo 16 mg (four 4 mg budesonide modified release capsules once daily [QD]) or placebo (4 matching capsules QD) for a 9-month Treatment Period.

Both Kinpeygo and placebo were provided as modified release capsules. The capsules were carefully matched in appearance, smell, and taste to ensure maintenance of treatment masking. Part A was blinded, and the blinding was planned to remain in place throughout Part B. The patients, investigators, and site staff conducting study procedures, evaluating patients, entering study data, and/or evaluating study data were blinded to treatment assignment.

Statistical methods

In the study, two populations are defined:

1. Part A Full Analysis Set (FAS) includes the first 201 patients randomised, regardless of whether the patient received study drug.

2. Safety Analysis Set (SAS) includes all patients who receive at least 1 dose of study drug up to the data cut-off. Therefore, this population includes data from patients who have not yet completed the 9-month treatment phase. The population comprises 294 patients in total: 150 patients who received Kinpeygo 16 mg and 144 patients who received placebo.

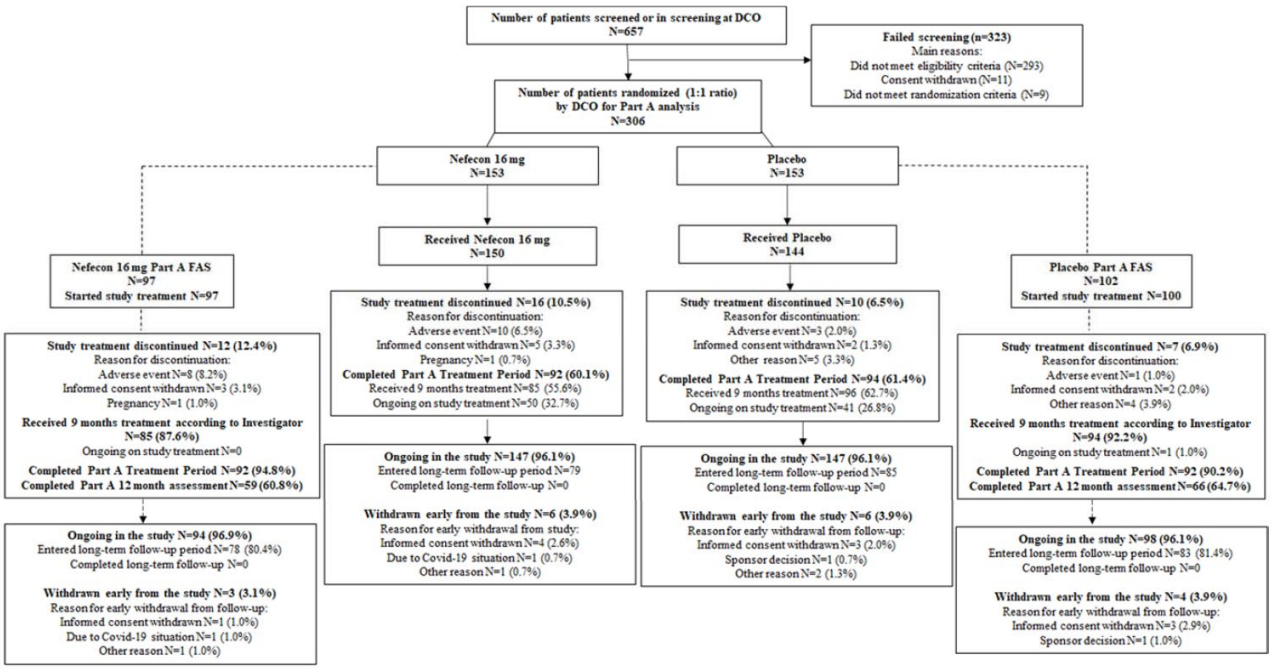
The primary efficacy endpoint for the Part A analysis, the ratio of UPCR at 9 months to baseline, was log-transformed prior to analysis, as were data from the other time points used in the analysis model. The treatment effect was expressed as a percent reduction in UPCR for Kinpeygo compared to placebo and was derived from the ratio of geometric least squares (LS) mean baseline ratios estimated at 9 months for each treatment group. The primary analysis of the log-transformed post-baseline to baseline ratios in UPCR was analysed using a mixed model repeated measures (MMRM) analysis based on the Part A FAS and incorporating UPCR data from 3, 6, 9, and 12 months. Baseline UPCR was included as a covariate and was calculated as the geometric mean of the 2 pre-randomisation UPCR measurements and log-transformed prior to inclusion in the analysis model. The model also included terms for treatment group, visit, log(baseline)-by-visit, and visit-by-treatment group interaction. A patient term was included as a random effect. An unstructured covariance matrix was used to model the within-patient correlation of data. The Kenward-Roger's degrees-of-freedom adjustment was used. Restricted maximum likelihood was used to obtain parameter estimates. The LS means were estimated by visit along with the associated 95% and 96% confidence interval (CI) and p-values with the primary analysis taken from the estimate at 9 months. Geometric LS mean values were obtained by exponentiating the LS means. Model assumptions of the MMRM were assessed using residual plots (such as q-q plots, histograms, box plots, and scatter plots).

The Part A secondary endpoint analysis of the ratio of eGFR at 9 and 12 months compared to baseline was analysed separately using robust regression having multiply imputed any missing data first in 3 phases: an imputation, analysis, and pooling phase, as described below. eGFR data were log-transformed prior to analysis.

Robust regression was selected because previous eGFR data from Kinpeygo trials suggested the possibility of a small sub-population of patients having extreme outlying data resulting from very rapid progression of disease. This method down-weights the contribution of outlying data using a pre-defined algorithm.

Results

Participant flow



Note: Completed Part A Treatment Period was defined as the patient has at least 1 valid UPCR value available in the 9-month visit window (Day 229 to Day 319).
Completed Part A 12 month assessment defined as the patient has at least one valid UPCR value available in the 12-month visit window, excluding any data post rescue therapy.
The number of patients ongoing on study treatment (N=91) + the number who received 9 months of treatment according to the Investigator (N=181) + the number who discontinued study treatment early (N=26) equals 298 rather than 294 (i.e., the number of patients dosed) because 4 of the patients who were randomized (1 to Nefecon 16 mg and 3 to placebo) but not dosed are included in the number of patients who discontinued study treatment early, due to the site completing the end of treatment eCRF.
a. In accordance with the study protocol, the first dose of study drug is administered at Visit 4 within 10 days of randomization. Any data collected after the DCO for the Part A analysis are not included, and so some patients randomized close to the DCO had not yet been dosed by the time of the DCO.
Covid-19 = Coronavirus Disease 2019; DCO = data cutoff; eCRF = electronic case report form; FAS = Full Analysis Set; UPCR = urine protein to creatinine ratio.

Figure 10 Patient disposition as of the Part A data cut-off

Recruitment

Part A first Patient first visit date: 05 September 2018; data cut-off date: 05 October 2020.

Conduct of the study

During the conduct of the study, several protocol amendments were made. Two of those changes might be of clinical relevance: (1) the inclusion criterion #2 (diagnosis of IgAN with biopsy verification) was changed from "within the past 5 years" to "within the past 10 years;" (16 March 2018) and (2) the lower limit of the eGFR value was reduced from 45 to 35 mL/min per 1.73 m2 (2 January 2019).

Table 13 Protocol deviations

Calliditas Therapeutics AB
Nef-301

Table 14.1.2.1
CSR Reportable Protocol Deviations
Part A Full Analysis Set

Deviation Category	Nefecon 16 mg (N= 97) n (%)	Placebo (N=102) n (%)	Total (N=199) n (%)
Any CSR reportable protocol deviations	64 (66.0)	62 (60.8)	126 (63.3)
Informed Consent	23 (23.7)	24 (23.5)	47 (23.6)
Investigational Product	22 (22.7)	17 (16.7)	39 (19.6)
Study Procedures	19 (19.6)	20 (19.6)	39 (19.6)
Entry Criteria Not Met	12 (12.4)	17 (16.7)	29 (14.6)
Visit Window	12 (12.4)	10 (9.8)	22 (11.1)
Excluded Medication Received	13 (13.4)	6 (5.9)	19 (9.5)
Sae Reporting	2 (2.1)	0 (0.0)	2 (1.0)
Wrong Treatment Or Incorrect Dose Received	0 (0.0)	1 (1.0)	1 (0.5)

% = 100 x n/N.

Source data: ADDV; Reference listing(s): 16.2.2.1
Program name: pd.sas

SDTM date: 28DEC2020 12:21
Analysis date: 21JAN2021 14:30

Baseline data

Table below displays patient demographics for the SAS and the Part A FAS, which were consistent between the analysis sets.

Table 14 Patient demographics – SAS and Part A FAS

Characteristic Statistic/Category	Safety Analysis Set		Part A FAS	
	Nefecon 16 mg (N=150)	Placebo (N=144)	Nefecon 16 mg (N=97)	Placebo (N=102)
Age (years)				
n	150	144	97	102
Median (range)	44 (21 to 69)	43 (22 to 73)	44 (25 to 69)	43 (23 to 73)
Age distribution, n (%)				
<45 years	79 (52.7)	82 (56.9)	52 (53.6)	56 (54.9)
≥45 and <65 years	64 (42.7)	60 (41.7)	39 (40.2)	44 (43.1)
≥65 years	7 (4.7)	2 (1.4)	6 (6.2)	2 (2.0)
Sex, n (%)				
Male	102 (68.0)	98 (68.1)	68 (70.1)	67 (65.7)
Female	48 (32.0)	46 (31.9)	29 (29.9)	35 (34.3)
Childbearing potential (female only), n (%)	N=48	N=46	N=29	N=35
Yes	37 (77.1)	35 (76.1)	25 (86.2)	27 (77.1)
No	11 (22.9)	11 (23.9)	4 (13.8)	8 (22.9)
Race, n (%)				
White	122 (81.3)	118 (81.9)	85 (87.6)	86 (84.3)
Asian	27 (18.0)	22 (15.3)	11 (11.3)	13 (12.7)
Black or African American	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Other	1 (0.7)	4 (2.8)	1 (1.0)	3 (2.9)
Ethnicity, n (%)				
Not Hispanic or Latino	135 (90.0)	136 (94.4)	88 (90.7)	94 (92.2)
Hispanic or Latino	15 (10.0)	7 (4.9)	9 (9.3)	7 (6.9)
Not reported	0 (0.0)	1 (0.7)	0 (0.0)	1 (1.0)
Baseline weight (kg)				
n	150	144	97	102
Median (interquartile range)	85 (72 to 97)	85 (72 to 93)	88 (74 to 100)	84 (71 to 94)
Min, Max	46, 145	46, 157	52, 145	52, 157
Baseline BMI (kg/m^2)				
n	150	143	97	102
Median (interquartile range)	28 (25 to 32)	27 (24 to 31)	29 (26 to 32)	28 (24 to 31)
Min, Max	19, 51	19, 48	19, 51	19, 48

Note: % = 100 × n/N.
Baseline was defined as the last measurement prior to the first dose of study drug.
BMI = body mass index; FAS = Full Analysis Set; max = maximum; min = minimum.
Sources: Post-text Tables 14.1.3.1 and 14.1.3.2

Table below describes baseline disease characteristics for the SAS and the Part A FAS, which were consistent between the analysis sets, and characterise a clinically relevant high-risk IgAN population.

Table 15 Baseline disease characteristics – SAS and Part A FAS

Characteristic Statistic/Category	Safety Analysis Set Nefecon 16 mg (N=150)	Safety Analysis Set Placebo (N=144)	Part A FAS Nefecon 16 mg (N=97)	Part A FAS Placebo (N=102)
Baseline systolic blood pressure (mmHg)				
n	150	144	97	102
Median (interquartile range)	126 (121 to 132)	124 (117 to 129)	128 (122 to 134)	124 (117 to 131)
Min, Max	91, 164	99, 157	103, 164	99, 157
Baseline diastolic blood pressure (mmHg)				
n	150	144	97	102
Median (interquartile range)	79 (76 to 84)	78 (73 to 83)	79 (76 to 84)	78 (73 to 83)
Min, Max	54, 96	63, 96	65, 94	63, 95
Baseline UACR (g/gram)				
n	150	144	97	102
Median (interquartile range)	0.99 (0.71 to 1.36)	0.95 (0.65 to 1.42)	0.98 (0.75 to 1.35)	0.98 (0.66 to 1.55)
Baseline total urine albumin (g/24 hours)				
n	150	144	97	102
Median (interquartile range)	1.78 (1.24 to 2.54)	1.70 (1.12 to 2.67)	1.81 (1.28 to 2.82)	1.74 (1.14 to 3.05)
Patients with microhematuria, n (%)	100 (66.7)	98 (68.1)	60 (61.9)	70 (68.6)
Baseline UPCR (g/gram)				
n	150	144	97	102
Median (interquartile range)	1.29 (0.92 to 1.71)	1.16 (0.83 to 1.75)	1.27 (0.95 to 1.75)	1.21 (0.87 to 1.79)
Baseline proteinuria (g/24 hours)				
n	150	144	97	102
Median (interquartile range)	2.32 (1.68 to 3.15)	2.18 (1.52 to 3.49)	2.33 (1.71 to 3.25)	2.25 (1.51 to 3.57)
Baseline proteinuria, n (%)				
<2 g/24 hours	61 (40.7)	64 (44.4)	39 (40.2)	43 (42.2)
≥2 and ≤3.5 g/24 hours	59 (39.3)	44 (30.6)	36 (37.1)	31 (30.4)
>3.5 g/24 hours	30 (20.0)	36 (25.0)	22 (22.7)	28 (27.5)
Baseline eGFR (CKD-EPI) (mL/min/1.73 m^2)				
n	150	144	97	102
Median (interquartile range)	55.49 (46.5 to 70.0)	54.96 (46.0 to 67.8)	54.85 (46.43 to 68.88)	55.53 (45.50 to 67.74)
Baseline eGFR (CKD-EPI), n (%)				
<60 mL/min/1.73 m^2	93 (62.0)	85 (59.0)	63 (64.9)	61 (59.8)
≥60 mL/min/1.73 m^2	57 (38.0)	59 (41.0)	34 (35.1)	41 (40.2)
Time from IgAN diagnosis to study entry (years)				
n	131	127	88	91
Median (interquartile range)	2.2 (0.5 to 6.4)	2.6 (0.5 to 6.3)	2.0 (0.8 to 6.1)	2.8 (0.5 to 7.1)
Min, Max	<0.1, 22	<0.1, 22	<0.1, 16	<0.1, 22
Patients with prior GCS or immunosuppressive use, n (%)	12 (8.0)	12 (8.3)	9 (9.3)	7 (6.9)
Patients recommended to make lifestyle choices as per protocol, n (%)	149 (99.3)	142 (98.6)	97 (100.0)	100 (98.0)

Note: % = 100 × n/N.
Baseline was defined as the last measurement prior to the first dose of study drug. Baseline for systolic and diastolic blood pressure was defined as the arithmetic mean of all measurements prior to the first dose of study drug. Baseline proteinuria, eGFR, and total urine albumin were calculated as the geometric mean of the 2 consecutive measurements prior to randomization.
CKD-EPI = Chronic Kidney Disease Epidemiology Collaboration; eGFR = estimated glomerular filtration rate; FAS = Full Analysis Set; GCS = glucocorticosteroid; IgAN = immunoglobulin A nephropathy; max = maximum; min = minimum; UACR = urine albumin to creatinine ratio; UPCR = urine protein to creatinine ratio.
Sources: Post-text Tables 14.1.3.1 and 14.1.3.2

Table below describes RAS inhibitor therapy at baseline for the SAS and the Part A FAS, which were consistent between the analysis sets.

Table 16 RAS inhibitor therapy at baseline – SAS and Part A FAS

Characteristic Statistic/Category	Safety Analysis Set		Part A FAS	
	Nefecon 16 mg (N=150)	Placebo (N=144)	Nefecon 16 mg (N=97)	Placebo (N=102)
Use of any RAS inhibitor therapy (ACEIs and/or ARBs), n (%)				
Patients on either ACEI or ARB	146 (97.3)	142 (98.6)	95 (97.9)	99 (97.1)
Patients on ACEI alone	72 (48.0)	57 (39.6)	54 (55.7)	44 (43.1)
Patients on ARB alone	68 (45.3)	78 (54.2)	38 (39.2)	48 (47.1)
Patients on both ACEI and ARB	6 (4.0)	7 (4.9)	3 (3.1)	7 (6.9)
Level of RAS blockade [1], n (%)	N=142	N=140	N=95	N=101
<50% of maximum allowed dose	34 (23.9)	28 (20.0)	22 (23.2)	20 (19.8)
≥50% and <80% of maximum allowed dose	31 (21.8)	42 (30.0)	22 (23.2)	33 (32.7)
≥80% of maximum allowed dose	77 (54.2)	70 (50.0)	51 (53.7)	48 (47.5)

Note: % = 100 × n/N.
Baseline was defined as the last measurement prior to the first dose of study drug. The data were derived using appropriate ATC classes if those therapies were ongoing at the point of randomization.
1. For patients taking both ACEIs and ARBs, the sum of the % of the maximum allowed dose for each were summarized. Patients who were not recorded as having received RAS blockade are included in the <50% category. The dose received was not recorded for some patients; these patients are not included in the summary.

ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin II type I receptor blocker; ATC = Anatomical Therapeutic Chemical; FAS = Full Analysis Set; RAS = renin-angiotensin system.
Sources: Post-text Tables 14.1.3.1 and 14.1.3.2

Table 24 summarises medical history that was present in >5% of patients in either treatment group by PT for the SAS and the Part A FAS. Other than IgAN, the most commonly reported conditions in the medical history were hypertension, hyperlipidemia (reported as either hypercholesterolemia, dyslipidemia, or hyperlipidemia), and hyperuricemia. Proteinuria and hematuria were each present in approximately 14% of patients.

Table 17 Medical history (>5% of patients in either treatment group) by PT – SAS and Part A FAS

Preferred Term	Safety Analysis Set		Part A FAS	
	Nefecon 16 mg (N=150) n (%)	Placebo (N=144) n (%)	Nefecon 16 mg (N=97) n (%)	Placebo (N=102) n (%)
Patients with any medical history	150 (100.0)	144 (100.0)	97 (100.0)	102 (100.0)
IgA nephropathy [1]	150 (100.0)	144 (100.0)	97 (100.0)	102 (100.0)
Hypertension	108 (72.0)	99 (68.8)	75 (77.3)	71 (69.6)
Hyperlipidemia [2]	51 (34.0)	40 (27.8)	33 (34.0)	26 (25.5)
Hyperuricemia	31 (20.7)	23 (16.0)	20 (20.6)	17 (16.7)
Chronic kidney disease	31 (20.7)	18 (12.5)	19 (19.6)	13 (12.7)
Proteinuria	18 (12.0)	19 (13.2)	14 (14.4)	15 (14.7)
Hematuria	18 (12.0)	15 (10.4)	15 (15.5)	13 (12.7)
Vitamin D deficiency	14 (9.3)	17 (11.8)	9 (9.3)	14 (13.7)
Gout	16 (10.7)	10 (6.9)	10 (10.3)	8 (7.8)
Gastroesophageal reflux disease	12 (8.0)	13 (9.0)	7 (7.2)	11 (10.8)
Obesity	12 (8.0)	11 (7.6)	9 (9.3)	5 (4.9)
Seasonal allergy	8 (5.3)	13 (9.0)	5 (5.2)	8 (7.8)
Hypothyroidism	10 (6.7)	10 (6.9)	7 (7.2)	4 (3.9)
Anxiety	9 (6.0)	8 (5.6)	7 (7.2)	7 (6.9)
Menopause	9 (6.0)	7 (4.9)	3 (3.1)	5 (4.9)
Diabetes [3]	13 (8.7)	5 (3.5)	9 (9.3)	1 (1.0)
Benign prostatic hyperplasia	9 (6.0)	3 (2.1)	5 (5.2)	2 (2.0)
Migraine	1 (0.7)	8 (5.6)	1 (1.0)	5 (4.9)

Note: % = 100 × n/N.
Medical history reported terms were coded using the Medical Dictionary for Regulatory Activities Version 22.0.
1. One patient had secondary IgA nephropathy and was excluded from the Part A FAS per the Statistical Analysis Plan.
2. Hyperlipidemia reported as either hypercholesterolemia, dyslipidemia, or hyperlipidemia.
3. Diabetes reported as either type 2 diabetes mellitus, type 1 diabetes mellitus, diabetes mellitus, or steroid diabetes.

FAS = Full Analysis Set; IgA = immunoglobulin A; PT = preferred term.
Sources: Post-text Tables 14.1.4.1 and 14.1.4.2

Table below presents treatment compliance based on capsule counts for the SAS and the Part A FAS. Compliance to study treatment was high in both treatment groups, with >93% of patients taking at least 80% of the expected number of capsules in the Part A FAS.

Table 18 Treatment compliance based on capsule counts – SAS and Part A FAS

Compliance (%)	Safety Analysis Set [1]		Part A FAS [2]	
	Nefecon 16 mg (N=150)	Placebo (N=144)	Nefecon 16 mg (N=97)	Placebo (N=102)
Median (range)	99 (0 to 121)	99 (31 to 106)	99 (0 to 121)	99 (0 to 106)
Compliance category, n (%)	N'=133	N'=132		
<50%	2 (1.5)	1 (0.8)	2 (2.1)	2 (2.0)
≥50% and <80%	4 (3.0)	6 (4.5)	3 (3.1)	5 (4.9)
≥80% and <120%	126 (94.7)	125 (94.7)	91 (93.8)	95 (93.1)
≥120%	1 (0.8)	0 (0.0)	1 (1.0)	0 (0.0)

Note: Percent compliance to the study treatment = 100 × total number of actual capsules taken / total number of expected capsules taken. The number of actual capsules taken = number of capsules dispensed - number of capsules returned. The number of capsules expected = (date of last dose - date of first dose + 1) × 4. The Tapering Period was not included in the compliance calculations.
1. For the Safety Analysis Set, % = 100 × n/N', where N' is the number of patients who were dosed and returned at least 1 bottle. Compliance could not be calculated for patients in the Safety Analysis Set who had not yet returned for a dispensing visit.
2. For the Part A FAS, % = 100 × n/N. Compliance was considered to be 0 for a patient who was not dosed. Note that 1 patient in the Part A FAS was dosed but did not return any bottles prior to the DCO; compliance for this patient was imputed to 0.

DCO = data cutoff; FAS = Full Analysis Set.
Sources: Post-text Tables 14.1.7.1 and 14.1.7.2

Patients were required to be on a stable dose of RAS inhibitor therapy (ACEIs and/or ARBs) at the maximum allowed dose or maximum tolerated dose according to the 2012 KDIGO guideline for the 3 months prior to randomisation. Table 19 summarises concomitant medications taken by >5% of total patients by ATC class for the SAS and the Part A FAS.

Table 19 Concomitant medications (>5% of total patients) by ATC class – SAS and Part A FAS

	Safety Analysis Set		Part A FAS	
ATC Class	Nefecon 16 mg (N=150) n (%)	Placebo (N=144) n (%)	Nefecon 16 mg (N=97) n (%)	Placebo (N=102) n (%)
Patients who took any concomitant medications	150 (100.0)	144 (100.0)	97 (100.0)	101 (99.0)
ARBs, plain [1]	63 (42.0)	82 (56.9)	36 (37.1)	53 (52.0)
ACEIs, plain [1]	74 (49.3)	59 (41.0)	55 (56.7)	48 (47.1)
HMG CoA reductase inhibitors	73 (48.7)	57 (39.6)	50 (51.5)	36 (35.3)
Dihydropyridine derivatives	52 (34.7)	48 (33.3)	37 (38.1)	35 (34.3)
Preparations inhibiting uric acid production	43 (28.7)	37 (25.7)	30 (30.9)	29 (28.4)
Anilides	29 (19.3)	39 (27.1)	21 (21.6)	31 (30.4)
Vitamin D and analogues	32 (21.3)	30 (20.8)	27 (27.8)	21 (20.6)
Other lipid modifying agents	38 (25.3)	21 (14.6)	23 (23.7)	14 (13.7)
Sulfonamides, plain	31 (20.7)	20 (13.9)	21 (21.6)	9 (8.8)
Beta blocking agents, selective	28 (18.7)	18 (12.5)	21 (21.6)	13 (12.7)
Proton pump inhibitors	23 (15.3)	19 (13.2)	17 (17.5)	15 (14.7)
Glucocorticoids	15 (10.0)	20 (13.9)	12 (12.4)	18 (17.6)
Alpha-adrenoreceptor antagonists	15 (10.0)	15 (10.4)	12 (12.4)	13 (12.7)
Thyroid hormones	14 (9.3)	14 (9.7)	9 (9.3)	6 (5.9)
Other antihistamines for systemic use	12 (8.0)	13 (9.0)	9 (9.3)	10 (9.8)
Opioids in combination with non-opioid analgesics	11 (7.3)	9 (6.3)	10 (10.3)	8 (7.8)
Platelet aggregation inhibitors, excluding heparin	11 (7.3)	9 (6.3)	6 (6.2)	8 (7.8)
Aldosterone antagonists	11 (7.3)	6 (4.2)	7 (7.2)	4 (3.9)
Piperazine derivatives	7 (4.7)	10 (6.9)	5 (5.2)	6 (5.9)
Preparations with no effect on uric acid metabolism	7 (4.7)	10 (6.9)	5 (5.2)	7 (6.9)
Benzodiazepine derivatives	6 (4.0)	10 (6.9)	6 (6.2)	10 (9.8)
Corticosteroids	6 (4.0)	10 (6.9)	6 (6.2)	8 (7.8)
Magnesium	8 (5.3)	8 (5.6)	6 (6.2)	6 (5.9)
Thiazides, plain	6 (4.0)	10 (6.9)	5 (5.2)	9 (8.8)
ARBs and diuretics	7 (4.7)	8 (5.6)	4 (4.1)	5 (4.9)

Note: % = 100 × n/N.
Concomitant medications were defined as medications that were taken on or after the first dose day of study treatment.
Medication reported terms were coded using the WHO Drug Dictionary (Version March 2019G B3).
1. These ATC classes were defined based on whether they were taken during treatment. These ATC classes are not inclusive of all RAS inhibitor therapy.
ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin II type I receptor blocker; ATC = Anatomical Therapeutic Chemical; FAS = Full Analysis Set; HMG CoA = 3-hydroxy-3-methyl-glutaryl-coenzyme A; RAS = renin-angiotensin system; WHO = World Health Organization.
Sources: Post-text Tables 14.1.5.3 and 14.1.5.4

Numbers analysed

The FAS has been used for the primary analyses of efficacy across all studies. The numbers of patients included in each of the analysis populations by study and for the pooled efficacy dataset are summarised in Table 20.

Table 20 Analysis sets by study and pooled dataset

	Number of patients						
	Nef-301		Nef-202			Pooled	
	Nefecon 16 mg	Placebo	Nefecon 16 mg	Nefecon 8 mg	Placebo	Nefecon 16 mg	Placebo
Patients randomized	153	153	51	51	51	204	204
Safety analysis set	150	144	49	51	50	199	194
Full Analysis Set[a]	97	102	48	51	50	145	152
Patients dosed[b]	97	100	49	51	50	146	150
Per Protocol analysis set	92	97	31	37	41	NA	NA

Source: Supportive Tables and Figures for SCE Table 2.7.3.1.1, Supportive Tables and Figures for SCS Table 2.7.4.1.1, Nef-301 CSR Table 7, and Nef-202 CSR Table 5.

[a] For Nef-301 this is defined as the Part A Full Analysis Set. For Nef-202 this is the Full Analysis Set at the time of the final analysis.

[b] For Nef-301 this is the number of patients in the Part A Full Analysis Set who received study treatment.

NA Not applicable. No pooled Per Protocol analyses performed.

Outcomes and estimation

Primary Efficacy Evaluation

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.

Table below presents an analysis of the ratio of UPCR at 9 months compared to baseline using MMRM for the Part A FAS.

Table 21 Analysis of the ratio of UPCR (g/gram) at 9 months compared to baseline using MMRM – Part A FAS

	Nefecon 16 mg (N=97)	Placebo (N=102)
Number of patients with valid UPCR result at 9 months	89	90
Ratio of geometric LS mean UPCR at 9 months compared to baseline (96% CI)	0.69 (0.61 to 0.79)	0.95 (0.83 to 1.08)
Corresponding percentage reduction (96% CI)	31% (21% to 39%)	5% (-8% to 17%)
Comparison of Nefecon 16 mg versus placebo		
Ratio of geometric LS means (96% CI)	0.73 (0.61 to 0.88)	
Corresponding percentage reduction (96% CI)	27% (12% to 39%)	
1-sided p-value	0.0003	

Note: All patients in the Part A FAS were included in the analysis at each time point, which implicitly imputed missing data for those patients without a valid UPCR result at the respective time point.
CI = confidence interval; FAS = Full Analysis Set; LS = least squares; MMRM = Mixed-Effects Model for Repeated Measures; UPCR = urine protein to creatinine ratio.
Sources: Post-text Tables 14.2.1.1.1 and 14.2.2.1

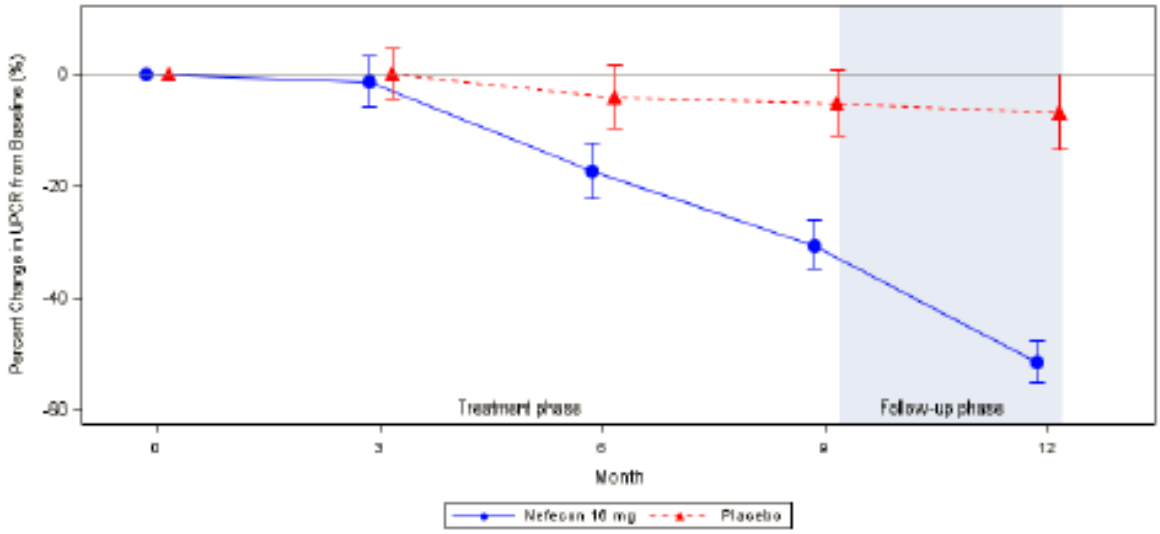
Table below presents an analysis of the ratio of UPCR at 3, 6, 9, and 12 months compared to baseline using MMRM for the Part A FAS.

Table 22 Analysis of the ratio of UPCR (g/gram) at 3, 6, 9, and 12 months compared to baseline using MMRM – Part A FAS

Time point (n, n)	Comparison of Nefecon 16 mg Versus Placebo	
	Ratio of Geometric LS Means (95% CI); 1-sided p-value	Corresponding Percentage Reduction (95% CI)
3 months (n = 93, 98)	0.99 (0.87 to 1.12); p=0.4129	1% (-12% to 13%)
6 months (n = 90, 94)	0.86 (0.73 to 1.02); p=0.0398	14% (-2% to 27%)
9 months (n = 89, 90)	0.73 (0.61 to 0.87); p=0.0003	27% (13% to 39%)
12 months (n = 59, 66)	0.52 (0.42 to 0.64); p<0.0001	48% (36% to 58%)

Note: n = number of patients in each treatment group (Nefecon 16 mg, placebo) with a valid UPCR result at the time point. All patients in the Part A FAS were included in the analysis at each time point, which implicitly imputed missing data for those patients without a valid UPCR result at the respective time point.
CI = confidence interval; FAS = Full Analysis Set; LS = least squares; MMRM = Mixed-Effects Model for Repeated Measures; UPCR = urine protein to creatinine ratio.
Sources: Post-text Tables 14.2.1.1.1, 14.2.2.1, and 14.2.2.5.1

Figure below presents the percentage change in UPCR from baseline for the Part A FAS. The reduction in UPCR with Kinpeygo 16 mg per day increased over time compared to placebo.



Note: Mean percent changes for each visit were calculated using ratio of geometric LS means from the model; both ratio of LS means and LS means ± standard error were transformed back into the original scale from MMRM estimates.
Baseline was defined as the geometric mean of the 2 consecutive measurements prior to randomization.
FAS = Full Analysis Set; LS = least squares; MMRM = Mixed-Effects Model for Repeated Measures; UPCR = urine protein to creatinine ratio.
Source: Post-text Figure 14.2.2.5.1a

Figure 11 Percentage change in UPCR (g/gram) from baseline – Part A FAS

Sensitivity analyses

Table 23 Supplementary and sensitivity analyses for the ratio of UPCR (g/gram) at 9 months compared to baseline

Analysis	N	Comparison of Nefecon 16 mg Versus Placebo Ratio of Geometric LS Means (95% CI); 1-sided p-value	Ratio of Geometric LS Mean UPCR at 9 Months Compared to Baseline (95% CI)	
			Nefecon 16 mg	Placebo
Primary MMRM analysis (Part A FAS)	199	0.73 (0.61 to 0.87) p=0.0003	0.69 (0.61 to 0.78) n=89	0.95 (0.84 to 1.07) n=90
1) Robust regression analysis to account for outliers (Part A FAS)	199	0.76 (0.65 to 0.89) p=0.0003	0.73 (0.65 to 0.81) n=89	0.95 (0.86 to 1.06) n=90
2) MMRM analysis to account for missing data (Part A FAS)	199	0.72 (0.60 to 0.87) p=0.0003	0.69 (0.61 to 0.78) n=89	0.95 (0.84 to 1.08) n=90
3) MMRM analysis including data post rescue treatment (Part A FAS)	199	0.69 (0.58 to 0.84) p<0.0001	0.66 (0.58 to 0.76) n=92	0.95 (0.84 to 1.09) n=92
4) MMRM analysis (Per Protocol Analysis Set)	189	0.78 (0.66 to 0.92) p=0.0016	0.72 (0.64 to 0.81) n=79	0.93 (0.83 to 1.04) n=85
5) MMRM analysis (all randomized patients)	306	0.71 (0.60 to 0.84) p<0.0001	0.65 (0.58 to 0.73) n=89	0.92 (0.82 to 1.04) n=92

Note: n = number of patients with a valid observed UPCR result at 9 months for each analysis (in all analyses, missing data were multiply imputed, either implicitly or explicitly, prior to analysis). N = total number of patients included who either had data observed or imputed.
CI = confidence interval; FAS = Full Analysis Set; LS = least squares; MMRM = Mixed-Effects Model for Repeated Measures; UPCR = urine protein to creatinine ratio.
Sources: Post-text Tables 14.2.1.1.1, 14.2.1.1.2, 14.2.1.1.3, 14.2.2.1, 14.2.2.2.1, 14.2.2.2.2, 14.2.2.2.3, 14.2.2.2.4, and 14.2.2.2.5

Secondary Efficacy Evaluations

1. Ratio of eGFR at 9 and 12 months compared to baseline

Table 24 Analysis of the ratio of eGFR (CKD-EPI) (mL/min/1.73 m2) at 9 months compared to baseline using robust regression – Part A FAS

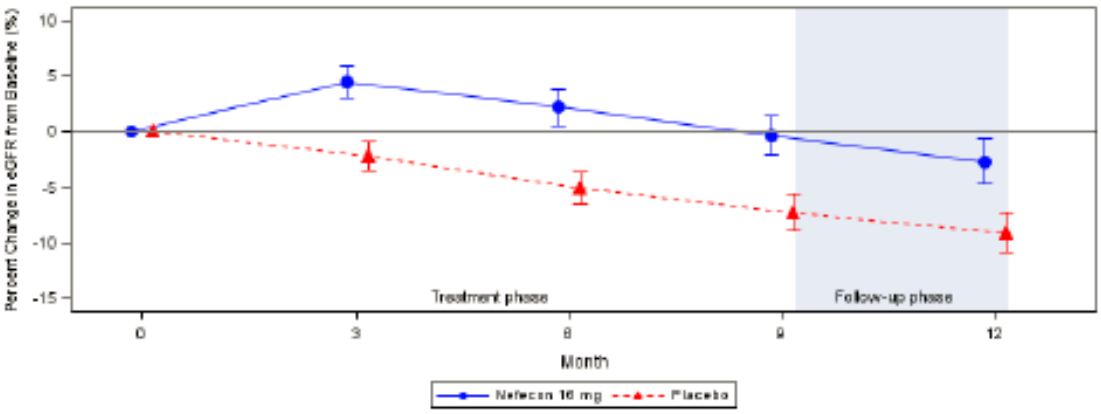
	Nefecon 16 mg (N=97)	Placebo (N=102)
Number of patients with valid eGFR result at 9 months	91	91
Ratio of geometric LS mean eGFR at 9 months compared to baseline (95% CI)	1.00 (0.96 to 1.03)	0.93 (0.90 to 0.96)
Corresponding percentage change (95% CI)	0% (-4% to 3%)	-7% (-10% to -4%)
Absolute change from baseline in eGFR at 9 months (mL/min/1.73 m^2)	-0.17	-4.04
Comparison of Nefecon 16 mg versus placebo		
Ratio of geometric LS means (95% CI)	1.07 (1.03 to 1.13)	
Corresponding percentage change (95% CI)	7% (3% to 13%)	
1-sided p-value	0.0014	
Difference in absolute change (mL/min/1.73 m^2)	3.87	

Note: Corresponding absolute changes from baseline were derived by multiplying the geometric LS mean ratio compared to baseline for each treatment arm with a value of 55.69 mL/min/1.73 m^2 and subtracting from the baseline value of 55.69 mL/min/1.73 m^2, where 55.69 is the geometric mean eGFR pooled across treatment groups.
All patients in the Part A FAS were included in the analysis at each time point, which implicitly imputed missing data for those patients without a valid eGFR result at the respective time point.
CI = confidence interval; CKD-EPI = Chronic Kidney Disease Epidemiology Collaboration; eGFR = estimated glomerular filtration rate; FAS = Full Analysis Set; LS = least squares.
Sources: Post-text Tables 14.2.1.2.1 and 14.2.2.3.1

Table 25 Analysis of the ratio of eGFR (CKD/EPI) (mL/min/1.73 m2) at 3, 5, 9, and 12 months compared to baseline using robust regression – Part A FAS

Time point (n, n)	Comparison of Nefecon 16 mg Versus Placebo		
	Ratio of Geometric LS Means (95% CI); p-value	Corresponding Percentage Change (95% CI)	Difference in Absolute Change (mL/min/1.73 m^2)
3 months (n = 92, 100)	1.07 (1.03 to 1.11); p=0.0003	7% (3% to 11%)	3.73
6 months (n = 89, 95)	1.08 (1.03 to 1.12); p=0.0005	8% (3% to 12%)	4.05
9 months (n = 91, 91)	1.07 (1.03 to 1.13); p=0.0014	7% (3% to 13%)	3.87
12 months (n = 58, 67)	1.07 (1.01 to 1.13); p=0.0106	7% (1% to 13%)	3.56

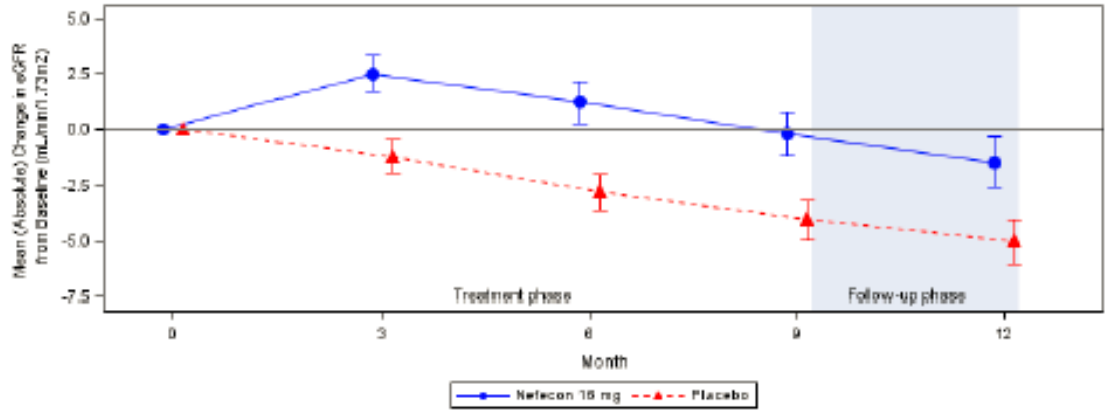
Note: n = number of patients in each treatment group (Nefecon 16 mg, placebo) with a valid eGFR result at the time point.
All patients in the Part A FAS were included in the analysis at each time point, which implicitly imputed missing data for those patients without a valid eGFR result at the respective time point.
CI = confidence interval; CKD-EPI = Chronic Kidney Disease Epidemiology Collaboration; eGFR = estimated glomerular filtration rate; FAS = Full Analysis Set; LS = least squares.
Sources: Post-text Tables 14.2.1.2.1, 14.2.2.3.1, 14.2.2.3.4, and 14.2.2.5.2



Note: Estimated mean percentage change ± standard error estimated from robust regression analysis of log-transformed post-baseline to baseline ratios at 3, 6, 9, and 12 months.
Baseline was defined as the geometric mean of the 2 consecutive measurements prior to randomization.
eGFR was calculated by the central laboratory using the CKD-EPI formula.
CKD-EPI = Chronic Kidney Disease Epidemiology Collaboration; eGFR = estimated glomerular filtration rate; FAS = Full Analysis Set.
Source: Post-text Figure 14.2.2.5.2a

Figure 12 Percentage change in eGFR (CKD-EPI) (mL/min/1.73 m2) from baseline – Part A FAS)

This figure presents the mean absolute change in eGFR (CKD-EPI) from baseline for the Part A FAS.



Note: Estimated mean percentage change ± standard error estimated from robust regression analysis of log-transformed post-baseline to baseline ratios at 3, 6, 9, and 12 months, and transformed back into the original scale.
Baseline was defined as the geometric mean of the 2 consecutive measurements prior to randomization.
eGFR was calculated by the central laboratory using the CKD-EPI formula.
CKD-EPI = Chronic Kidney Disease Epidemiology Collaboration; eGFR = estimated glomerular filtration rate; FAS = Full Analysis Set.
Source: Post-text Figure 14.2.2.5.2b

Figure 13 Mean absolute change in eGFR (CKD-EPI) (mL/min/1.73 m2) from baseline – Part A FAS

Sensitivity analyses

Table 26 Supplementary and sensitivity analyses for the ratio of eGFR (CKD-EPI) (mL/min/1.73 m2) at 9 months compared to baseline

Analysis	N	Comparison of Nefecon 16 mg Versus Placebo Ratio of Geometric LS Means (95% CI); 1-sided p-value; Absolute Change	Ratio of Geometric LS Mean eGFR at 9 Months Compared to Baseline (95% CI) Absolute Change (mL/min/1.73 m^2)	
			Nefecon 16 mg	Placebo
Primary robust regression analysis (Part A FAS)	199	1.07 (1.03 to 1.13); p=0.0014; 3.87	1.00 (0.96 to 1.03); -0.17; n=91	0.93 (0.90 to 0.96); -4.04; n=91
Robust regression analysis accounting for missing data (Part A FAS)	199	1.07 (1.02 to 1.13); p=0.0028; 3.72	0.99 (0.96 to 1.03); -0.44; n=91	0.93 (0.89 to 0.96); -4.16; n=91
Robust regression analysis (Per Protocol Analysis Set)	189	1.09 (1.04 to 1.15); p=0.0002; 4.79	1.02 (0.98 to 1.05); 0.85; n=81	0.93 (0.90 to 0.96); -3.95; n=86
Robust regression analysis (all randomized patients)	306	1.09 (1.04 to 1.15); p=0.0002; 4.75	1.00 (0.97 to 1.04); 0.10; n=91	0.92 (0.89 to 0.95); -4.65; n=93

Note: n = number of patients with a valid observed eGFR result at 9 months for each analysis (in all analyses, missing data were multiply imputed, either implicitly or explicitly, prior to analysis). N = total number of patients included who either had data observed or imputed.
CI = confidence interval; CKD-EPI = Chronic Kidney Disease Epidemiology Collaboration; eGFR = estimated glomerular filtration rate; FAS = Full Analysis Set; LS = least squares.
Sources: Post-text Tables 14.2.1.2.1, 14.2.1.2.2, 14.2.1.2.3, 14.2.2.3.1, 14.2.2.3.2, 14.2.2.3.3, and 14.2.2.3.6

Table 27 Supplementary and sensitivity analyses for the ratio of eGFR (CKD-EPI) (mL/min/1.73 m2) at 12 months compared to baseline

Analysis	N	Comparison of Nefecon 16 mg Versus Placebo Ratio of Geometric LS Means (95% CI); 1-sided p-value; Absolute Change	Ratio of Geometric LS Mean eGFR at 12 Months Compared to Baseline (95% CI) Absolute Change (mL/min/1.73 m^2)	
			Nefecon 16 mg	Placebo
Primary robust regression analysis (Part A FAS)	199	1.07 (1.01 to 1.13); p=0.0106; 3.56	0.97 (0.93 to 1.01); -1.47; n=58	0.91 (0.88 to 0.95); -5.03; n=67
Robust regression analysis (Per Protocol Analysis Set)	189	1.07 (1.01 to 1.14); p=0.0086; 3.75	0.98 (0.94 to 1.02); -1.02; n=49	0.91 (0.88 to 0.95); -4.77; n=62
Robust regression analysis (all randomized patients)	306	1.09 (1.03 to 1.16); p=0.0015; 4.67	0.98 (0.93 to 1.02); -1.32; n=58	0.89 (0.86 to 0.93); -5.99; n=67

Note: n = number of patients with a valid observed eGFR result at 12 months for each analysis (in all analyses, missing data were multiply imputed, either implicitly or explicitly, prior to analysis). N = total number of patients included who either had data observed or imputed.
Analysis accounts for missing data not performed at 12 months, as all patients have discontinued study treatment by 12 months.
CI = confidence interval; CKD-EPI = Chronic Kidney Disease Epidemiology Collaboration; eGFR = estimated glomerular filtration rate; FAS = Full Analysis Set; LS = least squares.
Sources: Post-text Tables 14.2.1.2.1, 14.2.1.2.2, 14.2.1.2.3, 14.2.2.3.4, 14.2.2.3.5, and 14.2.2.3.6

Supportive analysis of 1-year eGFR total slope

Table below presents a supportive analysis of 1-year eGFR total slope for the Part A FAS, which showed an improvement in slope of 3.37 mL/min/1.73 m2 per year with Kinpeygo 16 mg per day compared to placebo (95% CI 0.49 to 6.25; p=0.0111).

Table 28 Supportive analysis of 1-year eGFR (CKD-EPI) (mL/min/1.73m2 per year) total slope – Part A FAS

	Nefecon 16 mg (N=97)	Placebo (N=102)
1-year eGFR slope		
LS mean	-1.26	-4.63
95% CI LS mean	(-3.34 to 0.81)	(-6.64 to -2.63)
Difference in LS means vs placebo	3.37	
95% CI difference in LS means vs placebo	(0.49 to 6.25)	
p-value vs placebo	0.0111	

CI = confidence interval; CKD-EPI = Chronic Kidney Disease Epidemiology Collaboration; eGFR = estimated glomerular filtration rate; FAS = Full Analysis Set; LS = least squares.
Source: Post-text Table 14.2.2.3.7

2. Ratio of UACR at 9 months compared to baseline

Table 29 Analysis of the ratio of UACR (g/gram) at 9 months compared to baseline using MMRM – Part A FAS

	Nefecon 16 mg (N=97)	Placebo (N=102)
Number of patients with valid UACR result at 9 months	90	91
Ratio of geometric LS mean UACR at 9 months compared to baseline (95% CI)	0.64 (0.55 to 0.75)	0.93 (0.80 to 1.09)
Corresponding percentage reduction (95% CI)	36% (25% to 45%)	7% (-9% to 20%)
Comparison of Nefecon 16 mg versus placebo		
Ratio of geometric LS means (95% CI)	0.69 (0.55 to 0.86)	
Corresponding percentage reduction (95% CI)	31% (14% to 45%)	
1-sided p-value	0.0005	

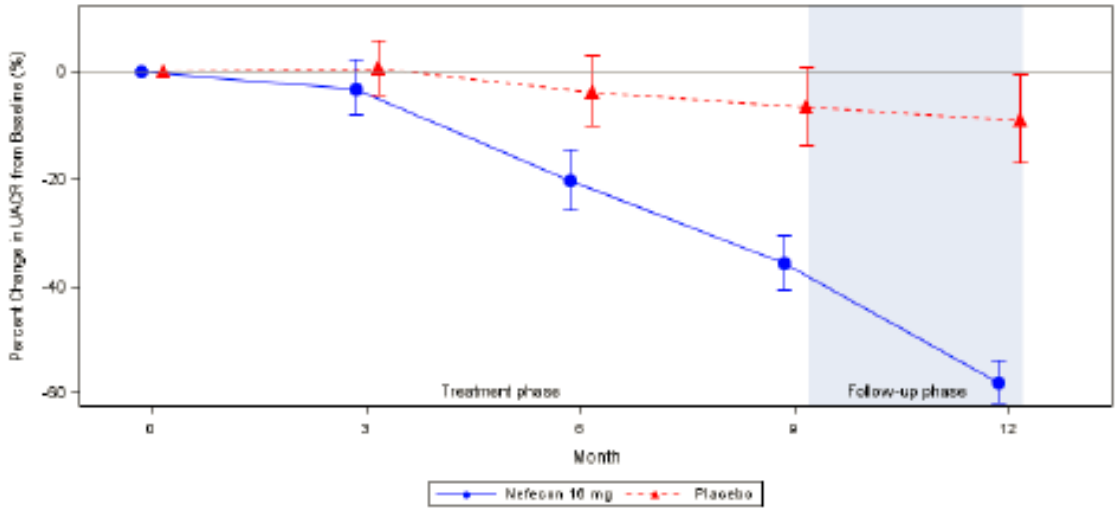
Note: All patients in the Part A FAS were included in the analysis at each time point, which implicitly imputed missing data for those patients without a valid UACR result at the respective time point.
CI = confidence interval; FAS = Full Analysis Set; LS = least squares; MMRM = Mixed-Effects Model for Repeated Measures; UACR = urine albumin to creatinine ratio.
Sources: Post-text Tables 14.2.1.3.1 and 14.2.2.4.1

Table 30 Analysis of the ratio UACR (g/gram) at 3, 6, 9, and 12 months compared to baseline using MMRM – Part A FAS

Time point (n, n)	Comparison of Nefecon 16 mg Versus Placebo	
	Ratio of Geometric LS Means (95% CI); 1-sided p-value	Corresponding Percentage Reduction (95% CI)
3 months (n = 93, 98)	0.96 (0.83 to 1.11); p=0.3068	4% (-11% to 17%)
6 months (n = 89, 94)	0.83 (0.68 to 1.01); p=0.0288	17% (-1% to 32%)
9 months (n = 90, 91)	0.69 (0.55 to 0.86); p=0.0005	31% (14% to 45%)
12 months (n = 60, 65)	0.46 (0.36 to 0.60); p<0.0001	54% (40% to 64%)

Note: n = number of patients in each treatment group (Nefecon 16 mg, placebo) with a valid UACR result at the time point. All patients in the Part A FAS were included in the analysis at each time point, which implicitly imputed missing data for those patients without a valid UACR result at the respective time point.
CI = confidence interval; FAS = Full Analysis Set; LS = least squares; MMRM = Mixed-Effects Model for Repeated Measures; UACR = urine albumin to creatinine ratio.
Sources: Post-text Tables 14.2.1.3.1, 14.2.2.4.1, and 14.2.2.5.3

Figure below presents the relative change in UACR from baseline for the Part A FAS.



Note: Estimated mean percentage change ± standard error estimated from MMRM analysis of log-transformed post-baseline to baseline ratios at 3, 6, 9, and 12 months.
Baseline was defined as the geometric mean of the 2 consecutive measurements prior to randomization.
FAS = Full Analysis Set; MMRM = Mixed-Effects Model for Repeated Measures; UACR = urine albumin to creatinine ratio.
Source: Post-text Figure 14.2.2.5.3a

Figure 14 Relative change in UACR (g/gram) from baseline – Part A FAS

3. Proportion of patients without microhematuria at baseline or at 9 months

Table 31 Proportion of patients without microhematuria at baseline or at 9 months – Part A FAS

	Nefecon 16 mg (N=97)	Placebo (N=102)
Baseline	37 (38.1)	32 (31.4)
9 months	62 (63.9)	38 (37.3)

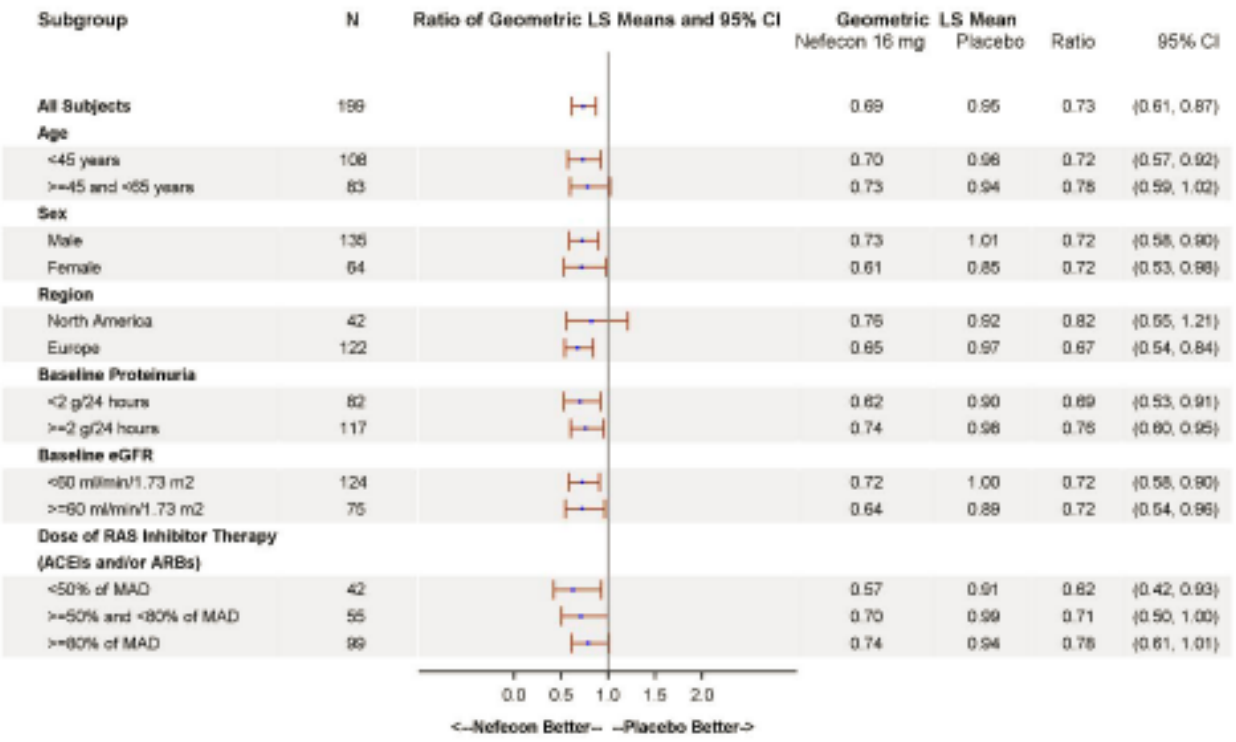
Note: Baseline was defined as the last measurement prior to randomization.
If the patient was tested negative in any of the occult blood assessments during Day 229 to Day 319, the patient was considered without microhematuria at 9 months. Patients who did not provide a test result were considered to have had microhematuria.
Patients were considered to be positive in the occult blood test if the result of Small, Moderate, or Large was reported; a result of Negative or Trace was considered as negative. The corresponding hemoglobin concentration is Trace = 0.015-0.062 mg/dL, Small = 0.062-0.2 mg/dL, Moderate = 0.2-1.0 mg/dL, and Large = >1.0 mg/dL.
FAS = Full Analysis Set.
Source: Post-text Table 14.2.1.6.1

Ancillary analyses

a) Primary efficacy endpoint:

Analyses of the ratio of UPCR at 9 months compared to baseline using MMRM were performed for subgroups of patients in the Part A FAS based on age (<45 years or ≥ 45 and <65 years); gender (male or female); region (Europe or North America); baseline proteinuria (<2 g/24 hours or ≥2 g/24 hours); baseline eGFR (<60 mL/min/1.73 m2 or ≥60 mL/min/1.73 m2); and dose of RAS inhibitor therapy (ACEIs and/or ARBs).

Figure below presents the subgroup analysis of the ratio of UPCR at 9 months compared to baseline using MMRM for the Part A FAS. UPCR results were generally consistent across the pre-defined subgroups. The UPCR treatment effect was highly consistent across subgroups. Interaction tests (p>0.05 for all subgroups) indicated no differential treatment effect on UPCR at 9 months for any baseline characteristics.

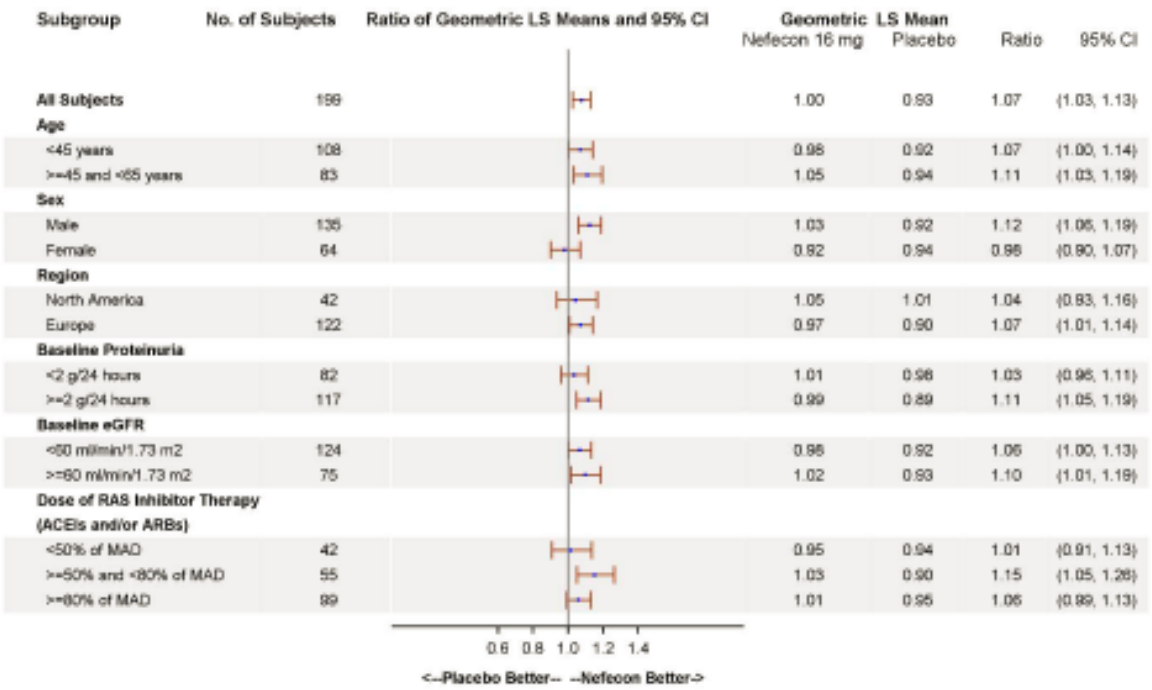


Note: If a subgroup had fewer than 20 patients exposed to Nefecon 16 mg, data in that subgroup level were not assessed.
ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin II type I receptor blocker; CI = confidence interval; eGFR = estimated glomerular filtration rate; FAS = Full Analysis Set; LS = least squares; MAD = maximum allowable dose; MMRM = Mixed-Effects Model for Repeated Measures; RAS = renin-angiotensin system; UPCR = urine protein to creatinine ratio.
Source: Post-text Figure 14.2.3.1

Figure 15 Subgroup analysis: Ratio of UPCR (g/gram) at 9 months compared to baseline using MMRM – Part A FAS

b) Secondary efficacy endpoint:

Analyses of the ratio of eGFR (CKD-EPI) at 9 months compared to baseline using robust regression were performed for subgroups of patients in the Part A FAS based on age (<45 years or ≥45 and <65 years); gender (male or female); region (Europe or North America); baseline proteinuria (<2 g/24 hours or ≥2 g/24 hours); baseline eGFR (<60 mL/min/1.73 m2 or ≥60 mL/min/1.73 m2); and dose of RAS inhibitor therapy (ACEIs and/or ARBs). Figure 17 presents the subgroup analysis of the ratio of eGFR (CKD-EPI) at 9 months compared to baseline using robust regression for the Part A FAS.



Note: If a subgroup had fewer than 20 patients exposed to Nefecon 16 mg, data in that subgroup level were not assessed.
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.
Source: Post-text Figure 14.2.3.2

Figure 16 Subgroup analysis: Ratio of eGFR (CKD-EPI) (mL/in/1.73 m2) at 9 months compared to baseline using robust regression – Part A FAS

Within the responses to the Day 90 List of Questions, the applicant provided pre-defined subgroup analyses for Nef-301 and Nef-202, including UPCR with a cut-off of 1.5 g/gram. A shortened version of these figures/tables is provided below:

UPCR

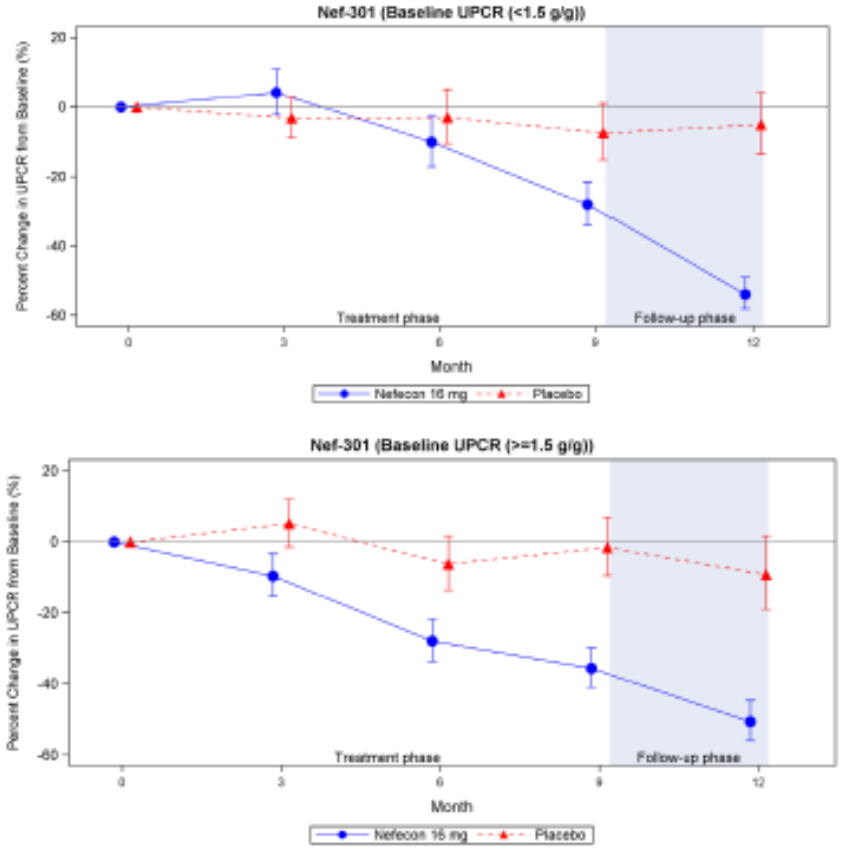


Table 32 Nef-301 Part A analysis of ratio (Kinpeygo 16 mg: Placebo) of UPCR (g/gram) at 3, 6, 9, and 12 months compared to baseline using MMRM by UPCR above and below 1.5 g/gram and compared to the overall population (FAS)

Timepoint	Comparison Nefecon 16 mg versus Placebo Percentage reduction (95% CI); 1-sided p-value, (n, n)		
	Baseline UPCR<1.5 g/gram	Baseline UPCR≥1.5 g/gram	Overall Population
3 months	-8% (-28% to 10%); p=0.7966 (n=58, 62)	14% (-3% to 28%); p=0.0534 (n=35, 36)	1% (-12% to 13%); p=0.4129 (n=93, 98)
6 months	7% (-17% to 26%); p=0.2556 (n=56, 59)	23% (3% to 39%); p=0.0123 (n=34, 35)	14% (-2% to 27%); p=0.0398 (n=90, 94)
9 months	22% (1% to 39%); p=0.0215 (n=58, 57)	35% (17% to 48%); p=0.0003 (n=31, 33)	27% (13% to 39%); p=0.0003 (n=89, 90)
12 months	51% (36% to 63%); p<0.0001 (n=37, 44)	46% (25% to 61%); p=0.0002 (n=22, 22)	48% (36% to 58%); p<0.0001 (n=59,66)

CI confidence interval; MMRM mixed model repeated measures; n number of patients in each treatment group (Nefecon 16 mg, placebo) with a valid UPCR result at the timepoint; UPCR urine protein creatinine ratio. Percentage reduction and 95% CI derived from (1-ratio of geometric LSmeans)×100.

eGFR

Additional eGFR slope data from 3 months onwards (not previously included in the MAA and hereafter referred to as "chronic slope") have been provided:

Table 33 Nef-301 Part A analysis of eGFR (mL/min/1.73 m2) at 3 and 12 months compared to baseline using robust regression analysis, and 1-year eGFR chronic slope from primary random coefficients analysis and sensitivity analysis using robust regression by baseline UPCR cut-off (FAS)

Baseline UPCR cut-off (g/gram)	N	Difference between Nefecon 16 mg and placebo			
		3-month eGFR treatment effect[a] (mL/min/1.73 m²)	12-month eGFR treatment effect[a] (mL/min/1.73 m²)	Difference in 1-year eGFR chronic slope (95% CI); 1-sided p-value (mL/min/1.73 m² per year)	
				Random coefficients analysis	Robust regression analysis
Overall population	199	3.73	3.56	-0.18 (-3.75 to 3.38); p=0.5406	0.46 (-3.36 to 4.28); p=0.4066
UPCR≥1.0	136	4.10	5.27	2.09 (-2.45 to 6.64); p=0.1817	2.66 (-2.13 to 7.46); p=0.1383
UPCR≥1.1	119	4.47	6.51	3.49 (-1.37 to 8.35); p=0.0787	4.21 (-0.86 to 9.28); p=0.0518
UPCR≥1.2	106	4.23	6.45	3.31 (-1.96 to 8.58); p=0.1077	3.95 (-1.41 to 9.31); p=0.0741
UPCR≥1.3	91	3.50	6.66	4.79 (-0.94 to 10.53); p=0.0500	5.79 (0.00 to 11.57); p=0.0249
UPCR≥1.4	81	3.53	7.68	6.33 (0.50 to 12.16); p=0.0169	7.04 (1.42 to 12.66); p=0.0071
UPCR≥1.5	73	3.64	8.98	7.62 (1.63 to 13.61); p=0.0068	8.19 (2.27 to 14.11); p=0.0033
UPCR≥1.6	62	3.20	7.70	6.02 (-0.87 to 12.90); p=0.0426	7.45 (0.49 to 14.42); p=0.0180
UPCR≥1.7	56	3.20	8.15	6.74 (-0.71 to 14.20); p=0.0375	7.65 (0.39 to 14.92); p=0.0194
UPCR≥1.8	48	3.33	7.87	6.51 (-2.07 to 15.10); p=0.0662	6.35 (-1.76 to 14.46); p=0.0624
UPCR≥1.9	43	2.99	7.80	5.06 (-3.94 to 14.07); p=0.1300	6.94 (-2.54 to 16.42); p=0.0758
UPCR≥2.0	39	3.28	8.34	6.02 (-3.14 to 15.17); p=0.0948	6.94 (-1.55 to 15.43); p=0.0545

Changes in eGFR according to level of proteinuria at baseline

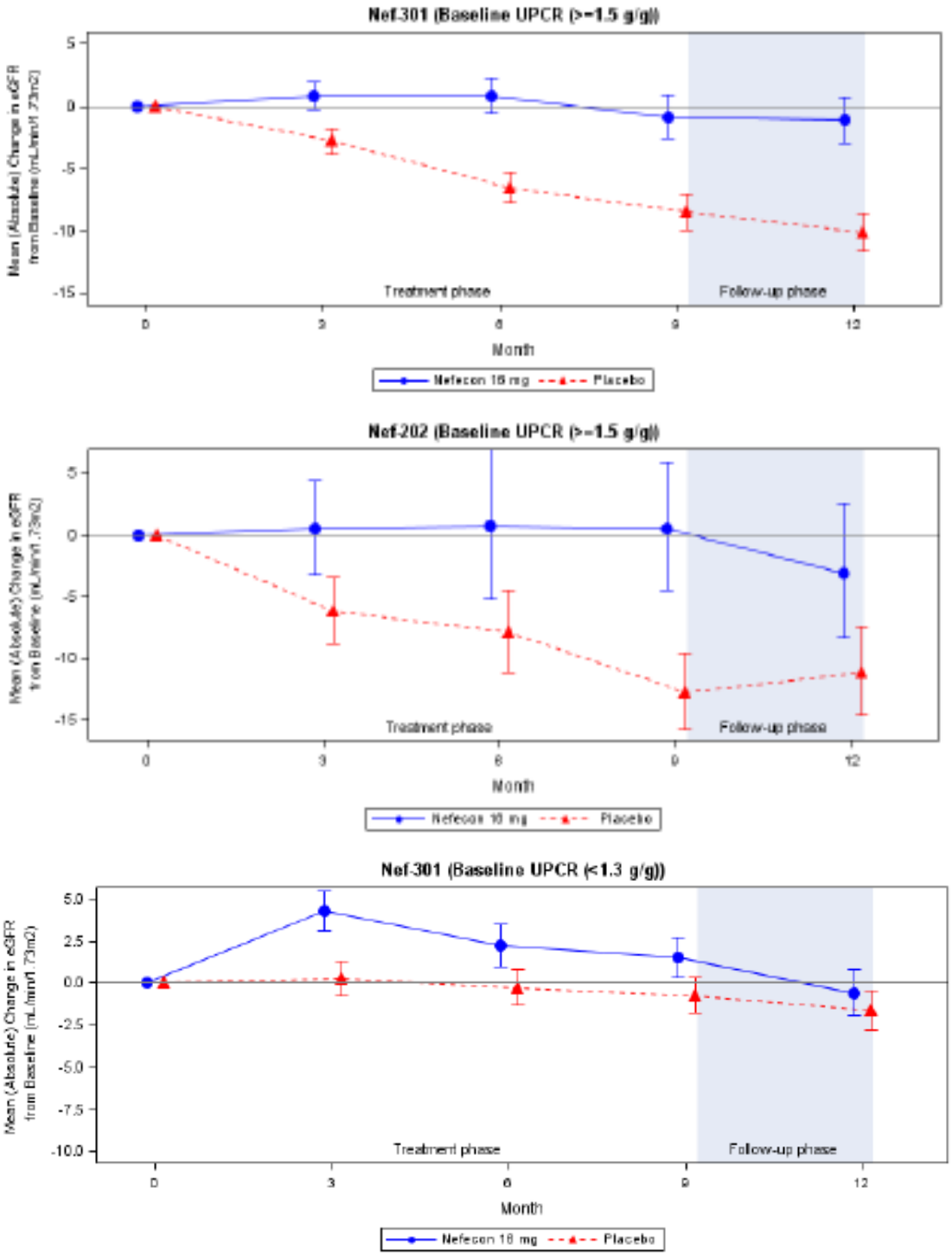


Figure 17 Nef-301 and Nef-202 absolute change in eGFR (mL/min/1.73 2) compared to baseline in patients with UPCR ≥ 1.5 g/gram (FAS)

Summary of main efficacy results

The following tables summarise the efficacy results from the main studies 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 below sections).

Table 34 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	This is an ongoing 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 optimized RAS inhibitor therapy.		
	Duration of Part A: Duration of Part B :		9 months ongoing
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, n = 97 randomised Placebo, 9 months, n = 102 randomised (both under continues RAS inhibitor therapy)
	Part B		observational follow-up 12 months (ongoing)
Endpoints and definitions	Primary 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
		UACR	Ratio of urine albumin to creatinine ratio (UACR) at 9 months compared to baseline
Database lock	05 October 2020		
Results and Analysis of Part A			
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; comparison of baseline to 9 months		
Descriptive statistics and estimate variability	Treatment group	Kinpeygo	Placebo
	Number of subject	89	90
	UPCR (ratio of mean at 9 months compared to baseline)	0.69	0.95
	96 % CI	0.61;0.79	0.83;1.08
Effect estimate per comparison	Primary endpoint UPCR	Comparison groups	Kinpeygo vs Placebo
		difference between groups	0.73 (= 27%)
		96 % CI	0.61;0.88 (12%;39%)
		P-value	0.0003
Notes	After 9 months of treatment, patients treated with Kinpeygo 16 mg once daily showed a statistically significant and clinically relevant 27% reduction in UPCR compared to placebo (96% CI 12% to 39%; p=0.0003). UPCR at 9 months was reduced from baseline by 31% in patients treated with Kinpeygo 16 mg once daily compared with 5% in placebo-treated patients.		
Analysis description	**Secondary analysis**		
Analysis population and time point description	Primary IgAN patients randomised to Kinpeygo or Placebo (1:1) both on a stable RAS inhibitor therapy; comparison of baseline to 9 months		
Descriptive statistics and estimate variability	Treatment group	Kinpeygo	Placebo
	Number of subject	91	91
	eGFR (ratio of mean at 9 months compared to baseline)	1.00	0.93
	95 % CI	0.96;1.03	0.90;0.96
Effect estimate per comparison	Secondary endpoint	Comparison groups	Kinpeygo vs Placebo

	eGFR	difference between groups	1.07 (= 7%)
		95 % CI	1.03;1.13 (3%;13%)
		P-value	0.0014
Notes	After 9 months of treatment, Kinpeygo 16 mg once daily provided a statistically significant and clinically relevant 7% treatment benefit on eGFR compared to placebo (p=0.0014).		
Descriptive statistics and estimate variability	Treatment group	Kinpeygo	Placebo
	Number of subject	90	91
	UACR (ratio of mean at 9 months compared to baseline)	0.64	0.93
	95 % CI	0.55;0.75	0.80;1.09
Effect estimate per comparison	Secondary endpoint UACR	Comparison groups	Kinpeygo vs Placebo
		difference between groups	0.69 (=31%)
		95 % CI	0.55;0.86 (14%;45%)
		P-value	0.0005
Notes	Consistent with the assessment of proteinuria reduction by UPCR, a 31% reduction in UACR compared to placebo was observed at 9 months (p=0.0005)		
Analysis population and time point description	Primary IgAN patients randomised to Kinpeygo or Placebo (1:1) both on a stable RAS inhibitor therapy; comparison of baseline to 12 months		
Effect estimate per comparison	Secondary endpoint eGFR	Comparison groups	Kinpeygo (n=58) vs Placebo (n=67)
		difference between groups	1.07 (= 7%)
		95 % CI	1.01;1.13 (1%;13%)

		P-value	0.0106
Notes	After 12 months of treatment, Kinpeygo 16 mg once daily provided a statistically significant and clinically relevant 7% treatment benefit on eGFR compared to placebo (p=0.0106).		

2.4.5.3. Clinical studies in special populations

Table 35 Summary of clinical studies in older patients (safety analysis set)

	n/N (%) of overall study population		
	Age 65-74	**Age 75-84**	**Age 85+**
Controlled Trials			
Nef-301 (Part A DCO)	9/294 (3.1%)	0	0
Nef-301 (D120 SU DCO)	10/366 (2.7%)	0	0
Nef-202[a]	2/150 (1.3%)	1/150 (0.7%)[a]	0
Pooled Nefecon 16 mg or placebo Part A DCO	10/393 (2.5%)	0	0
D120 SU DCO	11/465 (2.4%)	0	0
Non Controlled trials			
Nef-201 (Nefecon 8 mg)	0	0	0

[a]Numbers including Nefecon 8 mg dose group. The only patient aged ≥75 years of age received Nefecon 8 mg. N Total number of patients in the study or pooled population; n number of patients in the older age category.

2.4.5.4. Analysis performed across trials (pooled analyses and meta-analysis)

Given the comparable study designs, patient populations, study conduct, dosing regimen, and outcome measures in Nef-301 Part A and Nef-202, efficacy data were pooled to provide supportive efficacy estimates with increased precision compared with that of the individual trials. The final data from Nef-202, on completion of the study and including all randomised patients, have been used in the pooled efficacy analyses to provide the most complete analysis of the data for Kinpeygo 16 mg (N=145) compared to placebo (N=152). In order to best describe the cumulative evidence of efficacy, the statistical methodology used in Nef-301, that is now considered the optimal approach, has been applied consistently to the Nef-202 data prior to pooled analysis.

In general, prior to any pooling of efficacy data, Nef-202 endpoints were derived and re-analysed to correspond to the Nef-301 approach.

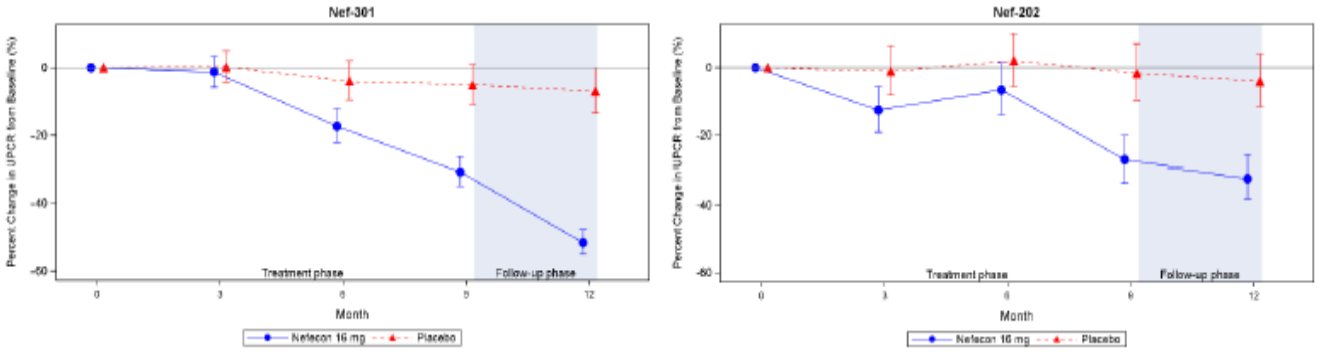
Pooled Nef-301 and Nef-202 efficacy results

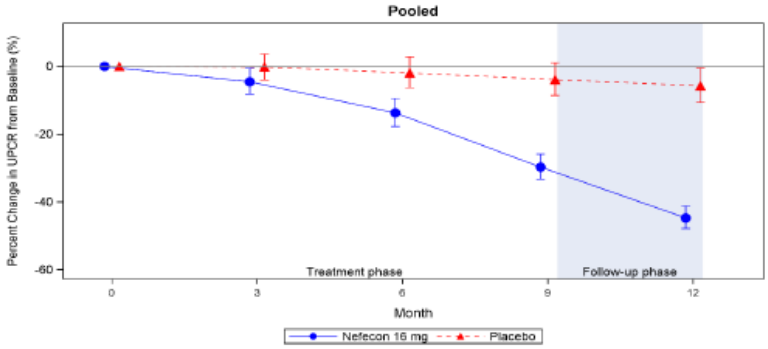
Table 36 Summary of UPCR analyses using MMRM at post-baseline visits across Nef-301, Nef-202, and the pooled datasets (full analysis set)

UPCR (g/gram)		Nef-301		Nef-202		Pooled	
		Nefecon 16 mg (N=97)	Placebo (N=102)	Nefecon 16 mg (N=48)	Placebo (N=50)	Nefecon 16 mg (N=145)	Placebo (N=152)
3 months	n	93	98	45	50	138	148
	Geometric LSmean change from baseline (95% CI)	0.99 (0.90 to 1.08)	1.00 (0.92 to 1.09)	0.87 (0.75 to 1.02)	0.99 (0.85 to 1.15)	0.96 (0.88 to 1.03)	1.00 (0.92 to 1.08)
	Comparison with placebo: Ratio of geometric LSmeans (95% CI) and percentage change (95% CI)	0.99 (0.87 to 1.12) 1% (-12% to 13%)		0.88 (0.71 to 1.09) 12% (-9% to 29%)		0.96 (0.86 to 1.07) 4% (-7% to 14%)	
	1-sided p-value	0.4129		0.1261		0.2170	
6 months	n	90	94	42	49	132	143
	Geometric LSmean change from baseline (95% CI)	0.83 (0.74 to 0.93)	0.96 (0.85 to 1.08)	0.93 (0.80 to 1.10)	1.02 (0.88 to 1.19)	0.86 (0.79 to 0.95)	0.98 (0.90 to 1.08)
	Comparison with placebo: Ratio of geometric LSmeans (95% CI) and percentage change (95% CI)	0.86 (0.73 to 1.02) 14% (-2% to 27%)		0.92 (0.73 to 1.14) 8% (-14% to 27%)		0.88 (0.77 to 1.01) 12% (-1% to 23%)	
	1-sided p-value	0.0398		0.2196		0.0303	
9 months Primary analysis timepoint	n	89	90	36	44	125	134
	Geometric LSmean change from baseline (95% CI)	0.69 (0.61 to 0.78)	0.95 (0.84 to 1.07)	0.73 (0.61 to 0.88)	0.98 (0.83 to 1.16)	0.70 (0.63 to 0.78)	0.96 (0.87 to 1.06)
	Comparison with placebo: Ratio of geometric LSmeans (95% CI) and percentage change (95% CI)	0.73 (0.61 to 0.87) 27% (13% to 39%)		0.74 (0.58 to 0.95) 26% (5% to 42%)		0.73 (0.64 to 0.85) 27% (15% to 36%)	
	1-sided p-value	0.0003		0.0100		<0.0001	
12 months	n	59	66	32	44	91	110
	Geometric LSmean change from baseline (95% CI)	0.48 (0.42 to 0.56)	0.93 (0.81 to 1.07)	0.68 (0.56 to 0.81)	0.96 (0.82 to 1.12)	0.55 (0.49 to 0.62)	0.94 (0.85 to 1.05)
	Comparison with placebo: Ratio of geometric LSmeans (95% CI) and percentage change (95% CI)	0.52 (0.42 to 0.64) 48% (36% to 58%)		0.71 (0.55 to 0.90) 29% (10% to 45%)		0.59 (0.51 to 0.69) 41% (31% to 49%)	
	1-sided p-value	<0.0001		0.0027		<0.0001	

Source: Supportive Tables and Figures for SCE Table 2.7.3.1.3 and Table 2.7.3.3.1.

CI confidence interval; LSmean least squares mean; MMRM mixed model repeated measures; n number of patients with a valid observed UPCR result at each timepoint for analysis - in all analyses missing data were multiply imputed, either implicitly or explicitly, prior to analysis; UPCR urine protein creatinine ratio. Corresponding percentage change and 95% CI is derived from (1-ratio of geometric LSmeans)×100.





Source: Supportive Tables and Figures for SCE Figure 2.7.3.3.1.
Estimated mean percentage change +/- standard error in UPCR estimated from MMRM analysis of log-transformed post-baseline to baseline ratios at 3, 6, 9, and 12 months. Baseline defined as the geometric mean of the 2 consecutive measurements prior to randomization.

Figure 18 Pooled Nef-301 and Nef-202 estimated percentage change in UPCR compared to baseline (full analysis set)

Table 37 Summary of eGFR analyses using robust regression at post-baseline visits across Nef-301, Nef-202, and the pooled datasets (full analysis set)

eGFR CKD-EPI (mL/min/1.73 m²)		Nef-301		Nef-202		Pooled	
		Nefecon 16 mg (N=97)	Placebo (N=102)	Nefecon 16 mg (N=48)	Placebo (N=50)	Nefecon 16 mg (N=145)	Placebo (N=152)
3 months	n	92	100	45	49	137	149
	Geometric LSmean change from baseline (95% CI)	1.05 (1.02 to 1.07)	0.98 (0.95 to 1.00)	0.99 (0.96 to 1.02)	0.96 (0.93 to 0.99)	1.02 (1.00 to 1.04)	0.97 (0.95 to 0.99)
	Absolute change (mL/min/1.73 m²)	2.54	-1.19	-0.95	-2.78	1.21	-1.79
	Comparison with placebo: Ratio of geometric LSmeans (95% CI) and percentage change (95% CI)	1.07 (1.03 to 1.11) 7% (3% to 11%)		1.03 (0.98 to 1.07) 3% (-2% to 7%)		1.05 (1.02 to 1.08) 5% (2% to 8%)	
	1-sided p-value	0.0003		0.1212		0.0004	
	Difference versus placebo in absolute change (mL/min/1.73 m²)	3.73		1.82		3.01	
6 months	n	89	95	41	48	130	143
	Geometric LSmean change from baseline (95% CI)	1.02 (0.99 to 1.06)	0.95 (0.92 to 0.98)	0.99 (0.95 to 1.03)	0.95 (0.92 to 0.98)	1.01 (0.99 to 1.04)	0.95 (0.93 to 0.97)
	Absolute change (mL/min/1.73 m²)	1.24	-2.81	-0.66	-3.95	0.63	-3.26
	Comparison with placebo: Ratio of geometric LSmeans (95% CI) and percentage change (95% CI)	1.08 (1.03 to 1.12) 8% (3% to 12%)		1.05 (0.99 to 1.10) 5% (-1% to 10%)		1.06 (1.03 to 1.10) 6% (3% to 10%)	
	1-sided p-value	0.0005		0.0427		0.0001	

eGFR CKD-EPI (mL/min/1.73 m²)		Nef-301		Nef-202		Pooled	
		Nefecon 16 mg (N=97)	Placebo (N=102)	Nefecon 16 mg (N=48)	Placebo (N=50)	Nefecon 16 mg (N=145)	Placebo (N=152)
	Difference versus placebo in absolute change (mL/min/1.73 m²)	4.05		3.30		3.89	
9 months Primary analysis timepoint	n	91	91	37	43	128	134
	Geometric LSmean change from baseline (95% CI)	1.00 (0.96 to 1.03)	0.93 (0.90 to 0.96)	0.99 (0.95 to 1.03)	0.94 (0.91 to 0.97)	0.99 (0.97 to 1.02)	0.93 (0.91 to 0.96)
	Absolute change (mL/min/1.73 m²)	-0.17	-4.04	-0.92	-4.49	-0.46	-4.21
	Comparison with placebo: Ratio of geometric LSmeans (95% CI) and percentage change (95% CI)	1.07 (1.03 to 1.13) 7% (3% to 13%)		1.05 (1.00 to 1.11) 5% (0% to 11%)		1.06 (1.03 to 1.10) 6% (3% to 10%)	
	1-sided p-value	0.0014		0.0271		0.0002	
	Difference versus placebo in absolute change (mL/min/1.73 m²)	3.87		3.57		3.75	
12 months	n	58	67	34	44	92	111
	Geometric LSmean change from baseline (95% CI)	0.97 (0.93 to 1.01)	0.91 (0.88 to 0.95)	0.99 (0.94 to 1.04)	0.93 (0.89 to 0.97)	0.98 (0.95 to 1.01)	0.92 (0.89 to 0.94)
	Absolute change (mL/min/1.73 m²)	-1.47	-5.03	-0.77	-5.24	-1.21	-5.15
	Comparison with placebo: Ratio of geometric LSmeans (95% CI) and percentage change (95% CI)	1.07 (1.01 to 1.13) 7% (1% to 13%)		1.07 (1.00 to 1.14) 7% (0% to 14%)		1.07 (1.02 to 1.11) 7% (2% to 11%)	
	1-sided p-value	0.0106		0.0256		0.0012	

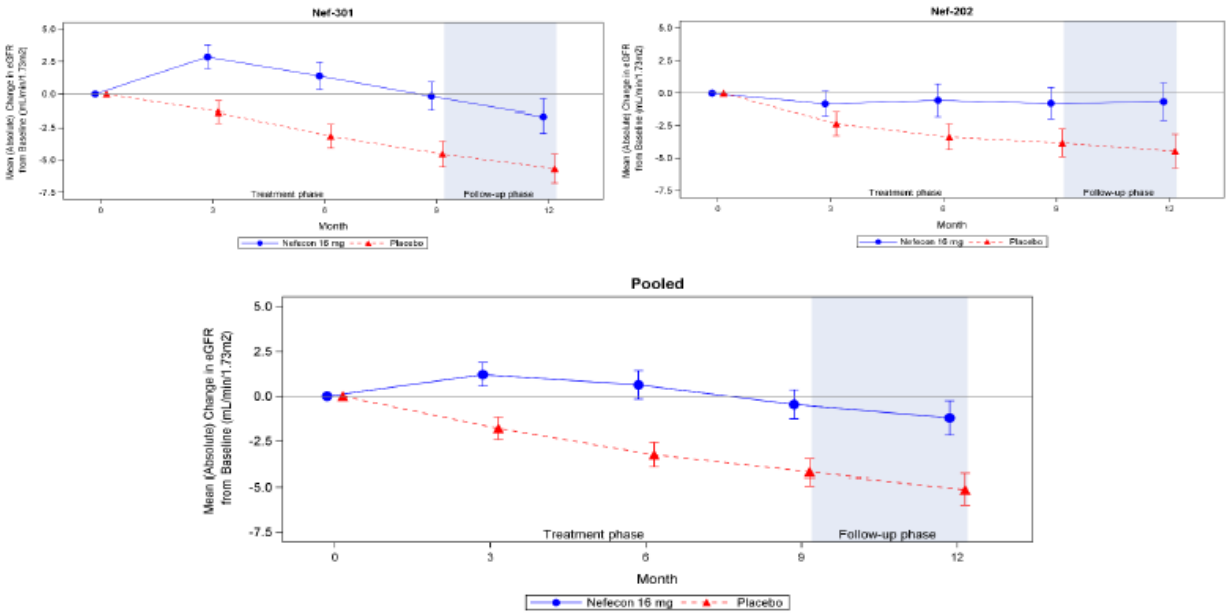
eGFR CKD-EPI (mL/min/1.73 m²)		Nef-301		Nef-202		Pooled	
		Nefecon 16 mg (N=97)	Placebo (N=102)	Nefecon 16 mg (N=48)	Placebo (N=50)	Nefecon 16 mg (N=145)	Placebo (N=152)
	Difference versus placebo in absolute change (mL/min/1.73 m²)	3.56		4.46		3.94	

Source: Supportive Tables and Figures for SCE Table 2.7.3.1.4 and Table 2.7.3.3.3.
CI confidence interval; LSmean least squares mean; n number of patients with a valid observed eGFR result at each timepoint for analysis - in all analyses missing data were multiply imputed, either implicitly or explicitly, prior to analysis; eGFR CKD-EPI estimated glomerular filtration rate estimated by Chronic Kidney Disease Epidemiology Collaboration calculation. Corresponding percentage change and 95% CI is derived from (ratio of geometric LSmeans-1)×100. The absolute change in eGFR is also derived directly from the robust regression model.

Table 38 Supportive analysis of 1-year eGFR slope across Nef-301, Nef-202, and the pooled datasets (full analysis set)

eGFR CKD-EPI (mL/min/1.73 m²)		Nef-301		Nef-202		Pooled	
		Nefecon 16 mg (N=97)	Placebo (N=102)	Nefecon 16 mg (N=48)	Placebo (N=50)	Nefecon 16 mg (N=145)	Placebo (N=152)
1-year slope	LS Mean slope (primary analysis)	-1.26	-4.63	0.61	-5.08	-0.70	-4.81
	Difference versus Placebo (95% CI)	3.37 (0.49 to 6.25)		5.69 (2.24 to 9.14)		4.11 (1.92 to 6.31)	
	p-value	0.0111		0.0007		0.0001	
	LS Mean slope (sensitivity analysis [a])	-0.11	-4.28	-1.87	-4.08	-0.73	-4.18
	Difference versus Placebo (95% CI)	4.17 (1.60 to 6.73)		2.20 (-1.74 to 6.15)		3.45 (1.33 to 5.57)	
	p-value	0.0007		0.1364		0.0007	

Source: Supportive Tables and Figures for SCE Table 2.7.3.3.7 and Table 2.7.3.3.8.
[a] In the sensitivity analysis each patient's slope was estimated from a separate linear regression fitted to each patient, with the resultant slope data compared between treatment groups using robust regression.



Source: Supportive Tables and Figures for SCE Figure 2.7.3.3.2b.
Estimated mean absolute change +/- standard error in eGFR estimated using robust regression analysis of log-transformed post-baseline to baseline ratios at 3, 6, 9, and 12 months and back-transformed to absolute changes. Estimated absolute change from baseline = baseline geometric mean for total × (geometric LS mean of Month X value / baseline value for each treatment arm - 1). Baseline defined as the geometric mean of the 2 consecutive measurements prior to randomization.

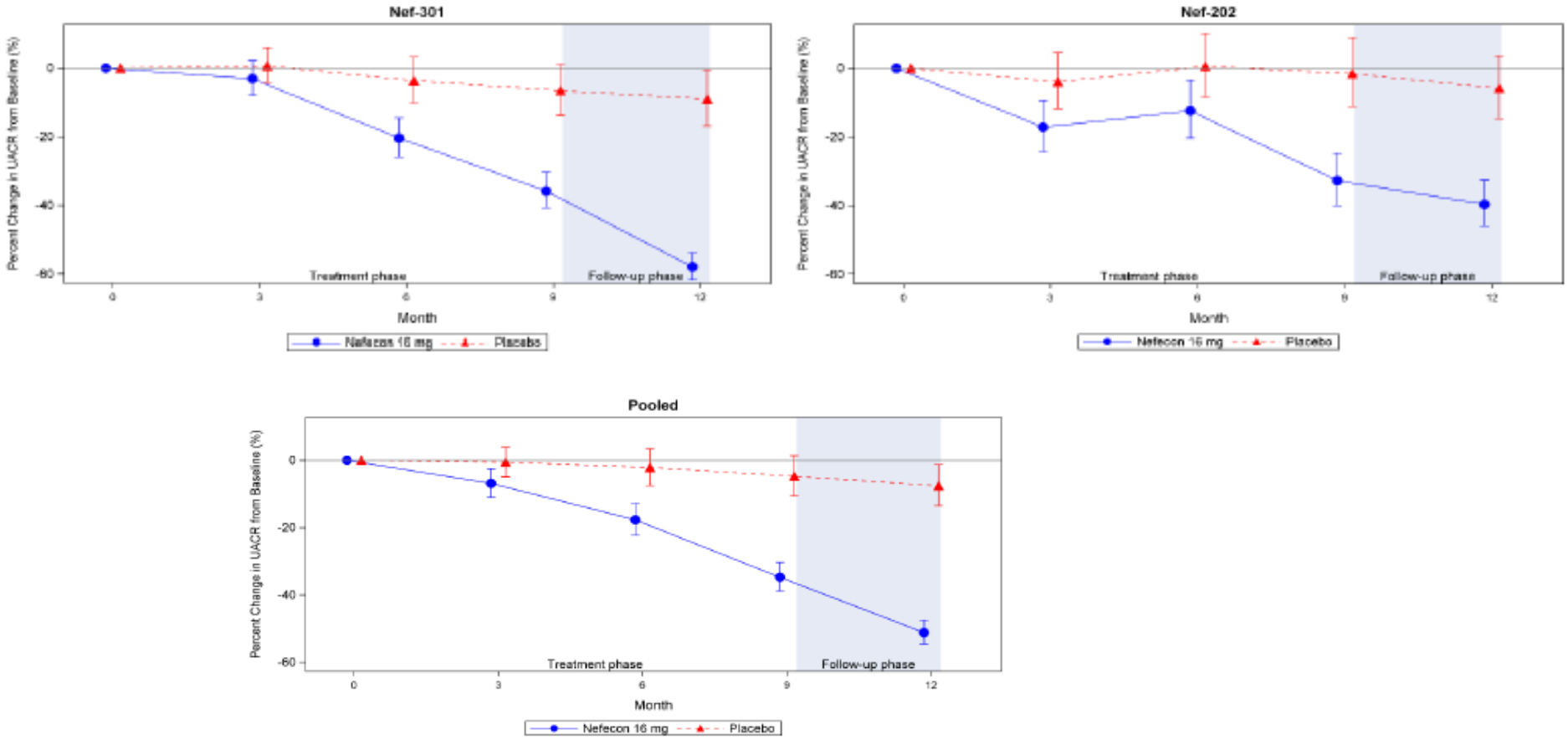
Figure 19 Pooled Nef-301 and Nef-202 absolute change in eGFR (ml/min/1.73m2) compared to baseline (full analysis set)

Table 39 Summary of UACR analyses using MMRM at post-baseline visits across Nef-301, Nef-202, and the pooled datasets (full analysis set)

UACR (g/gram)		Nef-301		Nef-202		Pooled	
		Nefecon 16 mg (N=97)	Placebo (N=102)	Nefecon 16 mg (N=48)	Placebo (N=50)	Nefecon 16 mg (N=145)	Placebo (N=152)
3 months	N	93	98	44	50	137	148
	Geometric LSmean change from baseline (95% CI)	0.97 (0.87 to 1.08)	1.01 (0.91 to 1.11)	0.83 (0.69 to 0.99)	0.96 (0.81 to 1.14)	0.93 (0.85 to 1.02)	0.99 (0.91 to 1.08)
	Comparison with placebo: Ratio of geometric LSmeans (95% CI) and percentage change (95% CI)	0.96 (0.83 to 1.11) 4% (-11% to 17%)		0.86 (0.67 to 1.10) 14% (-10% to 33%)		0.94 (0.83 to 1.06) 6% (-6% to 17%)	
	1-sided p-value	0.3068		0.1175		0.1485	
6 months	n	89	94	42	49	131	143
	Geometric LSmean change from baseline (95% CI)	0.80 (0.69 to 0.92)	0.96 (0.84 to 1.10)	0.88 (0.72 to 1.06)	1.00 (0.84 to 1.20)	0.82 (0.74 to 0.92)	0.98 (0.88 to 1.09)
	Comparison with placebo: Ratio of geometric LSmeans (95% CI) and percentage change (95% CI)	0.83 (0.68 to 1.01) 17% (-1% to 32%)		0.87 (0.67 to 1.14) 13% (-14% to 33%)		0.84 (0.72 to 0.99) 16% (1% to 28%)	
	1-sided p-value	0.0288		0.1543		0.0161	
9 months Primary analysis timepoint	n	90	91	36	44	126	135
	Geometric LSmean change from baseline (95% CI)	0.64 (0.55 to 0.75)	0.93 (0.80 to 1.09)	0.67 (0.54 to 0.84)	0.98 (0.80 to 1.21)	0.65 (0.57 to 0.74)	0.95 (0.84 to 1.08)
	Comparison with placebo: Ratio of geometric LSmeans (95% CI) and percentage change (95% CI)	0.69 (0.55 to 0.86) 31% (14% to 45%)		0.68 (0.51 to 0.93) 32% (7% to 49%)		0.69 (0.57 to 0.82) 31% (18% to 43%)	
	1-sided p-value	0.0005		0.0072		<0.0001	
12 months	n	60	65	32	44	92	109
	Geometric LSmean change from baseline (95% CI)	0.42 (0.35 to 0.51)	0.91 (0.76 to 1.09)	0.60 (0.48 to 0.75)	0.94 (0.78 to 1.14)	0.49 (0.42 to 0.56)	0.92 (0.81 to 1.05)
	Comparison with placebo: Ratio of geometric LSmeans (95% CI) and percentage change (95% CI)	0.46 (0.36 to 0.60) 54% (40% to 64%)		0.64 (0.48 to 0.86) 36% (14% to 52%)		0.53 (0.44 to 0.65) 47% (35% to 56%)	
	1-sided p-value	<0.0001		0.0016		<0.0001	

Source: Supportive Tables and Figures for SCE Table 2.7.3.1.5 and 2.7.3.3.5.

CI confidence interval; LSmean least squares mean; MMRM mixed model repeated measures; n number of patients with a valid observed UACR result at each timepoint for analysis - in all analyses missing data were multiply imputed, either implicitly or explicitly, prior to analysis; UACR urine albumin creatinine ratio. Corresponding percentage change and 95% CI is derived from (1-ratio of geometric LSmeans)×100.



Source: Supportive Tables and Figures for SCE Figure 2.7.3.3.3.
Estimated mean percentage change +/- standard error in UACR estimated from MMRM analysis of log-transformed post-baseline to baseline ratios at 3, 6, 9, and 12 months. Baseline defined as the geometric mean of the 2 consecutive measurements prior to randomization.

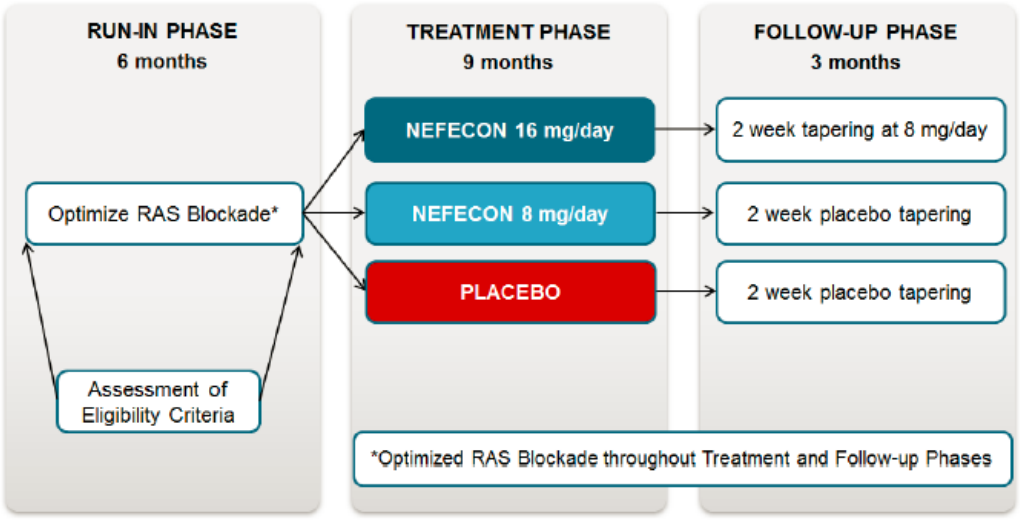
Figure 20 Pooled Nef-301 and Nef-202 estimated percentage change in UACR compared to baseline (full analysis set)

2.4.5.5. Supportive study

Supportive Phase 2b Nef-202 study: a multicentre, interventional treatment, randomised, double-blind, single group assignment, placebo-controlled study to evaluate the efficacy and safety of two different doses of Kinpeygo in primary IgA nephropathy patients at risk of developing end-stage renal disease.

Study period: first patient first visit: 11 December 2012; last patient last visit: 25 June 2015

The trial consisted of 3 phases: a 6-month run-in phase, a 9-month treatment phase and a 3-month follow-up phase, as outlined below. A schematic representation of the Nef-202 study is presented in figure below.



RAS: renin-angiotensin system.

Figure 21 Trial flow chart

Endpoints

Primary Efficacy Endpoint

- The primary endpoint was the mean reduction in UPCR at 9 months compared to baseline UPCR values. The mean reduction was measured as a ratio of UPCR at 9 months compared to baseline

Secondary Efficacy Endpoints

- Mean change in urine protein, urine albumin creatinine ratio (UACR) and urine albumin from baseline at Month 9
- Mean change in UPCR, urine protein, UACR and urine albumin from 9 to 12 months
- Mean change in serum creatinine, chronic kidney disease epidemiology collaboration equation (CKD-EPI) estimated GFR (eGFR), modification of diet in renal disease (MDRD) study equation eGFR [24, 25] and creatinine clearance from baseline at 9 months

Tertiary Efficacy Endpoints

- Achieving defined reductions (≥30%, ≥40%, ≥50%) in UPCR, urine protein, UACR and urine albumin at Month 9 compared to baseline
- Mean change in UPCR, urine protein, UACR and urine albumin from baseline at 1, 3, 6, 10.5 and 12 months
- Mean change in CKD-EPI from baseline at 1, 3, 6, 10.5, and 12 months
- Mean change in cystatin C-based eGFR from baseline at Month 9
- Proportion of patients with microhaematuria at Months 9 and 12

Efficacy Results

Primary endpoint

UPCR reduction from 9 months to baseline:

Following rejection of the null hypothesis versus UPCR at the interim, the follow-up of all randomised patients continued to 9 months and a full analysis was performed.

Geometric LSmean UPCR was reduced by approximately 20% from baseline (LSmean: 0.799) for Kinpeygo (16+8 mg/day combined) at 9 months based on the estimated back transformed LSmean from the model.

Table 40 Comparison of UPCR change from baseline at 9 months (full analysis set; final analysis)

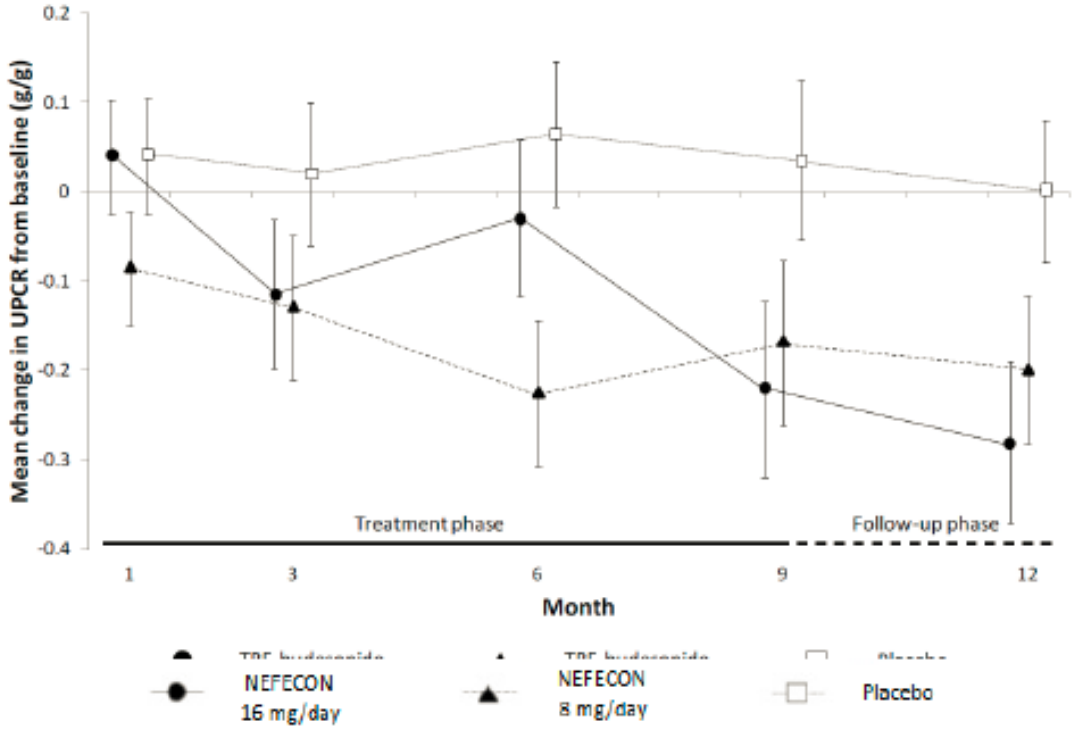
Treatment	n	Geometric LSmean (95% CI)	Comparison versus Placebo	
			Geometric LSmean (95% CI)	p-value
NEFECON (16+8 mg/day)	74	0.799 (0.694, 0.918)	0.768 (0.621, 0.951)	NA
Placebo	44	1.040 (0.870, 1.242)	NA	NA
NEFECON (16 mg/day)	34	0.746 (0.614, 0.907)	0.717 (0.556, 0.924)	NA
NEFECON (8 mg/day)	40	0.847 (0.705, 1.018)	0.813 (0.637, 1.039)	NA

Source Data: Table E1.1.1 and Table E2.1.1.
CI=confidence interval; LSmean=least squares mean; NA=not applicable; UPCR=urine protein creatinine ratio.

Secondary and tertiary endpoints

- Urine Protein Creatinine Ratio:

Reduction in UPCR at 9 months versus baseline showed Kinpeygo had a consistent effect on the relative change in UPCR.



The solid line shows the mean changes over the 9-month treatment phase and the dashed line the 3-month follow-up phase. Data are expressed as mean ± standard error of the mean.

Figure 22 Mean (absolute) change in UPCR from baseline

Mean UPCR further decreased from 9 to 12 months in all 3 treatment groups.

Table 41 Treatment comparison of urine protein creatinine ratio relative change from 9 to 12 months (full analysis set)

		NEFECON (16 mg/day)	NEFECON (8 mg/day)	Placebo
Change from 9 to 12 months	n	32	40	44
	Geometric LSmean (95% CI)	0.915 (0.767, 1.091)	0.959 (0.812, 1.132)	1.045 (0.894, 1.222)
Comparison vs. Placebo	Geometric LSmean (95% CI)	0.875[a] (0.695, 1.102)	0.917[b] (0.738, 1.140)	NA
	p-value	0.1267	0.2159	NA

Source Data: Table E9.1.1.

a. Comparison of NEFECON 16 mg/day vs. placebo.

b. Comparison of NEFECON 8 mg/day vs. placebo.

LSmean=least squares mean; CI=confidence interval; NA=not applicable.

- Estimated Glomerular Filtration Rate:

Mean eGFR CKD-EPI (serum creatinine) remained stable from baseline at 9 months in the Kinpeyo (=Nefecon) groups and decreased in the placebo group. All differences between Kinpeygo groups and placebo were statistically significant.

Table 42 Treatment comparison of eGFR CKD-EPI (creatinine) change from baseline at month 9 (full analysis set)

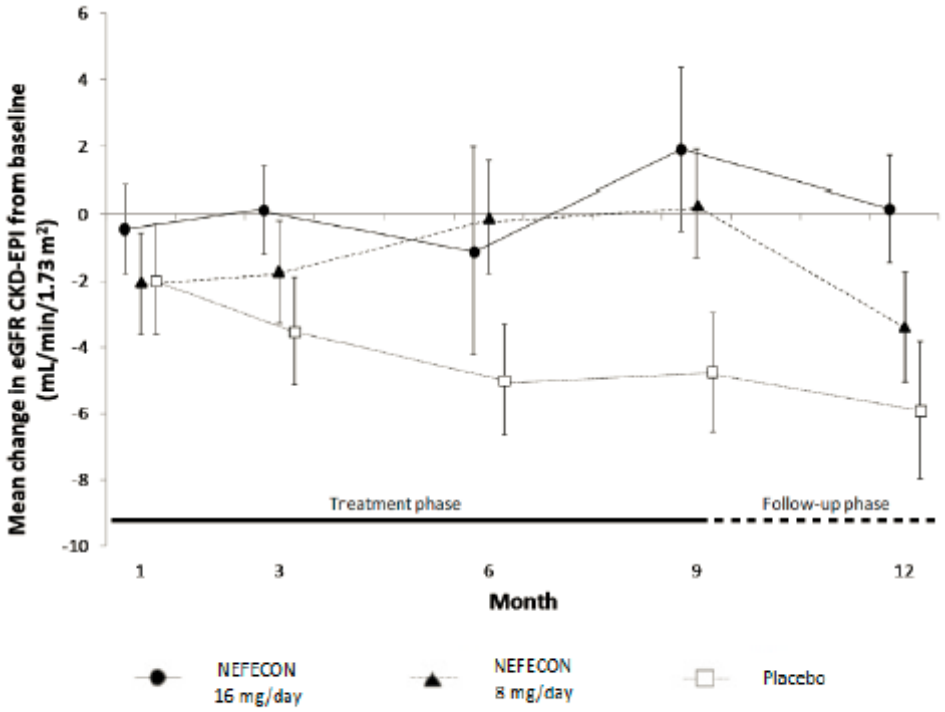
		NEFECON (16 mg/day)	NEFECON (8 mg/day)	Placebo
Change from Baseline at Month 9	n	34	41	42
	Geometric LSmean (95% CI)	1.006 (0.946, 1.070)	0.991 (0.934, 1.052)	0.902 (0.850, 0.956)
Comparison with Placebo	Geometric LSmean (95% CI)	1.116[a] (1.034, 1.205)	1.099[b] (1.021, 1.184)	NA
	p-value	0.0026	0.0064	NA

Source Data: Table E2.6.1.

a. Comparison of NEFECON 16 mg/day vs. placebo.

b. Comparison of NEFECON 8 mg/day vs. placebo.

LSmean=least squares mean; CI=confidence interval; NA=not applicable.



The solid line shows the mean changes over the 9-month treatment phase and the dashed line the 3-month follow-up phase. Data are expressed as mean ± standard error of the mean.

Figure 23 Mean (absolute) change in eGFR (CKD-EPI) from baseline

- Microhaematuria:

The percentage of patients with microhaematuria at 9 months was lower 53 (73.6%) in the Kinpeygo treatment groups than in the placebo group (37 [86.1%]). Results were similar at 12 months with 51 (70.8%) in the Kinpeygo treatment groups and 34 (82.9%) in the placebo group.

Table 43 Treatment comparison of microhaematuria proportion at Month 9 and Month 12 (FAS)

Month			NEFECON (16 mg/day)	NEFECON (8 mg/day)	Placebo
9	Microhaematuria Proportion	n	33	39	43
		n (%) of patients with haematuria	21 (63.64)	32 (82.05)	37 (86.05)
		Estimate (95% CI)	0.712 (–0.341, 1.766)	1.845 (0.724, 2.966)	2.224 (1.060, 3.388)
	Comparison with Placebo	Odds ratio (95% CI)	0.221 (0.072, 0.675)	0.684 (0.213, 2.195)	NA
		p-value	0.0041	0.2613	NA
12	Microhaematuria Proportion	n	34	38	41
		n (%) of patients with haematuria	24 (70.59)	27 (71.05)	34 (82.93)
		Estimate (95% CI)	0.899 (–0.121, 1.920)	1.204 (0.195, 2.212)	1.894 (0.811, 2.977)
	Comparison with Placebo	Odds ratio (95% CI)	0.370 (0.122, 1.126)	0.501 (0.170, 1.481)	NA
		p-value	0.0399	0.1056	NA

Source Data: Table E17.1 and Table E20.1.
a. Comparison of NEFECON 16 mg/day vs. placebo.
b. Comparison of NEFECON 8 mg/day vs. placebo.
CI=confidence interval; NA=not applicable.

Exploratory Nef-201 study

In addition, the applicant provided results derived from the exploratory study Nef-201, which was an open-label, un-controlled proof-of-concept study conducted at three clinical centres.

A total of 16 patients (10 men and 6 women, aged 29 to 46 years) were included.

The primary objective was to investigate the effect of Kinpeygo on albumin leakage and the secondary objectives were to investigate the effect of Kinpeygo on GFR in patients with IgA nephropathy as well as to study the safety of treatment with Kinpeygo.

The median relative reduction in urinary albumin excretion was -23% at six months of treatment (interquartile range: -0.36, -0.04; p=0.04). and -40% (interquartile range: -0.58, -0.15) two months after treatment discontinuation. Serum creatinine was reduced by 6% (interquartile range: -0.12, -0.02; p=0.003), and GFR (MDRD) increased approximately 8% (interquartile range: 0.02, 0.16; p=0.003) at six months of treatment.

These results show that the beneficial outcome on renal function as assessed by urine albumin excretion was maintained for at least two months posttreatment and are therefore indicative of a disease-modifying effect of Kinpeygo treatment in IgAN patients.

2.4.6. Discussion on clinical efficacy

Efficacy of Kinpeygo was investigated in two clinical studies: the pivotal phase 3 clinical trial Nef-301 and the supportive phase 2b study Nef-202.

Design and conduct of clinical studies

The supportive phase 2b study (Nef-202) was a randomised, double-blind, placebo-controlled study to evaluate the efficacy and safety of two different doses (16 vs 8 mg/d) of Kinpeygo in primary IgAN patients at risk of developing ESRD. In the final analysis set n = 149 patients were included (n=48 Kinpeygo 16mg/d; n=51 Kinpeygo 8mg/d; n = 50 placebo). The demographic and disease baseline characteristics of all study participants were well balanced, and as primary endpoint of this study, the mean reduction in UPCR at 9 months compared to baseline UPCR values has been evaluated

(measured as a ratio of UPCR at 9 months compared to baseline).

The pivotal phase 3 study (Nef-301) was 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. Only data from Part A (1 year treatment) have been submitted. Part B, a 12-month observational follow up period after treatment in Part A, is currently ongoing. The study included female and male patients ≥18 years of age with biopsy-verified primary IgAN, persistent proteinuria of ≥1 g/d and an eGFR of ≥35 mL/min per 1,73m^2 and ≤90 ml/min per 1,73m^2 using the CKD-EPI formula. The recruited population for the phase 3 trial Nef-301 is generally deemed acceptable.

The Part A FAS included data from 199 patients: 97 patients in the Kinpeygo 16 mg group and 102 patients in the placebo group. Subjects from the study group have been treated for 9 months with 16 mg Kinpeygo per day, which corresponds to 4 capsules at 4 mg budesonide. In order to prevent adrenal insufficiency, subjects were treated with 8 mg Kinpeygo for 2 weeks, before the observational Part B of the study has started. Based on the outcome of a previous Scientific advice, subjects not tolerating the full dose of 16 mg/d due to adverse events (AEs) were treated with only 8 mg (2 capsules) per day and continued after Part A for these 2 weeks also with the dose of 8 mg daily. Matching treatment in the placebo group has been performed accordingly.

In Part A, proteinuria, more specifically the ratio of UPCR (based on 24 hour urine collections) at 9 months following the first dose of study drug compared to baseline, was used as a single primary efficacy endpoint. There was intensive discussion about considering proteinuria as a robust primary surrogate endpoint as part of several Scientific Advices, therefore, the applicant followed the recommendation of the CHMP (EMEA/H/SA/2293/2/2017/PA/SME/III) and additionally provided a 1-year eGFR slope analysis from Part A as secondary endpoint.

In Part B of the pivotal trial, the AUC-based evaluation of eGFR over 2 years has been selected as a primary efficacy endpoint supplemented by a 2-year eGFR 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.

Statistical methods for efficacy analyses are generally appropriate to estimate the short-term (9/12 months) effects on UPCR and eGFR. The primary estimand (particularly the hypothetical strategy to address rescue medication) and estimation (missing at random assumption) can be questioned but are addressed in sensitivity analyses.

The 1-year eGFR was estimated *via* a robust regression model, which seems difficult to interpret and is seen critical due to possible down-weighting of subjects with "extreme" changes. The applicant was thus asked to estimate the 1-year changes from baseline using an MMRM model as for the primary endpoint considering an appropriate estimand and missing data handling. The evidence provided by the applicant on the adequacy of UPCR as a surrogate endpoint for renal function is generally considered appropriate, but the prediction of clinically relevant (long-term) outcomes reflecting renal change is seen critical due to the unclear treatment concept and uncertainties associated with the short-term treatment effect estimates (see further discussions on long-term clinical benefit).

During the conduct of the study, several protocol amendments were made. Two of those changes might be of clinical relevance, which allowed for the recruitment of sicker patients. The applicant responded that the adjustment in biopsy verification requirements and the inclusion of patients with lower baseline eGFR have not had a bearing on the overall results, and had these criteria been in place from the beginning of the study the results would remain unaltered. The pre-defined treatment period of 9 months is applicable to all patients in the trial, including those with more advanced disease.

Whether any particular subgroups of patients may benefit from an extended treatment period cannot be answered from the Nef-301 trial. This acceptable and it is not considered that this would have an impact on the integrity of the data.

Efficacy data and additional analyses

Supportive phase 2b study (Nef-202)

Upon 9 months treatment with Kinpeygo (16+8 mg/d, combined data) the UPCR was reduced approximately by 20% from baseline (LSmean 0.799; 8 mg/d: LSmean 0.847; 16 mg/d: 0.746) and additional minor decrease could be observed within the 3 months follow-up-phase (9 to 12 months) without further treatment. However, while the inclusion of a tapering phase during the 9 months of treatment within Part A allowing for dose reduction from 16 to 8 mg/d in case of arising safety issues is fully acknowledged, only borderline differences between the 16 mg/d and 8mg/d dosing regimen could be observed in any of the markers analysed. In a Scientific Advice, the selection of the dose of 16 mg for the pivotal clinical trial has been seen critical due to the lack of evidence provided by some interim analyses. However, it is acknowledged that the 16 mg dose has been used for the pivotal phase 3 trial, and since dose reduction was rare in the pivotal study and AEs were generally manageable, it was agreed not to include any guidance for dose reduction in the Kinpeygo SmPC.

Pivotal phase 3 study (Nef-301)

The efficacy data from Part A show that the ratio of UPCR at 9 months to baseline was 0.69 in the Kinpeygo treatment arm and 0.95 in the placebo arm (CI 95%). This means a reduction of proteinuria (UPCR) of 31 % for Kinpeygo and 5 % for placebo during a treatment course of 9 months. The ratio of geometric LS means comparing Kinpeygo/placebo was 0.73 (27%, p 0.0003). 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.

The secondary efficacy analysis was about to determine (1) the ratio of eGFR at 9 and 12 months compared to baseline as well as (2) the ratio of UACR at 9 months compared to baseline. The ratio of geometric mean eGFR at 9 months compared to baseline showed a change of the eGFR of 0% in the Kinpeygo arm and a -7% change in the placebo arm. Comparing Kinpeygo versus placebo revealed a ratio of mean eGFR of 1.07 (= 7% more reduction of eGFR in the placebo arm). In contrast to proteinuria (primary endpoint), this effect was not pronounced after 12 months, which is not surprising because 1 year treatment/observation phase, especially under continues RAS treatment, is probably too short to see any effect at the level of eGFR. Additionally, the ratio of UACR at 9 months compared to baseline has been evaluated using MMRM analysis for Part A data. This ratio was 0.64 (= 36 % reduction) for the Kinpeygo arm and 0.93 (= 7% reduction) for the placebo arm following a very similar kinetics (3 -12 months) as shown for UPCR ratios (primary endpoint). Correspondingly, also the number of patients without microhematuria was higher at 9 months compared to baseline in the Kinpeygo treatment arm (Kinpeygo: from 38.1 to 63.9% versus placebo: from 31.4 to 37.3%).

While acknowledging the robustness of the 9-month treatment effect on UPCR, it was unclear why the treatment difference gets even larger at 12 month and why the phase 3 results are not consistent with those observed in the phase 2 study (Nef-202). The (mean) eGRF values differ even more between studies. There is a peculiar (mean) increase of eGRF after 3 months treatment in Nef-301, and thereafter the eGFR decrease appears to be similar in the two arms. In the Nef-202 study the (mean) decrease in both arms appears linear and the slopes differ. These data raised questions about the ability of the drug to slow the rate of loss of kidney function and have a meaningful effect on

progression to kidney failure. The applicant was asked to discuss the observed increase of eGFR at 3 months in study Nef-301 and respective differences to the phase 2 data.

According to the applicant the observed increase of eGFR at 3 months in Nef-301 is considered most likely due to a direct anti-inflammatory effect on the kidney, as a consequence of low-level systemic exposure to budesonide.

The applicant further pointed out that eGFR deteriorates more rapidly in patients with higher baseline levels of proteinuria and that the early acute increase in eGFR observed in the overall Nef-301 population is reflected in a stabilisation of eGFR with Kinpeygo treatment relative to the more immediate deterioration of eGFR for placebo-treated patients with high baseline proteinuria.

Regarding the difference in the eGFR curves between Nef-301 and Nef-202 the applicant argued, that a lower rate of eGFR decline in the placebo arm of Nef-301 (compared to Nef-202) for patients with UPCR<1.5 g/gram may have contributed to the difference between studies. The applicant´s discussion can be followed and is acknowledged.

Since the applicant initially claimed approval of budesonide in a rather broad population of patients with IgAN, the applicant was requested to submit additional data to substantiate the use in a broad target population. In response, the applicant submitted additional pre-specified subgroup analyses of treatment effects on UPCR at 9 months and eGFR up to 1 year for the subgroups of patients with UPCR <1.5 g/g versus ≥1.5 g/g at baseline. UPCR sub-category (defined by <1.5 g/g versus ≥1.5 g/g) were consistent with the primary efficacy findings. In the subgroup analyses of UPCR at 9 months, there was no differential treatment effect on UPCR at 9 months according to baseline proteinuria or UPCR, in either the individual trials or the pooled analysis (Nef-202 and Nef-301). However, there was a statistically significant interaction for the eGFR treatment effect at 9 months according to baseline UPCR (p=0.0046) and baseline total proteinuria (p=0.0012) in the pooled analysis (Nef 202, Nef 301). The eGFR treatment effect was larger in patients with higher baseline levels of proteinuria, with similar patterns observed in the individual trials. The additional data provided for Kinpeygo in patients with a UPCR ≥1.5 g/g (a pre-specified subgroup) suggest evidence of relevant clinical benefit in terms of slowing the chronic rate of loss of renal function (eGFR), in patients with higher levels of UPCR at baseline. This subgroup was also noted to be at particular risk of rapid disease progression over a relatively short time period.

The applicant argued that in patients with lower levels of proteinuria at baseline, where significant improvement in proteinuria is observed later in the treatment course (at 9 and 12 months), increasing separation of the eGFR curves has not yet had time to occur. The applicant’s statement is acknowledged; however, this will need to be demonstrated when corresponding data are available from the ongoing phase 3 study (Nef-301).

Overall, uncertainties regarding the interpretability of the eGFR data persist in spite of additional analyses provided. The applicant’s confidence that the eGFR curves will continue to separate after treatment discontinuation is not yet shared. As stated by the applicant, there is no significant difference in treatment effect in terms of eGFR in the overall study population

Given the limited data on the efficacy and safety currently available for Kinpeygo, 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. Thus, a cut-off value for proteinuria was proposed in section 4.1 of the SmPC, i.e. a UPCR ≥ 1.5 g/gram.

Within the day 180 responses the applicant agreed to restrict the Kinpeygo indication at the time of this CMA but proposed a lower cut-off value with a UPCR ≥1.3 g/g. The argumentation put forward by the applicant was that the Kinpeygo treatment effect on the rate of loss of renal function estimated by the difference in 1-year chronic slope (from 3 months onwards) first becomes statistically significant at

a baseline UPCR threshold of 1.3 g/gram. The applicant further stated that the pre-specified level of 1.5g/gram was chosen arbitrarily and should therefore not be considered as a meaningful cut-off value. This is not considered a valid argument. The arbitrary selection of a threshold does not render it meaningless in the context of a confirmatory trial setting. Only patients with a baseline proteinuria of >1.5g/gram were a pre-specified subpopulation that showed a statistically significant treatment effect over placebo in eGFR. Therefore, this is the only cut-off value that could be considered for the restriction of the target population.

The CHMP recommended to restrict the indication to the treatment of primary IgAN in adults at risk of rapid disease progression with a UPCR ≥1.5 g/gram. This was accepted by the applicant.

Long term clinical benefit/Treatment concept

Overall, epidemiologic data indicate a strong and consistent relationship between the level and duration of proteinuria and loss of kidney function in patients with IgAN. However, since there are knowledge gaps regarding the minimal magnitude and duration of proteinuria reduction that confers to a protective effect, the applicant was asked to further justify the relevance of the clinical results. It is generally agreed with the applicant that the data provided so far from the Kinpeygo trials demonstrate statistically significant and clinically relevant treatment benefits for UPCR/UACR and, partly, for eGFR, which distinguishes the Kinpeygo results from STOP-IgAN trial that failed to show any treatment effect on eGFR (Lennartz DP et al.[37]).

It is acknowledged that the evidence presented suggest a high probability that UPCR could be considered a viable candidate for surrogacy in regard to long term clinical benefit. In addition, it is appreciated that the applicant has pointed out possible issues with the assumption of proportional hazard over the duration of the follow up period. However, there is only limited evidence that this is the case.

If this assumption does not hold, the estimates of the median time to clinical outcome cannot be considered reliable. So, while the modelling document provided in the initial MAA as well as the additional reasoning provided by the applicant is seen as favourable evidence for the efficacy of Kinpeygo, the suggested effect size of 35.0 years (95% CI 19.2 to 71.6 years) is not seen as sufficiently robust to support such a claim. From a regulatory perspective, UPCR is still not a validated endpoint for renal outcome and a positive benefit risk assessment cannot be made on the basis of a robust UPCR effect at 9 or 12 months alone. In fact, there is little evidence of renal benefit for the pre-specified subgroup of patients with lower levels of baseline proteinuria (cut-off value of <1.5 g/gram) based on the eGFR values. Thus, uncertainties regarding the interpretability of the surrogacy endpoint UPCR still persist.

Since it is assumed that based on the pathophysiology of IgAN and due to the fluctuations in disease severity, life-long treatment cycles with Kinpeygo might be required, and major concerns were raised about the intended treatment concept of Kinpeygo. Especially because in the pivotal phase 3 study (Nef-301), a single 9-months treatment period (Part A) was used, but no limitation in the length of treatment was initially proposed in section 4.2 of the SmPC. In its response the applicant clarified that Kinpeygo should be seen as a treatment that can potentially delay disease progression rather than cure patients and suggested specifying the duration of a treatment cycle, 9 months, in section 4.2 of the SmPC. This proposal is deemed acceptable. Treatment duration of 9 months at a 16 mg once daily dose is supported by the pivotal phase 3 study (Nef-301 Part A) and the phase 2b study Nef 202.

Dual RAS blockade

[37] Lennartz DP et al. Single versus dual blockade of the renin-angiotensin system in patients with IgA nephropathy. Journal of Nephrology. 2020 Dec;33(6):1231-1239.

In both studies Nef-301 and 202, patients were on optimised ACEI and/or ARB therapy prior to randomisation and throughout the treatment and follow-up periods. Of note, in study Nef-202, 22% received both an ACEI and an ARB. In study Nef-301, a considerably smaller subset was on dual RAS blocking therapy: 3 patients (3.1%) in the budesonide group and 7 patients (6.9%) in the placebo group. It is known that inhibition of the RAS system leads to reduction in blood pressure and reduces proteinuria in IgAN. However, evidence from clinical trials showed that dual RAS blockade is associated with adverse drug reactions like severe hypotension, hyperkaliaemia and renal failure (e. g. ONTARGET study[38]). In addition, a post-hoc analysis of the STOP-IgAN trial which investigated single versus dual RAS blockade on renal endpoints in IgAN showed higher proteinuria with dual blockade over the 3-year trial (Lennartz DP et al[37]). Hence, recent KDIGO guidelines do not support dual blockade and recommend therapy with either an ACEi or ARB "Recommendation 2.3.2. *We recommend that all patients with proteinuria >0.5 g/d, irrespective of whether they have hypertension, be treated with either an ACEi or ARB".*

Analyses submitted by the applicant investigating the small subgroup of patients in studies Nef-202 and Nef-301 who received dual blockade (ACEI plus ARB) did not hint at a worse benefit/risk profile compared to the overall study population. However, as evidence from literature indicates that dual RAS blockade is associated with adverse drug reactions like severe hypotension, hyperkaliaemia and renal failure, the applicant committed to provide a sensitivity analysis excluding patients who received background therapy with both an ACEI and an ARB with the results of the ongoing phase 3 study (Nef-301). As the latest KDIGO recommendations do not recommend dual blockade, it is expected that in the future no patients will be treated with both an ACEI and an ARB.

Additional efficacy data needed in the context of a conditional MA

Conditional approval is sought on the basis of proteinuria reduction, measured by UPCR, supported by 1-year eGFR data from the Part A of the pivotal phase 3 Nef-301 study.

As the basis for a proposed full approval the primary objective of Part B of the Nef-301 study is to assess the effect of Kinpeygo 16 mg on the clinical consequences of proteinuria reduction, as measured by eGFR recorded over 2 years compared to placebo. The primary efficacy endpoint for the Part B analysis is a time-weighted average of eGFR recordings observed at each time point over 2 years ($AUC_{(0-2)}$).

Additional analyses investigating the relationship of clinical outcome (e.g. time to first occurrence of a composite of death, ESKD, or a decline exceeding 40% in eGFR) and eGFR slope are expected for conversion of the conditional into a full Marketing Authorisation. In addition, the requested subgroup analysis excluding patients who received background therapy with both an ACEI and an ARB is expected to provide a cleared picture on renal clinical outcome events.

Therefore, in order to confirm the efficacy and safety of budesonide for the treatment of primary IgAN and more particularly to assess the clinical consequences of proteinuria reduction, as measured by eGFR, the applicant 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. This specific obligation is reflected in Annex II of the product information.

[38] Mann JFE et al. Renal outcomes with telmisartan, ramipril, or both, in people at high vascular risk (the ONTARGET study): a multicentre, randomised, double-blind, controlled trial. Lancet. 2008 Aug 16;372(9638):547-53.

2.4.7. Conclusions on clinical efficacy

While the primary endpoint UPCR is statistically significant in the overall study population, there is little evidence of renal benefit for the pre-specified subgroup of patients with lower levels of baseline proteinuria (cut-off value of <1.5 g/gram) based on the eGFR values provided. Therefore, a restriction of the target population in section 4.1 to patients with higher levels of baseline proteinuria (cut-off value of ⩾1.5 g/gram) is recommended.

2.4.8. Clinical safety

2.4.8.1. Patient exposure

The safety analysis set consists of 294 patients of which 150 have been treated with Kinpeygo and 144 with placebo with a cut-off date of 5th October 2020. The trial Nef-202 also contributes to the safety profile of Kinpeygo, where patients were treated with 8/16mg of Kinpeygo or placebo. The study included 3 phases: a 6-month run in phase, a 9-month treatment phase and a 3-month follow-up phase which included an initial 2-week tapering period. Besides these two main studies, several pharmacology studies were performed with healthy volunteers.

In the pivotal Nef-301, two populations are defined:

1. FAS Part A included the first 201 patients randomised, regardless of whether the patient received study drug (the primary population for evaluation of Part A efficacy). For the purposes of safety analyses in this population for the summary of clinical safety, only patients who received at least one dose of study treatment are included, with all safety summaries presented by treatment received. Only these patients will have had the opportunity to have received the intended 9 months of therapy.

2. SAS included all patients who receive at least 1 dose of study drug up to the data cut-off. Therefore, this population includes data from patients who have not yet completed the 9-month treatment phase. The population comprises 294 patients in total: 150 patients who received Kinpeygo 16 mg and 144 patients who received placebo.

Overall exposure in clinical studies

Table 44 Analysis sets by study and pooled safety datasets

	Number of patients						
	Nef-301		Nef-202			Pooled	
	Nefecon 16 mg	Placebo	Nefecon 16 mg	Nefecon 8 mg	Placebo	Nefecon 16 mg	Placebo
Patients randomized[a]	153	153	51	51	51	204	204
Safety Analysis Set	150	144	49	51	50	199	194
Total patient years exposure[b]	94.3	96.2	29.3	34.1	35.9	123.6	132.1
Full Analysis Set (patients dosed)[c]	97	100	49	51	50	146	150
Total patient years exposure[b]	71.7	75.8	29.3	34.1	35.9	101.0	111.7

Source: Table 4 in Module 2.7.3.

[a] As of the DCO for Nef-301 there were 12 patients randomized and not dosed. In Nef-202 there were 3 patients randomized and not dosed. These patients are not included in the safety evaluation.

[b] Total patient years exposure estimated from mean exposure×number of patients.

[c] For Nef-301 this is the number of patients in the Part A Full Analysis Set who received study treatment.

Duration of exposure

Table 45 Nef-301 study drug exposure as of the DCO of 5 October 2020 (SAS and Part A FAS)

	Safety Analysis Set		Part A Full Analysis Set	
	Nefecon 16 mg (N=150)	Placebo (N=144)	Nefecon 16 mg (N=97)	Placebo (N=100)
Overall Exposure (days)[a]				
n	150	144	97	100
Median [inter-quartile range]	279 [187 to 288]	282 [224 to 288]	286 [280 to 291]	286 [281 to 289]
Range	8 to 348	5 to 333	12 to 348	5 to 333
Exposure to 16 mg dose prior to tapering period (days)[b]				
n	150	144	97	100
Median [inter-quartile range]	266 [175 to 273]	269 [221 to 274]	272 [266 to 277]	272 [268 to 275]
Range	8 to 316	5 to 309	12 to 316	5 to 309
Exposure to a reduced 8 mg dose prior to tapering period (days)[b]				
n	5	3	4	1
Median [inter-quartile range]	28 [21 to 97]	14 [10 to 251]	63 [25 to 168]	251
Range	19 to 238	10 to 251	21 to 238	251
Exposure during tapering period (days)[c]				
n	86	92	85	91
Median [range]	14 [12 to 80]	14 [12 to 62]	14 [12 to 80]	14 [12 to 62]

Source: Nef-301 CSR Table 25.

[a] Overall exposure = Date of last dose (including the tapering period) – date of first dose +1. Dose interruptions not accounted for in any of these exposure calculations.

[b] Exposure to 8 mg and 16 mg doses calculated as date of last dose of 16 mg or 8 mg prior to tapering period – date of first dose of 16 mg or 8 mg prior to tapering period + 1.

[c] Exposure during tapering period calculated as date of last dose – date of first dose in tapering period + 1. Note that the reason for some apparent long tapering periods was either a result of a delay in data entry or that the appropriate eCRF had not yet been completed prior to the DCO.

Table 46 Nef-402 summary of treatment exposure (FAS)

Variable	Statistic	Nefecon 16 mg (N=48)[a]	Nefecon 8 mg (N=51)	Placebo (N=50)
Duration of exposure [days]	Mean	222.7	244.4	262.5
	Median [inter-quartile range]	271 [178 to 277]	274 [259 to 280]	274 [267 to 281]
	Range	28 to 297	35 to 302	63 to 317

Source: Nef-202 CSR Table 24 and Nef-202 CSR Table D6.1.

[a] One patient completed the run-in phase and was randomized to Nefecon 16 mg/day, but had difficulty swallowing the capsules and was withdrawn from the trial after 1 dose. This patient was included in the Safety Analysis Set but excluded from the Full Analysis Set.

Demographics and baseline characteristics

Table 47 Summary of demographic and disease characteristics and RAS inhibitor therapy in Nef-301, Nef-202, and the pooled dataset (SAS)

	Nef-301		Nef-202			Pooled	
	Nefecon 16 mg N=150	Placebo N=144	Nefecon 16 mg N=49	Nefecon 8 mg N=51	Placebo N=50	Nefecon 16 mg N=199	Placebo N=194
Median Age [range] (years)	44 [21 to 69]	43 [22 to 73]	38 [18 to 64]	40 [20 to 82]	37 [18 to 69]	42 [18 to 69]	41 [18 to 73]
Sex (n, % male)	102 (68.0)	98 (68.1)	34 (69.4)	37 (72.5)	35 (70.0)	136 (68.3)	133 (68.6)
BMI (kg/m^2)	28 [25 to 32]	27 [24 to 31]	27 [23 to 31]	26 [24 to 30]	27 [23 to 30]	28 [25 to 32]	27 [24 to 30]
Weight (kg)	85 [72 to 97]	85 [72 to 93]	86 [75 to 97]	79 [74 to 92]	82 [71 to 97]	85 [73 to 97]	84 [71 to 94]
Race (n, %): White	122 (81.3)	118 (81.9)	48 (98.0)	49 (96.1)	48 (96.0)	170 (85.4)	166 (85.6)
Black	0	0	0	0	0	0	0
Asian	27 (18.0)	22 (15.3)	1 (2.0)	1 (2.0)	1 (2.0)	28 (14.1)	23 (11.9)
Other	1 (0.7)	4 (2.8)	0	1 (2.0)	1 (2.0)	1 (0.5)	5 (2.6)
Ethnicity (n, %)							
Hispanic/Latino	15 (10.0)	7 (4.9)	7 (14.3)	11 (21.6)	3 (6.0)	22 (11.1)	10 (5.2)
Non-Hispanic/Non-Latino	135 (90.0)	136 (94.4)	42 (85.7)	40 (78.4)	47 (94.0)	177 (88.9)	183 (94.3)
Systolic blood pressure (mm Hg)	126 [121 to 132]	124 [117 to 129]	127 [120 to 134]	129 [116 to 136]	130 [120 to 138]	126 [120 to 133]	125 [118 to 132]
Diastolic blood pressure (mm Hg)	79 [76 to 84]	78 [73 to 83]	78 [70 to 84]	80 [72 to 86]	80 [71 to 88]	79 [75 to 84]	79 [73 to 84]
UPCR (g/gram)	1.29 [0.92 to 1.71]	1.16 [0.83 to 1.75]	0.79 [0.55 to 1.27]	0.81 [0.55 to 1.16]	0.84 [0.53 to 1.59]	1.18 [0.78 to 1.58]	1.09 [0.77 to 1.72]
Total urine protein (g)/24 hours	2.32 [1.67 to 3.15]	2.18 [1.52 to 3.49]	1.32 [0.92 to 2.11]	1.16 [0.88 to 1.72]	1.34 [0.98 to 2.54]	2.04 [1.41 to 2.94]	1.99 [1.33 to 3.35]
UACR (g/gram)	0.99 [0.70 to 1.36]	0.95 [0.65 to 1.42]	0.69 [0.44 to 1.12]	0.71 [0.44 to 1.08]	0.72 [0.44 to 1.26]	0.92 [0.60 to 1.24]	0.89 [0.58 to 1.40]
Total urine albumin (g)/24 hours	1.78 [1.24 to 2.54]	1.70 [1.12 to 2.67]	1.08 [0.85 to 1.81]	1.00 [0.68 to 1.43]	1.15 [0.81 to 2.05]	1.63 [1.13 to 2.31]	1.59 [1.02 to 2.59]
eGFR CKD-EPI (mL/min/1.73 m^2)	55.5 [46.5 to 70.0]	55.0 [46.0 to 67.8]	78.1 [63.0 to 101.8]	71.1 [53.5 to 87.4]	71.1 [53.3 to 92.6]	59.1 [48.5 to 74.5]	58.5 [48.5 to 73.5]
Patients with microhematuria (n, %)	100 (66.7)	98 (68.1)	43 (87.8)	34 (66.7)	42 (84.0)	143 (71.9)	140 (72.2)
Time from diagnosis to start of treatment (years)	2.3 [0.5 to 6.4]	2.6 [0.5 to 6.3]	2.8 [0.7 to 6.5]	4.9 [1.1 to 11.0]	2.4 [0.3 to 7.4]	2.4 [0.6 to 6.4]	2.6 [0.5 to 6.4]
Prior treatment with corticosteroids or immunosuppressants (n, %) [a]	12 (8.0)	14 (9.7)	6 (12.2)	14 (27.5)	7 (14.0)	18 (9.0)	21 (10.8)
RAS inhibitor therapy: Patients on ACEI alone (n, %)	72 (48.0)	57 (39.6)	26 (53.1)	25 (49.0)	21 (42.0)	98 (49.2)	78 (40.2)
Patients on ARB alone (n, %)	68 (45.3)	78 (54.2)	14 (28.6)	14 (27.5)	16 (32.0)	82 (41.2)	94 (48.5)
Patients on both ACEI and ARB (n, %)	6 (4.0)	7 (4.9)	9 (18.4)	12 (23.5)	13 (26.0)	15 (7.5)	20 (10.3)
Level of RAS blockade (n, %) [b]:	n=142	n=140	n=49	n=51	n=50	n=191	n=190
<50% of MAD	34 (23.9)	28 (20.0)	5 (10.2)	6 (11.8)	5 (10.0)	39 (20.4)	33 (17.4)
≥50 to <80%	31 (21.8)	42 (30.0)	12 (24.5)	15 (29.4)	8 (16.0)	43 (22.5)	50 (26.3)
≥80%	77 (54.2)	70 (50.0)	32 (65.3)	30 (58.8)	37 (74.0)	109 (57.1)	107 (56.3)

Source: Supportive Tables and Figures for SCS Table 2.7.4.1.3.

[a] Patients previously treated with corticosteroids or immunosuppressants was for any indication in Nef-301, but was for IgAN in Nef-202.

[b] Patients who were not recorded as receiving either an ACEI or an ARB were included in the <50% group. For patients taking both ACEIs and ARBs, the sum of the % of the maximum allowed dose for each were summarized. The dose of RAS inhibitor therapy was not recorded for some patients; these patients are not included in the level of RAS blockade summary.

Data are presented as median [inter-quartile range] unless otherwise stated.

ACEI angiotensin converting enzyme inhibitor; ARB angiotensin II type I receptor blocker; BMI body-mass index; CKD-EPI Chronic Kidney Disease Epidemiology Collaboration; eGFR estimated glomerular filtration rate; MAD maximum allowed dose; RAS renin-angiotensin system; UACR urine albumin creatinine ratio; UPCR urine protein creatinine ratio.

Concomitant medications

Table 48 Summary of concomitant medications in >5% of either pooled treatment group for Nef-301, Nef-202, and the pooled dataset (Nef-301 Part A FAS for safety, NEF-202 SAS and Pooled)

Concomitant medication ATC Class	Nef-301		Nef-202			Pooled	
	Nefecon 16 mg N=97	Placebo N=100	Nefecon 16 mg N=49	Nefecon 8 mg N=51	Placebo N=50	Nefecon 16 mg N=146	Placebo N=150
Any concomitant medication	97 (100.0)	100 (100.0)	49 (100.0)	51 (100.0)	50 (100.0)	146 (100.0)	150 (100.0)
ACEIs, plain [a]	55 (56.7)	47 (47.0)	34 (69.4)	36 (70.6)	33 (66.0)	89 (61.0)	80 (53.3)
ARBs, plain [a]	36 (37.1)	53 (53.0)	23 (46.9)	27 (52.9)	26 (52.0)	59 (40.4)	79 (52.7)
HMG-CoA reductase inhibitors	50 (51.5)	36 (36.0)	22 (44.9)	18 (35.3)	17 (34.0)	72 (49.3)	53 (35.3)
Dihydropyridine derivatives	37 (38.1)	35 (35.0)	11 (22.4)	14 (27.5)	12 (24.0)	48 (32.9)	47 (31.3)
Preparations inhibiting uric acid production	30 (30.9)	29 (29.0)	12 (24.5)	9 (17.6)	10 (20.0)	42 (28.8)	39 (26.0)
Anilides	21 (21.6)	31 (31.0)	7 (14.3)	7 (13.7)	11 (22.0)	28 (19.2)	42 (28.0)
Vitamin D and analogues	27 (27.8)	21 (21.0)	8 (16.3)	10 (19.6)	7 (14.0)	35 (24.0)	28 (18.7)
Other lipid modifying agents	23 (23.7)	14 (14.0)	4 (8.2)	8 (15.7)	3 (6.0)	27 (18.5)	17 (11.3)
Sulfonamides, plain	21 (21.6)	9 (9.0)	8 (16.3)	4 (7.8)	4 (8.0)	29 (19.9)	13 (8.7)
Beta blocking agents, selective	21 (21.6)	13 (13.0)	5 (10.2)	5 (9.8)	2 (4.0)	26 (17.8)	15 (10.0)
Proton pump inhibitors	17 (17.5)	15 (15.0)	10 (20.4)	7 (13.7)	7 (14.0)	27 (18.5)	22 (14.7)
Glucocorticoids [b]	12 (12.4)	18 (18.0)	3 (6.1)	2 (3.9)	5 (10.0)	15 (10.3)	23 (15.3)
Alpha-adrenoreceptor antagonists	12 (12.4)	13 (13.0)	1 (2.0)	3 (5.9)	2 (4.0)	13 (8.9)	15 (10.0)
Thyroid hormones	9 (9.3)	6 (6.0)	4 (8.2)	4 (7.8)	3 (6.0)	13 (8.9)	9 (6.0)
Other antihistamines for systemic use	9 (9.3)	10 (10.0)	5 (10.2)	3 (5.9)	2 (4.0)	14 (9.6)	12 (8.0)
Opioids in combination with non-opioid analgesics	10 (10.3)	8 (8.0)	2 (4.1)	0	2 (4.0)	12 (8.2)	10 (6.7)
Platelet aggregation inhibitors, excluding heparin	6 (6.2)	8 (8.0)	3 (6.1)	1 (2.0)	0	9 (6.2)	8 (5.3)
Aldosterone antagonists	7 (7.2)	4 (4.0)	3 (6.1)	0	0	10 (6.8)	4 (2.7)
Propionic acid derivatives	7 (7.2)	4 (4.0)	4 (8.2)	2 (3.9)	6 (12.0)	11 (7.5)	10 (6.7)
Piperazine derivatives	5 (5.2)	6 (6.0)	1 (2.0)	0	5 (10.0)	6 (4.1)	11 (7.3)
Preparations with no effect on uric acid metabolism	5 (5.2)	7 (7.0)	1 (2.0)	1 (2.0)	1 (2.0)	6 (4.1)	8 (5.3)
Benzodiazepine derivatives	6 (6.2)	10 (10.0)	2 (4.1)	1 (2.0)	2 (4.0)	8 (5.5)	12 (8.0)
Corticosteroids [b]	6 (6.2)	8 (8.0)	1 (2.0)	0	2 (4.0)	7 (4.8)	10 (6.7)
Magnesium	6 (6.2)	6 (6.0)	6 (12.2)	1 (2.0)	4 (8.0)	12 (8.2)	10 (6.7)
Thiazides, plain	5 (5.2)	9 (9.0)	6 (12.2)	5 (9.8)	2 (4.0)	11 (7.5)	11 (7.3)
ARBs and diuretics	4 (4.1)	5 (5.0)	1 (2.0)	1 (2.0)	3 (6.0)	5 (3.4)	8 (5.3)

Source: Supportive Tables and Figures for the SCS Table 2.7.4.1.10.

[a] These ATC classes are not inclusive of all RAS inhibitor therapy.

[b] These ATC classes of glucocorticoids and corticosteroids include rescue treatment for IgAN, as well as glucocorticosteroid treatments administered for other reasons.

Medication reported terms were coded using the WHO Drug Dictionary Version WHO Drug_Mar2019G B3.

ACEI angiotensin converting enzyme inhibitor; ARB angiotensin II type I receptor blocker; HMG-CoA 3-hydroxy-3-methylglutaryl-coenzyme A.

2.4.8.2. Adverse events

Analysis of Adverse events

Table 49 Nef-301 overview of adverse events as of the DCO of 5 October 2020 (SAS and Part A FAS)

		Safety Analysis Set						Part A Full Analysis Set			
		Nefecon 16 mg (N=150)			Placebo (N=144)			Nefecon 16 mg (N=97)		Placebo (N=100)	
		n (%)	E	CI9 %	n (%)	E	CI9 %	n (%)	E	n (%)	E
Any TEAE[a]		114 (76.0)	522	83.1	87 (60.4)	352	65.8	84 (86.6)	429	73 (73.0)	300
Maximum severity	Mild	66 (44.0)	401	47.9	53 (36.8)	285	39.6	49 (50.5)	330	46 (46.0)	243
	Moderate	43 (28.7)	116	32.0	32 (22.2)	64	24.0	31 (32.0)	95	26 (26.0)	56
	Severe	5 (3.3)	5	3.9	2 (1.4)	3	1.4	4 (4.1)	4	1 (1.0)	1
Any drug-related TEAEs[b]		65 (43.3)	204	46.8	27 (18.8)	68	20.7	47 (48.5)	167	24 (24.0)	62
Maximum severity	Mild	42 (28.0)	157	30.2	18 (12.5)	51	13.8	31 (32.0)	129	17 (17.0)	49
	Moderate	22 (14.7)	46	15.8	7 (4.9)	14	4.4	15 (15.5)	37	6 (6.0)	12
	Severe	1 (0.7)	1	0.7	2 (1.4)	3	1.4	1 (1.0)	1	1 (1.0)	1
Any AESI		3 (2.0)	3	2.5	1 (0.7)	1	0.7	2 (2.1)	2	0	0
Treatment-emergent SAEs (TESAEs)		14 (9.3)	21	10.9	6 (4.2)	7	2.9	11 (11.3)	16	5 (5.0)	5
Any drug-related TESAEs[b]		3 (2.0)	3	2.2	3 (2.1)	4	1.4	2 (2.1)	2	2 (2.0)	2
Any SAEs leading to death		0	0	0	0	0	0	0	0	0	0
Any TEAEs leading to discontinuation of study treatment		12 (8.0)	31	8.9	3 (2.1)	8	2.2	9 (9.3)	27	1 (1.0)	5

Source: Nef-301 CSR Table 28.

[a] TEAEs defined as AEs that occurred for the first time after dosing with study drug, or existed before but worsened in severity or relationship to study drug after dosing. Adverse events that started >14 days after the last dose of the treatment are excluded from this summary. The last dose is defined as the last dose patient received including the tapering period, regardless of the duration of therapy.

[b] Drug-related based on Investigator assessment of whether or not there was a reasonable possibility of a causal relationship between the event and study treatment. If missing then considered drug-related.

AESI Adverse Event of Special Interest; CI9 estimated cumulative incidence of events by 9 months based on both the observed incidence of events in the FAS and the cumulative incidence of events at earlier timepoints from patients only included in the Safety Analysis Set, assuming their subsequent incidence of events increased at the same rate as observed in the FAS; DCO data cut-off; E number of events; FAS Full Analysis Set; N number of patients dosed; n number of patients with an AE; SAE serious adverse event; TEAE treatment-emergent adverse event.

Table 50 Summary of TEAEs in the pooled dataset (Nef-301 Part A FAS for safety and SAS)

	Nef-301		Nef-202			Pooled	
	Nefecon 16 mg	Placebo	Nefecon 16 mg	Nefecon 8 mg	Placebo	Nefecon 16 mg	Placebo
Part A Full Analysis Set	**N=97**	**N=100**	**N=49**	**N=51**	**N=50**	**N=146**	**N=150**
Patients with any TEAE	84 (86.6)	73 (73.0)	42 (85.7)	46 (90.2)	39 (78.0)	126 (86.3)	112 (74.7)
Drug-related TEAE[a]	47 (48.5)	24 (24.0)	27 (55.1)	29 (56.9)	18 (36.0)	74 (50.7)	42 (28.0)
TEAE graded severe	4 (4.1)	1 (1.0)	4 (8.2)	2 (3.9)	1 (2.0)	8 (5.5)	2 (1.3)
TEAE leading to discontinuation of study treatment[b]	9 (9.3)	1 (1.0)	11 (22.4)	6 (11.8)	3 (6.0)	20 (13.7)	4 (2.7)
Patients with any TESAE	11 (11.3)	5 (5.0)	5 (10.2)	0	2 (4.0)	16 (11.0)	7 (4.7)
Drug-related TESAE[a]	2 (2.1)	2 (2.0)	1 (2.0)	0	2 (4.0)	3 (2.1)	4 (2.7)
Patients with any AESI	2 (2.1)	0	1 (2.0)	0	0	3 (2.0)	0
Safety Analysis Set	**N=150**	**N=144**	**N=49**	**N=51**	**N=50**	**N=199**	**N=194**
Patients with any TESAE	14 (9.3)	6 (4.2)	5 (10.2)	0	2 (4.0)	19 (9.5)	8 (4.1)
Patients with any AESI	3 (2.0)	1 (0.7)	1 (2.0)	0	0	4 (2.0)	1 (0.5)
Deaths	0	0	0	0	0	0	0

Source: Supportive Tables and Figures for SCS Table 2.7.4.2.1 and Table 2.7.4.2.2.

[a] Drug-related TEAE based on Investigator-assessed causality of at least possibly drug-related. This differs to overview of adverse events table in Nef-202 CSR (Table 14) which only summarized those considered to be probably drug- related.

[b] The Nef-202 CSR reported TEAEs that led to discontinuation from the study. For the pooled analyses, TEAEs that led to discontinuation of study treatment have been summarized for both studies.

Treatment-emergent adverse events that start either before or within 14 days of completion of the tapering period in Nef-301 or within 28 days of the end of study treatment in Nef-202 are included in this summary. Note this differs to the Nef-202 CSR in which all TEAEs during treatment and follow-up were reported together.

AESI adverse event of special interest; N number of patients in the analysis set; SAE serious adverse event; TEAE treatment-emergent adverse event; TESAE treatment-emergent SAE.

The most common treatment-emergent adverse events (TEAEs) reported in ≥5% of Kinpeygo-treated patients with a >5% higher frequency in the Kinpeygo 16 mg/day group compared to placebo were hypertension, edema peripheral, muscle spasms, acne, dermatitis, dyspnea, face edema, hirsutism, and ligament sprain.

Other common TEAEs reported in ≥5% of Kinpeygo-treated patients such as nasopharyngitis, headache, nausea, diarrhea, upper respiratory tract infection, abdominal pain, dyspepsia, and fatigue were reported at a similar frequency in both treatment groups.

Table 51 Nef-301 TEAEs reported by ≥5% of patients in either treatment group by preferred term (SAS and Part A FAS for safety)

Treatment Emergent Adverse Event (Preferred Term) [a]	Safety Analysis Set						Part A Full Analysis Set			
	Nefecon 16 mg (N=150)			Placebo (N=144)			Nefecon 16 mg (N=97)		Placebo (N=100)	
	n (%)	E	CI9 %	n (%)	E	CI9 %	n (%)	E	n (%)	E
Patients with any TEAE	114 (76.0)	522	83.1	87 (60.4)	352	65.8	84 (86.6)	429	73 (73.0)	300
Hypertension [a]	17 (11.3)	19	13.5	3 (2.1)	3	2.2	15 (15.5)	17	2 (2.0)	2
Edema peripheral [a]	20 (13.3)	25	14.0	4 (2.8)	5	2.2	14 (14.4)	18	4 (4.0)	5
Muscle spasms	17 (11.3)	22	13.2	4 (2.8)	5	3.4	13 (13.4)	18	4 (4.0)	5
Nasopharyngitis	13 (8.7)	14	9.5	13 (9.0)	17	9.7	13 (13.4)	14	12 (12.0)	14
Headache	15 (10.0)	19	11.2	12 (8.3)	13	9.6	11 (11.3)	13	11 (11.0)	12
Acne	15 (10.0)	15	11.5	2 (1.4)	2	1.5	11 (11.3)	11	2 (2.0)	2
Dermatitis [a]	8 (5.3)	8	5.0	1 (0.7)	2	0.7	7 (7.2)	7	1 (1.0)	2
Weight increased	8 (5.3)	8	6.2	4 (2.8)	4	2.9	7 (7.2)	7	3 (3.0)	3
Dyspnea	6 (4.0)	6	NC	0 (0.0)	0	NC	6 (6.2)	6	0 (0.0)	0
Face edema [a]	9 (6.0)	9	6.8	1 (0.7)	1	0.7	6 (6.2)	6	1 (1.0)	1
Nausea	8 (5.3)	8	5.9	10 (6.9)	10	7.8	6 (6.2)	6	9 (9.0)	9
Diarrhea	8 (5.3)	8	6.0	7 (4.9)	7	5.6	6 (6.2)	6	7 (7.0)	7
Upper respiratory tract infection	6 (4.0)	6	4.6	9 (6.3)	14	6.8	5 (5.2)	5	9 (9.0)	14
Abdominal pain [a]	6 (4.0)	6	NC	6 (4.2)	6	NC	5 (5.2)	5	6 (6.0)	6
Dyspepsia	7 (4.7)	11	NC	2 (1.4)	2	NC	5 (5.2)	9	2 (2.0)	2
Fatigue	5 (3.3)	5	NC	5 (3.5)	6	NC	5 (5.2)	5	2 (2.0)	3
Hirsutism [a]	5 (3.3)	5	NC	0 (0.0)	0	NC	5 (5.2)	5	0 (0.0)	0
Ligament sprain	5 (3.3)	6	NC	0 (0.0)	0	NC	5 (5.2)	6	0 (0.0)	0
Abdominal discomfort [a]	6 (4.0)	6	NC	6 (4.2)	6	NC	4 (4.1)	4	6 (6.0)	6
Vomiting	5 (3.3)	8	NC	5 (3.5)	9	NC	4 (4.1)	7	5 (5.0)	9
Rash	4 (2.7)	6	NC	5 (3.5)	9	NC	4 (4.1)	6	5 (5.0)	9
Oropharyngeal pain	4 (2.7)	5	NC	5 (3.5)	7	NC	3 (3.1)	4	5 (5.0)	7
Pain in extremity	2 (1.3)	3	NC	7 (4.9)	9	NC	2 (2.1)	3	5 (5.0)	6
Back pain	2 (1.3)	2	NC	6 (4.2)	6	NC	0 (0.0)	0	6 (6.0)	6
Pyrexia	0 (0.0)	0	NC	7 (4.9)	7	NC	0 (0.0)	0	6 (6.0)	6

Source: Nef-301 CSR Table 30.

[a] Preferred Terms are grouped for hypertension (hypertension and essential hypertension); edema peripheral (edema peripheral and peripheral swelling), dermatitis (dermatitis, hand dermatitis, perioral dermatitis, seborrheic dermatitis, and eczema), face edema (face edema and swelling face), abdominal pain (abdominal pain, abdominal pain upper, and abdominal pain lower), hirsutism (hirsutism and hypertrichosis); and abdominal discomfort (abdominal discomfort, abdominal tenderness, and abdominal distension).

CI9 Estimated cumulative incidence of events by 9 months; E number of events; N number of patients dosed; n number of patients with TEAE; NC Not calculated when percentage of patients with TEAE<5%; TEAE treatment-emergent adverse event.

TEAEs that started or worsened after the start of study treatment up until 14 days after the end of the tapering period are included.

Adverse events considered related to by the investigator

Table 52 Summary of TEAEs in the pooled dataset (Nef-301 Part A FAS for safety and SAS)

	Nef-301		Nef-202			Pooled	
	Nefecon 16 mg	Placebo	Nefecon 16 mg	Nefecon 8 mg	Placebo	Nefecon 16 mg	Placebo
Part A Full Analysis Set	**N=97**	**N=100**	**N=49**	**N=51**	**N=50**	**N=146**	**N=150**
Patients with any TEAE	84 (86.6)	73 (73.0)	42 (85.7)	46 (90.2)	39 (78.0)	126 (86.3)	112 (74.7)
Drug-related TEAE[a]	47 (48.5)	24 (24.0)	27 (55.1)	29 (56.9)	18 (36.0)	74 (50.7)	42 (28.0)
TEAE graded severe	4 (4.1)	1 (1.0)	4 (8.2)	2 (3.9)	1 (2.0)	8 (5.5)	2 (1.3)
TEAE leading to discontinuation of study treatment[b]	9 (9.3)	1 (1.0)	11 (22.4)	6 (11.8)	3 (6.0)	20 (13.7)	4 (2.7)
Patients with any TESAE	11 (11.3)	5 (5.0)	5 (10.2)	0	2 (4.0)	16 (11.0)	7 (4.7)
Drug-related TESAE[a]	2 (2.1)	2 (2.0)	1 (2.0)	0	2 (4.0)	3 (2.1)	4 (2.7)
Patients with any AESI	2 (2.1)	0	1 (2.0)	0	0	3 (2.0)	0
Safety Analysis Set	**N=150**	**N=144**	**N=49**	**N=51**	**N=50**	**N=199**	**N=194**
Patients with any TESAE	14 (9.3)	6 (4.2)	5 (10.2)	0	2 (4.0)	19 (9.5)	8 (4.1)
Patients with any AESI	3 (2.0)	1 (0.7)	1 (2.0)	0	0	4 (2.0)	1 (0.5)
Deaths	0	0	0	0	0	0	0

Source: Supportive Tables and Figures for SCS Table 2.7.4.2.1 and Table 2.7.4.2.2.

[a] Drug-related TEAE based on Investigator-assessed causality of at least possibly drug-related. This differs to overview of adverse events table in Nef-202 CSR (Table 14) which only summarized those considered to be probably drug- related.

[b] The Nef-202 CSR reported TEAEs that led to discontinuation from the study. For the pooled analyses, TEAEs that led to discontinuation of study treatment have been summarized for both studies.

Treatment-emergent adverse events that start either before or within 14 days of completion of the tapering period in Nef-301 or within 28 days of the end of study treatment in Nef-202 are included in this summary. Note this differs to the Nef-202 CSR in which all TEAEs during treatment and follow-up were reported together.

AESI adverse event of special interest; N number of patients in the analysis set; SAE serious adverse event; TEAE treatment-emergent adverse event; TESAE treatment-emergent SAE.

The frequencies of treatment-related TEAEs with a reasonable possibility of a causal relationship between the event and study treatment, as assessed by the investigator, were higher with Kinpeygo 16 mg (48.5%) than with placebo (24.0%), in the Part A FAS. Similar frequencies were observed in the SAS (43.3% versus 18.8% for the Kinpeygo and placebo treatment groups, respectively). The most common TEAEs considered by the investigator to have a reasonable possibility of being treatment-related were AEs that would be anticipated with budesonide treatment.

Table 53 Nef-301 drug-related TEAEs reported by ≥4% of patients in either treatment group of the Part A FAS for safety preferred term (SAS and Part A FAS for safety)

Drug-related TEAE[a] (Preferred Term)	Safety Analysis Set				Part A Full Analysis Set			
	Nefecon 16 mg (N=150)		Placebo (N=144)		Nefecon 16 mg (N=97)		Placebo (N=100)	
	n (%)	E	n (%)	E	n (%) E	E	n (%)	E
Patients with any drug-related TEAE[a]	65 (43.3)	204	27 (18.8)	68	47 (48.5)	167	24 (24.0)	62
Acne	13 (8.7)	13	2 (1.4)	2	9 (9.3)	9	2 (2.0)	2
Weight increased	6 (4.0)	6	4 (2.8)	4	6 (6.2)	6	3 (3.0)	3
Hypertension	6 (4.0)	6	0	0	5 (5.2)	5	0	0
Headache	5 (3.3)	5	2 (1.4)	2	5 (5.2)	5	2 (2.0)	2
Edema peripheral [b]	6 (4.0)	8	2 (1.4)	3	4 (4.1)	5	2 (2.0)	3
Dyspepsia	5 (3.3)	7	1 (0.7)	1	4 (4.1)	6	1 (1.0)	1
Mood swings [b]	5 (3.3)	5	1 (0.7)	1	4 (4.1)	4	1 (1.0)	1
Face edema [b]	7 (4.7)	7	1 (0.7)	1	4 (4.1)	4	1 (1.0)	1
Cushingoid [b]	4 (2.7)	4	0	0	4 (4.1)	4	0	0
Hirsutism [b]	4 (2.7)	4	0	0	4 (4.1)	4	0	0
Upper respiratory tract infection	0	0	4 (2.8)	6	0	0	4 (4.0)	6

Source: Nef-301 CSR Table 32.

[a] Drug-related based on Investigator assessment of whether or not there was a reasonable possibility of a causal relationship between the event and study treatment. If missing then considered drug-related.

[b] Preferred Terms are grouped for edema peripheral (edema peripheral and peripheral swelling), mood swings (mood swings, mood altered, and irritability), face edema (face edema and swelling face), cushingoid (cushingoid and Cushing's syndrome), and hirsutism (hirsutism and hypertrichosis).

E number of events; FAS Full Analysis Set; N number of patients dosed; n number of patients with TEAE; TEAE treatment-emergent adverse event. TEAEs that started or worsened after the start of study treatment are included.

Adverse events of special interest

The following, which are established potentially clinically significant consequences of steroid treatment, were considered adverse event of special interest (AESIs) in Nef-301 study:

- Severe infection requiring hospitalisation;
- New onset of diabetes mellitus;
- Confirmed fracture;
- New osteonecrosis;
- Gastrointestinal bleeding that requires hospitalisation;
- Reported occurrence of cataract formation, and
- Reported onset of glaucoma.

Glucocorticosteroids are also known to increase the risk of adverse gastrointestinal effects, such as gastritis, ulcer formation, and gastrointestinal bleeding (Messer et al 1983). As Kinpeygo directs the release of the active substance budesonide to the ileum, GI AEs were also evaluated across the patient studies.

Table 54 Nef-301 adverse event of special interest (SAS)

Adverse Event of Special Interest	Number (%) of patients			
	During treatment up to 14 days after last dose		During follow-up >14 days after last dose	
	Nefecon 16 mg (N=150)	Placebo (N=144)	Nefecon 16 mg (N=79)	Placebo (N=85)
Patients with any AESI	3 (2.0)	1 (0.7)	1 (1.3)	1 (1.2)
Severe infection that required hospitalization	0	0	0	0
New onset of diabetes mellitus	2 (1.3)	0	1 (1.3)	0
Confirmed fracture	0	1 (0.7)	0	1 (1.2)
New osteonecrosis	0	0	0	0
Gastrointestinal bleeding that required hospitalization	1 (0.7)	0	0	0
Reported occurrence of cataract formation	0	0	0	0
Reported onset of glaucoma	0	0	0	0

Source: Nef-301 CSR Table 34.

AESI Adverse Event of Special Interest; N during the treatment period is the number of patients in the Safety Analysis Set; N during follow-up is the number of patients in the Safety Analysis Set attending a study visit more than 14 days after completion of the tapering period.

2.4.8.3. Serious adverse event/deaths/other significant events

There have been two deaths reported in the Kinpeygo treatment group; one was a fatal coronavirus infection that occurred during the "on treatment" phase and one was a cerebral haemorrhage that occurred during follow-up. Neither was considered by the investigator to be potentially related to study treatment.

Table 55 Nef-301 summary of treatment-emergent serious adverse events by preferred term (Part A FAS for safety)

Treatment-emergent SAE (Preferred Term)	Number (%) of patients	
	Nefecon 16 mg (N=97)	Placebo (N=100)
Patients with any treatment-emergent SAE	11 (11.3)	5 (5.0)
Pulmonary embolism	2 (2.1)	0
Renal impairment	2 (2.1)	0
Nephrotic syndrome	1 (1.0)	0
Diverticulitis	0	1 (1.0)
Erysipelas	1 (1.0)	0
Dyspnea	1 (1.0)	0
Hypertension	1 (1.0)	0
Hypertensive urgency	1 (1.0)	0
Post thrombotic syndrome	1 (1.0)	0
Inguinal hernia	0	1 (1.0)
Chest pain	1 (1.0)	0
Face edema	1 (1.0)	0
Edema peripheral	1 (1.0)	0
Rhabdomyolysis	0	1 (1.0)
Meningioma	1 (1.0)	0
Transient ischemic attack	0	1 (1.0)
Abortion spontaneous	1 (1.0)	0
Suicidal ideation	0	1 (1.0)
Rash generalized	1 (1.0)	0

Source: Nef-301 CSR Table 36.
N number of patients dosed; SAE serious adverse event. Treatment-emergent SAEs that started or worsened after the start of study treatment up until 14 days after the end of the tapering period are included.

Table 56 Summary of treatment-emergent serious adverse events reported by >1 Kinpeygo-treated patients in the pooled dataset (SAS)

Preferred Term	Number (%) of patients						
	Nef-301		Nef-202			Pooled	
	Nefecon 16 mg (N=150)	Placebo (N=144)	Nefecon 16 mg (N=49)	Nefecon 8 mg (N=51)	Placebo (N=50)	Nefecon 16 mg (N=199)	Placebo (N=194)
Patients with any treatment emergent SAE	14 (9.3)	6 (4.2)	5 (10.2)	0	2 (4.0)	19 (9.5)	8 (4.1)
Nephrotic syndrome	1 (0.7)	0	1 (2.0)	0	0	2 (1.0)	0
Renal impairment	2 (1.3)	0	0	0	0	2 (1.0)	0
Pulmonary embolism	2 (1.3)	0	0	0	0	2 (1.0)	0

Source: Supportive Tables and Figures for SCS Table 2.7.4.3.1.
Treatment-emergent SAEs that start either before or within 14 days of completion of the tapering period in Nef-301 or within 28 days of the end of study treatment in Nef-202 are included in this summary.

2.4.8.4. Laboratory findings

Clinical chemistry

In the patient studies, there were no clinically relevant changes in median values of any clinical chemistry parameters observed over time between Kinpeygo and placebo. Any dose-related trends observed between Kinpeygo 16 mg and Kinpeygo 8 mg, relative to placebo were not considered clinically relevant.

In Nef-301, 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 Kinpeygo treatment were not considered clinically relevant and resolved after the end of the treatment period.

Numerical increases in median LDH, calcium, sodium, and phosphate levels and a small decline in median creatine kinase observed during Kinpeygo treatment were not considered clinically relevant and returned to baseline levels after the end of the treatment period.

Hematology

There were no clinically relevant changes in median values in any hematology parameters observed over time between Kinpeygo and placebo.

In Nef-301, small, predictable increases in white cell counts, hemoglobin, and hematocrit, and a small, expected decrease in eosinophils were observed during Kinpeygo treatment, which returned to baseline levels after the end of treatment. These non-clinically significant changes in white cell counts and other hematological parameters are an expected effect related to GCS use and were also observed in Nef-202.

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 no patients with type 1 or type 2 diabetes mellitus were allowed in the Nef-202 study. A markedly higher percentage of patients in the Kinpeygo 16 mg group of Nef-301 had a medical history of diabetes compared to the placebo group (9 patients [9.3%] versus 1 patient [1.0%] respectively in the Part A FAS; and 13 patients [8.7%] versus 5 patients [3.5%] respectively in the SAS.

In addition, more Kinpeygo-treated patients had pre-diabetic levels of HbA1c ≥ 5.7% or FBG≥100 mg/dL at baseline, as compared to placebo-treated patients (46% and 32% respectively). At a group level, a small numerical increase in median HbA1c levels was observed during Kinpeygo treatment, with some outliers also evident in the Kinpeygo treatment group.

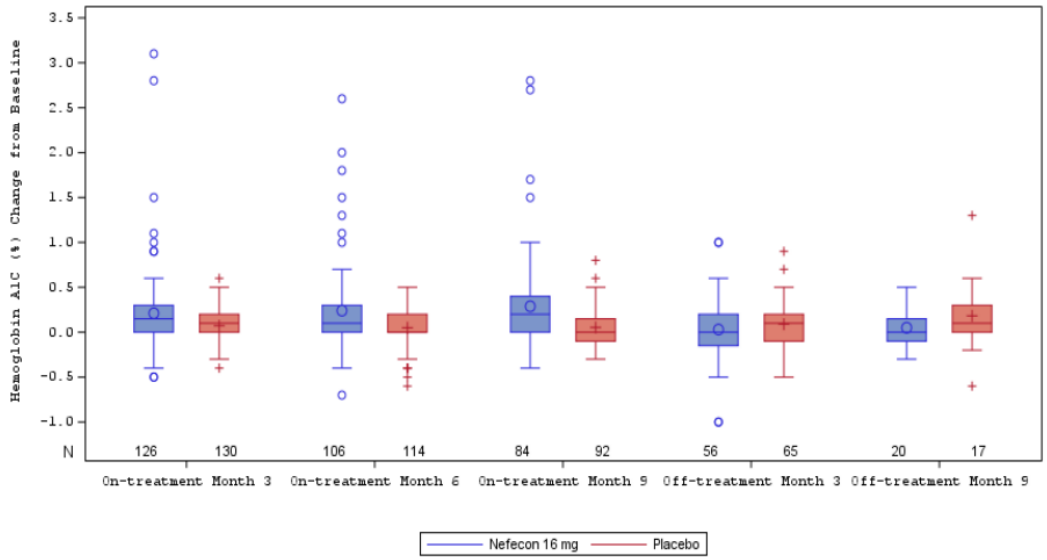


Figure 24 Nef-301 Percentage change from baseline in HbA1c over time (SAS)

2.4.8.5. Safety in special populations

As for other oral budesonide products (e.g., Entocort), 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 Kinpeygo 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 hypertension, edema peripheral, and acne. 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.

Table 57 Summary of the number and percentage of patients reporting treatment-emergent AEs during the "on treatment" phase by age group (D120 SU pooled Saf-301 and Nef-202 SAS)

MedDRA Terms	Number (percentage of patients)			
	Age <65 years		Age 65-74 years[a]	
	Nefecon 16 mg (N=226)	Placebo (N=228)	Nefecon 16 mg (N=7)	Placebo (N=4)
Total TEAEs	183 (81.0)	148 (64.9)	7 (100)	2 (50)
Serious TEAEs	19 (8.4)	9 (3.9)	2 (28.6)	0
Fatal	1 (0.4)	0	0	0
New or prolonged hospitalization	18 (8.0)	8 (3.5)	2 (28.6)	0
Life-threatening	1 (0.4)	1 (0.4)	0	0
Disability	0	0	0	0
Important medical event	4 (1.8)	3 (1.3)	1 (14.3)	0
TEAEs leading to discontinuation	26 (11.5)	6 (2.6)	1 (14.3)	0
Psychiatric disorders [b]	26 (11.5)	18 (7.9)	0	0
Nervous system disorders [b]	37 (16.4)	29 (12.7)	2 (28.6)	0
Accidents and injuries [c]	12 (5.3)	11 (4.8)	1 (14.3)	0
Cardiac disorders [b]	8 (3.5)	5 (2.2)	1 (14.3)	0
Vascular disorders [b]	33 (14.6)	11 (4.8)	3 (42.9)	0
Cerebrovascular disorders [c]	0	1 (0.4)	0	0
Infections and infestations [b]	77 (34.1)	64 (28.1)	1 (14.3)	0
Anticholinergic syndrome [d]	1 (0.4)	0	0	0
Sum of postural hypotension, falls, black outs, syncope, dizziness, ataxia, fractures [e]	5 (2.2)	10 (4.4)	1 (14.3)	0
Other TEAE appearing more frequently in older patients (preferred term):				
Oedema peripheral	27 (11.9)	8 (3.5)	2 (28.6)	0

[a] There have been no patients treated with Nefecon 16 mg or placebo aged ≥75 years.
[b] Based on System Organ Class.
[c] Based on Standard MedDRA Queries.
[d] Anticholinergic syndrome events were defined as at least one adverse event from each of the following 3 medical conditions, concurrently: neuropsychiatric/ophthalmological event + dryness event + vital sign abnormality; or a single adverse event of 'anticholinergic syndrome'.
[e] In addition to the preferred terms listed, hypotension cases were also reviewed. These cases were evenly distributed and were not consistent with orthostatic (postural) hypotension or vasovagal symptoms, and thus not included.
N Number of patients in each age category and treatment group for the pooled Nef-301 and Nef-202 Safety Analysis Set; TEAE treatment-emergent adverse event.

2.4.8.6. Immunological events

No immunological events were reported. However, a high local steroid exposure of the gut could potentially affect immunological gastrointestinal functions.

2.4.8.7. 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.

2.4.8.8. Discontinuation due to adverse events

Table 58 Summary of TEAEs that led to discontinuation of study treatment in >1 Kinpeygo-treated patients in the pooled dataset (Nef-301 Part A FAS for safety pooled with Nef-202 SAS)

Preferred Term	Number (%) of patients						
	Nef-301		Nef-202			Pooled	
	Nefecon 16 mg (N=97)	Placebo (N=100)	Nefecon 16 mg (N=49)	Nefecon 8 mg (N=51)	Placebo (N=50)	Nefecon 16 mg (N=146)	Placebo (N=150)
Patients with a TEAE leading to discontinuation of study treatment	9 (9.3)	1 (1.0)	11 (22.4)	6 (11.8)	3 (6.0)	20 (13.7)	4 (2.7)
Acne	0	0	4 (8.2)	0	0	4 (2.7)	0
Cushingoid	1 (1.0)	0	3 (6.1)	1 (2.0)	0	4 (2.7)	0
Lipohypertrophy	1 (1.0)	0	3 (6.1)	0	0	4 (2.7)	0
Edema peripheral	2 (2.1)	0	1 (2.0)	0	0	3 (2.1)	0
Insomnia	0	1 (1.0)	2 (4.1)	1 (2.0)	0	2 (1.4)	1 (0.7)
Hirsutism	0	0	2 (4.1)	1 (2.0)	0	2 (1.4)	0
Agitation	1 (1.0)	0	1 (2.0)	1 (2.0)	0	2 (1.4)	0
Mood swings	1 (1.0)	1 (1.0)	1 (2.0)	0	0	2 (1.4)	1 (0.7)
Hypertension	2 (2.1)	0	0	0	0	2 (1.4)	0
Skin striae	0	0	2 (4.1)	0	0	2 (1.4)	0
Abdominal pain upper	1 (1.0)	0	1 (2.0)	0	0	2 (1.4)	0
Headache	2 (2.1)	0	0	1 (2.0)	0	2 (1.4)	0
Nephrotic syndrome	1 (1.0)	0	1 (2.0)	0	0	2 (1.4)	0

Source: Supportive Tables and Figures for SCS Table 2.7.4.3.6.

2.4.8.9. Post marketing experience

No post-marketing data are available. The medicinal product has not been marketed in any country.

2.4.9. Discussion on clinical safety

The safety database consists of data from the pivotal phase 3 clinical study (Nef-301) and the supportive phase 2 study (Nef-202). In the pivotal study Nef-301, 294 patients were randomised 1:1 to treatment with 16 mg budesonide (150 patients), or placebo (140 patients). In the supportive Nef-202 study, 153 patients were randomised at 1:1:1 ratios (16 mg budesonide, 8 mg budesonide, or placebo).

The safety data based on Nef-301 consist of 2 parts i) FAS Part A with the first 201 randomised patients (superseded by the 9-Month Safety Cohort in the updated safety data report D120 SU data cut-off, in which all patients included received the full 9 months treatment; 134 – Kinpeygo, and 132 – Placebo) and ii) a SAS including further patients already randomised for Part B (n= 374). The phase 3 SAS includes all available safety data from all visits in all 374 patients who had received at least one dose of study drug by the time of the data cut-off (cut-off 15 March 2021) and therefore includes some patients who have not yet completed the 9-month treatment phase. As part of the day 90 responses, updated safety information from study Nef-301 was provided. Overall, the provided data demonstrated an acceptable safety profile.

The patient populations between the pivotal Nef-301 and supportive study Nef-201 vary in their baseline characteristics, with patients in the Nef-301 trials suffering from more advanced disease while also taking concomitant medication. None of the baseline characteristics appeared to be correlating with an increased risk factor to develop certain AEs. Thus, the pooled data are considered acceptable to assess the safety profile for Kinpeygo.

The study population included in Nef-301 is considered representative for the intended target population and thus suitable to assess budesonide safety in the intended indication. 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=10). The small size of the exposed population also favours confounding effects caused by baseline imbalances. For example, an analysis of glucocorticoid-related AEs in the subgroups of patients with baseline UPCR below or above 1.5 g/gram is hampered by the fact that a greater proportion of patients with UPCR<1.5 g/gram was included in Nef-202 as compared to Nef-301 and that glucocorticosteroid-related AEs were probably over-reported in Nef-202 in contrast to Nef-301 (AEs solicited using a questionnaire in Nef-202). The sparse safety data submitted (exposure below 300-600 patients as recommended in CPMP/ICH/375/95) might be partially compensated by the fact, that budesonide is a long-established medical drug. Furthermore, there may be yet unknown safety-related issues associated with its special pharmacokinetics and its use in a highly special target population. These will be monitored in post-marketing surveillance via periodic safety updates reports (PSURs) and in the ongoing phase 3 study (Nef-301).

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 – none 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.

Budesonide is metabolised by cytochrome P450 3A4 (CYP3A4) – hence all drugs that induce or inhibit CYP3A4 affect the plasma concentration. Nevertheless, because of the delayed release mode of action, the systemic exposure should be significantly lower than when budesonide is administered systemically. Instead, the capsules pass through the GI tract to deliver its constituents mainly locally in the Ileum. The applicant has alleviated concerns regarding the influence of medication that can affect gastric pH.

The incidence of TEAEs was balanced between the treatment arms – 85.8% in patients treated with budesonide compared to 69.7% in the placebo group. The most common TEAEs compared to placebo across both studies ranging from 10-20% of affected patients were hypertension, muscle spasms, edema peripheral, and acne – all known side effects from budesonide treatment.

Updated safety data demonstrated that in patients with BMI≥30 kg/m^2, 11 (12.9%) Kinpeygo-treated patients reported TEAEs of hypertension compared to none in the placebo-treated patients. The applicant has provided a discussion whether a warning for increased rate of hypertension in patients that have a BMI≥30 kg/m^2 in section 4.4 should be included. The main counterargument was that there is no statistical difference between hypertension occurrence in BMI≥30 kg/m^2 and BMI≤30 kg/m^2 for Kinpeygo and placebo-treated patients. It is considered that the statistical test used lacks the power to rule out that hypertension is increased in BMI≥30 kg/m^2 patients. However, since hypertension is already included in 4.8 of the SmPC, this issue is not pursued further.

Regarding body weight, the changes in mean body weight are not considered clinically relevant. Several outliers with body weight increase of ≥ 10 kg specifically occurred in the Kinpeygo group, but not with placebo. This weight gain was probably caused by increased appetite, edema and fluid retention as an effect of budesonide and/or a consequence of the underlying kidney disease. It is somewhat re-assuring that the incidence of severe infections requiring hospitalisation was not increased in the budesonide group, but on the other hand, the study population may not have been large enough to detect such events. However, the frequency of non-serious, specifically bacterial, infections appears to be numerically increased. Thus, the increased risk of infections is mentioned in section 4.8 of the SmPC, where adverse drug reactions typical of systemic glucocorticosteroids are listed. In analogy to the corresponding section of the SmPC of the reference product Entocort, this list has been extended by further examples of potential glucocorticoid-related AEs.

Rates of serious TEAEs are low and distributed equally across treatment groups, 10.4% in the budesonide group versus 5.3% in placebo. Most serious TEAEs occurred once in single patients, with the exception of pulmonary embolism (2 events). In general, thromboembolic events are an issue as these are known to be associated with glucocorticoid therapy and occurred 5 times (3x deep vein/ venous thrombosis and 2x pulmonary embolism) during the Nef-301 and Nef-202 studies. The assessment of these events is complicated by risk factors and concomitant medications. The applicant also discussed the relationship between thromboembolic events and (locally delivered) budesonide and concluded based on literature and low systemic exposure that an inclusion in the SmPC is not needed. The applicant will closely monitor these events in upcoming periodic safety update single assessment (PSUSA) procedures and review the literature. There have been two deaths reported in the Kinpeygo treatment group; one was a fatal coronavirus infection that occurred during the "on treatment" phase and one was a cerebral haemorrhage that occurred during follow-up. Neither was considered by the investigator to be potentially related to study treatment. In addition, no immunological events were reported. However, a high local steroid exposure of the gut could potentially affect immunological gastrointestinal functions. Updated analysis and medical data review of the data by the applicant showed this is likely not the case.

During the clinical development program, 24 patients that received the highest dose of Kinpeygo (16 mg) were discontinued, 6 discontinued patients received the 8 mg dose, and 6 patients were on

placebo. All TEAEs that were the cause of study discontinuation occurred also in other patients and all TEAEs were expected from the safety profile of budesonide.

Routine pharmacovigilance activities will include the 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 has been included in the risk management plan (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 periodic safety update reports (PSUSRs) accordingly.

From the safety database all the adverse reactions reported in clinical trials have been included in the Summary of Product Characteristics.

2.4.10. Conclusions on the clinical safety

The safety profile of Kinpeygo has been well characterised in the clinical development program 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. Risk Management Plan

2.5.1. Safety concerns

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

2.5.2. Pharmacovigilance plan

The pharmacovigilance plan consists of routine pharmacovigilance activities including the collection, assessment and processing of individual case safety reports, an ongoing safety surveillance and periodic signal detection. Further, the following routine pharmacovigilance activities beyond adverse reactions reporting and signal detection will address the missing information 'use in pregnancy and lactation':

- Specific adverse reaction follow-up questionnaire: Targeted Pregnancy/ Breast-feeding follow-up questionnaire. The purpose of the targeted questionnaire is to closely follow-up events in pregnant/ breast-feeding women as well as the foetus/ born child and/or breast-fed child including but not limited to spontaneous miscarriage, elective termination, normal birth, or congenital abnormality of patient exposed to Kinpeygo during pregnancy and breast-feeding as well as any complications occurring in the foetus, the born child and/ or breast-fed child of patients exposed to Kinpeygo.

- Other forms of routine pharmacovigilance activities: Cumulative review of case reports on the use of Kinpeygo in pregnancy and lactation, which will be included in the PSUR

There will be no additional pharmacovigilance activities.

2.5.3. Risk minimisation measures

Safety concerns	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/ Breastfeeding 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

2.5.4. Conclusion

The CHMP and PRAC considered that the risk management plan version 0.5 is acceptable.

2.6. Pharmacovigilance

2.6.1. Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.6.2. Periodic Safety Update Reports submission requirements

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.

Based on the fact that IgAN is a new indication for budesonide and will be authorised under a conditional marketing authorisation awaiting confirmatory efficacy results from part B of the pivotal study Nef-301, the PRAC is of the opinion that a separate entry in the EURD list for Kinpeygo is needed, as it cannot follow the already existing entry for budesonide. The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. The applicant did request the alignment of the new PSUR cycle with the international birth date (IBD). The IBD is 15 December 2021. The new EURD list entry will therefore use the IBD to determine the forthcoming Data Lock Points.

2.7. Product information

2.7.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

2.7.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Kinpeygo (budesonide) is included in the additional monitoring list as it is approved under a conditional marketing authorisation (Reg Art 14-a).

Therefore, the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-risk balance

3.1. Therapeutic Context

3.1.1. Disease or condition

Kinpyego (budesonide) is 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 request of the CHMP to restrict the previously claimed broader indication.

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.

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 (National Organization for Rare Disorders [NORD]).

3.1.2. Available therapies and unmet medical need

There are currently no treatments approved for the management of patients with primary IgAN. Supportive treatment recommendations have been provided in the KDIGO 2021 guideline.

Standard of care comprises of supportive therapy, which focuses on a lowering the proteinuria and optimal blood pressure control by maximum tolerated inhibition of the RAS, together with a low sodium diet (KDIGO 2021, Trimarchi et al 2019). For patients with persistent proteinuria >1 g/day, rigorous blood pressure control with ACEIs and/or ARBs [RAS inhibitor therapy] to achieve blood pressure targets of <130/80 mm Hg is the cornerstone of therapy.

When proteinuria persists despite the optimal RAS inhibition with ACEIs/ARBs, patients are at risk of progression to ESRD, there are no further recommended treatments, and management options are generally limited to consideration of an off-label 6-month treatment course of high-dose systemic glucocorticosteroid.

Additional immunosuppressants beyond glucocorticosteroid, such as cyclophosphamide, are suggested for specific situations only, for example in cases of crescentic IgAN where renal function is rapidly deteriorating. Notably, the KDIGO 2021 guideline suggests that mycophenolate mofetil should not be used in IgAN patients due to heterogeneity of outcomes and potential side effects.

Considering the lack of approved therapies, the severe side effects associated with systemic glucocorticosteroid use, and the possibility of progression to ESRD, dialysis and transplantation, there is an unmet medical need for an efficacious and safe treatment, especially for patients with persistent proteinuria despite optimized RAS inhibition.

3.1.3. Main clinical studies

The main evidence of efficacy is based on pivotal data from Part A of the phase 3, randomised, double-blind, placebo-controlled study of Kinpeygo 16 mg (N=97) once daily compared with placebo (N=102) in patients with primary IgAN on a background of optimized RAS inhibitor therapy (Nef-301).

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.

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.

Additional efficacy data were provided from the supportive phase 2b randomised, double-blind, placebo-controlled study (Nef-202).

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 (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.

Efficacy results in the supportive Phase 2b study (Nef-202)

- After 9 months of treatment, patients treated with Kinpeygo 16 mg once daily showed a 26% reduction in UPCR compared to placebo ($p=0.0051$).
- After 9 months of treatment, Kinpeygo 16 mg once daily provided a 12% (7.63 mL/min/1.73 m^2) treatment benefit on eGFR ($p=0.0026$), compared to placebo. This corresponded to a stabilisation of eGFR (minor increase of 0.44 mL/min/1.73 m2 from baseline) in patients who received Kinpeygo 16 mg once daily and a deterioration from baseline of 7.19 mL/min/1.73 m^2 in patients who received placebo.

In the pooled dataset comparing Kinpeygo 16 mg/day with placebo, the UPCR treatment effect was consistent across subgroups.

3.3. Uncertainties and limitations about favourable effects

- UPCR as surrogate endpoint of renal function is not considered fully validated and representative on its own for benefits in clinical outcome. Therefore, the benefit-risk assessment also included measures of eGFR values to evaluate Kinpeygo's effect on renal

function. Long term effects will be further assessed with the results of the ongoing phase 3 study (Nef-301).

- The rate of loss of renal function (eGFR chronic slope) does not reach statistical significance in the overall study population and in subgroups with baseline UPCR levels <1.3 g/gram. Therefore, the indication was restricted to patients at risk of rapid disease progression with a UPCR ≥1.5 g/gram.
- Inconsistencies between the Nef-301 and Nef-202 trials in regard to eGFR curves were observed: There is a peculiar (mean) increase of eGFR after 3 months treatment in Nef-301, and thereafter the eGFR decrease appears to be similar in the two arms suggesting that there is no difference between the two arms in the rate of loss of kidney function from month 3 through 12. In the Nef-202 study the (mean) decrease in both arms appears linear and the slopes differ. These data raised questions about the ability of the drug to slow the rate of loss of kidney function and have a meaningful effect on progression to kidney failure. However, these uncertainties have been addressed for now for a subgroup of patients with higher levels of baseline proteinuria in the context of a conditional marketing authorisation application
- There were also uncertainties with respect to the relationship between the results of the surrogate endpoints and clinical outcome (e.g. time to first occurrence of a composite of death, ESKD, or a decline exceeding 40% in eGFR) which could not be resolved by the modelling data provided due to methodological concerns. However, despite these uncertainties an acceptable positive benefit/risk was concluded. In addition, these concerns will be addressed with the results of the ongoing phase 3 study (Nef-301).

3.4. Unfavourable effects

- The frequency of TEAEs leading to discontinuation of study drug in Nef-301 study was 13 (9.7%) in Kinpeygo 16 mg-treated patients vs. 2.3% in the placebo group, with 6 Kinpeygo-treated patients undergoing dose reduction. In total, 13.1% of patients discontinued due to TEAEs versus 3.3% in the placebo group.
- The incidence of TEAEs was balanced between the treatment arms – 85.8% in patients treated with budesonide compared to 69.7% in the placebo group.
- The most common TEAEs compared to placebo across both studies (Nef 202, Nef-301) ranging from 10-20% of affected patients were muscle spasms, muscle spasms, hypertension, edema peripheral, and acne – all known side effects from budesonide treatment.
- Rates of serious TEAEs were low in Part A of study Nef-301 (10.4% in the budesonide group versus 5.3% in placebo).
- Two deaths have been reported across the clinical development program, both in the Kinpeygo treated patients. Both were reported as not related to the treatment (corona infection and a case of cerebral haemorrhage during follow up 300+ days after last dose).

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=10).

3.6. Effects Table

Table 59 Effects table for Kinpeygo in 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 (data cut-off: 15 March 2021)

Effect	Short Description	Unit	9 months		12 months		Study Ref
			Kinpeygo 16 mg	Placebo	Kinpeygo 16 mg	Placebo	
Favourable Effects							
UPCR	Ratio of geometric LSmean UPCR compared to baseline (96% CI)	(g/g)	0.69 (0.61 to 0.79)	0.95 (0.83 to 1.08)	0.48 (0.42 to 0.56)	0.93 (0.81 to 1.07)	Nef 301
	Percentage reduction (96% CI)	%	31% (21% to 39%)	5% (-8% to 17%)	52% (44% to 58%)	7% (-7% to 19%)	Nef 301
	Kinpeygo 16 mg versus Placebo		0.73 (0.61 to 0.88); p=0.0003 27% (12% to 39%)		0.52 (0.42 to 0.64); p<0.0001 48% (36% to 58%)		Nef 301
eGFR	Ratio of geometric LSmean eGFR compared to baseline (95% CI)	mL/ min/ 1.73 m2	1.00 (0.96 to 1.03)	0.93 (0.90 to 0.96)	0.97 (0.93 to 1.01)	0.91 (0.88 to 0.95)	Nef 301
	percentage reduction (95% CI)	%	0% (-4% to 3%)	-7% (-10% to -4%)	-3% (-7% to 1%)	-9% (-12% to -5%)	Nef 301
	Change in eGFR from baseline	mL/ min/ 1.73 m2			-1.1	-10.1	Nef 301

Effect	Short Description	Unit	9 months		12 months		Study Ref
			Kinpeygo 16 mg	Placebo	Kinpeygo 16 mg	Placebo	
	Kinpeygo 16 mg versus Placebo		1.07 (1.03 to 1.13); p=0.0014 7% (3% to 13%)		1.07 (1.01 to 1.13); p=0.0106 7% (1% to 13%) 3.56		Nef 301
UPCR	Percentage reduction in UPCR at 9 months compared to baseline (95% CI)		25% (9% to 39%)	-4% (-24% to 13%)	32% (18% to 43%)	-0.0% (-18% to 14%)	Nef 202
	Ratio of geometric LSmean UPCR compared to baseline (95% CI)	(g/gram)	0.75 (0.61, 0.91)	1.04 (0.87, 1.24)	0.68 (0.57, 0.82)	1.00 (0.86, 1.18)	Nef 202
	Kinpeygo 16 mg versus Placebo		0.72 (0.56, 0.92); p=0.0051 28% (8% to 44%)		0.68 (0.54, 0.85); p=0.0005 32% (15% to 46%)		Nef 202
eGFR	Ratio of geometric LSmean eGFR compared to baseline (95% CI)	mL/min/1.73 m2	1.01 (0.95, 1.07)	0.90 (0.85, 0.96)	0.99 (0.92, 1.07)	0.89 (0.83, 0.95)	Nef 202
	percentage reduction (95% CI)	%	1% (-5% to 7%)	-10% (-15% to -4%)	-1 (-8% to 7%)	-11% (-17% to -5%)	Nef 202
	Kinpeygo 16 mg versus Placebo		1.12 (1.03, 1.21); p=0.0026 12% (3% to 21%)		1.11 (1.01, 1.23); p=0.0134 11% (1% to 23%)		Nef 202
Unfavourable Effects							

Effect	Short Description	Unit	9 months		12 months		Study Ref
			Kinpeygo 16 mg	Placebo	Kinpeygo 16 mg	Placebo	
discontinuation of the drug	frequency of TEAEs leading to discontinuation of study drug	%	13.1	3.3			Pooled Nef 301and Nef202
TESAE	Patients with any TESAE	%	9.0	3.9			Pooled Nef 301 and Nef202

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Importance of favourable effects

The primary endpoint of the pivotal study, reduction of proteinuria (UPCR) at 9 months compared to baseline, was met. The reduction of proteinuria could be observed already at earlier stages after starting the treatment (at 3 months and 6 months) but was more pronounced at 12 months. 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 % treatment benefit compared to placebo. In contrast to proteinuria (primary endpoint), this effect was not pronounced after 12 months, which is not surprising because 1 year treatment/observation phase, especially under continuous RAS treatment, is too short to see any effect at the level of eGFR.

Additional analyses indicated that the difference in 1-year eGFR chronic slope between Kinpeygo and placebo first became statistically significant at a UPCR threshold of 1.3 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 (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.

Treatment duration of 9 months at a 16 mg once daily dose is supported by the pivotal phase 3 study (Nef-301 Part A) and the phase 2b study (Nef 202). Nevertheless, IgAN is a chronic autoimmune disease and repetition of treatment cycles may become necessary. Part B of the Nef-301 study and the open-label extension study (phase 3b Nef-301) will provide additional information on duration of efficacy and relapse for both single and repeated 9-months treatment cycles (see Annex II).

Importance of unfavourable effects

The safety profile of Kinpeygo has been well characterised in the clinical development program and is in line with the known safety profile of already approved budesonide medicinal products. The most commonly reported adverse drug reactions were acne reported in approximately 10% of patients, hypertension, peripheral oedema, face oedema, and dyspepsia, each occurring in approximately 5% of patients; these were mainly of mild or moderate severity and reversible, reflecting the low systemic exposure to budesonide after oral administration. Overall, the data demonstrated an acceptable safety profile consistent with the known active ingredient.

3.7.2. Balance of benefits and risks

Overall, the conduct of two double-blinded, placebo-controlled trials in an orphan disease with an acceptable large number of patients at intermediate to high-risk for disease progression is positively recognised. Treatment was generally well-tolerated, with a safety profile consistent with the known active ingredient.

The evidence provided by the applicant on the adequacy of UPCR as a surrogate endpoint for renal function is generally considered appropriate.

However, in addition to the UPCR measures, the benefit-risk assessment needs to include measured eGFR values to evaluate Kinpeygo's effect on renal function. While the primary endpoint UPCR is statistically significant in the overall study population, there is little evidence of renal benefit in terms of slowing the decline of renal function as measured by eGFR for the pre-specified subgroup of patients with lower levels of baseline proteinuria (cut-off value of <1.5 g/gram) based on the eGFR values provided.

Therefore, the limitation of approval to the subgroup with higher levels of proteinuria appears justified for the following reasons. First, the primary endpoint reduction in UPCR has shown robust and statistically significant results in both the broad population and the pre-specified subgroup with UPCR ≥ 1.5 g/gram at baseline. Second, the secondary endpoint on eGFR slope, necessary to support the clinical relevance of the surrogate primary endpoint on proteinuria, has revealed a convincing outcome only in the proposed subgroup, but not in the overall patient population. Third, the earlier reduction of UPCR in the pre-defined subgroup, which is reflected in a significantly delayed decline in eGFR over 1 year when compared with placebo, provides a plausible rationale for the effect in the subgroup.

Therefore, the indication is restricted to patients with higher levels of baseline proteinuria (cut-off value of ≥ 1.5 g/gram). The efficacy of Kinpeygo for the treatment of primary IgAN and more particularly the clinical consequences of proteinuria reduction, as measured by eGFR, will be confirmed with the results of Part B of study Nef 301 (see Annex II).

The safety profile of Kinpeygo has been well characterised in the clinical development program and is in line with the known safety profile of already approved budesonide medicinal products.

3.7.3. Additional considerations on the benefit-risk balance

Conditional marketing authorisation

As comprehensive data on the product are not available yet, a conditional marketing authorisation was requested by the applicant in the initial submission.

The product falls within the scope of Article 14-a of Regulation (EC) No 726/2004 concerning conditional marketing authorisations, as it aims at the treatment of a life-threatening disease. In addition, the product is designated as an orphan medicinal product.

Furthermore, the CHMP considers that the product fulfils the requirements for a conditional marketing authorisation:

- The benefit-risk balance is positive, as discussed in section 3.7.2.
- It is likely that the applicant will be able to provide comprehensive data on safety and efficacy through the phase 3 study (Nef-301).

Data of eGFR slope were provided for UPCR cut-offs from ⩾1.0 to 2.0 g/gram at baseline. These analyses indicate that the difference in 1-year eGFR chronic slope between Kinpeygo and placebo first becomes statistically significant at a UPCR threshold of 1.3 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 (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. Clinical benefit in this patient population is considered likely to be confirmed at the time of the final analysis of the phase 3 study (Nef-301).

- Unmet medical needs will be addressed, as

There are no treatments approved for the management of patients with primary IgIAN. Patients with baseline UPCR ⩾1.3 g/gram are at risk of rapid disease progression to ESRD over a short period of time and represent a group of patients for whom the unmet medical need is considerable. Without treatment, an eGFR deterioration of 9.36 mL/min/1.73 m^2 per year would be expected (1-year eGFR slope in the placebo group of the phase 3 trial), and as a result these patients are at significant risk of requiring dialysis or kidney transplantation in the near term.

Although long term data are currently missing on whether the effects on proteinuria and eGFR are sustained over a longer time period and despite some uncertainties regarding the claimed locally acting targeted-release effect on the Peyer´s Patch, it is considered that the product will fulfil an unmet medical need in the approved indication for the treatment of primary IgAN in adults at risk of rapid disease progression with a UPCR ⩾1.5 g/gram.

- The benefits to public health of the immediate availability outweigh the risks inherent in the fact that additional data are still required.

Considering the lack of approved therapies, the serious side effects associated with the use of systemically acting GCSs and the high likelihood of progression to ESRD, dialysis and transplantation, there is a high unmet medical need for an efficacious and safe treatment for IgAN, to prevent or reduce further deterioration in renal function, thereby preserving residual functionality and avoiding progression to ESRD.

Efficacy of Kinpeygo has been demonstrated in a subgroup of patients with higher level of proteinuria. The profile safety of Kinpeygo containing a well-known active substance, budesonide, is considered acceptable. Long-term efficacy and safety will be addressed in the study Nef-301.

In light of the above, it is agreed, that the benefits to public health of the immediate availability of the medicinal product outweigh the risks inherent in the fact that additional data are still required.

3.8. Conclusions

The overall benefit/risk balance of Kinpeygo is positive, subject to the conditions stated in section 'Recommendations'.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Kinpeygo is favourable in the following 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.

The CHMP therefore recommends the granting of the conditional marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to medical prescription.

Other conditions and requirements of the marketing authorisation

- ***Periodic Safety Update Reports***

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.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency.
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Specific Obligation to complete post-authorisation measures for the conditional marketing authorisation

This being a conditional marketing authorisation and pursuant to Article 14-a of Regulation (EC) No 726/2004, the MAH shall complete, within the stated timeframe, the following measures:

Description	**Due date**
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.	September 2023

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States.

Not applicable