Medicinrådet

Bilag til Medicinrådets anbefaling vedrørende TRF-budesonid til behandling af primær immunglobulin A-nefropati hos voksne med risiko for hurtig sygdoms-progression med et urinprotein-til-kreatinin-forhold ≥ 1,5 g/g

Vers. 1.0

Bilagsoversigt

1. Ansøgers notat til Rådet vedr. budesonid
2. Forhandlingsnotat fra Amgros vedr. budesonid
3. Ansøgers endelige ansøgning vedr. budesonid

Notat til Medicinrådets udkast til anbefaling vedr. Kinpeygo til behandling af primær immunglobulin A (IgA)-nefropati (IgAN) hos voksne med risiko for hurtig sygdomsprogression med et urinprotein-til-kreatinin-forhold ≥ 1,5 g/g.

STADA Nordic vil gerne takke sekretariatet for et godt samarbejde og den fleksibilitet, der har præget processen med ansøgningen samt de spørgsmål, der er opstået undervejs. Vi ser frem til Medicinrådets beslutning og bidrager gerne med nedenstående input.

I Danmark følger behandlingen af patienter med IgA-nefropati retningslinjerne fra KDIGO (Kidney Disease: Improving Global Outcomes). Dansk Nefrologisk Selskabs arbejdsgruppe er enig i KDIGO GN 2021 -retningslinjerne, som fraråder brug af antikoagulation, azathioprin, MMF, CNI, RTX, fiskeolie eller hydroxychloroquin til disse patienter. Arbejdsgruppen anbefaler, at patienter med høj risiko for forværring af nyrefunktionen (på trods af optimal antiproteinurisk behandling i 3-6 måneder) kan tilbydes behandling med Prednisolon i 7-9 måneder eller henvises til en nefrologisk afdeling, der deltager i afprøvning af nye lægemidler. (Dansk Nefrologisk Selskab)

KDIGO-retningslinjerne for behandling af IgAN er dog for nylig blevet opdateret og offentliggjort med en foreløbig version, der er åben for kommentarer. Opdateringen er ventet i betragtning af de mange kliniske aktiviteter på området i de seneste år, herunder FDA's og EMA's godkendelse af 2 IgAN-specifikke lægemidler og flere, der i øjeblikket er i fase 2 og 3. De nye retningslinjer gør at nogle af anbefalingerne i 2021-versionen er blevet forældede.

Der foreligger i øjeblikket ingen head-to-head-studier, der direkte sammenligner effektiviteten eller sikkerheden af Kinpeygo med systemiske kortikosteroider. På grund af forskelle i studiedesign og baseline-karakteristika er det ikke muligt at lave direkte sammenligninger mellem de enkelte studier. En indirekte sammenligning (ITC) mellem Kinpeygo og systemiske kortikosteroider kan dog være mulig via et netværk af relevante studier. Forskelle i baseline-karakteristika og behandlingsregimer (inklusive baggrundsbehandlinger) gør det imidlertid vanskeligt at kontrollere for variationer mellem studierne og risiko for bias.

I NefIgArd-studiet er forekomsten af infektioner sammenlignelig mellem behandlingsgrupperne, alvorlige bivirkninger (SAEs) er jævnt fordelt, og nye tilfælde af diabetes er sjældne. Den tilgængelige evidens indikerer derfor, at Kinpeygo har en bedre sikkerhedsprofil sammenlignet med systemiske kortikosteroider.

Når vi ser på sikkerhedsprofilen for Kinpeygo i forhold til andre glukokortikoidprodukter, vurderer vi, at sikkerheden ved eksisterende immunosuppressive behandlinger er usikker. Brugen af systemiske kortikosteroider bør kun overvejes efter nøje overvejelse og diskussion med patienten, og kun i udvalgte patientgrupper. I STOP-IgAN-studiet, der omhandlede en kaukasisk population, viste immunosuppressiv behandling ingen fordele i forhold til renal overlevelse over 10 år sammenlignet med understøttende behandling alene, men resulterede i flere bivirkninger. TESTING-studiet af methylprednisolon mod placebo i asiatiske patienter med IgAN viste, at methylprednisolon var overlegen i forhold til placebo til nyreoverlevelse, men studiet blev afsluttet tidligt på grund af en høj forekomst af alvorlige bivirkninger i methylprednisolongruppen, især alvorlige infektioner. Derfor anses systemiske kortikosteroider ikke som standardbehandling ifølge retningslinjerne og er derfor ikke en relevant sammenligningsbehandling i kliniske studier for Kinpeygo.

Vi har gennemgået udkastet til vurderingsrapporten og vil gerne opfordre Medicinrådet til at tage højde for, at der er væsentlige forskelle mellem patientbehandlingen i dansk klinisk praksis og de eksisterende studier.

På baggrund af de nye KDIGO-retningslinier mener vi, at Kinpeygo bør være et standardtilbud til danske patienter:

1. Nefecon (Kinpeygo) er den eneste behandling, der til dato har vist sig at reducere niveauerne af patogene former af IgA og IgA-immunkomplekser (Public Review Draft, KDIGO 2024).
2. NICE-komitéen har vurderet, at målrettet budesonid som tillæg til optimeret standardbehandling sandsynligvis er en omkostningseffektiv anvendelse af NHS' ressourcer sammenlignet med standardbehandling alene. Der er dog begrænset data om gentagen brug af målrettet budesonid, men behandlingen blev godkendt i december 2023. (www.nice.org.uk/guidance/ta937)
3. Ifølge det seneste KDIGO Public Review Draft foreslås det, at en 9-måneders behandling med Nefecon (Kinpeygo) bør tilbydes patienter med risiko for progression af nyrefunktionstab ved IgAN (Public Review Draft, KDIGO 2024).

På baggrund af ovennævnte retningslinier forventer vi, at flere sammenlignelige lande vil følge disse, hvilket vil føre til yderligere studier og post-marketing overvågning.

Hvis Medicinrådet ønsker yderligere data for at bekræfte fund og effekt af ovennævnte retningslinier vil vi gerne kunne tilbyde danske patienter behandlingen ud fra en individuel klinisk vurdering, så danske speciallæger kan opnå erfaring og indsigt, samtidig med at andre europæiske lande, der følger NICE og/eller KDIGO-retningslinjerne vil komme med yderligere data. Vi håber derfor, at Rådet vil være åbne for en senere revurdering, når flere data og eventuelle danske erfaringer er tilgængelige.

Vi planlægger lancering og aftale med Amgros, så Kinpeygo vil blive tilgængeligt i Danmark, med henblik på at enkelte speciallæger kan vælge at ordinere til udvalgte patienter på en individuel godkendelse.

Med venlig hilsen

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30.08.2024
DBS/CAF

Forhandlingsnotat

Dato for behandling i Medicinrådet	25.09.2024
Leverandør	Stada Nordic
Lægemiddel	Kinpeygo (TRF-Budesonid)
Ansøgt indikation	TRF-budesonid til behandling af primær immunglobulin A nefropati hos voksne med risiko for hurtig sygdomsprogression med et urinprotein-til-kreatinin-forhold ≥ 1,5 g/g
Nyt lægemiddel / indikationsudvidelse	Formulering: kapsler med ny styrke og modificeret udløsning

Prisinformation

Amgros har forhandlet følgende pris på Kinpeygo (budesonid):

Tabel 1: Forhandlingsresultat, betinget pris

Lægemiddel	Styrke	Pakningsstørrelse	AIP (DKK)	Forhandlet SAIP (DKK)	Rabatprocent ift. AIP
Kinpeygo	4 mg	120 stk.	59.294,01	[redacted]	[redacted]

Prisen er betinget af Medicinrådets anbefaling.

Hvis ikke Medicinrådet anbefaler Kinpeygo, indkøbes lægemidlet til følgende pris:

Tabel 2: Forhandlingsresultat, ubetinget pris

Lægemiddel	Styrke	Pakningsstørrelse	AIP (DKK)	Forhandlet SAIP (DKK)	Rabatprocent ift. AIP
Kinpeygo	4 mg	120 stk.	59.294,01	[redacted]	[redacted]

Aftaleforhold

Amgros indgår en aftale med leverandøren på enten det betingede pristilbud eller det ubetingede pristilbud alt afhængig af Medicinrådets beslutning. [redacted]

[redacted] Budesonid findes i dag i mange formuleringer og alle formuleringer er udbudt med samme betingelser.

Konkurrencesituationen

TRF-budesonid er det første lægemiddel med indikation til behandling af primær immunglobulin A nefropati (IgAN). TRF-budesonid er dermed en ny styrke og formulering af et ældre lægemiddel. Der er mange forskellige formuleringer af budesonid til andre indikationer. Der findes en pakning med en styrke på 3 mg, der også har en formulering med modificeret udløsning. [redacted]

Tabel 3 viser lægemiddeludgiften for 9 måneders behandling med TRF-budesonid.

Tabel 3: Lægemiddeludgifter pr. patient

Lægemiddel	Styrke	Paknings-størrelse	Dosering	Pris pr. pakning (SAIP, DKK)	Lægemiddeludgift for 9 måneder (SAIP, DKK)
Kinpeygo	4 mg	120 stk.	16 mg dagligt	[redacted]	[redacted]

Status fra andre lande

Tabel 4: Status fra andre lande

Land	Status	Link
Norge	Under evaluering	Link til vurderingen
England	Godkendt	Link til anbefaling

Konklusion

Amgros vurderer, at leverandøren på nuværende tidspunkt ikke kan give en bedre pris fordi der ikke er mulighed for at få en aftale med en fortrolig pris. Denne ene formulering på 4 mg bliver inkluderet i et normalt udbud på linje med andre lægemidler med indholdsstoffet budesonid.

[redacted]

Application for the assessment of Kinpeygo (TRF-budesonide) for primary immunoglobulin A nephropathy (IgAN)

Contact information

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Table of contents

Tables and Figures

List of Tables

List of Figures

Abbreviations

Abbreviation	Definition
ACEi	Angiotensin-converting enzyme inhibitor
ACTH	Adrenocorticotropic hormone
ADPKD	Autosomal dominant polycystic kidney disease
AE	Adverse event
AESI	Adverse event of special interest
AIC	Akaike Information Criterion
AQoL	Assessment of Quality of Life
ARB	Angiotensin II receptor blocker
AUC	Area under the curve
BIC	Bayesian Information Criterion
BMI	Body-mass index
BP	Blood pressure
CE	Cost-effectiveness
CEM	Cost-effectiveness model
CFB	Change from baseline
CI	Confidence interval
CKD	Chronic kidney disease
CKD-EPI	Chronic kidney disease epidemiology collaboration
CL	Confidence limit
Covid-19	Coronavirus Disease 2019
CrI	Credible interval
CRP	C-reactive protein
CSR	Clinical study report
CTP	Clinical trial protocol
CV	Cardiovascular
CVD	Cardiovascular disease
CYP3A4	Cytochrome P450 3A4
DAPA	Dapagliflozin
DAPA-CKD	Dapagliflozin and Prevention of Adverse Outcomes in Chronic Kidney Disease
DB	Data cutoff
DBP	Diastolic blood pressure
DKK	Danish Krone
DM	Diabetes mellitus
DNSL	Dansk Nefrologisk Selskabs Landsregister
DSA	Deterministic sensitivity analysis
DSU	Decision Support Unit
EBMR	Evidence Based Medicine Reviews
eCRF	Electronic case report form
eGFR	Estimated glomerular filtration rate
EMA	European Medicine Agency
EQ-5D	EuroQol-5 Dimension
ESRD	End-stage renal disease
ESS	Effective sample size
FAS	Full analysis set
FDA	Food and Drug Administration
FE	Fixed effect
GCS	Glucocorticosteroid
gd	Galactose-deficient
GFR	Glomerular filtration rate
GI	Gastrointestinal
GN	Glomerulonephritis
GP	General practitioner

h	Hours
HIV	Human immunodeficiency virus
HR	Hazard ratio
HRQoL	Health-related quality of life
HSU	Health state utility
HSUV	Health state utility value
HTA	Health technology assessment
HUI	Health Utilities Index
ICER	Incremental cost-effectiveness ratio
IgA	Immunoglobulin A
IgAN	Immunoglobulin A nephropathy
IPD	Individual patient data
IQR	Interquartile range
IRT	Interactive response technology
IS	Immunosuppressant
IST	Immunosuppressive therapy
ITC	Indirect treatment comparison
KDIGO	Kidney Disease – Improving Global Outcomes
KM	Kaplan-Meier
KOL	Key opinion Leader
LS	Least Squares
LSI	Life Satisfaction Index
MAIC	Matching-adjusted indirect comparison
MCMC	Markov chain Monte Carlo
MCS	Mental component score
MD	Mean difference
MesPGN	Mesangioproliferative GN
MHRA	Medicines and Healthcare products Regulatory Agency
mL/min	Millilitres per minute
mm Hg	Millimetres of mercury
MMF	Mycophenolate mofetil
MMRM	Mixed-effects model for repeated measures
MRU	Medical resource use
MTD	Maximum tolerated dose
N	Number of patients
N/A	Not applicable
N/E	Not estimated
NICE	National Institute for Health and Care Excellence
NMA	Network meta-analysis
NR	Not reported
od	Once daily
OLE	Open-label extension
OR	Odds ratio
PCS	Physical component score
PF	Prognostic factor
PLD	Patient level data OR pseudo patient level data
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PSA	Probabilistic sensitivity analysis
PT	Preferred term
QALY	Quality-adjusted life years
QLI	Quality of Life Index
RaDaR	National Registry of Rare Kidney Diseases
RAS	Renin-angiotensin system
RASi	Renin-angiotensin system inhibitor
RCT	Randomised controlled trial
RE	Random effect

Ref	Reference
RRT	Renal replacement therapy
SAE	Serious adverse event
SAS	Safety analysis set
SBP	Systolic blood pressure
SD	Standard deviation
SE	Standard error
SEM	Standard error of the mean
SF	Short Form health survey
SF-36	Short Form-36
SG	Standard gamble
SGLT2i	Sodium-glucose cotransporter-2 inhibitor
SLR	Systematic literature review
SMC	Scottish Medicines Consortium
SMD	Standardised mean difference
SMR	Standardised mortality ratio
SoC	Standard of care
STOP-IgAN	Supportive therapy with vs. without immunosuppressive treatment
TEAE	Treatment-emergent adverse event
TEAESI	Treatment-emergent serious adverse event of special interest
TEM	Treatment-effect modifier
TESAE	Treatment-emergent serious adverse event
TESTING	Therapeutic Effects of Steroids in IgA Nephropathy Global
TRF	Targeted-release formulation
TRF-BUD	Targeted-release formulation budesonide
TSD	Technical Support Document
TTD	Time to treatment discontinuation
TTO	Time trade-off
tx	Treatment
UACR	Urine albumin-to creatinine ratio
UK RaDaR	United Kingdom National Registry of Rare Kidney Diseases
UPCR	Urine protein-to-creatinine ratio
US	United States
UTI	Urinary tract infection
VAS	Visual analogue scale
WBC	White blood cell

1. Regulatory information on the medicine

Overview of the medicine	
Proprietary name	Kinpeygo
Generic name	TRF-budesonide
Therapeutic indication as defined by EMA	Primary IgAN in adults at risk of rapid disease progression with a UPCR ≥1.5 g/g [1, 2]
Marketing authorization holder in Denmark	Calliditas Therapeutics AB
ATC code	A07EA06
Combination therapy and/or co-medication	No
Date of EC approval	15 July 2022

Overview of the medicine	
Has the medicine received a conditional marketing authorization?	Yes, conditional approval was granted for the subgroup UPCR ≥1.5 g/g. Application for the full trial population (patients with IgAN) in the NefIgArd trial has been submitted.
Accelerated assessment in the European Medicines Agency (EMA)	No
Orphan drug designation (include date)	Yes, November 2016 [3]
Other therapeutic indications approved by EMA	No
Other indications that have been evaluated by the DMC (yes/no)	No
Dispensing group	NBS
Packaging – types, sizes/number of units and concentrations	4 mg capsules, 120-tablet (30-day) pack

2. Summary table

Table 1. Summary table of application

Summary	
Therapeutic indication relevant for the assessment	Primary IgAN in adults at risk of rapid disease progression with a UPCR ≥1.5 g/g [1, 2]
Dosage regiment and administration	The recommended dose is 16 mg administered orally, once daily, in the morning at least one hour before a meal.[4] Each capsule strength is 4 mg and the duration of therapy is 9 months, followed by a tapering period. [4]
Choice of comparator	Corticosteroids (prednisolone)
Prognosis with current treatment (comparator)	As presented in Section 8.1.2.2, more patients are progressing to later (more severe) CKD stages in the corticosteroids arm than in the Kinpeygo arm.
Type of evidence for the clinical evaluation	Indirect comparison (NMA and MAIC)
Most important efficacy endpoints (Difference/gain compared to comparator)	[redacted]

Summary	
	[redacted]
Most important serious adverse events for the intervention and comparator	No individual serious adverse event (SAE) occurred in ≥5% of patients treated with Kinpeygo. [redacted] In the STOP-IgAN trial (investigating corticosteroids), there were more events of non-severe and severe infections in the immunosuppression group, predominantly of the GI and respiratory tracts, of which 25% were thought to be related to study treatment.[6] the rates of SAEs and total number of infections were higher among patients receiving immunosuppression compared with those receiving supportive care alone in both subgroups, regardless of baseline eGFR levels.[7]
Impact on health-related quality of life	Clinical documentation: SF-36 data was collected in NefIgArd NEF-301 part A, however, it was not used in the model since patients in Part A of NefIgArd Nef-301 were observed for up to 12 months and no patients progressed to ESRD; therefore, the observed patient-reported outcome data, in the form of the SF-36, would only be available to inform QoL estimates in the CKD 1–4 health states. As patients with IgAN are not expected to experience substantial changes in QoL until they reach ESRD, where dialysis or a transplant is required, using one source to inform the utility values in the CKD 1–5 health states was deemed most appropriate. Furthermore, mapping the trial SF-36 data to the EQ-5D would have introduced additional uncertainty to the model due to the lack of IgAN-specific mapping studies. Health economic model: the model relies on EQ-5D values from the literature (Cooper et al. 2020 [8]) to inform patient utility assumptions. Patients treated with corticosteroids progress to CKD stage 5 faster than those on Kinpeygo, resulting in a lower HRQoL.
Type of economic analysis that is submitted	Type of analysis: Cost-utility Type of model: Markov model (cohort state-transition model)
Data sources used to model the clinical effects	Kinpeygo (TRF-budesonide): • Effects: ○ NefIgArd NEF-301 Part A and B subgroup data for UPCR ≥ 1.5 g/g [5, 9-11] ○ Danish KOL [12], and Sugrue *et al*. 2019 [13] for patient risks of CKD 5, dialysis and kidney transplant ○ UK RaDaR for risk of mortality from CKD stages 1-5, transplant, and dialysis.[14-16] • Adverse events: NefIgArd NEF-301 Part B [5, 10]

Summary	
	Corticosteroids (prednisolone): the ITC was informed by the STOP-IgAN trial, as the TESTING trial comprised a primarily Asian population, not considered relevant to Danish clinical practice [6]
Data sources used to model the health-related quality of life	Cooper *et al*. 2020 [8] In the absence of utility data from the clinical trial, an alternative published study in CKD was identified as a source of HSUVs in the economic model and subsequently validated by clinical opinion.
Life years gained	[redacted]
QALYs gained	[redacted]
Incremental costs	[redacted]
ICER (DKK/QALY)	[redacted]
Uncertainty associated with the ICER estimate	The one-way sensitivity analysis revealed that the three parameters with greatest impact on the ICER results were [redacted]
Number of eligible patients in Denmark	**Year** / 2019 / 2020 / 2021 / 2022 / 2023 **Incidence** / 24 / 24 / 24 / 24 / 24 **Prevalence** / 380 / 404 / 428 / 452 / 476
Budget impact (in year 5)	[redacted]

Note: AUC-based endpoint calculated as a time-weighted average of log-eGFR baseline ratio of measurements at each post-baseline visit compared with baseline for Month 3, 6, 9, 12, 18 and 24 respectively, where recordings made at 18 and 24 months receive twice as much weight as those made at 3, 6, 9, and 12 months; if a subgroup level has fewer than 20 patients exposed to Kinpeygo 16 mg, data in that subgroup level were not assessed; a subgroup is analysed only when it has at least 2 levels assessed; baseline is defined as the geometric mean of the 2 consecutive measurements prior to randomisation

[redacted] Collaboration; eGFR, estimated glomerular filtration rate; FAS, full analysis set; LS, least squares; RAS, renin-angiotensin system; UPCR, urine protein-to-creatinine ratio

Source: DOF (NEF-301 Part B additional tables and figures)[17]

3. The patient population, intervention, choice of comparator(s) and relevant outcomes

3.1 The medical condition

3.1.1 Immunoglobulin A nephropathy (IgAN)

IgAN is a rare disease [18], with a low prevalence which resulted in Kinpeygo being granted an orphan designation.[3] IgAN is a progressive CKD type with a specific underlying pathophysiology implicating the gut-kidney axis and immune-mediated responses.[18-23] Patients often have high levels of galactose-deficient (gd) immunoglobulin As (IgAs), which are produced primarily by the Peyer's patches in the distal ileum of the gastrointestinal (GI) tract. Immune complexes with gd-IgAs and autoantibodies deposit in the kidneys, leading to inflammation and fibrosis, which in some cases results in ESRD.[18-23]

IgAN presents with a broad range of signs and symptoms, including proteinuria,[24, 25] haematuria,[24] tiredness,[25] fatigue[25] and pain,[25, 26] which can cause physical limitations and restrict daily activities.[25] Patients with IgAN suffer anxiety, depression,[25, 27] and fear of progression to ESRD[25] requiring dialysis or transplantation.[28]

Diagnosis

IgAN can only be diagnosed with a renal biopsy that detects IgA deposition in the glomerular mesangium.[18, 29] Diagnosis is based on the MEST-C score, which includes five histological features.[18, 29, 30] There are no validated diagnostic serum or urine biomarkers for IgAN.[29] Patients are often not diagnosed until they present with evidence of renal disease such as gross haematuria, hypertension, renal insufficiency, and significant proteinuria. [31]

Aetiology and risk factors

The exact causes of IgAN are unknown[18, 32] and the source of the high levels of gd-IgAs in IgAN remains an area of investigation.[18] Hypotheses include the triggering of increased production of gd-IgAs due to hereditary causes,[19] or by an initial trauma such as mucosal infection (e.g., tonsillitis), stress, or exposure to toxins.[23]

IgAN is a heterogeneous disease, with different clinical and pathologic features across ethnic populations.[29, 32] Several genetic loci have been identified that are associated with IgAN pathogenesis.[32-35]

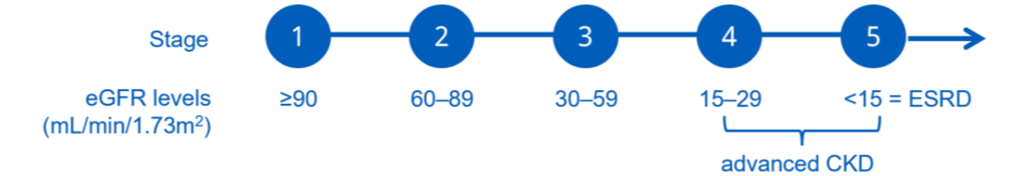
3.1.2 Disease course and progression

IgAN is a type of CKD that follows a slowly-progressive course,[23, 26] which is generally defined by kidney damage, based on estimated glomerular filtration rate (eGFR) levels (Figure 1).[36]

Normal eGFR is generally considered to be ≥90 mL/min/1.73 m2, although levels decrease with age. As a severe reduction in eGFR is defined as ESRD, then, by definition, eGFR decline is on the path of progression to ESRD.[37] Decline in eGFR over time (measured by eGFR slope) is associated with an elevated risk of progression to ESRD and an increased mortality risk.[38-41]

Progression can lead to ESRD (CKD stage 5, kidney failure),[29, 42] where patients require renal replacement therapy (RRT) in the form of a kidney transplant or chronic dialysis;[28] eGFR <15 mL/min/1.73 m2 corresponds to CKD stage 5 or ESRD (Figure 1).[36]

Figure 1. Stages of CKD based on eGFR levels



Stage	Description	eGFR levels (mL/min/1.73 m^2)*
1	Kidney damage† with normal or increased eGFR	≥90
2	Kidney damage† with mildly decreased eGFR	60 to 89
3	Moderate decreased eGFR	30 to 59
4	Severe decreased eGFR	15 to 29
5	Kidney failure (ESRD)	<15 or dialysis

*eGFR estimated from serum creatinine using the Modification of Diet in Renal Disease (MDRD) study equation based on age, gender, race, and calibration for serum creatinine
†For stages 1 and 2, kidney damage was assessed by spot albumin-to-creatinine ratio >17 mg/g (men) or >25 mg/g (women) on two measurements
CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; Source: Chronic kidney disease guidelines, 2004 (AJKD)[36]

3.1.3 Risk factors for progression to ESRD

The disease course and rate of progression varies across individuals with IgAN, but is more rapid in patients with high levels of proteinuria and decreased eGFR levels, as both are associated with high risk of progression to ESRD[16, 24, 38, 43-46] and mortality.[28-30, 47, 48]

Proteinuria is a key risk factor for progression to ESRD in IgAN[24] with consistent evidence linking sustained proteinuria with loss of kidney function, progression to ESRD[24, 38, 43, 44] and mortality.[30, 47, 48] A large retrospective, multicentre study (13 European countries) in 1,147 patients with IgAN receiving treatment (VALIGA) showed that time-averaged proteinuria had predictive value for 5- and 10-year kidney survival.[30] Specifically, time-averaged proteinuria <0.5 g/day was significantly associated with better renal outcomes (measured by the combined endpoint of 50% decrease in eGFR and/or ESRD) compared with proteinuria 0.5–0.9 g/day (p<0.0001).[30] Additional data from individual-patient meta-analyses and retrospective studies are available, showing that reduction in proteinuria was associated with lower risk of progression to ESRD[43, 44, 47, 48] and mortality.[43]

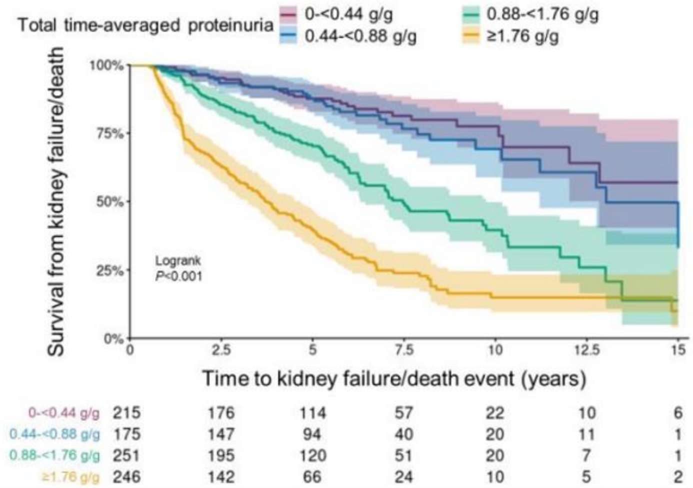
In a study of patients from the IgAN cohort of the RaDaR, (2,299 adults, 140 children), 50% of patients reached kidney failure or died during the study period (median follow-up: 5.9 years; Q1, Q3: 3.0, 10.5).[16] In adults, median kidney survival was 10.8 years (95% CI 10.0 to 12.0), mean age at kidney failure/death was only 49 years (SD, 14 years) for adults, and most patients progressed to kidney failure within 10 to 15 years from diagnosis (Figure 2).[16] Once kidney failure occurs, patients require RRT, either dialysis or a renal transplant, for the rest of their lives.[26, 28] This means that many patients could need dialysis for at least 20 to 30 years.

UK RaDaR analyses show that higher levels of proteinuria are associated with faster rates of disease progression.[16] Kaplan-Meier survival analyses showed that patients with time-averaged proteinuria >0.88 g/g (>100 mg/mmol) were likely to progress to ESRD or death more quickly than patients with time-averaged proteinuria <0.88g/g, see Figure 2 (Table 133 shows the clinical outcomes based on the total follow-up time for patients from the UK RaDaR IgAN cohort.[16] Patients with low time-averaged proteinuria of <0.88 g/g UPCR (equivalent to protein excretion of 1 g/day; n=390) had a median time to ESRD or death of >15 years. However, this decreased to approximately 7.5 years in patients with UPCR 0.88 to <1.76 g/g (n=251), and further decreased to approximately 3 years in patients with UPCR ≥1.76 g/g (n=246). Preserving kidney function earlier rather than later in the disease course is thus expected to provide the most benefit, when there is more residual kidney function left to protect.[16]

In a cohort of adults with baseline UPCR ≥0.88 g/g, considered comparable with protein excretion ≥1 g/d, and eGFR ≥30 ml/min per 1.73 m2, each 10% decrease in proteinuria from baseline was associated with a significant increase in the risk of kidney failure or death (HR 0.89; 95% CI, 0.87 to 0.92) after adjusting for age, sex, baseline eGFR, and time from diagnosis to baseline.[16]

In the incident population, 85% of patients with time-averaged UPCR of ≥1.76 g/g experienced ESRD or death within 10 years, compared with 60% of those with UPCR of 0.88 g/g to <1.76 g/g, 31% of those with UPCR 0.44 to <0.88 g/g, and 22% of those with UPCR <0.44 g/g.[16]

Figure 2. Kaplan-Meier survival curves (95% CI) of time to kidney failure/death event based on total follow-up time-averaged proteinuria for patients from the UK RaDaR IgAN cohort



Abbreviations: CI, confidence interval; IgAN, immunoglobulin A nephropathy; UK RaDaR, United Kingdom National Registry of Rare Kidney Diseases.
Source: Pitcher et al. 2023[16]

Low eGFR levels at renal biopsy and decreases in eGFR levels over time are associated with an elevated risk of progression to ESRD and an increased mortality risk in patients with IgAN[38, 49] and CKD. Patients with CKD with an eGFR <30 mL/min/1.73 m2 have a 314% increased all-cause mortality risk versus those with normal eGFR.[50] A recent study that pooled data from 13 IgAN trials showed that the 1-year eGFR slope is an important independent and predictor of clinical outcomes and therefore a clinically relevant surrogate endpoint for clinical trials in IgAN.[10]

Reducing proteinuria slows the progression of CKD and is accepted as a surrogate endpoint for improved outcomes in IgAN by KDIGO and the Food and Drug Administration (FDA) [24, 29, 37]. Reducing proteinuria is also key in long-term prevention of CKD and kidney failure by the EMA[51] and clinical guidelines.[29] Accepted measurements of proteinuria include UPCR and/or urine albumin-to-creatinine ratio (UACR), measured from early morning samples (untimed "spot" urine sample), as discussed by the EMA,[51] the KDIGO 2021 Glomerular Diseases Workgroup,[29] and the US National Kidney Foundation.[37] Additionally, a decline in eGFR from baseline over a 2 to 3 year period is considered an acceptable surrogate outcome measure for ESRD in clinical trials in patients with IgAN by the EMA,[51] clinical guidelines,[29] and the US National Kidney Foundation.[37]

Progression to ESRD

Patients with advanced CKD have a high symptom burden[26, 28] and symptoms become more severe as the disease progresses, including pain, oedema[26] and fatigue.[25, 26, 52] As mentioned above, median kidney survival in the UK RaDaR registry was 10.8 years (95% CI 10.0 to 12.0), and the mean age at kidney failure/death was only 49 years (SD, 14 years).[16] Progression was even faster in the target patient population for Kinpeygo, with a median time to ESRD or death of 3 years in patients with UPCR ≥1.76 g/g.[16] Therefore, patients could require regular, burdensome dialysis for at least 20 to 30 years.[18, 26, 28]

3.2 Patient population

IgAN is an orphan disease, affecting approximately 4 in 10,000 people in the European Union (EU).[3] The worldwide annual incidence of IgAN is at least 2.5 per 100,000 people [18, 53] and in Europe is between 0.7 to 2.3 per 100,000 people per year.[54]

IgAN is more frequently diagnosed in males than females, with ratios ranging from less than 2:1 in East Asia[55, 56] to as high as 6:1 in Northern Europe and United States (US).[56] Recent Asian[57] and international studies,[6, 58, 59] in patients with IgAN reported a ratio of 2:1. Caucasian and Asian populations are more prone to developing IgAN compared with Black populations.[56]

In Europe, the rate of IgAN diagnosis in adult patients undergoing kidney biopsy ranges from 6.4%[60] to 27.3%.[61] The rates of IgAN diagnosis across countries vary widely,[18, 53] likely due to differences in screening and biopsy practices across countries.[21, 54] Mean age at diagnosis of IgAN in Europe varies between 23[62] to 53 years old.[63] In the large adult IgAN cohort of the UK National Registry of Rare Kidney Diseases (UK RaDaR; n=2,299; recruitment initiated in 2013), the mean age at diagnosis was 42 years (SD, 14 years).[16]

No high-quality data is publicly available on Danish IgAN patients.[64] A Danish study, presenting a prevalence of 748 people per million inhabitants in 2014 with glomerulonephritis (GN), is deemed as the most accurate existing source for estimating IgAN patients in Denmark.[65] For most of the patients with kidney biopsies in the study, it was noted that the correct diagnosis was probably IgA GN and not primarily mesangioproliferative GN (MesPGN). The results from the study point to a prevalence of biopsy verified MesPGN of around 1,026 patients in Denmark and an incidence of 11 patients per million inhabitants as of 2014.[65] More patients are expected to exist as the study cohort only includes patients up to 2014, and that IgAN only can be diagnosed with a kidney biopsy, which is reserved for patients with progressive renal failure or a high degree of proteinuria, hence suggesting that the incidence and prevalence are covering mainly patients at high risk of CKD progression.[64] In addition, younger patients with monosymptomatic haematuria and normal renal function will rarely be biopsied, since the presumptive diagnosis is IgAN, and the treatment is non-specific.[65] Only a smaller group of these patients are expected to be eligible for Kinpeygo treatment.

Therefore, due to lack of data, estimations must be made to give an indication of the number of Danish patients anticipated to be eligible for Kinpeygo treatment (with urine protein-to-creatinine ratio (UPCR) ≥1.5 g/gram). In the NefIgArd trials, patients with ≥1.5 g/gram represented 37% of all patients. As the inclusion criteria for the trial specified that patients must have UPCR ≥0.8 g/gram in 2 consecutive measurements, this means that the study only included patients with high risk of progression according to the KDIGO guidelines (proteinuria >0.75–1 g/d despite ≥90 days of optimized supportive care).[29, 66] Similarly, the Danish study used for epidemiological data above only included patients with a biopsy, which are those with the clinical factors indicating a high risk of progression.[65] Therefore, we can assume that about 37% of the patients in the Danish study would have UPCR ≥1.5 g/gram and thus be eligible for Kinpeygo treatment.[65] Based on this assumption, the prevalence of patients matching the Kinpeygo eligibility criteria is approximately 380 patients (0.37*1,026) and the incidence around 24 patients (0.37*11 ppm*5.8 based on a Danish population of 5.8 million inhabitants).

A Danish clinical expert confirmed our estimations of the prevalence of patients with IgAN and the share of patients eligible for Kinpeygo.[12] In addition, the clinical expert informed that all patients eligible for Kinpeygo are considered as chronic patients (defined as per KDIGO guidelines as either proteinuria or reduced eGFR > 3 months [12, 29]) and the vast majority (>90%) of patients eligible for Kinpeygo i.e., with proteinuria, will be treated on the hospital level.[12] It was also mentioned that, in terms of high risk of progression, the majority of patients who were biopsied would fall into this category of patients at high risk of progression. Therefore, using biopsy-confirmed cases (as from the Danish study) gives a good estimate of the number of patients who would be possible candidates for second-line treatment including Kinpeygo.[12]

Table 2 Incidence and prevalence in the past 5 years

Year	2019	2020	2021	2022	2023
Incidence in Denmark	24	24	24	24	24
Prevalence in Denmark	380	404	428	452	476
Swedish estimations*	262	346	430	514	598

Note: Due to lack of data, since the prevalence and incidence estimates are based on one year, it is assumed that the prevalence the following years is equal to the prevalence + the incidence, with the same logic for the earlier years. For

example, if the prevalence and incidence estimate is based on data for year 2022, the estimates for 2019-2021 is based on the 2022 prevalence but deducting the annual incidence per year.
*Swedish estimations for high risk IgAN patients (same patient population as presented for Denmark) based on clinical expert input. The estimation for Sweden is lower than that for Denmark in the first year since the total population in Sweden is double the size of that in Denmark.

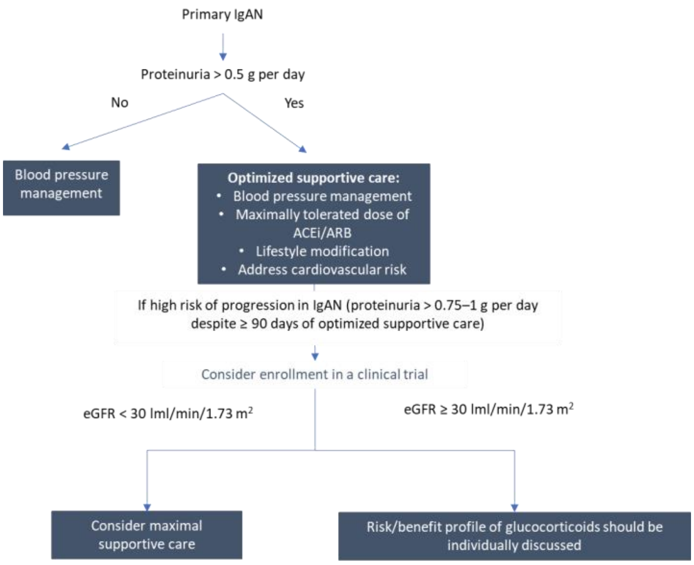
Table 3 Estimated number of patients eligible for treatment

Year	Year 1	Year 2	Year 3	Year 4	Year 5
Number of patients in Denmark who are eligible for treatment in the coming years	380	404	428	452	476

3.3 Current treatment options

Patients with IgAN at risk of progression to ESRD have limited treatment options. Danish clinicians follow a combination of the KDIGO guidelines, the national treatment guidelines from the Danish Society of Nephrology and local practical instructions. The recommendations of these guidelines are detailed below, except for the local practical instructions that are usually a regional interpretation of the national guidelines and most of them are not publicly available.[64]

Figure 3. Treatment algorithm from the KDIGO IgAN treatment guidelines



Abbreviations: ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; BP, blood pressure, eGFR, estimated glomerular filtration rate; IgAN, immunoglobulin A nephropathy. Source: [29].

The KDIGO guidelines recommend that proteinuria levels and eGFR are the main considerations when deciding a treatment regimen.[29] The primary focus of management in patients with IgAN is optimised supportive care, which consists of management of blood pressure with lifestyle modifications and/or renin-angiotensin system (RAS) blockade (angiotensin-converting enzyme inhibitors [ACEi] or angiotensin receptor blockers [ARB]). Controlling blood pressure can slow the progression of CKD and reduce cardiovascular risk in CKD populations, and there is no evidence to suggest that the benefits are different for patients with CKD due to IgAN. [29]

In patients with IgAN at high risk of progression to ESRD, there are limited treatment options, especially in Caucasian populations.[18, 29] Enrolment in clinical trials is recommended by the clinical guidelines. In patients not eligible for clinical trial enrolment, corticosteroids can be considered [18, 29], but only cautiously due to their questionable benefit-to-risk ratio, as they are associated with serious adverse events (AEs), particularly infections.[18, 29, 42]

The Danish Society of Nephrology published treatment guidelines for IgAN In 2020, with an updated version released in May 2023.[67, 68] These guidelines provide recommendations for different patient groups affected with IgAN, and it is aligned with the KDIGO guidelines. For patients with normal kidney function with or without microscopic haematuria and with or without albuminuria (< 0.5 g/d) or proteinuria (< 0.75 g/d) and for patients with chronic renal insufficiency with eGFR below 30 ml/min, the disease is treated symptomatically with general antiproteinuric treatment including RAS blockade is recommended, regardless of the degree of albuminuria and blood pressure control. For patients with albuminuria (> 0.5 g/d) or proteinuria (> 0.75 g/d) and eGFR above 30 ml/min, symptomatic treatment as described above is used for 3 to 6 months. If symptoms continue, steroid monotherapy should be considered. If so, the recommended corticosteroid treatment is monotherapy using prednisolone for 7-9 months or referral to a clinical trial. [68]

According to a clinical expert interviewed by STADA, treatment for IgAN patients at risk of progression usually includes lifestyle changes and maximum tolerated dose of RAS blockade. Systemic glucocorticoids in the form of prednisolone are used to varying extent in the regions and in low doses as according to those used in the TESTING trial.[12, 57, 69]

In patients who have progressed to ESRD, the only treatment option is RRT, either in the form of a kidney transplant or chronic dialysis. [70]

3.4 The intervention – Kinpeygo (TRF-budesonide)

Kinpeygo is the first approved treatment specifically designed for patients with IgAN.[71] Kinpeygo is anticipated to address the remaining unmet need for patients with IgAN at high risk of disease progression due to 1) its targeted mode of action in patients with IgAN and 2) supportive clinical trial data specifically for patients with IgAN. Table 4 provides an overview of Kinpeygo.

Table 4. Overview of Kinpeygo

Overview of intervention	
Therapeutic indication relevant for the assessment	Primary IgAN in adults at risk of rapid disease progression with a UPCR ≥1.5 g/g [1, 2]
Method of administration	Oral
Dosing	The recommended dose is 16 mg administered orally, once daily, in the morning at least one hour before a meal.[4]
Dosing in the health economic model (including relative dose intensity)	16 mg once daily for 9 months

Overview of intervention	
Should the medicine be administered with other medicines?	Kinpeygo can be administered as adjunct therapy to standard of care (ACEis/ARBs). No medicine needs to be co-administered during Kinpeygo's administration.
Treatment duration / criteria for end of treatment	The duration of therapy is 9 months, followed by a tapering period.[4]
Necessary monitoring, both during administration and during the treatment period	Patients should be monitored for any signs and symptoms of the following conditions/diseases: [72] • Hepatic impairment • Symptoms of steroid withdrawal in patients transferred from systemic corticosteroids • Infections • Patients with special diseases • Visual disturbance • Concomitant treatment with potent CYP3A4 inhibitors • ACTH stimulation test • Fructose intolerance, glucose-galactose malabsorption or sucrose-isomaltase insufficiency
Need for diagnostics or other tests (e.g. companion diagnostics). How are these included in the model?	UPCR and/or UACR to evaluate proteinuria reduction.
Package size(s)	4 mg capsules, 120-tablet (30-day) pack

Abbreviations: ACEis, angiotensin-converting enzyme inhibitors; ACTH, adrenocorticotropic hormone; ARBs, angiotensin receptor blockers; CYP3A4, cytochrome P450 3A4; UACR, urine albumin creatinine ratio; UPCR, urine protein-to-creatinine ratio.

Mechanism of action

Kinpeygo is a second-generation, potent corticosteroid, with potent glucocorticoid activity and weak mineralocorticoid activity.[4, 22] It exerts anti-inflammatory and immunosuppressive effects via glucocorticoid receptors.[4] The working hypothesis for Kinpeygo's proposed mechanism of action in IgAN is that it blocks communication via cytokines in the Peyer's patches in the ileum, thereby cutting off the signals required for clonal expansion and differentiation of antigen-specific T and B cells, and inhibiting their proliferation and differentiation into plasma cells that produce mucosal gd-IgAs.[1, 22, 73] Consequently, it is expected that the occurrence of gd-IgA antibodies and formation of immune complexes in the systemic circulation will be suppressed, therefore preventing downstream effects of the deposition of immune complexes in the kidneys, such as kidney inflammation, damage and loss of function.

3.4.1 The intervention in relation to Danish clinical practice

There is currently no approved treatment for the patient with primary IgAN who are on optimized supportive care, including a stable dose of maximally tolerated RAS blockade therapy, and are at risk of rapid disease progression with a UPCR ≥1.5 g/g (Kinpeygo's indication). In Denmark, IgAN patients at high risk of progression are enrolled in clinical trials or treated with treatments that are not specifically targeting IgAN due to lack of options, such as systemic corticosteroids (e.g., budesonide or prednisolone).[74]

Treatment with systemic steroids in IgAN has been a controversial topic over the years[75] due to uncertainty around their benefit-to-risk ratio.[76] Systemic corticosteroids are associated with high rates of serious AEs, particularly serious infections [6, 7, 57, 77], with one randomized controlled trial (RCT) being terminated early due to an increased risk of serious adverse events.[57] A meta-analysis of 10 RCTs of 791 patients with IgAN showed that glucocorticoid treatment improved renal function (relative risk [RR], 0.34; 95% confidence interval [CI], 0.13 to 0.89) and reduction in daily proteinuria levels (standardised mean difference [SMD], -0.69; 95% CI, 0.8 to -0.53; p<0.00001) but was linked to a marked increase in the risk of gastrointestinal AEs (RR, 3.10; 95% CI, 1.37 to 6.98; p=0.006).[78]

Evidence for the use of corticosteroids in IgAN predominantly comes from two RCTs: the Supportive Versus Immunosuppressive Therapy from the Treatment of Progressive IgAN (STOP-IgAN) trial (supportive therapy with vs. without immunosuppressive treatment) [6, 7, 77] and the TESTING trial (methylprednisolone vs. placebo). [57, 79] These trials showed that efficacy outcomes were generally improved in patients receiving corticosteroids compared with those who did not, although renal outcomes were inconsistent, with no significant eGFR benefit observed in the STOP-IgAN trial.[6, 57, 79] Overall, due to the moderate-quality evidence available, clinical guidelines present a weak and cautious recommendation for use of corticosteroids in patients with IgAN at high risk of progression to ESRD, due to the significant risk of toxicity with the therapy.[18, 29]

Existing formulations of budesonide are used to treat immune-mediated GI diseases, such as Crohn’s disease, as well as liver and respiratory diseases.[22] As budesonide is rapidly absorbed in the proximal GI tract when taken orally, formulations used to treat Crohn’s disease use pH-sensitive, enzymatically-triggered and/or time-dependent coatings to target the drug delivery to the bowel. However, unlike Kinpeygo, these formulations have not been specifically designed to target IgAN’s cause of disease[22] and their efficacy and safety in patients with IgAN is unknown.[80, 81]

A high unmet medical need exists in this patient population with a reduced life expectancy and double the mortality rate of the general population.[38, 82] Patients suffer from a broad range of symptoms which restrict daily activities in early stages and a higher symptom burden in the advanced CKD stages [26, 28], including RRT. A recent UK register study in IgAN patients showed that a requirement for dialysis/renal transplant or death happens within 15 years for most patients with proteinuria ≥1.76 g/g .[15, 16] The rate at which patients progress is also faster for patients with higher rates of proteinuria, e.g. 50% of patients with proteinuria ≥1.76 g/g progress to ESRD or death within approximately 3 years [16]. Kinpeygo is anticipated to address the remaining unmet need for patients with IgAN at high risk of disease progression due to its targeted mode of action in patients with IgAN and supportive clinical trial data specifically for patients with IgAN.

Positioning of Kinpeygo (Kinpeygo)

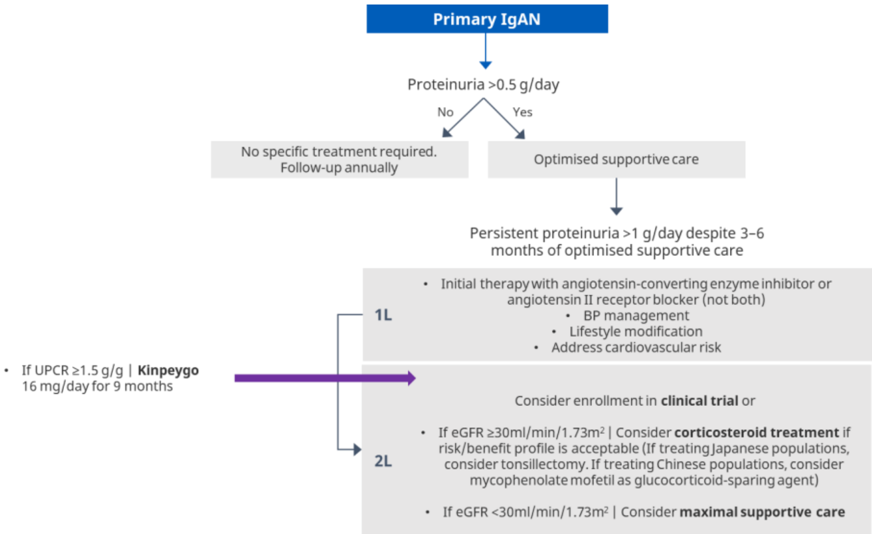
Kinpeygo is the first treatment specifically designed for patients with IgAN[71], and it has an orphan designation [3]. In Europe, Kinpeygo was granted an accelerated assessment procedure by the CHMP in April 2021.[83] Calliditas submitted a Marketing Authorisation Application on 28 May 2021 and the European Commission granted conditional marketing authorisation in the EU in July 2022.[66] The current EU indication for Kinpeygo is for the treatment of primary IgAN in adults at risk of rapid disease progression with a UPCR ≥1.5 g/g. [1, 2]

Kinpeygo is anticipated to be used in adult patients with primary IgAN who:

- are receiving optimised supportive care, which includes lifestyle modification, blood pressure management, maximum-tolerated RAS blockade, and statins to provide cardiovascular protection
- are at risk of rapid disease progression with a UPCR ≥1.5 g/g.[4]

The anticipated positioning of Kinpeygo is as second-line treatment as presented in Figure 4. Kinpeygo is expected to replace the current use of corticosteroids (i.e., prednisolone), since prednisolone is currently used off-label, and has a significant risk of toxicity.[18, 29]

Figure 4. Anticipated place in treatment pathway for Kinpeygo (Kinpeygo)



Notes: BP control is recommended for all patients; SGLT2is are now also considered for their renal protective properties in addition to CV protection; hydroxychloroquine can also be considered for Chinese patients
Abbreviations: BP, blood pressure; CV, cardiovascular; eGFR, estimated glomerular filtration rate; IgAN, Immunoglobulin A nephropathy; SGLT2i, sodium-glucose cotransporter-2 inhibitor.
Sources: KDIGO, 2021;[29] Pattrapornpisut *et al*, 2021[18]

3.5 Choice of comparator(s)

According to the treatment guidelines for patients with glomerulonephritis in Denmark, issued by Dansk Nefrologisk Selskab [69], the treatment alternative for patients with UPCR ≥1.5 g/g is low doses of prednisolone (as based on the TESTING doses [57]). A Danish clinical expert has confirmed the use of prednisolone for these patients.[12] Although prednisolone is not specifically targeting patients with IgAN and is associated with high risks of adverse events.[18, 29, 42] DMC has requested the comparison against prednisolone. Therefore, in this application, Kinpeygo is compared to corticosteroids (prednisolone).

An overview of the chosen comparator is presented in Table 5.

Table 5. Overview of comparator - prednisolone

Overview of comparator	
Generic name	Prednisolone
ATC code	H02AB06 [84]
Mechanism of action	Prednisolone is a glucocorticoid similar to cortisol used for its anti-inflammatory, immunosuppressive, anti-neoplastic, and vasoconstrictive effects.[85]
Method of administration	Oral [84]
Dosing	0.5mg/kg/day for 9 months [12, 57, 69]
Dosing in the health economic model (including relative dose intensity)	Same dosing scheme as from TESTING trial and Danish guidelines (verified by a Danish KOL) [12, 57, 69]: 0.5mg/kg/day for 9 months (total number of administrations in the model: 272.97 [30.33 days * 9 months]).
Should the medicine be administered with other medicines?	No
Treatment duration/ criteria for end of treatment	9 months [57, 69]
Need for diagnostics or other tests (i.e. companion diagnostics)	None [84]
Package size(s)	5 mg tablets, 100 tablets per package [84]

Note that the relative efficacy data used in the health economic model (CEM) is based on an ITC which includes the STOP-IgAN trial, in which the treatments included corticosteroids followed by immunosuppressants (azathioprine and cyclophosphamide).[6] The ITC did not include the TESTING trial [57] since the study population was found to be heterogeneous to the population of Kinpeygo, as it primarily consisted of an Asian population (for more information, see Section 6.1.1.2). Genetic predisposition is recognised to play a major role in discrepancies in disease prevalence, clinical presentation, outcomes, and treatment responses; with the Asian population showing much faster disease progression than the global population [86-89]. Asian patients progressed faster in the NefIgArd study versus the global population in NefIgArd and Kinpeygo had much greater treatment effect in this patient population versus the global population (24 months mean change in eGFR from baseline, mL/min/1.73 m^2, for Asian patients with Kinpeygo -7.09 and placebo -20.97 versus global patients with Kinpeygo -6.11 and placebo -12.0).[89]

On the contrary, the dosing scheme in the model is based on the TESTING doses (low doses of prednisolone), since it is recommended by the Danish treatment guidelines and confirmed by a Danish clinical expert.[12, 68] See more information in Section 7 and Section 11.1.

3.6 Cost-effectiveness of the comparator(s)

There is no cost-effectiveness analysis conducted for the chosen comparator. However, the comparator, corticosteroids (prednisolone) is considered as the relevant comparator by the DMC’s Fagudvalg and a Danish clinical expert has confirmed that patients with IgAN are currently treated with prednisolone in Denmark (in addition to SoC, i.e., RAS blockade).

3.7 Relevant efficacy outcomes

3.7.1 Definition of efficacy outcomes included in the application

Table 6 shows the efficacy outcome measures from NefIgArd part B, which are relevant for this application. Additional definitions and measures are presented in Table 67.

Table 6 Efficacy outcome measures relevant for the application

Outcome measure	Time point*	Definition	How was the measure investigated/method of data collection
UPCR [Included NefIgArd Part B]	12 and 24 months	1. Ratio of UPCR compared with baseline averaged over time points between 12 and 24 months. **Definition of UPCR** Reducing proteinuria (assessed by measuring proteinuria over 24 hour, UPCR, and/or UACR) slows the progression of CKD and is accepted as a surrogate endpoint for improved outcomes in IgAN by KDIGO and the FDA.[24, 29, 37] UPCR and UACR measured from early morning samples are accepted as simple measurements of proteinuria.[37] In patients with time-averaged UPCR ≥1.76 g/g (n=246) approximately 85% developed kidney failure within 10 years.[16] In those with time-averaged UPCR of 0.88 to <1.76 g/g (n=251) the rate was approximately 60%, and among those with time-averaged UPCR of 0.44 to <0.88 g/g (n=175) the rate was approximately 30%. Even in those with low time-averaged UPCR <0.44 g/g (n=215), approximately one-fifth developed kidney failure at 10 years.[16]	1. UPCR based on 24-hour urine collections UPCR were calculated by the central laboratory and recorded at 3, 6, 9, 12, 18, and 24 months.[5] The secondary endpoints that assess time-averaged parameters (UPCR and UACR) between 12 and 24 months were log-transformed prior to analysis and were analyzed using a MMRM model with separate visit terms for 3, 6, 9, 12, 18, and 24 months. The visits at 12, 18, and 24 months were given equal weight to obtain the geometric mean treatment effect averaged over these time points.
eGFR [Included NefIgArd Part B]	24 months (12 months for one analysis)	1. AUC-based endpoint of eGFR calculated as a time-weighted average of eGFR recordings observed at each time point over 2 years (analysis performed when the last patient randomised completed Visit 17b). 2. 2-year eGFR slope. 3. time to 30% reduction from baseline in eGFR. 4. ratio of eGFR compared with baseline averaged over time points between 12 and 24 months.	1. Time-weighted average of eGFR recordings observed at each time point over 2 years, with eGFR (CKD-EPI) calculated by a central laboratory at each timepoint. The eGFR at baseline and 2 years was repeated to provide a second value obtained within 14 to 35 days (eGFR recorded was the geometric mean of the two assessments) Each timepoint was weighted in proportion to the time elapsed since the previous recording. Therefore, recordings made at 18 and 24 months received twice as much weight as those made at 3, 6, 9, and

Outcome measure	Time point*	Definition	How was the measure investigated/method of data collection
		<u>Definition of eGFR:</u> Glomerular filtration rate is generally considered the most useful overall measure of kidney function. As eGFR levels are used to define CKD stages, and below 15 mL/min/1.73 m^2 is defined as kidney failure, then by definition, eGFR decline is on the path of progression to kidney failure.[37] Decline in eGFR over time (measured by eGFR slope) is associated with an elevated risk of progression to ESRD and an increased mortality risk.[38-41] and is an accepted valid surrogate end point in RCTs.[37] Meta-analyses consistently show that an effect on 2-year eGFR slope is a major, independent predictor of treatment effect on long-term clinical outcomes in IgAN.[45, 90, 91] **<u>Composite endpoint eGFR reduction:</u>** In addition to the eGFR and UPCR endpoints included in the NefIgArd trial, a composite endpoint of time from randomisation to confirmed 30% reduction in eGFR or confirmed kidney failure provides additional supportive evidence that Kinpeygo affects longer-term outcomes.	12 months. The weights totalled 1 so that the treatment effect could be interpreted as the average effect over 2 years. Robust regression was used to prevent outlying data having undue influence on the results. A multiple imputation procedure was used to handle missing data. Data were log-transformed before analysis. 2. Primary supportive analysis of 2-year eGFR total slope using a random coefficients analysis was planned prior to unblinding Part A; however, this analysis method underestimates the magnitude of the Kinpeygo treatment effect. Therefore 2-year total slope was estimated as half of the between-arm difference in mean change from baseline to 2 years derived from a robust regression analysis of the multiply imputed values of log-transformed eGFR at 2 years used in the primary endpoint calculation. An analysis of 2-year eGFR total slope using a linear spline mixed-effects analysis, with a fixed knot at 3 months, was also pre-specified prior to unblinding the full study to provide a more accurate estimate of the magnitude of the 2-year eGFR total slope 3. Composite endpoint of time from randomisation to confirmed 30% reduction in eGFR (CKD-EPI formula; confirmed by two values over ≥4 weeks) or confirmed kidney failure (defined as dialysis for ≥1 month, kidney transplantation, sustained [≥1 month] eGFR <15 mL/min per 1.73 m^2, or kidney-related death). The time to a 30% reduction in eGFR (CKD-EPI) was measured from the time of the first dose of study drug or the time of randomization (if the patient randomized did not receive any study drug) and included all data not impacted by the use of rescue medication. 4. Average over time points between 12 and 24 months, inclusive, following the first dose of study drug eGFR were calculated by the central laboratory and recorded at 3, 6, 9, 12, 18, and 24 months.[5]

* Time point for data collection used in analysis (follow up time for time-to-event measures)

Abbreviations: AUC, area under the curve, CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; eGFR, estimated glomerular filtration rate; UACR, urine albumin-to-creatinine ratio; UPCR, urine protein-to-creatinine ratio

Source: DOF (NEF-301 CSR)[11]; Barratt *et al*, 2023[92], Lafayette *et al*, 2023, Supplementary Appendix;[93] DOF (NEF-301 Part B CSR)[5]

3.7.1.1 Validity of outcomes

In line with other chronic kidney diseases, the overall treatment goal for patients with primary IgAN at risk of progressing to ESRD is to reduce proteinuria and albuminuria and slow the decline in glomerular filtration rate (GFR). An ongoing decline in GFR is predictive of later ESRD, and beneficial effects of treatment on proteinuria, as measured by UPCR, have been associated with corresponding beneficial effects on the decline in eGFR. The available literature has shown that across all kidney diseases, there is a direct link between UPCR and early changes in eGFR to later clinical changes in GFR and important clinical endpoints, including ESRD, eGFR <15 mL/min/1.73 m2, or sustained doubling of serum creatinine. [10, 24, 37, 43, 91, 94] Hence, treatment effects on UPCR and eGFR are considered likely to predict longer term clinical benefit.

3.7.1.1.1 UPCR/UACR

Reducing proteinuria slows the progression of CKD and is accepted as a surrogate endpoint for improved outcomes in IgAN by KDIGO and the Food and Drug Administration (FDA). [24, 29, 37] Reducing proteinuria is also key in long-term prevention of CKD and kidney failure by the EMA[51] and clinical guidelines.[29] Accepted measurements of proteinuria include UPCR and/or urine albumin-to-creatinine ratio (UACR), measured from early morning samples (untimed “spot” urine sample), as discussed by the EMA,[51] the KDIGO 2021 Glomerular Diseases Workgroup,[29] and the US National Kidney Foundation.[37]

3.7.1.1.2 eGFR

A decline in eGFR from baseline over a 2 to 3 year period is considered an acceptable surrogate outcome measure for ESRD in clinical trials in patients with IgAN by the EMA,[51] clinical guidelines,[29] and the US National Kidney Foundation.[37] Furthermore, IgAN progression is defined by eGFR-based CKD stages [36].

4. Health economic analysis

4.1 Model structure

A cost-utility analysis was conducted, and the incremental cost-effectiveness ratio (ICER) was expressed as a cost per quality-adjusted life-year (QALY).

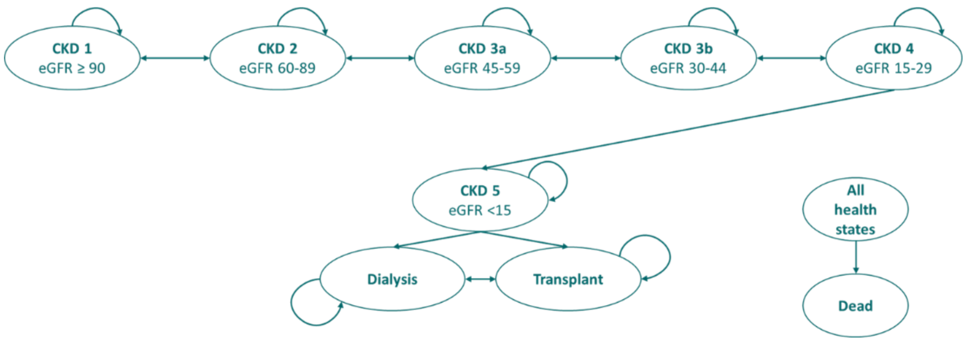
The CEM was developed in Microsoft® Excel (Microsoft, Washington, USA, 2022), using Visual Basic for Applications functionality to determine the cost-effectiveness of Kinpeygo versus relevant comparators.

Due to the lack of published cost-effectiveness analyses specific to IgAN at the time of model development, the relative strengths of patient-level and cohort-level approaches to the decision problem were considered. Despite the reduced flexibility, a cohort-level approach would be optimal as it requires fewer data inputs than a patient-level simulation approach. A cohort-level approach was also the most commonly used structure in previous CKD HTA submissions identified in the economic SLR [95-101], which was considered by clinicians to be a good proxy for patients with IgAN [102].

The chosen CEM structure is presented in Figure 5. Aspects of the model structure used in the single technology appraisal NICE submission TA775 were used in the model structure. As per the TA775 submission, the model's health states are mostly defined by CKD state; that is, by eGFR levels. Although eGFR was a secondary endpoint in NefIgArd Nef-301 study and UPCR was the primary endpoint, the published cost-effectiveness precedent in CKD has linked CKD health states to patient utility, health resource use, and transition probability data. Furthermore, there is no such precedent for UPCR-defined states in CKD, and as noted, no identified published CEM precedent is specific to IgAN. Therefore, defining health states by eGFR was deemed most appropriate for the economic evaluation.

Within the model, there are eight health states and an absorbing mortality state. An identical cohort enters each treatment arm of the model, distributed across the CKD health states in a manner that reflects the baseline distribution of CKD states in the NefIgArd Nef-301 Part A study. The arrows in Figure 5 represent the permitted transitions between health states.

Figure 5- Kinpeygo CEM structure schematic



Note: The arrows represent the permitted transitions between health states.
Abbreviations: CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate (eGFR measured as 35mL/min/1.73m2).

Reflecting the observed patient movements in the NefIgArd Nef-301 study, clinician feedback, and given the relatively short monthly CEM time cycle for a chronic disease, movements between CKD states were assumed to be restricted to immediate neighboring CKD states at each cycle. To account for the bias of slight changes in eGFR readings around threshold values, transitions to better health states (observed in the trial) were also incorporated. The assumption that patients could transition to better health states in CKD 1–4 was validated by clinical experts at an advisory board [102]. Furthermore, an assumption that patients could transition to improved health states was deemed acceptable for decision making purposes in the economic models used in the NICE TA775 [97] and SMC SMC2428 [103] submissions (dapagliflozin for treating chronic kidney disease).

As indicated by Figure 5, the CEM assumes it is not possible to move from CKD 5 to an improved CKD state. Movements between dialysis and transplant health states are assumed to be possible due to patients experiencing transplant rejection and recurrent disease. However, transitions to improved states from these states are not possible. This approach for transitioning to CKD 5 was also adopted in the TA775 [97] and SMC2428 [103] model structures.

As indicated by Figure 5, movements to the ’Dead‘ state are possible from each alive health state, at every cycle. No long-term data was available from the NefIgArd Nef-301 study and due to the relatively low mortality risk in early CKD stages, no mortality data from NefIgArd Nef-301 were available to directly inform the CEM. Therefore, the CEM relies on real-world evidence from the national registry of rare kidney diseases (UK RaDaR) to inform the risk of death from all health states (further described in Section 8.4).

The risk of CKD 5 was also informed by real-world evidence from UK RaDaR because insufficient data on the number of patients who transitioned to CKD 5 during the NefIgArd Nef-301 study was available.

Within this model structure it is possible to capture a predicted benefit for Kinpeygo in terms of delaying patient progression through CKD health states, delaying expected time to CKD 5 and associated dialysis and potential kidney transplant burden, and ultimately delaying expected time to death.

The model structure presented in Figure 5 was validated by international experts gathered at an advisory board held in February 2023 [102].

4.2 Model features

Table 7 Features of the economic model

Model features	Description/chosen value	Justification
Patient population	Primary IgAN in adults at risk of rapid disease progression with a UPCR ≥1.5 g/g [1, 2] The experience of NefIgArd Nef-301 trial patients is assumed to be representative of the Kinpeygo-eligible patient experience in routine practice, across jurisdictions.	No deviations from section 3.2. Baseline characteristics are assumed similar to Danish patients, with an average age at diagnosis of approximately 45 years.
Perspective	Limited societal perspective	According to DMC guidelines
Time horizon	Lifetime (58 years)	To capture all health benefits and costs in line with DMC guidelines, although the user may change this up to a maximum time horizon of 70 years. Based on mean age at diagnosis (42.4 years). Validated by Danish clinical expert.
Cycle length	Monthly (30.4375 days)	IgAN is a chronic disease. Therefore, a monthly cycle length is appropriate. Cycle length was validated by KOLs [102]
Model structure	Cohort state-transition model	A cohort state-transition model requires fewer data assumptions than a patient-level approach. Cohort state-transition models have also been used in previous submissions in similar disease areas (CKD).
Half-cycle correction	Yes	
Discount rate	3.5 %	The DMC applies a discount rate of 3.5 % for all years
Intervention	Kinpeygo	
Comparator	Prednisolone (corticosteroids, CS)	According to national treatment guideline. Validated by Danish clinical expert. [12, 69]
Outcomes	eGFR, UPCR, UACR	See Section 3.7.1 and Table 67.
Source of efficacy for Kinpeygo	NefIgArd Nef-301 trial subgroup data for UPCR ≥1.5 g/g**[104]**	The clinical trial for Kinpeygo.
Source of efficacy for CS	STOP-IgAN trial [6]	The most relevant trial assessing the efficacy of corticosteroids, seen to the included patient population. TESTING trial not included in the ITC due to heterogeneity in the study population (predominantly Asian population) vs. that of Kinpeygo. See more information in Section 3.5 and Table 79.
Retreatment eligibility	Yes, 2 total treatment rounds, i.e., 1 retreatment.	Data from the NefIgArd-OLE study which includes patients that are potentially eligible for retreatment with Kinpeygo is not currently available. Therefore, the retreatment eligibility criteria align with the

Model features	Description/chosen value	Justification
	[redacted]	NefIgArd eligibility criteria (UPCR ≥1.5 g/g and eGFR ≥35 mL/min/1.73m^2). Only patients in CKD stages 1 to 3b at the time of retreatment are assumed to be eligible to receive retreatment with TRF-budesonide, as per the NefIgArd Nef-301 eligibility criteria (eGFR ≥35 mL/min/1.73m2). [redacted]
Retreatment efficacy	Although clinical experts do not expect that Kinpeygo's treatment effect will diminish with retreatment cycles, it was conservatively assumed that Kinpeygo would have a 90% treatment effect in subsequent rounds of retreatment.	While the MHRA [106] and EMA [107] licence wording states retreatment may be considered at the discretion of the treating physician, there is no available safety or efficacy data regarding subsequent treatment courses of Kinpeygo. Furthermore, based on its mechanism of action, clinicians do not expect patients to develop resistance to Kinpeygo if receiving multiple treatment rounds. However, it was conservatively assumed Kinpeygo would experience a treatment waning effect of 10% in subsequent rounds of treatment compared to the safety and efficacy data for the initial treatment of Kinpeygo. This strategy is more conservative than treatment guidelines from KDIGO 2021 in which therapies with similar dosing patterns are advised for those who relapse with no diminished efficacy. For example, patients with membranous nephropathy may be retreated with rituximab, or frequently relapsing patients with minimal change disease may be retreated with glucocorticoids.
Source of AE rates for Kinpeygo	NefIgArd Nef-301 Part B study	The NefIgArd Nef-301 trial is the most robust source of evidence for AEs associated with Kinpeygo
Source of AE rates for CS	STOP-IgAN	The STOP-IgAN trial is the most robust source of evidence for AEs associated with corticosteroids. TESTING trial not included in the ITC due to heterogeneity in the study population (predominantly Asian population) vs. that of Kinpeygo. See more information in Section 3.5 and Table 79.
Adverse events for Kinpeygo	All TEAEs and TESAEs that occur in more than one patient are included in the model.	Treatment related TEAEs that would likely incur costs from the model's perspective are included. TESAEs were restricted to AEs that occurred in more than one patient to avoid the inclusion of anomaly adverse events and to ensure a manageable list to model
Adverse events for CS	Severe adverse events (SAEs) from the STOP-IgAN trial that were deemed possibly/probably/definitely related to treatment by local physicians were included in the model	This assumption ensures that only SAEs that would likely incur costs from the model's perspective are included in the model

Model features	Description/chosen value	Justification
Source of utilities	Cooper et al. 2020 [8]	In the absence of utility data from the clinical trial, an alternative published study in CKD was identified as a source of HSUVs in the economic model and subsequently validated by clinical opinion.
Transitions between CKD health states	Patients can only transition to CKD health states that neighbour the patients current CKD state	Reflecting the observed patient movements in the NefIgArd Nef-301 study, and given the short CEM time cycle, movements between CKD states are assumed to be restricted to immediate neighbour states at each cycle.
Transitions to CKD 5	Risk of progression to CKD 5 is only possible from CKD 4 health state	Assumption validated by international clinical experts

Abbreviations: ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blockers; CEM, cost-effectiveness model; CKD, chronic kidney disease; CS, corticosteroids; EMA, European Medicines Agency; HTA, health technology assessment; IS, immunosuppressant; KDIGO, Kidney Disease Improving Global Outcomes; MHRA, Medicines and Healthcare products Regulatory Agency; OLE, open label extension; SAE, serious adverse event; TESAE, treatment-emergent serious adverse events; TRF, targeted-release formulation; UPCR, urine protein-to-creatinine ratio.

5. Overview of literature

5.1 Literature used for the clinical assessment

A systematic literature review (SLR) was conducted to assess the efficacy and safety in patients with primary IgAN treated Kinpeygo in comparison to established treatment, including corticosteroids. The studies used for the clinical assessment in this application are presented in Table 8. For more information, see Appendix H.

Table 8 Relevant literature included in the assessment of efficacy and safety

Reference (Full citation incl. reference number)*	Trial name*	NCT identifier	Dates of study (Start and expected completion date, data cut-off and expected data cut-offs)	Used in comparison of*
RCT: Barratt J, Lafayette RA, Kristensen CM, *et al*. Results from part A of the multi-center, double-blind, randomized, placebo-controlled NefIgArd trial, which evaluated targeted-release formulation of budesonide for the treatment of primary immunoglobulin A nephropathy. *Kidney International*. 2023;103:391–402. **CSR:** Calliditas Therapeutics AB. Clinical Study Report. A Randomized, Double-Blind, Placebo Controlled Study to Evaluate Efficacy and Safety of Nefecon in Patients With Primary IgA Nephropathy at Risk of Progressing to End-	NefIgArd NEF-301 Part A	NCT03643965	Start: September 2018 Completion: 5/10/2020 Data-cut-off: 5/10/2020	Kinpeygo vs placebo for adult patients with primary IgAN at risk of rapid disease progression with a UPCR ≥1.5 g/g.

Reference (Full citation incl. reference number)*	Trial name*	NCT identifier	Dates of study (Start and expected completion date, data cut-off and expected data cut-offs)	Used in comparison of*
Stage Renal Disease (NefIgArd) | Data cutoff date of 05 October 2020 for Part A analysis | Protocol number Nef-301 | v1.0. 27 January 2021, 2020.[11]				
RCT: Lafayette RA, Kristensen J, Stone A, et al. Efficacy and safety of a targeted-release formulation of budesonide in patients with primary IgA nephropathy (NefIgArd): 2-year results from a randomised phase 3 trial. Lancet. 2023;402(10405):859-870. [104] **CSR:** Calliditas Therapeutics AB. Clinical Study Report. A Randomized, Double-Blind, Placebo Controlled Study to Evaluate Efficacy and Safety of Nefecon in Patients With Primary IgA Nephropathy at Risk of Progressing to End-Stage Renal Disease (NefIgArd). Data cutoff date of 06 February 2023 for the full data set (Part B analysis). 31 May 2023, 2023[5]	NefIgArd NEF-301 Part B	NCT03643965	Start: September 2018 Completion: 6/2/2023 Data cut-off: 6/2/2023	Kinpeygo vs placebo for adult patients with primary IgAN at risk of rapid disease progression with a UPCR ≥1.5 g/g.
Fellstrom BC, Barratt J, Cook H, *et al*. Targeted-release budesonide versus placebo in patients with IgA nephropathy (NEFIGAN): a double-blind, randomised, placebo-controlled phase 2b trial. *Lancet*. 2017;389(10084):2117-2127[59]	NEFIGAN NEF-202	NCT01738035	Start: December 2012 Completion: September 2015	Not used in the submission/model.
Rauen T, Eitner F, Fitzner C, Sommerer C, Zeier M, Otte B, Panzer U, Peters H, Benck U, Mertens PR, Kuhlmann U, Witzke O, Gross O, Vielhauer V, Mann JF, Hilgers RD, Floege J; STOP-IgAN Investigators. Intensive Supportive Care plus Immunosuppression in IgA Nephropathy. N Engl J Med. 2015 Dec 3;373(23):2225-36. Doi: 10.1056/NEJMoa1415463. PMID: 26630142[6]	STOP-IgAN	NCT00554502	Start: 29/10/2007 Completion: 22/09/2015	Corticosteroids and immunosuppressive treatment vs placebo for patients with primary IgA nephropathy confirmed on biopsy; an age of 18 to 70 years; and a proteinuria level above 0.75 g per day of urinary protein excretion. Used in the submission/model in the ITC for the comparison of Kinpeygo vs corticosteroids.

* If there are several publications connected to a trial, include all publications used.

5.2 Literature used for the assessment of health-related quality of life

No EQ-5D HRQoL data were collected during the NefIgArd Nef-301 trial that could be incorporated in the model. Therefore, the model relies on EQ-5D values from the literature to inform patient utility assumptions. See more information in Section 10.1. An SLR was conducted to identify literature for HRQoL, however, since no UK-specific EQ-5D studies were identified in the economic SLR for patients with IgAN, the literature used to inform HRQoL (Cooper *et al*. 2020 [8]) was instead found in the reference list of a previous NICE HTA submission (TA775) [97].

Table 9 Relevant literature included for (documentation of) health-related quality of life (See section 10)

Reference (Full citation incl. reference number)	Health state/Disutility	Reference to where in the application the data is described/applied
Cooper JT, Lloyd A, Sanchez JJG, Sörstadius E, Briggs A, McFarlane P. Health related quality of life utility weights for economic evaluation through different stages of chronic kidney disease: a systematic literature review. Health Qual Life Outcomes. 2020 Sep 21;18(1):310. doi: 10.1186/s12955-020-01559-x. PMID: 32957990; PMCID: PMC7507735.	Health state utility values, CKD1-5, peritoneal dialysis and post-transplant.	See Section 10.3.

5.3 Literature used for inputs for the health economic model

An SLR was conducted, however, the health economic model does not include data from sources identified in the SLR. Instead, targeted literature reviews were in some cases conducted to find the inputs that were not sourced from the NefIgArd trial. For example, some resource use inputs, adverse event disutilities and costs were identified and used in the model. For more information, see Section 10.3.4.2 and Section 11. An overview of the literature used for inputs to the health economic model is presented in Table 10.

Table 10 Relevant literature used for input to the health economic model

Reference (Full citation incl. reference number)	Input/estimate	Method of identification	Reference to where in the application the data is described/applied
Cooper JT, Lloyd A, Sanchez JJG, Sörstadius E, Briggs A, McFarlane P. Health related quality of life utility weights for economic evaluation through different stages of chronic kidney disease: a systematic literature review. Health Qual Life Outcomes. 2020 Sep 21;18(1):310. doi: 10.1186/s12955-020-01559-x. PMID: 32957990; PMCID: PMC7507735.[8]	Health state utility values, CKD1-5, peritoneal dialysis and post-transplant.	Reference list of a previous NICE HTA submission (TA775) [97]	Section 10.3.4.1 Table 41
Sullivan et al. (2006)[108]	Adverse event disutility	Targeted literature review	Section 10.3.4.2 Table 43
Sullivan et al. (2011)[109]	Adverse event disutility	Targeted literature review	Section 10.3.4.2 Table 43
Eriksson D, Karlsson L, Eklund O, Dieperink H, Honkanen E, Melin J, Selvig K, Lundberg J. Real-world costs of autosomal dominant polycystic kidney disease in the Nordics. BMC Health Serv Res. 2017 Aug 15;17(1):560. doi: 10.1186/s12913-017-2513-8. PMID: 28806944; PMCID: PMC5556351.[110]	Annual resource utilisation and annual costs for health stated CKD 1-5 and other medical resource use.	Targeted literature review	Section 11.4 Table Table 46
Danish Society of Nephrology [111]	Frequency of hospital and home haemodialysis	Targeted literature review	Section 11.4 Table Table 46

6. Efficacy

6.1 Efficacy of Kinpeygo compared to placebo and corticosteroids for patients with IgAN

6.1.1 Relevant studies

Table 11 outlines the clinical studies assessing the efficacy of Kinpeygo versus placebo for adult patients with primary IgAN. The indication for Kinpeygo and the population relevant for this application is adult patients with primary IgAN at risk of rapid disease progression with a UPCR ≥ 1.5. This subpopulation is included in the pivotal trial NefIgArd Part A and B. The efficacy results outlined in this section only include Part B data, since it includes the same patient population as Part A (+ an additional 160 patients) for a longer time period (longer follow-up). Part B is an interim readout (not an additional study) to Part A. Part B is includes the main results for which this assessment (and model) is based. Part A results is also presented in Appendix B for transparency. In addition, a summary of the results for the full trial population in NefIgArd Part B and NefIgAN is also presented in the following efficacy section (6.1.3.1), for transparency.

The subpopulation was pre-defined in the study protocol. The table also includes the STOP-IgAN trial, assessing immunosuppression including corticosteroids plus supportive care versus supportive care. This study serves as basis for the indirect treatment comparison between Kinpeygo and corticosteroids. For detailed study characteristics refer to Appendix A. This the following efficacy section presents results from the NefIgArd Part B trial as well as the STOP-IgAN trial.

Table 11 Overview of study design for studies included in the comparison

Trial name, NCT-number (reference)		Study design	Trial objective	Study duration		Patient population	Intervention	Comparator	Outcomes and follow-up period
NefIgArd NEF-301, NCT03643965 Part A: Barratt *et al*, 2023[92] Part B: Lafayette *et al*, 2023[104]	Part A	Phase III, double-blind, RCT Part A evaluated Kinpeygo's efficacy and safety Completed, start date: September 2018, End date: October 2020	To evaluate the efficacy, safety and tolerability of Kinpeygo 16 mg/day in patients with primary IgAN at risk of progressing to ESRD, despite maximum tolerated RAS blockade	26.5 months (total)	Up to 35 days screening, 9 months treatment, 3 months follow-up.	Patients ≥18 years with biopsy-confirmed primary IgAN, eGFR ≥35 and ≤90 mL/min per 1.73 m2, proteinuria ≥1 g/day or UPCR ≥0.8 g/g	Optimised RASi therapy plus Kinpeygo 16 mg/day or placebo (1:1 randomisation stratified by baseline proteinuria, baseline eGFR and geographic region)	Placebo	Primary outcomes: Ratio of UPCR at 9 months compared with baseline. Secondary outcomes: • Ratio of eGFR at 9 and 12 months compared with baseline; • ratio of UACR at 9 months compared with baseline; • supportive analyses of the above endpoints at time points up to 12 months; • 1-year eGFR slope; • safety variables. 3 months follow-up.
	Part B	Phase III, double-blind, RCT Part B is evaluating Kinpeygo			Additional 12 months (+14 to 35 days)		Optimised RASi therapy (maximally tolerated doses) was continued but patients did		Primary outcomes: AUC-based endpoint of eGFR calculated as a time-weighted average of eGFR recordings observed at each time point over 2 years (analysis performed when the last patient randomised completed Visit 17b) Secondary outcomes:

Trial name, NCT-number (reference)	Study design	Trial objective	Study duration	Patient population	Intervention	Comparator	Outcomes and follow-up period
	for long-term renal function preservation Completed, End date: February 2023		follow-up		not receive Kinpeygo		• 2-year eGFR slope; • time to 30% reduction from baseline in eGFR; • time to rescue medication; • ratio of UPCR, UACR, and eGFR compared with baseline averaged over time points between 12 and 24 months, inclusive; • proportion of patients without microhaematuria in at least two time points; • proportion of patients receiving rescue treatment; • SF-36 at 9 and 24 months; • exploratory analyses on blood and urine; • safety variables 12 months follow-up.
NefIgAN NEF-202, NCT01738035[59]	Phase IIb, double-blind, RCT	To evaluate the safety and efficacy of two doses of Kinpeygo in patients with IgAN at risk of progression to ESRD despite optimised RAS blockade	6 months run-in, 9 months treatment, 3 months follow-up.	Patients ≥18 years biopsy-confirmed primary IgAN, eGFR ≥45 mL/min per 1.73 m2, and UPCR >0·5 g/g or urine	Optimised RASi therapy plus Kinpeygo 16 mg/day or Kinpeygo 8 mg/day or placebo (1:1:1 randomisation stratified by baseline UPCR).	Placebo	Primary outcomes: Mean change from baseline in UPCR over the 9-month treatment phase Secondary outcomes: • Mean changes from baseline in: ○ UPCR, ○ eGFR, ○ 24-h urine protein excretion, ○ UACR, and ○ 24-h urine albumin excretion - assessed at various timepoints, presence/absence of microhaematuria

Trial name, NCT-number (reference)	Study design	Trial objective	Study duration	Patient population	Intervention	Comparator	Outcomes and follow-up period
				protein ≥0.75 g/24-h			3 months follow-up.
STOP-IgAN, NCT00554502[7]	Multicenter, open-label, randomized, controlled trial with a two-group, parallel, group-sequential design.	To evaluate the outcomes of immunosuppressive therapy, when added to supportive care, in patients with IgA nephropathy.		Patients who had persistent proteinuria with urinary protein excretion of at least 0.75 g per day.	Immunosuppressive therapy (incl. corticosteroids). Corticosteroids: patients with eGFR ≥60 ml per minute per 1.73 m2, treatment for 6 months (methylprednisolone IV 1 g per day for 3 days at the start of months 1, 3, and 5; and oral prednisolone at a dose of 0.5 mg per kilogram per 48 hours on the other days). Cyclophosphamide: patients with an eGFR between 30 and 59 ml per minute per 1.73 m2, 1.5 mg/kg/day for 3 months Azathioprine: month 4 through 36 at a dose of 1.5 mg/kg/day	SoC (RAS blockade, blood pressure control, dietry counseling, NSAID, statins if necessary	Primary outcomes: • Full clinical remission (defined as proteinuria with a protein-to-creatinine ratio of <0.2 and stable renal function with a decrease in the eGFR of <5 ml per minute per 1.73 m^2 from the baseline eGFR at the end of the 3-year trial phase). • Decrease in the eGFR of at least 15 ml per minute per 1.73 m2 from the baseline eGFR. Secondary outcomes: • Absolute decrease in the eGFR, • A decrease in the eGFR of at least 30 ml per minute per 1.73 m2 from the baseline eGFR, • The need for dialysis (onset of end-stage renal disease), • The mean annual change in the slope of the reciprocal of serum creatinine concentration, • Proteinuria at 12 and 36 months, and • Disappearance of microhematuria as determined by means of a dipstick or urinary sediment test.

Trial name, NCT-number (reference)	Study design	Trial objective	Study duration	Patient population	Intervention	Comparator	Outcomes and follow-up period
					plus oral prednisolone 440ng/day, tapered to 10 mg/day the first 3 months of study, 10mg/day months 4-6 and 7.5 mg/day during month 7-36.		
NefIgArd-OLE, NCT04541043 [112, 113]Not used or presented further in the application since it is ongoing.	Phase IIIb open-label, single-arm, extension trial with active treatment	To evaluate the efficacy and safety of Kinpeygo 16 mg/day in patients with IgAN who completed the NefIgArd trial, and particularly to evaluate retreatment in patients who were treated with Kinpeygo in NefIgArd	9-months treatment, 3 months follow-up	Patients who completed the NefIgArd Phase III trial	Optimised RASi therapy plus Kinpeygo 16 mg/day (all patients)	Placebo	Primary outcomes: Ratios of eGFR and of UPCR at 9 months compared with baseline Secondary outcomes: • Ratio of UACR at 9 months compared with baseline; • SF-36 QoL assessment at 12 months compared with baseline; • proportion of patients with microhaematuria at 9 months compared with baseline; • proportion of patients receiving rescue treatment and time to receiving rescue treatment; • proportion of patients on dialysis, undergoing kidney transplantation, or with eGFR <15 mL/min per 1.73 m2; • cortisol suppression at 9 and 12 months, compared with baseline; • incidence of TEAEs from enrolment up to 12 months 3 months follow-up.

Abbreviations: eGFR, estimated glomerular filtration rate; h, hour; IgAN, immunoglobulin A nephropathy; OLE, open-label extension; QoL, quality of life; RASi, renin-angiotensin system inhibitor; RCT, randomised controlled trial; SF-36, Short Form-36; TEAE, treatment-emergent adverse event; UPCR, urine protein-to-creatinine ratio; UACR, urine albumin-to-creatinine ratio; UPCR, urine protein-to-creatinine ratio. Sources: DOF (NEF-301 CSR);[11] Barratt et al, 2021 (abstract);[9] Fellström et al, 2017;[59] DOF (NEF-202 CSR)[114]; ClinicalTrials.gov[113]; Barratt et al, 2023;[92] Lafayette et al, 2023;[104] DOF (NEF-301 Part B CSR)[5]; DOF (OLE study protocol)[112]

6.1.1.1 Comparability of studies

The comparative analysis between Kinpeygo and corticosteroids is undertaken through an ITC (network meta-analysis, NMA) informed by change from baseline (CFB) to 24 months based on data from the NefIgArd Part B trial data for the ≥1.5 g/g population (for Kinpeygo), and the STOP-IgAN trial (for corticosteroids) [6], since a majority of the patient population comprised of Caucasians, a population generalizable to the UK, which was assumed relevant for Danish clinical practice). The other study investigating the efficacy of corticosteroids, TESTING trial [79], primarily comprised of an Asian population, which is not considered relevant to European clinical practice due to the differences in outcomes and treatment responses seen between Asian and Caucasian populations [86-88]. It was therefore not deemed relevant for the Danish population and this submission.

However, the TESTING study was considered relevant to inform the dosing scheme for the CS arm versus Kinpeygo for Danish patients, since the treatment guidelines and a Danish clinical expert have informed that patients are treated with low doses of prednisolone, as based on the dosing scheme in the TESTING trial. [12, 57, 69] Therefore, the model includes TESTING doses as the dosing scheme for prednisolone, but efficacy data from the STOP-IgAN trial.

6.1.1.2 Comparability of patients across studies

NMA methods may lack robustness where there are observed differences between studies; if there are differences in patient characteristics, this may undermine the results of the NMA. For example, there are differences between studies in terms of ethnicity and race between the NefIgArd and STOP-IgAN trial, where the NefIgArd trial includes a large proportion of white/Caucasian patients. The STOP-IgAN trial did not report the ethnicity of patients, however, the study was conducted across 32 centres in Germany.[7, 77] Rauen 2018 also reported in the discussion section of the long-term follow-up publication that STOP-IgAN evaluated a majority white European population.[7]

A recent review suggested significant heterogeneity in epidemiology, progression, and outcomes of IgAN across different ethnic populations.[88] This was particularly related to significant differences observed in disease progression in ethnically Caucasian patients compared with ethnically Asian patients. E.g., Asian patients progressed faster in the NefIgArd study versus the global population in NefIgArd and Kinpeygo had much greater treatment effect in this patient population versus the global population (24 months mean change in eGFR from baseline, mL/min/1.73 m^2, for Asian patients with Kinpeygo -7.09 and placebo -20.97 versus global patients with Kinpeygo -6.11 and placebo -12.0).[89] This may hinder comparisons where there are substantial difference in the ethnic composition of clinical trials. However, the current NMA compares outcomes between predominantly Caucasian studies: STOP-IgAN, and NefIgArd. Therefore, this factor is not expected to confound the NMA results.

Another notable difference between studies was baseline UPCR and proteinuria. This is important as baseline proteinuria is a significant predictor of patient outcomes and these factors may be considered as treatment-effect modifiers. One key assumption underpinning an NMA is that the trials compared do not differ in any characteristics that impact the treatment-effect. Potential sources of between-study heterogeneity may affect the robustness of an NMA and may introduce bias into the results of an indirect comparison, limiting the interpretability and applicability of the results. Furthermore, patients in the NefIgArd trial were those with baseline UPCR ≥1.5 g/g, however, the average (mean) UPCR was less than this value in comparator trials (for example, the mean baseline UPCR pooled across arms in STOP-IgAN was 1.1 g/g). Similarly, mean proteinuria was 1.70 g/day in the STOP-IgAN study, compared to [redacted] in the NefIgArd trial, [redacted] Therefore, there may be little overlap in study populations' baseline UPCR and/or proteinuria.[6, 115]

Alternative statistical methodology has also been explored (results presented in Appendix C, Section C.1.2) in an attempt to overcome some of the issues identified around the NMA approach (e.g. observed differences in study populations); this included a population-adjusted approach (specifically, a series of anchored MAIC analyses). This form of ITC is considered to be a targeted approach which utilises IPD from the index trial (i.e. the NefIgArd trial), and differences in observed effect modifiers are accounted for through the use of population-adjustment methods and re-weighting, prior to estimation of treatment-effects. Data from the NefIgArd trial were re-weighted in an attempt to match the population of each comparator study, and the treatment-effect (MD in CFB) was estimated using these weighted data.[115] For comparison purposes, results from the unadjusted (i.e. unweighted) NefIgArd data are also presented.

The MAIC analyses presented in in Appendix C, Section C.1.2 may be used to support the findings from the NMA presented in this report.

There may also be concerns regarding the accuracy of data included in the ITCs (including both the NMA and MAIC analysis). For example, both UPCR and eGFR data from STOP-IgAN were based on digitisation of graphical figures in the absence of reported data.[6] Additionally, within-trial uncertainty was not always reported, particularly where results were only presented graphically, meaning that assumptions were required to estimate the uncertainty around the CFB.

Table 12 presents the baseline characteristics from the NefIgArd Part B trial for adult primary IgAN patients with UPCR ≥ 1.5 g/g and patients from the STOP-IgAN trial.

Table 12. Comparison of NefIgArd Phase III Part B trial baseline patient characteristics for adult primary IgAN patients UPCR ≥1.5 g/g vs. STOP-IgAN trial for corticosteroids

	[redacted]		STOP-IgAN trial[6]	
	[redacted]	[redacted]	Supportive care + immunosuppression (incl. CS) (N=82)	Supportive care (N=80)
Age median (range) [mean marked with ¤]	[redacted]	[redacted]	42.8 ± 13.1	45.8 ± 12.5
Age distribution, n (%)			NR	NR
<45 years	[redacted]	[redacted]	NR	NR

	[redacted]		STOP-IgAN trial[6]	
	[redacted]	[redacted]	Supportive care + immunosuppression (incl. CS) (N=82)	Supportive care (N=80)
≥45 years and <65 years	[redacted]	[redacted]	NR	NR
≥65 years	[redacted]	[redacted]	NR	NR
Sex, n (%)				
Male	[redacted]	[redacted]	62 (76)	65 (81)
Female	[redacted]	[redacted]	20 (24)	15 (19)
Race, n (%)				
White	[redacted]	[redacted]	NR	NR
Asian	[redacted]	[redacted]	NR	NR
Black or African American	[redacted]	[redacted]	NR	NR
Other	[redacted]	[redacted]	NR	NR
Baseline BMI, kg/m2				
n	[redacted]	[redacted]	NR	NR
Median (IQR)	[redacted]	[redacted]	27.0 ± 5.0	28.6 ± 5.3
Baseline SBP, mmHG				
Median (IQR)	[redacted]	[redacted]	124 ± 9.7	127 ± 8.5
Baseline DBP, mmHg				
Median (IQR)	[redacted]	[redacted]	77 ± 7.0	78 ± 7.0
Baseline UPCR, g/g				
Median (IQR)	[redacted]	[redacted]	1.1 ± 0.6	1.0 ± 0.5
Baseline proteinuria, g/24 h				
Median (IQR)	[redacted]	[redacted]	NR	NR
<2 g/24 h, n (%)	[redacted]	[redacted]	NR	NR
≥2 g/24 h and <3.5 g/24 h, n (%)	[redacted]	[redacted]	NR	NR
>3.5 g/24 h, n (%)	[redacted]	[redacted]	NR	NR
Unrinary protein excretion rate g/24 h	[redacted]	[redacted]	1.8 ± 0.8	1.6 ± 0.7
Creatinine clearance, ml/min	[redacted]	[redacted]	76.3 ± 36.4	76.2 ± 31.0
Baseline UACR, g/g				
Median (IQR)	[redacted]	[redacted]	NR	NR
Baseline total urine albumin, g/24 h				
Median (IQR)	[redacted]	[redacted]	NR	NR
Baseline eGFR*, mL/min/1.73 m²				
Median (IQR)	[redacted]	[redacted]	61.1 ± 29.0	57.4 ± 24.9
<60 mL/min per 1.73 m², n (%)	[redacted]	[redacted]	NR	NR
≥60 mL/min per 1.73 m², n (%)	[redacted]	[redacted]	NR	NR

	[redacted]		STOP-IgAN trial[6]	
	[redacted]	[redacted]	Supportive care + immunosuppression (incl. CS) (N=82)	Supportive care (N=80)
Microhaematuria at randomisation, n (%)				
Yes	[redacted]	[redacted]	NR	NR
No	[redacted]	[redacted]	NR	NR
Time from IgAN diagnosis biopsy to informed consent, years				
n	[redacted]	[redacted]	N/A	N/A
Median (IQR)	[redacted]	[redacted]	N/A	N/A
Patients with prior systemic GCS or immunosuppressive use				
n (%)	[redacted]	[redacted]	N/A	N/A
Use of any RAS inhibitor therapy, n (%)				
Patients on ACEi alone	[redacted]	[redacted]	49	34
Patients on ARB alone	[redacted]	[redacted]	15	30
Patients on both ACEi and ARB	[redacted]	[redacted]	36	32
Maximum daily ACEi dose	[redacted]	[redacted]	48	37
Maximum daily ARB dose	[redacted]	[redacted]	17	33
Maximum ACEi and ARB dose	[redacted]	[redacted]	6	6
Level of RAS blockade as a % of maximum allowable dose				
n	[redacted]	[redacted]	See above	See above
<50%, n (%)	[redacted]	[redacted]	See above	See above
≥50% and <80%, n (%)	[redacted]	[redacted]	See above	See above
≥80%	[redacted]	[redacted]	See above	See above

[redacted]

Abbreviations: ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin II type I receptor blocker; BMI, body-mass index; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; FAS, full analysis set; GCS, glucocorticosteroid; h, hours; IgAN, immunoglobulin A nephropathy; IQR, interquartile range; n, number; N/A, not applicable; NR, not reported; RAS, renin-angiotensin system; SAS, safety analysis set; SBP, systolic blood pressure; UACR, urine albumin-to-creatinine ratio; UPCR, urine protein–creatinine ratio
Source: DOF (NEF-301 Part B additional tables and figures)[17], STOP-IgAN trial.[6]

6.1.2 Comparability of the study population(s) with Danish patients eligible for treatment

Table 13 summarises the characteristics in the relevant Danish population and in the health economic model. Further details are provided in Appendix A. The mean age at diagnosis in

Denmark is 45 years, which is slightly higher than in the NefIgArd trial (42 years), which is used in the health economic model.

Table 13 Characteristics in the relevant Danish population and in the health economic model

	Value in Danish population (reference)	Value used in health economic model (reference if relevant)
Age	45 years [64]	[redacted]
Gender (proportion female, %)	Assumed to be similar to the Danish population.	[redacted]
Average weight		[redacted]
Baseline distribution across CKD states		
CKD stage 1	Assumed to be similar to the Danish population.	1.4%
CKD stage 2		34.3%
CKD stage 3a		37.1%
CKD stage 3b		27.1%
CKD 4		0.0%

6.1.3 Efficacy results: NefIgArd Phase III trial (Part B)

The efficacy results outlined in this section only include Part B data, since it is an interim readout (not an additional study), and it includes the same patient population as Part A (+ an additional 160 patients) for a longer time period (longer follow-up). Part B is therefore including the main results for which this assessment (and model) is based. Part A results is also presented in Appendix B for transparency. Full results from the NefIgAN study is presented in Appendix B, Section B.1.3. Results for the subgroup of patients with UPCR ≥ 1.5 g/g, for which this application considers, is presented in the following section (Section 6.1.3.1). All results are presented in Appendix B, sections B.1.1.2 and B.1.1.4.

The pre-planned Part B analysis of the NefIgArd trial is the final analysis of the overall 2-year global Phase III trial. The DCO occurred on 6 February 2023 when the last patient randomised in the trial had the opportunity to complete Visit 17b, which could occur up to 35 days after Visit 17a (the 24-month visit).

Regarding patients discontinuing treatment, in the FAS, discontinuations due to TEAEs occurred in 17 (9%) of 182 patients in the Kinpeygo group and three (2%) of 182 in the placebo group (FAS).[104] In the SAS, 17 (9%) patients in the Kinpeygo group and 3 (2%) patients in the placebo group discontinued study treatment due to a TEAE.[5] See more information in Appendix E, Sections E.1.3.5 and E.1.3.6.

A full description of the trial design is included in Appendix A, and an overview is provided in Table 11.

The key results for the full trial population in NefIgArd Part B and NefIgAN study are presented in Table 15 and all results are presented in Appendix B, Section B.1.1.1 and B.1.1.3, and B.1.3 for NefIgAN.

6.1.3.1 Kinpeygo efficacy in baseline UPCR ≥1.5 g/g subgroup

In patients with baseline UPCR ≥1.5 g/g, 9 months of treatment with Kinpeygo provided a statistically significant and clinically relevant reduction in decline of eGFR; the treatment effect of [redacted] was maintained during the 15-month observational follow-up.[17]

At 9 months, mean absolute change in eGFR from baseline (mL/min/1.73 m2) was [redacted] for Kinpeygo versus [redacted] for placebo (absolute difference [redacted]) and equivalent figures at 2 years were [redacted] for Kinpeygo versus [redacted] for placebo, absolute difference [redacted].

The size of the eGFR benefit versus placebo achieved after 9 months of treatment was maintained over the 15-month off-drug observational period.[17] Over 2 years, eGFR was on average [redacted] with Kinpeygo compared with placebo.

Key results from Part B in patients with UPCR ≥1.5 g/g are presented in this section. All results can be found in Appendix B, Section B.1.

6.1.3.1.1 Primary outcome: AUC-eGFR (time weighted average of eGFR over 2 years)

In patients with baseline UPCR ≥1.5 g/g, the ratio of AUC over 2 years of time-weighted averages of eGFR compared with baseline showed a statistically significant treatment benefit of [redacted] with Kinpeygo 16 mg/day versus placebo (ratio of LS means [redacted]), Table 14.[17]

The absolute change in eGFR from baseline over 2 years reported with Kinpeygo was [redacted] mL/min per 1.73 m^2 [redacted] and reported with placebo was [redacted].[17] Over 2 years, eGFR was on average [redacted] with Kinpeygo compared with placebo.[17]

Table 14. Ratio of AUC over 2 years of time-weighted averages compared with baseline of eGFR (CKD-EPI) (mL/min/1.73m2) using robust regression by subgroups (Part B FAS – baseline UPCR ≥1.5 g/g subgroup)

	Kinpeygo 16 mg/day* [redacted]	Placebo* [redacted]
eGFR $AUC_{(0-2)}$ geometric LS mean (95% CI)**	[redacted]	[redacted]
Kinpeygo vs. placebo		
Ratio of Geometric LS Means vs. placebo	[redacted]	
p value	[redacted]	
Estimated absolute change from baseline over 2 years (mL/min/1.73 m²)†	[redacted]	[redacted]
Estimated absolute change vs. placebo	[redacted]	

Note: AUC-based endpoint calculated as a time-weighted average of log-eGFR baseline ratio of measurements at each post-baseline visit compared with baseline for Month 3, 6, 9, 12, 18 and 24 respectively, where recordings made at 18 and 24 months receive twice as much weight as those made at 3, 6, 9, and 12 months; if a subgroup level has fewer than 20 patients exposed to Kinpeygo 16 mg, data in that subgroup level were not assessed; a subgroup is analysed only when it has at least 2 levels assessed; baseline is defined as the geometric mean of the 2 consecutive measurements prior to randomisation
*Treatment in addition to RAS inhibition
**For each post-baseline visit, the geometric mean of all available measurements within the corresponding analysis window is used

[†]Estimated absolute change from baseline = baseline geometric mean for total x (geometric LS mean of ratio of AUC over 2 years compared with baseline for each treatment arm −1)
Abbreviations: AUC, area under the curve; CI, confidence interval; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; eGFR, estimated glomerular filtration rate; FAS, full analysis set; LS, least squares; RAS, renin-angiotensin system; UPCR, urine protein-to-creatinine ratio
Source: DOF (NEF-301 Part B additional tables and figures)[17]

6.1.3.1 Efficacy results per study – full trial population summary

Key efficacy results for NefIgArd Part B and NefigAN are presented in Table 15 for the full trial population. Key results for the subgroup of patients with UPCR ≥1.5 g/g in the NefIgArd study, for which this assessment is considering, is presented in Section 6.1.3.1.

Table 15. Overview of key efficacy results from NefIgArd (Part B) and NefIgAN for the full population

NefIgArd NEF-301 (Phase III, full results – Part B)		NefIgAN NEF-202 (Phase IIb)	
Kinpeygo 16 mg*	**Placebo***	**Kinpeygo 16 mg ***	**Placebo***
Absolute change from baseline in eGFR over 2 years (mL/min/1.73 m²)			
(**n=182**) −2.47 (−3.88 to −1.02)	(n=182) −7.52 (−8.83 to −6.18)		
Comparison of Kinpeygo* 16 mg versus placebo* (n=182, 182)			
Percentage change in eGFR $AUC_{(0–2)}$** (95% CI) 10% (6% to 15%); p<0.0001			
Mean absolute change in eGFR from baseline at 2 years (95% CI), mL/min per 1.73 m² per year		**Mean % change in eGFR from baseline at 9 months (95% CI)**	
(**n=149**) −6.11 (−8.04 to −4.11)	(n=146) −12.00 (−13.76 to −10.15)	(n=48) 0.6%	(n=50) −9.8%
Comparison of Kinpeygo* 16 mg versus placebo*			
(n=**149, 146**) Ratio of LS means: 1.13 (1.07 to 1.20) Corresponding to a % change of 13% (7% to 20%) Absolute difference in eGFR at 2 years: 5.89 mL/min/1.73 m²; p<0.0001		(n=48, 50) Ratio of LS means: 1.12 (1.03, 1.21) Corresponding % change: 12% (3% to 21%) p=0.0026	
% change in UPCR from baseline at 2 years (95% CI)		**% change in UPCR from baseline at 9 months (95% CI); interim analysis**	
(**n=145**) −31% (−39% to −22%)	(n=142) −1% (−13% to 12%)	(n=48) −27%	(n=50) 3%
Comparison of Kinpeygo* 16 mg versus placebo*			
(n=145, 142) Ratio of LS means: 0.70 (0.59 to 0.84) Corresponding % reduction[§]: 30% (16% to 42%), p<0.0001		(n=48, 50) Ratio of LS means: 0.71 (0.53 to 0.94) Corresponding % reduction: 29% (6% to 47%), p=0.0092	
Composite endpoint of time to confirmed 30% reduction in eGFR or kidney failure, n (%)			
(**n=182**) 21 (12%)	(n=182) 39 (21%)		
Comparison of Kinpeygo* 16 mg versus placebo* (n=182, 182)			
HR 0.45 (95% CI 0.26 to 0.75), p=0.0014			
Patients without microhaematuria during the observational follow-up period[‡], n (%)			
(**n=182**) 94 (59%)	(n=182) 59 (39%)		
Comparison of Kinpeygo* 16 mg versus placebo* (n=182, 182)			
OR[§] 2.5 (95% CI 1.6 to 4.1), p=0.0001			

*Treatment in addition to RAS inhibition; **AUC(0–2) is a time-weighted average of eGFR observed at each time point over 2 years, with the treatment effect interpreted as the average effect of Kinpeygo over 2 years; §Corresponding percentage reduction and confidence interval is derived from (1 – ratio of geometric LS means) × 100; †In patients with two or more valid urine dipstick results during the observational follow-up period, patients' urine dipstick result returned a result of negative, trace, or 0.03 mg/dL on at least two visits in the observational follow-up period; §Estimated using logistic regression model with treatment, log-baseline UPCR, log-baseline eGFR, and geographical region as defined in the stratification variable as covariates, where CI is estimated using a profile-likelihood approach and the p value is from a likelihood-ratio test. Abbreviations: CI, confidence interval; eGFR, estimated glomerular filtration rate; LS, least square; RAS, renin-angiotensin system; SEM, standard error of the mean; UPCR, urine protein-to-creatinine ratio. Source: Lafayette et al, 2023;[104] Lafayette et al, 2023, Supplementary Appendix;[93] DOF (NEF-301 Part B CSR);[5] Barratt et al, 2023;[92] DOF (NEF-301 CSR);[11] Fellström et al, 2017;[59] DOF (NEF-202 CSR)[114]§

6.1.1 Efficacy results STOP-IgAN trial

The study could not confirm the hypothesis that additional immunosuppressive therapy would provide substantial kidney-related benefits in patients with high-risk IgA nephropathy. Although the addition of immunosuppressive therapy to supportive care was superior to supportive care alone in inducing remission of proteinuria in a proportion of patients, there was no significant difference between the two study groups with respect to the second primary end point of decreasing the rate of fast decreases in the eGFR.

This section includes the results for the primary outcome. Secondary outcomes are presented in Appendix B, Section B.1.4.

6.1.1.1 Primary outcome

6.1.1.1.1 Full clinical remission

The 3-year trial phase was completed by 76 patients (95%) in the supportive-care group and by 78 patients (95%) in the immunosuppression group. In the full-analysis set, 4 of the 80 patients (5%) in the supportive-care group, as compared with 14 of the 82 patients (17%) in the immunosuppression group, had a full clinical remission at the final visit (Figure 30, Panel A). An analysis of all available cases yielded similar results — 4 of 72 patients (6%) in the supportive-care group had a full clinical remission at the final visit, as compared with 14 of 71 (20%) in the immunosuppression group.

Additional analyses that included a permutation test, multiple imputation of missing information, and per-protocol analyses confirmed significant differences between the groups. Patients who had a remission had a lower mean (±SD) baseline level of proteinuria than did those who did not have a remission (protein-to-creatinine ratio of 0.7±0.3 vs. 1.1±0.6; P<0.001 by Welch's t-test). Renal function and blood pressure at baseline were similar in these groups. The higher rate of full clinical remission in the immunosuppression group than in the supportive-care group was related exclusively to the remission of proteinuria (9 patients in supportive-care group vs. 20 patients in the immunosuppression group); there was no significant difference between the two study groups in the number of patients with a decrease in the eGFR of less than 5 ml per minute per 1.73 m^2 during the trial (38 patients in each group).

6.1.1.1.2 Decrease in the eGFR of at least 15 ml per minute per 1.73 m2 from the baseline eGFR

With respect to the second primary end point (a decrease in the eGFR of at least 15 ml per minute per 1.73 m^2), there was no significant difference between the groups (full-analysis set: 22 of 80 patients [28%] in the supportive-care group and 21 of 82 [26%] in the immunosuppression group; Figure 30 in Appendix B, Section B.1.4.1.1, Panel B). Similarly, in the analysis of all available cases, 18 of 76 patients (24%) in the supportive-care group and 17 of 78 (22%) in the immunosuppression group had a decrease in the eGFR of at least 15 ml per minute per 1.73 m^2. When measured creatinine clearance instead of eGFR was used to assess this end point, there was also no significant difference between the study groups (odds ratio for a decrease in creatinine clearance of ≥15 ml per minute per 1.73 m^2 in the immunosuppression group, 1.15; 95% confidence interval, 0.62 to 2.14; P=0.66).

7. Comparative analyses of efficacy

To assess comparative efficacy of Kinpeygo versus comparators of interest (i.e., corticosteroids, including prednisolone), a systematic literature review (SLR) was undertaken (completed in March 2023) and included evidence assessing corticosteroid therapy. Indirect treatment comparison (ITC) analyses were completed in August 2023 using 12-month data from Part A of the NefIgArd trial.[116, 117] Note that the comparison is also made to immunosuppressive therapies (azathioprine and cyclophosphamide), since the STOP-IgAN trial included both corticosteroids and immunosuppressive therapies.

To ensure the ITC reflects the latest and most comprehensive data available, this analysis is based on the 24-month data from Part B of the NefIgArd trial. This section details results from an ITC analysis informed by change from baseline (CFB) to 24 months based on data from the NefIgArd Part B trial data for the ≥1.5 g/g population.[115]

ITC methods included network meta-analysis (NMA) as well as population-adjusted indirect comparisons using matching-adjusted indirect comparisons (MAIC) (to further explore comparative efficacy between Kinpeygo and key comparators, and to supplement the findings obtained from the NMA). Assumptions were required to facilitate a quantitative analysis, which may limit the robustness of the analyses performed.

As mentioned in Section 6.1.1.1, the MAIC was conducted as an alternative statistical methodology in an attempt to overcome some of the issues identified around the NMA approach (e.g. observed differences in study populations) and therefore, this following section will present the results from the NMA only, and the MAIC results are presented in Appendix C, Section C.1.2.2.

The detailed description of methodology adopted for the analysis are presented in Appendix A, Section A.4.

7.1.1 Differences in definitions of outcomes between studies

Differences in the definitions of outcomes between studies used for the comparative analysis of efficacy of Kinpeygo versus corticosteroids (prednisolone), i.e., NefIgArd and STOP-IgAN, is presented below, For information on differences in definitions of outcomes between studies for the population-adjusted indirect comparison (MAIC), see Appendix C, Section C.1.3.

Network meta-analysis (NMA)
For eGFR, NefIgArd reported data in regard to mean CFB to 24 months, along with a corresponding 95% confidence interval (CI) from which the standard error (SE) was deduced.

[115] STOP-IgAN only reported 24-month follow-up data in graphical format, requiring digitisation to obtain estimates of the required CFB data.[6, 118]The CFB in eGFR to 24 months, the SE of the CFB estimate was calculated using baseline and 24-month data using the formula that is presented in Appendix C (C.1.1.2).

7.1.2 Method of synthesis

A Bayesian NMA approach was adopted for synthesis of the evidence base, and both random-effects (RE) and fixed-effect (FE) models were fitted to the data to estimate relative treatment-effects between Kinpeygo and relevant comparators. Results from the RE models are presented in the main body of the report; these models are considered to be more conservative and appropriate in the presence of observed heterogeneity in the network. Furthermore, findings from the ITC feasibility assessment identified several observed differences between studies, meaning that between-study heterogeneity is likely to be present in the evidence base. The approach adopted for synthesis was based on a model structure reported in the NICE guidance published by the Decision Support Unit (DSU) Technical Support Document (TSD).[119] Independent NMA were conducted for each outcome. An arm-based treatment-effect model using a Normal likelihood with identity link function was fitted to the data, evaluating the mean CFB in UPCR or eGFR along with the associated SE.

In the RE NMA, an informative prior distribution based on using Turner's prior was used, with an adjustment made for analysis of outcomes measured on a continuous scale, using recommendations published by Ren 2018.[120, 121]

Bayesian statistical software, WinBUGS (v1.4.3) – a Markov chain Monte Carlo (MCMC) simulation-based software, was adopted for all analyses.[122] For each analysis, 50,000 initial samples were discarded as burn-in and 10,000 samples were retained to inform summary parameter estimates. A thinning interval of 10 was utilized to mitigate the issue of autocorrelation.

7.1.3 Results from the comparative analysis

A summary of the results from the NMA for eGFR is presented in Table 16. A summary of the available data for eGFR for the trials included in the NMA is presented in Table 80 in C.1.1.4.

A summary of the available data for eGFR is presented in Table 80. Note: analyses using 24-month data are based on outcomes previously explored using data related to CFB to 12 months in eGFR.

Results from the MAIC is presented in Appendix C, section C.1.2.2.

Table 16 Results (pairwise comparisons) from the comparative analysis of Kinpeygo vs. corticosteroids (prednisolone) for primary IgAN in adults at risk of rapid disease progression with a UPCR ≥1.5 g/g

[redacted]		[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]

[redacted]		[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]

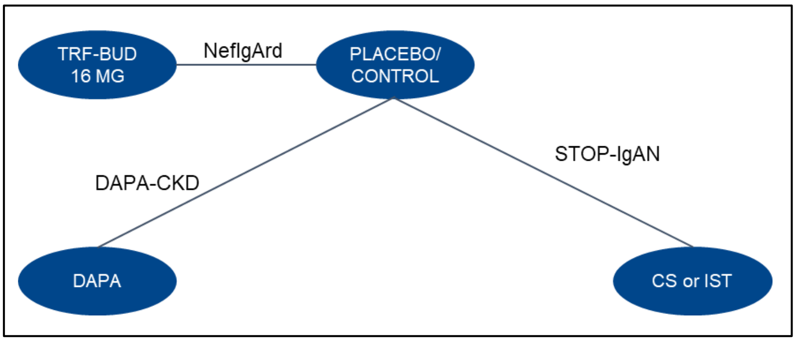
[redacted]

7.1.4 Efficacy – results per change from baseline to 24 months in eGFR (NMA)

Three studies are included in the analysis which evaluate CFB to 24 months in eGFR; the network diagram is presented in Figure 6.[115, 118, 123] Data from the STOP-IgAN and DAPA-CKD trials were reported graphically and were digitised accordingly. A comparison was possible between Kinpeygo versus CS or IST and dapagliflozin (DAPA in figure). Note: data from the NefIgArd trial is based on the subgroup of patients with baseline UPCR ≥1.5 g/g.[115]

The comparison relevant for this assessment is versus CS or IST. The results for dapagliflozin will therefore not be included.

Figure 6. Network – CFB to 24 months in eGFR (NMA)



Abbreviations: CFB, change from baseline; CS, corticosteroid; DAPA, dapagliflozin; eGFR, estimated glomerular filtration rate; IST, immunosuppressive therapy; N, number of studies; TRF-BUD, targeted-release formulation budesonide.

A forest plot showing the relative effects from the RE model showing the MD between Kinpeygo versus each comparator is presented in .

[redacted]

Figure 7. Forest plot (Kinpeygo versus comparator) – MD in CFB to 24 months in eGFR (RE model) (NMA)

[redacted]

[redacted]

8. Modelling of efficacy in the health economic analysis

8.1 Presentation of efficacy data from the clinical documentation used in the model

The transition probabilities for CKD stage 1-4 for Kinpeygo and corticosteroids are presented in Section 8.1.2, whereas for stage CKD 5 to dialysis and kidney transplant, and from dialysis to transplant are presented in Section 8.2.2. The extrapolation of efficacy related to the risk of progressing to CKD 5 for Kinpeygo and corticosteroids, including a description of its transition probabilities are presented in Section 8.2.1.1. The risk of transitioning to the death state is described in Section 8.4.

8.1.1 Extrapolation of efficacy data

8.1.1.1 Extrapolation of [effect measure 1]

Not applicable.

Table 17 Summary of assumptions associated with extrapolation of [effect measure]

Method/approach	Description/assumption
Not applicable	

8.1.2 Calculation of transition probabilities

The transition probabilities presented in this section for CKD 1-5 and death are considered applicable to the Danish population, as it is not expected that it would differ between European countries, assuming similar patient characteristics between the countries. In addition, transition probabilities for CKD 5 to dialysis and transplant, and dialysis to transplant were informed by a Danish clinical expert.

8.1.2.1 CKD 1-4 health state transition matrices for Kinpeygo

8.1.2.1.1 Transitions between 0-24 months

Data from NefIgArd Nef-301 was used to inform transition probabilities from baseline to 24 months [124]. During NefIgArd Nef-301, patients received treatment for 9 months and were followed up to 24 months after initial treatment. Transition probabilities between CKD 1–4 health states in the Kinpeygo and SoC arm were estimated by modelling the log odds of improvement and worsening in CKD states using the NefIgArd Nef-301 patient level data and logistic regression within the statistical software R (version 4.1.1). Note that the SoC arm is mentioned here since the transition probabilities for the corticosteroids arm are partly based on the transition probabilities for SoC. See more information in this section.

eGFR values were mapped to CKD stages at baseline and after 24-months from receiving initial treatment. Patients are considered to have 'transitioned' if they were in a different CKD stage after 24 months of treatment compared with baseline, with the likelihood of transitioning evaluated by treatment arm and baseline CKD stage.

The output of the logistic regression produced log odds ratios for each coefficient (CKD stage at baseline and treatment arm) is presented in Table 18.

Table 18. NefIgArd Nef-301 logistic regression output

[redacted]		[redacted]		[redacted]	
[redacted]					
[redacted]		[redacted]		[redacted]	
[redacted]		[redacted]		[redacted]	
[redacted]		[redacted]		[redacted]	
[redacted]		[redacted]		[redacted]	
[redacted]		[redacted]		[redacted]	
[redacted]		[redacted]		[redacted]	
[redacted]					
[redacted]		[redacted]		[redacted]	
[redacted]		[redacted]		[redacted]	
[redacted]		[redacted]		[redacted]	
[redacted]		[redacted]		[redacted]	
[redacted]		[redacted]		[redacted]	

[redacted]

The log odds in Table 18 were converted to 24-month probabilities as follows:

$$p = \frac{e^{(\beta_0 + \beta_1 x_1 + \cdots + \beta_n x_n)}}{1 + e^{(\beta_0 + \beta_1 x_1 + \cdots + \beta_n x_n)}}$$

Where p is the 24-month probability, β_0 is the log odds of the intercept (placebo CKD stage 3b) and $\beta_1 x_1, \ldots, \beta_n x_n$ are log odds ratios for each group compared to the intercept.

The 24-month probabilities were converted to monthly probabilities, to align with the model cycle length, using the equations below:

$$r = -\frac{\ln(1-p)}{t}$$

Where r is the rate, p is the 24-month probability and t is time-period (24 months).

$$p = 1 - e^{\frac{-r}{t}}$$

Where r is the rate, p is the monthly probability and t is time-period (30.4375 days).

The resultant transition probabilities are presented in Table 19.

Patients that discontinue treatment still incur the Kinpeygo transition probabilities presented in Table 19. This implicitly assumes that the transition probabilities from the trial data included patients that discontinued treatment before 9 months and therefore the transition probabilities account for the disease progression of patients that discontinued Kinpeygo treatment.

Table 19. Transitions in the health economic model - Kinpeygo and SoC

To From	CKD 1	CKD 2	CKD 3a	CKD 3b	CKD 4	Total	Description of method	Reference
Kinpeygo transition probabilities								
CKD 1	[redacted]	[redacted]				100.0%		
CKD 2	[redacted]	[redacted]	[redacted]			100.0%		
CKD 3a		[redacted]	[redacted]	[redacted]		100.0%		
CKD 3b			[redacted]	[redacted]	[redacted]	100.0%		
CKD 4				[redacted]	[redacted]	100.0%	See Section 8.1.2.1.1	NefIgArd Nef-301 [124]
SoC transition probabilities								
CKD 1	[redacted]	[redacted]				100.0%		
CKD 2	[redacted]	[redacted]	[redacted]			100.0%		
CKD 3a		[redacted]	[redacted]	[redacted]		100.0%		
CKD 3b			[redacted]	[redacted]	[redacted]	100.0%		
CKD 4				[redacted]	[redacted]	100.0%		

Abbreviations: CKD, chronic kidney disease; SoC, standard of care; TRF, targeted-release formulation.

Kinpeygo retreatment transition probabilities

Patients that undergo subsequent treatment rounds of Kinpeygo incur the 0–24-month Kinpeygo transition probabilities (presented in Table 19) that have been weighted by Kinpeygo's retreatment waning effect, which is assumed to be [redacted]. The weighted 0-24-month transition probabilities are applied to patients undergoing retreatment from the time point where retreatment is initiated plus the time point from where no treatment effect is assumed (2 years). Beyond this time point, the beyond 24 months SoC transition probabilities are applied.

Patients that do not receive a subsequent round of Kinpeygo are assumed to only receive SoC and therefore the beyond 24 months SoC transition probabilities are applied to these patients.

8.1.2.1.2 Transitions beyond 24 months

No data from NefIgArd Nef-301 beyond 24 months from baseline were available at the time of submission. As such, the transition probabilities beyond 24 months in the SoC arm are assumed equivalent to observed transition probabilities in the NefIgArd Nef-301 SoC arm [124], as presented in Table 19 in Section 8.1.2.1.1.

The transition probabilities in the NefIgArd Nef-301 Kinpeygo arm are only applied up until the treatment effect duration, which in the base case is 2 years, after which point the beyond 24-month transition probabilities are assumed equivalent to observed transition probabilities in the NefIgArd Nef-301 SoC arm, as presented in Table 19 in Section 8.1.2.1.1.

8.1.2.2 CKD 1-4 health state transition matrices for corticosteroids

8.1.2.2.1 Transitions between 0-24 months

The 0–24-month transition probabilities in the CS and IS plus SoC arm are calculated by applying a factor to the SoC transition probabilities. A goal seek analysis was run within Excel to determine what factor needed to be applied to the SoC transition probabilities to obtain CS and IS probabilities that achieved the difference in eGFR over 24 months between CS and IS therapy in the STOP-IgAN trial and SoC, as seen in the ITC [125]. To calculate the change in eGFR over 24 months, the proportion of patients in each of the CKD 1-4 health states in the SoC and CS and IS plus SoC engines in each cycle were multiplied by the mid-point eGFR range corresponding to the health state (Table 20). The difference in eGFR over 24-months was then calculated by subtracting the change in eGFR observed in the corticosteroids arm from the change in eGFR observed in the SoC arm. [redacted]. Applying this factor to the SoC transition probabilities produced the transition probabilities presented in Table 21.

Table 20. eGFR ranges and mid-point

	Lower eGFR value	Upper eGFR value	Mid-point
CKD 1	90	100	95
CKD 2	60	89	74.5
CKD 3a	45	59	52
CKD 3b	30	44	37
CKD 4	15	29	22

Abbreviations: CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate

Table 21. Transitions in the health economic model – corticosteroids (CS)

To From	CKD 1	CKD 2	CKD 3a	CKD 3b	CKD 4	Total	Description of method	Reference
Corticosteroid (CS) transition probabilities								
CKD 1	[redacted]	[redacted]				100.0%	See Section 8.1.2.1.1	STOP-IgAN
CKD 2	[redacted]	[redacted]	[redacted]			100.0%		
CKD 3a		[redacted]	[redacted]	[redacted]		100.0%		

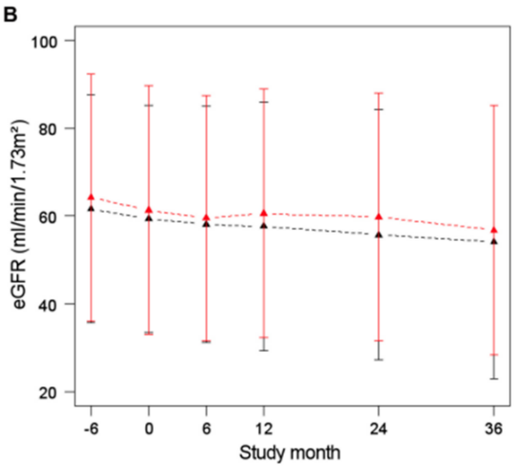
CKD 3b		[redacted]	[redacted]	[redacted]	100.0%	trial. [6, 125]
CKD 4			[redacted]	[redacted]	100.0%	

Abbreviations: CKD, chronic kidney disease; CS, corticosteroids.

The model assumes corticosteroids only have a treatment effect duration of 2 years. This assumption was based on the findings of Rauen et al. 2015 [6] who demonstrated the absolute eGFR change at 24 months after randomization, was significantly lower in the immunosuppression group compared to those in the supportive-care group. At month 36, the difference in eGFR from baseline was no longer significant (Figure 8).

The graph presented in Figure 8 demonstrates the change in eGFR over the trial time horizon and was digitised using Engauge Digitizer 12.1 software [126].

Figure 8. Estimated eGFR over the duration of STOP-IgAN study



▲ corticosteroid/immunosuppressant therapy plus SoC arm ▲ SoC arm
Source: Rauen et al, 2015[6]

The digitised data as presented in Table 22 shows eGFR level are different time-points of the STOP-IgAN trial.

Table 22. Digitized data showing estimated eGFR in STOP-IgAN

Time (months)	SoC eGFR (ml/min per 1.73 m²)	Corticosteroids plus SoC eGFR (ml/min per 1.73 m²)
[redacted]	[redacted]	[redacted]
[redacted]		

The data presented in Table 22 was used to calculate the change in eGFR from baseline to 24-months and 24-months to 36-months in the SoC and CS and IS plus SoC arms of the STOP-IgAN trial (presented in Table 23). However, as shown in Table 23, the change in eGFR between 24–36 months suggest SoC is more effective than CS and IS plus SoC.

Table 23. Change in eGFR in STOP-IgAN trial

Time (months)	SoC	Corticosteroids plus SoC	Treatment difference†
Change in eGFR between baseline and 24 months	[redacted]	[redacted]	[redacted]
Change in eGFR between 24 -36 months	[redacted]	[redacted]	[redacted]

† Treatment difference calculated by subtracting the change in eGFR in the CS and IS plus SoC arm from the change in eGFR in the SoC arm

This demonstrates that CS and IS plus SoC have a greater treatment effect compared to SoC for 2 years. Beyond 2 years, SoC has a greater treatment effect on eGFR. Therefore, the transition probabilities beyond 24 months in the model are assumed equivalent to the SoC transition probabilities.

8.1.2.2.2 Transitions beyond 24 months

As presented in Section 8.1.2.2.1, CS and IS plus SoC have a greater treatment effect compared to SoC for 2 years. Beyond 2 years, SoC has a greater treatment effect on eGFR. Therefore, the transition probabilities beyond 24 months in the model are assumed equivalent to the SoC transition probabilities as presented in Table 19 in Section 8.1.2.1.1.

8.1.2.3 Health state occupancy plots

The proportion of patients in each health state per cycle for Kinpeygo and corticosteroids is presented in Figure 9.

Figure 9 Distribution of patients in the model's stages over the model's time horizon

[redacted]

[redacted]

Abbreviations: CKD, Chronic kidney disease.

8.2 Presentation of efficacy data from other sources

8.2.1 Extrapolation of efficacy data

8.2.1.1 Extrapolation of risk of CKD 5 (eGFR <15 mL/min/1.73m^2)

The risk of CKD 5 in the Kinpeygo and corticosteroids arms is informed by applying a hazard ratio (HR) to the risk of CKD 5 in the SoC arm. This section first presents how the risk for SoC was extrapolated from the UK RaDaR database study (Table 24), and secondly it describes how the risk for Kinpeygo and corticosteroids arms was calculated.

Table 24 Summary of assumptions associated with extrapolation of risk of CKD 5 (eGFR <15 mL/min/1.73m^2)

Method/approach	Description/assumption
Data input	UK RaDaR database study [127] for SoC, HR from Inker et al. 2019 [128] for Kinpeygo and corticosteroids.

Method/approach	Description/assumption
Model	Exponential Generalized gamma Log-normal Weibull Gompertz Gamma Log-logistic
Assumption of proportional hazards between intervention and comparator	Not applicable
Function with best AIC fit	Kinpeygo, SoC and corticosteroids: Gamma
Function with best BIC fit	Kinpeygo, SoC and corticosteroids: Gamma
Function with best visual fit	On visual inspection of the extrapolated curves, the log-logistic and log-normal models did not provide a good fit to the tail of the KM and appear to overestimate time to ESRD. Additionally, the Gompertz model results in a curve that plateaus, suggesting that a proportion of patients (~5%) do not transition to ESRD. This was not considered to be clinically plausible given the progressive nature of the disease. Therefore, the statistical fit was used to determine the best fitting model out of those that were considered to be clinically and visually plausible.
Function with best fit according to evaluation of smoothed hazard assumptions	Not applicable
Validation of selected extrapolated curves (external evidence)	The choice of parametric model to inform the CKD 4 to CKD 5 transition was further validated by experts at the advisory board using visual inspection [102].
Function with the best fit according to external evidence	Not applicable
Selected parametric function in base case analysis	Gamma
Adjustment of background mortality with data from Statistics Denmark	Yes
Adjustment for treatment switching/cross-over	No
Assumptions of waning effect	No
Assumptions of cure point	No

SoC arm

As per the model structure in Section 4, only patients with CKD 4 can transition to CKD 5. In the model base case, the risk of CKD 5 is informed by real world evidence from patients with IgAN and UPCR ≥1.5 g/g collected in the UK RaDaR database [127]. [redacted]

Figure 10. UK RaDaR KM curve estimating time to diagnosis of ESRD

[redacted]

[redacted]

The KM curve presented in Figure 10 was digitised using Engauge Digitizer 12.1 software [126]. Pseudo patient level data (PLD) was generated from the sdigitised data using the R packages [129] “MASS” and “splines”.

The KM curve presented in Figure 10 was digitised using Engauge Digitizer 12.1 software [126]. Pseudo patient level data (PLD) was generated from the digitised data using the R packages [129] “MASS” and “splines”. As data were only available for up to 4 years, parametric survival modelling was fitted to these data to extrapolate beyond the currently available data, using the R packages “survival” and “flexsurv” [129]. Figure 11 presents the extrapolated and digitised KM data with seven parametric extrapolations fitted.

Figure 11. Digitised UK RaDaR KM data and fitted parametric extrapolations to estimate time to CKD 5

[redacted]

[redacted]

The AIC and BIC both ranked gamma as the model that best fits the observed data, as presented in Table 25. The gamma model is used in the base case since it provides the numerically best fit according to both AIC and BIC statistics. Alternative model extrapolations are explored in scenario analyses.

The choice of parametric model to inform the CKD 4 to CKD 5 transition was further validated by experts at the advisory board using visual inspection [102]. On visual inspection of the extrapolated curves, the log-logistic and log-normal models did not provide a good fit to the tail of the KM and appear to overestimate time to ESRD. Additionally, the Gompertz model results in a curve that plateaus, suggesting that a proportion of patients (~5%) do not transition to ESRD. This was not considered to be clinically plausible given the progressive nature of the disease. Therefore, the statistical fit was used to determine the best fitting model out of those that were considered to be clinically and visually plausible.

Table 25. AIC and BIC statistics for time to CKD 5 models

Model	AIC	AIC rank	BIC	BIC rank
Exponential	[redacted]	4	[redacted]	3
Generalised gamma	[redacted]	3	[redacted]	6
Gompertz	[redacted]	5	[redacted]	4
Log-logistic	[redacted]	6	[redacted]	5
Log-normal	[redacted]	7	[redacted]	7
Weibull	[redacted]	2	[redacted]	2
Gamma	[redacted]	**1**	[redacted]	**1**

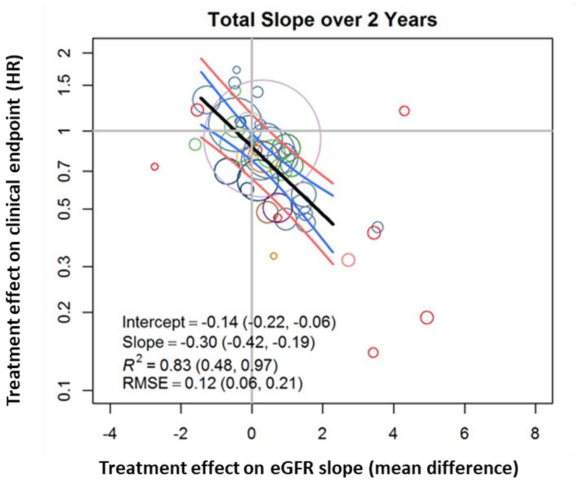
Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion; CKD, chronic kidney disease.

Kinpeygo (TRF-budesonide) arm

The risk of CKD 5 in the Kinpeygo arm is informed by applying a hazard ratio (HR) to the risk of CKD 5 in the SoC arm (presented in Figure 11).

In the model base case, movements from the CKD 4 health state to the CKD 5 health state in the Kinpeygo arm are calculated by applying a HR of [redacted] to the extrapolated KM data presented in Figure 11. Published meta-analyses [128] were used to estimate the reduction in risk of the clinical outcome (HR), and associated 95% CI, allowing for the uncertainty in the Kinpeygo 16 mg treatment effects on 2-year eGFR slope and the relationship between endpoints. The observed treatment effect on [redacted] in NefIgArd Nef-301 arm predicts a HR of [redacted] for the clinical outcome.

Figure 12. Relationship between treatment effect on 2-year eGFR slope and clinical outcome, with predicted HR for Kinpeygo 16 mg



Abbreviations: eGFR, estimated glomerular filtration rate; HR, hazard ratio; TRF, targeted release.
Source: Adapted from Figure 5 of Inker et al. 2019. The meta-analysis of 47 trials in chronic kidney disease (Inker et al. 2019 supplement eFigure5) relating treatment effects on 2-year eGFR total slope to long-term clinical outcomes in IgAN was used to predict the HR associated with the treatment effect on 2-year eGFR total slope for Kinpeygo 16 mg versus placebo in Nef-301.

The equation used to calculate the HR using the coefficients presented in Figure 12 and the observed treatment effect on 2-year eGFR total slope of 3.83 mL/min/1.73 m^2 per year is presented below:

$$HR = e^{(intercept+[slope \times eGFR\ treatment\ effect])}$$

$$HR = e^{(-0.14+[-0.30\times 3.83])} = $$ [redacted]

Figure 13 presents the risk of transitioning to the CKD 5 health state while receiving Kinpeygo by applying the HR of [redacted] to the digitised KM data and fitted survival models in Figure 11.

Figure 13. Digitised UK RaDaR KM data with fitted gamma extrapolation and HR of 0.28 applied.

[redacted]

[redacted]

The HR of [redacted] is only applied to the SoC curve for as long as Kinpeygo is assumed to have a treatment effect within the model. The base case treatment effect duration is 2 years (further detail in Section 8.1.2.1.1). After this time point, patients in the Kinpeygo arm of the model are assumed to experience an equivalent hazard of transitioning to CKD 5 as those in the SoC arm, unless the patient undergoes another round of Kinpeygo treatment.

Corticosteroids arm

Movements from the CKD 4 health state to the CKD 5 health state in the corticosteroids arm are calculated by applying a HR of [redacted] to the extrapolated KM data presented in Figure 13. Using published meta-analyses and the formula presented in Section 8.1.2.1.1, the observed treatment effect on 2-year eGFR total slope in the sub-population of patients with baseline UPCR ≥1.5 g/g of [redacted] This predicts a HR of [redacted] for the clinical outcome. This HR is only applied to the SoC curve for the first 2-years of the model as this is how long CS+IST is assumed to have a treatment effect. After this time point, patients in the corticosteroids arm of the model are assumed to experience an equivalent hazard of transitioning to CKD 5 as those in the SoC arm.

8.2.2 Calculation of transition probabilities from CKD 5, dialysis, and kidney transplant health states

No IgAN-specific data was available to inform the transition probability between CKD 5 and dialysis due to the inclusion criteria of the NefIgArd Nef-301 trial limiting recruitment to patients classified as CKD 1-3b only. The transition from transplant to dialysis were sourced from a systematic literature review by Sugrue *et al.* (2019)[13], which aimed to review published economic models simulating long-term outcomes of kidney disease to inform cost-effectiveness evaluations of CKD treatments, and converted to monthly probabilities for the CEM.[13] The transitions from CKD 5 to dialysis and transplant and from dialysis to transplant were based on clinical expert input, to better reflect the Danish context as more than 80% of patients expected to progress to dialysis straightaway when reaching CKD 5, 20-30% of patients expected to receive transplant after dialysis and 10-20% of patients expected to progress to transplant straightaway when reaching CKD 5.[12] The clinical expert provided annual rates of patients transitioning between the health state dialysis to transplant, which were then converted to monthly probabilities through the rate and probability formula presented in Section 8.1.2.1.1, to be aligned with the 30-day cycle length, and are applied in the CEM as reported in Table 26.

The same transition probabilities from CKD 5, dialysis and transplant were applied over time for both Kinpeygo, SoC and corticosteroids. In this, it was assumed that there is no difference (i.e., no lasting treatment effect) for Kinpeygo patients compared with SoC and corticosteroids once patients reach the CKD 5 health state. Table 26 presents the monthly transition probabilities from CKD 5, dialysis, and transplant used in the model.

Table 26. Monthly transition probabilities from CKD 5, dialysis, and transplant

Health state	CKD 5	Dialysis	Transplant	Total
CKD 5 [12]	[redacted]	[redacted]	[redacted]	100%
Dialysis [12]		[redacted]	[redacted]	100%
Transplant [13]		[redacted]	[redacted]	100%

Abbreviations: CKD, chronic kidney disease

8.3 Modelling effects of subsequent treatments

N/A, no subsequent treatments are included in the model.

8.4 Other assumptions regarding efficacy in the model - mortality

As no long-term survival data were available from the NefIgArd Nef-301 clinical trial, no mortality data were available to directly inform the CEM. Therefore, the CEM relies on real-world evidence to inform the risk of death from all health states.

In any instance, where the background risk of death was greater for the general population compared with the modelled population, general population background mortality was applied. The probability of death for the general population was age- and sex-adjusted in line with data sourced from the general mortality for the Danish population as per DMC guidelines. [130]

During retreatment with Kinpeygo no explicit changes were made to the mortality data as the risk of death were assumed to only be dependent on disease progression rather than treatment received.

8.4.1 Risk of death from CKD 1-5, dialysis, and transplant health states

Data from UK RaDaR were used to inform the risk of mortality from CKD stages 1–5, transplant, and dialysis. The standardised mortality rates from the UK RaDaR data were calculated by building a cox regression model with age, sex, and CKD stage as covariates. The 10-year survival rates were used to calculate the standardised mortality ratios (SMR). The SMR weights used in the CEM for the CKD stages and dialysis health states are presented in Table 27.

Table 27. Standard mortality ratios

Health state	SMR
CKD 1	[redacted]
CKD 2	[redacted]
CKD 3a	[redacted]
CKD 3b	[redacted]
CKD 4	[redacted]
CKD 5	[redacted]
Renal replacement therapy (dialysis and transplant)	[redacted]

Abbreviations: CKD, chronic kidney disease; SMR, standardised mortality ratio.
Note: Renal replacement therapy estimate was used for patients in both the dialysis and transplant health states.

8.5 Overview of modelled average treatment length and time in model health state

The transitions in the model were mostly informed by transition probabilities, as opposed to effect measures. Hence, Table 28 on effect measure estimates was considered not applicable in this submission.

Table 28 Estimates in the model

	Modelled average [effect measure] (reference in Excel)	Modelled median [effect measure] (reference in Excel)	Observed median from relevant study
Not applicable			

Regarding treatment duration, as per SmPC, which requires a daily dose of 16 mg for 9 months, the model assumes all treatment will stop after 9 months [72]. Prior to 9 months, the number of patients that continue treatment each month was informed by the TTD data from Part B full analysis set of the NefIgArd Nef-301 study. This data is presented in Figure 14.

Figure 14 Digitised KM curve of time to discontinuation of study treatment – TRF-budesonide

[redacted]

[redacted]

It should be noted that patients were censored at their final follow-up appointment of the NefIgArd Nef-301 study even if they were continuing treatment. Therefore, patients that had a follow-up before month 9 were censored despite not discontinuing their treatment. This explains the sharp decline in the proportion of patients that are on treatment before month 9. The data in Figure 14 does not include patients that received a reduced/tapering dose for 2 weeks after 9 months of treatment. Therefore, it is assumed that all patients on treatment at the start of the month 9 received the reduced dose for 2 weeks. As well as a tapering dose for another 2 weeks.

The modelled average treatment length (time to treatment discontinuation) in the model for Kinpeygo and corticosteroids are presented in Table 29. There is no variation in treatment length between health states.

Table 29 Overview of modelled average treatment length and time in model health state, undiscounted and not adjusted for half cycle correction (adjust the table according to the model)

Treatment	Treatment length [months]	Health state 1 [months]	Health state 2 [months]
Kinpeygo	[redacted]	N/A	N/A
Corticosteroids	[redacted]	N/A	N/A

9. Safety

9.1 Safety data from the clinical documentation

This section contains data on safety and tolerability of Kinpeygo from NefIgArd Part B trial, for both FAS and the subgroup of patients with UPCR ≥ 1.5 g/g relevant for this assessment, and from the NefIgAN trial. The section also includes safety data for corticosteroids (prednisolone) from the STOP-IgAN study, see Section 9.1.3.

The Part B Per Protocol Set included all patients in the Part B FAS for whom no protocol deviations occurred during the study that were considered to have the potential to impact the efficacy evaluation.[5, 104] For more information on the analysis populations in the trials, see Appendix A, Section A.1.6.

An overview of key safety results from NefIgArd Part B for the full population and for the subgroup of patients with UPCR ≥ 1.5 g/g which is relevant for this assessment, is presented in Table 30 and Table 87, respectively. Additional safety results are presented in Appendix E.1.3. An overview of key safety results from the NefIgAN study can be found in Appendix E.1.4, and a comparison of the NefIgArd trial and NefIgAN trial results is presented in Appendix E.1.1.

Table 30 Overview of safety events in the full population from NefIgArd Part B, during treatment for 9 months.

	NefIgArd NEF-301 (Phase III) Part B FAS		Difference, % (95 % CI)
	Kinpeygo 16 mg*	Placebo*	
Number of adverse events, n	[redacted]	[redacted]	n/a
Number and proportion of patients with ≥1 adverse events, n (%)	[redacted]	[redacted]	n/a
Number of serious adverse events, n	[redacted]	[redacted]	n/a
Number and proportion of patients with ≥ 1 serious adverse events, n (%)	[redacted]	[redacted]	n/a
Number of CTCAE grade ≥ 3 events, n	[redacted]	[redacted]	n/a
Number and proportion of patients with ≥ 1 CTCAE grade ≥ 3 events, n (%)	[redacted]	[redacted]	n/a
Number of adverse reactions, n	[redacted]	[redacted]	n/a
Number and proportion of patients with ≥ 1 adverse reactions, n (%)	[redacted]	[redacted]	n/a
Number and proportion of patients who had a dose reduction, n (%)	[redacted]	[redacted]	n/a
Number and proportion of patients who discontinue treatment regardless of reason, n (%)	[redacted]	[redacted]	n/a
Number and proportion of patients who discontinue	[redacted]	[redacted]	n/a

	NefIgArd NEF-301 (Phase III) Part B FAS		Difference, % (95 % CI)
	Kinpeygo 16 mg*	Placebo*	
treatment due to adverse events, n (%)			
TEAEs leading to discontinuations	[redacted]	[redacted]	n/a
AEs leading to death	[redacted]	[redacted]	n/a

Table 31. Overview of safety events in the subgroup UPCR ≥1.5 g/g from NefIgArd Part B (relevant for this assessment), during treatment.

	NefIgArd NEF-301 (Phase III) Part B SAS		Difference, % (95 % CI)
	Kinpeygo 16 mg [redacted]	Placebo [redacted]	
Number of treatment emergent adverse events, n	[redacted]	[redacted]	[redacted]
Number and proportion of patients with ≥1 adverse events, n (%)	[redacted]	[redacted]	[redacted]
Number of serious adverse events, n	[redacted]	[redacted]	[redacted]
Number and proportion of patients with ≥ 1 serious adverse events, n (%)	[redacted]	[redacted]	[redacted]
Number of CTCAE grade ≥ 3 events, n	[redacted]	[redacted]	[redacted]
Number and proportion of patients with ≥ 1 CTCAE grade ≥ 3 events, n (%)	[redacted]	[redacted]	[redacted]
Number of adverse reactions, n	[redacted]	[redacted]	[redacted]
Number and proportion of patients with ≥ 1 adverse reactions, n (%)	[redacted]	[redacted]	[redacted]
Number and proportion of patients who had a dose reduction, n (%)	[redacted]	[redacted]	[redacted]
Number and proportion of patients who discontinue treatment regardless of reason, n (%)	[redacted]	[redacted]	[redacted]
Number and proportion of patients who discontinue treatment due to adverse events, n (%)	[redacted]	[redacted]	[redacted]
Any AE leading to death	[redacted]	[redacted]	[redacted]
Any TEAE leading to discontinuation of study treatment	[redacted]	[redacted]	[redacted]

* A serious adverse event is an event or reaction that at any dose results in death, is life-threatening, requires hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or results in a congenital anomaly or birth defect (see the ICH's complete definition).
§ CTCAE v. 5.0 must be used if available.

9.1.1 NefIgArd Part B - Safety and tolerability

Kinpeygo was well tolerated, with a safety profile as expected for a locally acting oral budesonide product.[104] The safety results for the baseline UPCR ≥1.5 g/g subgroup were consistent with those observed for the full NefIgArd trial population [17].

Safety data are summarised for the SAS (all 389 patients who received at least 1 dose of study drug), as well as for the Part B FAS (all 364 patients randomised at the completion of recruitment to the global part of the study [with the exception of the 2 incorrectly enrolled patients who were also excluded from the Part A FAS]) (see Appendix A, Section A.1.6). Adverse events tables are presented as 'during treatment' (i.e., from the first day of study treatment through 14 days after the last dose of study treatment, including tapering) or 'during follow-up' (defined as >14 days after the last dose of study treatment, including tapering).[5]

See Appendix E, Section E.1.3 for all safety results, in addition to those presented in Table 30 and Table 31.

9.1.1.1 Serious AEs

During treatment, in the FAS, 18 (10%) patients in the Kinpeygo 16 mg/day group and 9 (5%) patients in the placebo group reported TESAEs.[104] In the SAS, [redacted].[5].The TESAEs considered by the Investigator to be possibly related to Kinpeygo treatment were pneumonia, pulmonary embolism, hypertension, and generalized rash.[5]

In the SAS, [redacted] patients in the Kinpeygo and [redacted] patients in the placebo group reported new TESAEs during observational follow-up (any previously reported TEAE had to be reported at a higher severity during follow-up to be counted as a new AE in the follow-up period).[5] [redacted]

Table 32 Serious adverse events (time point)

Adverse events	Kinpeygo [redacted]		Placebo [redacted]	
	Number of patients with adverse events	Number of adverse events	Number of patients with adverse events	Number of adverse events
Adverse event, n (%)	No separate serious adverse events occurred in ≥ 5% of patients, [redacted]			

9.1.1.2 Kinpeygo safety in baseline UPCR ≥1.5 g/g subgroup

The safety results for the baseline UPCR ≥1.5 g/g subgroup were consistent with those observed for the full NefIgArd trial population[17]See all results presented in Appendix E Section E.1.3.6.

9.1.2 NefIgAN - Safety and tolerability

The safety results from the NefIgArd Phase III trial were consistent with those from the NefigAN Phase IIb trial. Information about treatment exposure, treatment emergent adverse events (TEAEs), serious adverse events (AEs), discontinuations, deaths and changes in laboratory parameters or vital signs were recorded. The results are presented in Appendix E, E.1.4.

9.1.3 STOP-IgAN trial

Systemic corticosteroids are associated with high rates of serious AEs, particularly serious infections,[6, 7, 57, 77] with the TESTING trial being terminated early due to an increased risk of SAEs.[57] Although the reduced-dose cohort of the TESTING trial experienced fewer treatment-related AEs,[79] the efficacy results are not considered relevant to European clinical practice due to the differences in outcomes and treatment responses seen between Asian and Caucasian populations.[86-88] Therefore, the efficacy and safety of corticosteroids for this application is based on the STOP-IgAN trial.

In STOP-IgAN, there were more events of non-severe and severe infections in the immunosuppression group, predominantly of the GI and respiratory tracts, of which 25% were thought to be related to study treatment (Table 33).[6]

- Importantly, the rates of SAEs and total number of infections were higher among patients receiving immunosuppression compared with those receiving supportive care alone in both subgroups, regardless of baseline eGFR levels.[7]
- The investigators concluded that immunosuppressive therapy with glucocorticoids ± cyclophosphamide, in addition to supportive care, increased the risk of infections in patients with IgAN.[6, 77]

Table 33. Key safety data - STOP-IgAN trial[77]

Adverse events, n (%)	Supportive care + immunosuppression* (incl. CS) (N=82)	Supportive care (N=80)	p-value
Patients with ≥1 SAE, n (%)	29 (36.3)	21 (25.6)	0.24
SAE (n)	33	29	0.18
Non-severe and severe infections[6]	174	111	0.07
Total SAE of infection (n)	8	3	0.21
Diverticulitis or appendicitis	3	1	0.62
Pneumonia or respiratory tract infection	3	1	0.62
Viral exanthema	1	1	1.00
Knee empyema	1	0	1.00
Death (n)†	1	1	1.00
Additional AEs of interest (n)			
≥1 incidence of increase in liver-enzyme level (i.e., alanine aminotransferase >50 IU/ml)	13	12	1.00
≥1 incidence of observed leukopenia (i.e., leukocyte count <4000/µl)	2	3	1.00
Malignant neoplasm	2	0	0.50

Impaired glucose tolerance or diabetes mellitus	9	1	0.02
Gastrointestinal bleeding	0	0	Not determined
Fracture	1	0	1.00
Osteonecrosis (n)	0	0	Not determined
Weight gain (≥5 kg within first year)	14	5	0.049

*Patients randomly assigned to the immunosuppression group who had an eGFR ≥60 mL/min/1.73 m^2 received glucocorticoid monotherapy for 6 months (intravenous [IV] methylprednisolone 1 g/day for three days at the start of months 1, 3, and 5, and oral prednisolone 0.5 mg/kg/48 hours on the other days). Patients with an eGFR 30–59 mL/min/1.73 m^2 received cyclophosphamide 1.5 mg/kg/day for three months, followed by azathioprine 1.5 mg/kg/day during months 4–36, plus oral prednisolone 40 mg/day, tapered to 10 mg/day, over the first three months of the study, 10 mg/day during months 4–6, and 7.5 mg/day during months 7–36)[77]
†One patient who received supportive care alone died in a motor vehicle accident, and one patient who received additional immnosuppression died of pneumogenic sepsis, which corresponds to a ”suspected unexpected serious adverse reaction” in clinical trials.
Abbreviations: SAE, serious adverse event

9.1.4 Safety data in the health economic model

The adverse events rates for both the Kinpeygo and SoC arm were sourced from Part B NefIgArd Nef-301 CSR (Safety Analysis Set [SAS])[5]. All treatment-related AEs occurring in ≥4% of patients in either treatment arm of the full analysis set (FAS) were included in the model. However, the adverse event rates used in the model were sourced from the SAS; this was because the SAS contained a larger sample of patients. Limiting the TEAEs to all TEAEs occurring in ≥4% of patients in either treatment arm of the SAS would have reduced the number of TEAEs included and therefore it was more conservative, and comprehensive, to define the TEAE list using the FAS.

Additionally, treatment related treatment-emergent severe adverse events (TESAEs) occurring in more than one patient were also included in the analysis. Data from the SAS also informed the rates of TESAEs.

The AEs included in the model are presented in Table 34 for Kinpeygo and for corticosteroids.

Table 34 Adverse events used in the health economic model – NefIgArd trial and STOP-IgAN

Treatment-emergent adverse events (TEAE)	Kinpeygo 16 mg [redacted] n (%)	Placebo [redacted] n (%)	Corticosteroids (N=82) n (%)		
	Frequency used in economic model for intervention			**Source Kinpeygo and placebo**	**Source corticosteroids**
Treatment-related treatment-emergent AE (≥4% of patients in either treatment group)					
[redacted]	[redacted]	[redacted]	NR	DOF (NEF-301 Part B CSR)[5]; Lafayette et al, 2023[104]	STOP-IgAN CSR, Table S3 [6]
[redacted]	[redacted]	[redacted]	NR		
[redacted]	[redacted]	[redacted]	NR		
[redacted]	[redacted]	[redacted]	NR		
[redacted]	[redacted]	[redacted]	NR		
[redacted]	[redacted]	[redacted]	NR		
[redacted]	[redacted]	[redacted]	NR		
[redacted]	[redacted]	[redacted]	NR		
[redacted]	[redacted]	[redacted]	NR		
Treatment-emergent severe/serious AE (occurring in >1 patient)					

Treatment-emergent adverse events (TEAE)	Kinpeygo 16 mg [redacted] n (%)	Placebo [redacted] n (%)	Corticosteroids (N=82) n (%)		
[redacted]	[redacted]	[redacted]	0 (0.0%)	DOF (NEF-301 Part B CSR)[5]; Lafayette et al, 2023[104]	STOP-IgAN CSR, Table S3 [6]
[redacted]	[redacted]	[redacted]	0 (0.0%)		
[redacted]	[redacted]	[redacted]	NR		
[redacted]	[redacted]	[redacted]	NR		
[redacted]	[redacted]	[redacted]	NR		
[redacted]	[redacted]	[redacted]	NR		
[redacted]	[redacted]	[redacted]	1 (1.2%)		
[redacted]	[redacted]	[redacted]	1 (1.2%)		
[redacted]	[redacted]	[redacted]	1 (1.2%)		
[redacted]	[redacted]	[redacted]	1 (1.2%)		
[redacted]	[redacted]	[redacted]	1 (1.2%)		
[redacted]	[redacted]	[redacted]	1 (1.2%)		
[redacted]	[redacted]	[redacted]	1 (1.2%)		
[redacted]	[redacted]	[redacted]	1 (1.2%)		
[redacted]	[redacted]	[redacted]	1 (1.2%)		
[redacted]	[redacted]	[redacted]	2 (2.4%)		
[redacted]	[redacted]	[redacted]	1 (1.2%)		
[redacted]	[redacted]	[redacted]	1 (1.2%)		

Abbreviations: AE, adverse event; NR, not reported; SAEs, serious adverse events; TRF, targeted-release formulation.

[redacted]

Sources: Calliditas Therapeutics AB. Data on file, NEF-301 Part B CSR[5]; Lafayette et al, 2023[104], Rauen et al., 2015 [6]

9.2 Safety data from external literature applied in the health economic model

N/A, no safety data from external literature was applied in the health economic model.

Table 35 Adverse events that appear in more than X % of patients

Adverse events	Intervention (N=x)			Comparator (N=x)			Difference, % (95 % CI)	
	Number of patients	Number of	Frequenc y used in economi	Number of patients	Number of	Frequenc y used in economi	Number of patients	Number of

Adverse events	Intervention (N=x)			Comparator (N=x)			Difference, % (95 % CI)	
	with adverse events	adverse events	c model for intervention	with adverse events	adverse events	c model for comparator	with adverse events	adverse events
Adverse event, n	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A

10. Documentation of health-related quality of life (HRQoL)

No EQ-5D HRQoL data were collected during the NefIgArd Nef-301 trial that could be incorporated in the model. Although SF-36 data were collected in NefIgArd Nef-301, patients in Part A of NefIgArd Nef-301 were observed for up to 12 months and no patients progressed to ESRD; therefore, the observed patient-reported outcome data, in the form of the SF-36, would only be available to inform QoL estimates in the CKD 1–4 health states. As patients with IgAN are not expected to experience substantial changes in QoL until they reach ESRD, where dialysis or a transplant is required, using one source to inform the utility values in the CKD 1–5 health states was deemed most appropriate. Furthermore, mapping the trial SF-36 data to the EQ-5D would have introduced additional uncertainty to the model due to the lack of IgAN-specific mapping studies. Therefore, the model relies on EQ-5D values from the literature to inform patient utility assumptions. These assumptions were validated by clinical experts at the STADA UK advisory board [102] and accepted by NICE in the HTA submission for Kinpeygo.

An overview of the included HRQoL instruments is presented in Table 36, and the HSUV utilized in the model is presented in Section 10.3.

Table 36 Overview of included HRQoL instruments

Measuring instrument	Source	Utilization
EQ-5D-5L	Cooper et al. (2020) [8]	Cooper et al. (2020) were used to inform the following health states: CKD stages 1, 2, 3a, 3b, 4, 5, haemodialysis, peritoneal dialysis, and transplant.

10.1 Presentation of the health-related quality of life

N/A, since health-related quality of life (HRQoL) in the model is not based on the studies informing the clinical effectiveness, information on HRQoL will be presented in Section 10.3.

10.1.1 Study design and measuring instrument

N/A, since health-related quality of life (HRQoL) in the model is not based on the studies informing the clinical effectiveness, information on HRQoL will be presented in Section 10.3.

10.1.2 Data collection

N/A, since health-related quality of life (HRQoL) in the model is not based on the studies informing the clinical effectiveness, information on HRQoL will be presented in Section 10.3.

Table 37 Pattern of missing data and completion

Time point	HRQoL population N	Missing N (%)	Expected to complete N	Completion N (%)
	Number of patients at randomization	Number of patients for whom data is missing (% of patients at randomization)	Number of patients “at risk” at time point X	Number of patients who completed (% of patients expected to complete)
Baseline	N/A	N/A	N/A	N/A

10.1.3 HRQoL results

N/A, since health-related quality of life (HRQoL) in the model is not based on the studies informing the clinical effectiveness, information on HRQoL will be presented in Section 10.3.

Example of figure displaying the mean change from baseline through the different data collection time points for both the intervention and comparator (Not applicable)

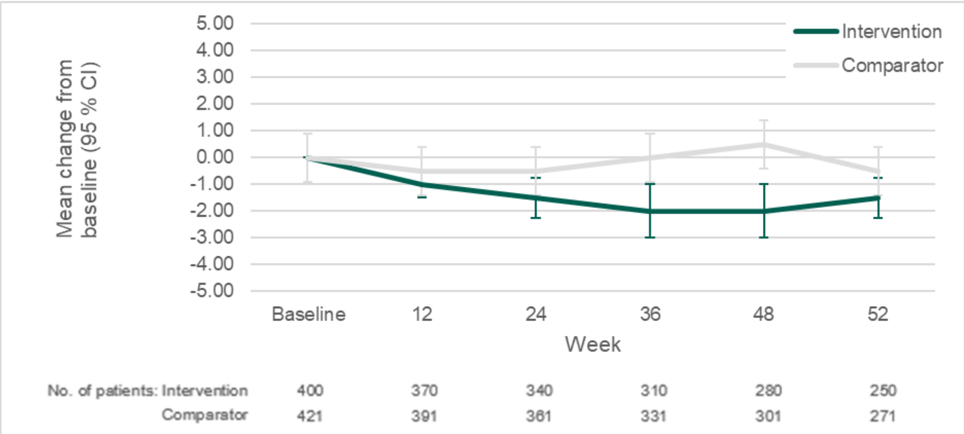


Table 38 HRQoL [instrument 1] summary statistics

	Intervention		Comparator		Intervention vs. comparator
	N	Mean (SE)	N	Mean (SE)	Difference (95% CI) p-value
Baseline	N/A	N/A	N/A	N/A	N/A

10.2 Health state utility values (HSUVs) used in the health economic model

See information in Section 10.3.

10.2.1 HSUV calculation

See information in Section 10.3.

10.2.1.1 Mapping

See information in Section 10.3.

10.2.2 Disutility calculation

See information in Section 10.3.

10.2.3 HSUV results

See more information in Section 10.3.4.1. Table 39 summarizes the health state utility values used in the model.

Table 39 Overview of health state utility values

	Results [SE]	Instrument	Tariff (value set) used	Comments
HSUVs				
CKD 1	0.85 [0.08]	EQ-5D-5L	UK	Since STADA does not have access to the individual patient data from the original trial, it was not possible to calculate utility values using the Danish preference weights.
CKD 2	0.85 [0.08]	EQ-5D-5L	UK	
CKD 3a	0.80 [0.08]	EQ-5D-5L	UK	
CKD 3b	0.80 [0.08]	EQ-5D-5L	UK	
CKD 4	0.74 [0.06]	EQ-5D-5L	UK	
CKD 5	0.73 [0.10]	EQ-5D-5L	UK	
Haemodialysis	0.44 [0.03]	EQ-5D-5L	UK	
Peritoneal dialysis	0.53 [0.07]	EQ-5D-5L	UK	
Post transplant	0.71 [0.02]	EQ-5D-5L	UK	

Abbreviations: CKD, chronic kidney disease; SE, Standard error. Standard error calculated as (1-mean)/(1.96*2). Source: Cooper et al. 2020. [8]

10.3 Health state utility values measured in other trials than the clinical trials forming the basis for relative efficacy

Given the absence of EQ-5D data from the NefIgArd Nef-301 trial, literature sources were consulted to inform health state utility values in the model.

No UK or Danish-specific EQ-5D studies were identified in the economic systematic literature review (SLR) for patients with IgAN. Moreover, no trials reporting EQ-5D-5L values for the population of interest were found. Instead, the references listed in recent CKD submissions to NICE were cross-checked. Cooper *et al.* 2020 was included in the TA775 NICE HTA submission reference list [97]. Cooper *et al*. 2020, report an SLR of HRQoL utility weights for CKD stages used in economic evaluations (using the EQ-5D-3L questionnaire). Hence, the health economic model (CEM) incorporates HSUV from Cooper *et al.* 2020 [131].

10.3.1 Study design

Cooper *et al*. 2020 [131] reported utility values for each CKD stage according to instrument and country in Table 4 of the publication, with multiple values presented for health states considered in the CEM. Utility values calculated using the EQ-5D-3L questionnaire from studies conducted in the UK were selected for use in the CEM in line with the NICE reference case [132]. These values were used to inform the following health states: CKD stages 1, 2, 3a, 3b, 4, 5, haemodialysis, peritoneal dialysis, and transplant. CKD stage 4 EQ-5D-3L analysis was conducted by Jesky *et al.* 2016 [133], as referenced by Cooper *et al*. 2020 [131].

It should be noted that the Cooper *et al*. 2020 study incorrectly labelled this value from Jesky *et al.* 2016 as based on a US population in Table 4 (of the publication), when it was in fact based on a UK population. However, Jesky *et al*. 2016 is a UK study exploring the relationship between pre-dialysis CKD and HRQoL outcomes using the EuroQol EQ-5D-3L.

For patient utility in the dialysis and transplant health states, utility values were also sourced from Cooper *et al.* 2020.[8] Patients in the dialysis health state are assumed to receive either haemodialysis (79.8%) or peritoneal dialysis (20.2%) based on the distribution reported in the Annual report from the Danish Society of Nephrology (Dansk Nefrologisk Selskab, DNS) from 2022.[134] As patient utility differs between haemodialysis and peritoneal dialysis, different patient utilities were assigned based on modality in the CEM (haemodialysis or peritoneal dialysis), distributed per the proportions reported in the DNS Annual report.[134]

A key limitation of this approach was that Cooper *et al.* 2020 did not analyse patient groups with characteristics matched to NefIgArd Nef-301 patient characteristics. While this is a limitation of the evidence base, the utility values sourced from CKD studies were considered reasonable proxies to inform the CEM, as determined from expert clinical opinion [102].

Since STADA does not have access to the individual patient data from the original trial, it was not possible to calculate utility values using the Danish preference weights.

10.3.2 Data collection

Each study included in Cooper *et al.* 2020 was assessed against the following criteria [8]:

- The study was conducted in a CKD population
- The study reports original empirical HSU weights
- Data were collected using a generic HRQoL measure (i.e. EQ-5D, short-form 6-dimention [SF-6D] or a mappable equivalent such as short-form 36 [SF-36] or short-form 12 [SF-12]; or the Health Utility Index [HUI])
- The study sample size was at least 25 patients
- The study was conducted in a country of interest (i.e., USA, Canada, Australia, China, UK, Spain, Italy, France or Germany)
- HSU weights were presented in a comprehensive way that is useful to inform cost-effectiveness analysis (e.g. HSU weights were available by CKD stage)

To weigh both data quality and data appropriateness as recommended by Brazier and colleagues (2019)[135], each study that met the critical appraisal at stage 1 was then reviewed in full in stage 2 and graded from 1 to 3 with consideration to the presence of bias, alignment with HTA criteria, and general compliance with the initial selection criteria (Table 40).[8] To assess bias, each study's methodology was examined for selection bias, bias in data analysis or interpretation, drop out or missing data, or bias in study execution such as unblinding in randomised control trials.[8]

Grade 1 studies were considered most appropriate for HTA. If data for a specific health state was not available using Grade 1 studies, then, Grade 2 studies would be reviewed to identify a missing value following the iterative approach recommended by Brazier and colleagues (2019). Grade 3 studies were considered to be inappropriate.[8]

All analysed studies met the grade 1 screening requirements, and therefore the overall study quality was high. Quality assessment reported a lack of clarity in 7 studies regarding drop out or missing data rates.[8]

Table 40. Record Grading Scale

Record Grading Scale
Study meets all HTA selection criteria and has no apparent sources of significant bias
Study meets HTA selection criteria but may be subject to bias (e.g. may need the application of a mapping algorithm to derive HSU weights or there may be study methodology bias)
Study does not meet HTA selection criteria (e.g. not a population representative of the CKD population)

Abbreviations: CKD chronic kidney disease, HTA health technology assessment, HSU health state utility. Sources: Cooper et al. (2020)[8]

10.3.3 HRQoL Results

See Section 10.3.4.

10.3.4 HSUV and disutility results

10.3.4.1 HSUV

Table 41 presents the health state utility values (HSUV) from Cooper *et al.* (2020) which are used in the health economic model (CEM).[8] Table 42 summarizes the literature-based health state utility values from Cooper *et al.* (2020).[8]

Table 41 Overview of health state utility values

	Results [SE]	Instrument	Tariff (value set) used	Comments
HSUV				
CKD 1	0.85 [0.08]	EQ-5D-5L	UK	Since STADA does not have access to the individual patient data from the original trial, it was not possible to calculate utility values using the Danish preference weights.
CKD 2	0.85 [0.08]	EQ-5D-5L	UK	
CKD 3a	0.80 [0.08]	EQ-5D-5L	UK	
CKD 3b	0.80 [0.08]	EQ-5D-5L	UK	
CKD 4	0.74 [0.06]	EQ-5D-5L	UK	
CKD 5	0.73 [0.10]	EQ-5D-5L	UK	
Haemodialysis	0.44 [0.03]	EQ-5D-5L	UK	
Peritoneal dialysis	0.53 [0.07]	EQ-5D-5L	UK	

	Results [SE]	Instrument	Tariff (value set) used	Comments
Post transplant	0.71 [0.02]	EQ-5D-5L	UK	

Abbreviations: CKD, chronic kidney disease; SE, Standard error. Standard error calculated as (1-mean)/(1.96*2). Source: Cooper et al. 2020. [8]

Table 42 Overview of literature-based health state utility values

		Results [SE]	Instrument	Tariff (value set) used	Comments
Cooper et al. 2020. [8]	CKD 1	0.85 [0.08]	EQ-5D-5L	UK	Since STADA does not have access to the individual patient data from the original trial, it was not possible to calculate utility values using the Danish preference weights.
	CKD 2	0.85 [0.08]	EQ-5D-5L	UK	
	CKD 3a	0.80 [0.08]	EQ-5D-5L	UK	
	CKD 3b	0.80 [0.08]	EQ-5D-5L	UK	
	CKD 4	0.74 [0.06]	EQ-5D-5L	UK	
	CKD 5	0.73 [0.10]	EQ-5D-5L	UK	
	Haemodialysis	0.44 [0.03]	EQ-5D-5L	UK	
	Peritoneal dialysis	0.53 [0.07]	EQ-5D-5L	UK	
	Post transplant	0.71 [0.02]	EQ-5D-5L	UK	

Abbreviations: CKD, chronic kidney disease; SE, Standard error. Standard error calculated as (1-mean)/(1.96*2).

10.3.4.2 Adverse event disutility

AEs occurred in both NefIgArd arms (Kinpeygo and placebo). The cost and quality of life implications of these AEs should be accounted for in the CEM, and for this an accurate proportion of patients who experienced each AE is required.

Table 34 in Section 9.1.4 presents the AE proportions obtained from the NefIgArd SAS sample (195 Kinpeygo patients versus 194 placebo patients), sourced from the CSR, which are used to inform AE occurrence by treatment arm in the CEM.

Disutility due to AEs were applied as a one-off utility decrement in the first on-treatment cycle to all patients in each arm. Assumptions for the duration and disutility of AEs captured in the CEM were informed by literature sources obtained from a targeted literature review. Where data were not identified in the literature, a simplifying assumption of no associated disutility was assumed. Additionally, where data were not available to inform AE duration, a simplifying assumption of a one-week duration was made.

When retreatment with Kinpeygo is enabled in the CEM, the utility decrement associated with AEs is applied in the first model cycle of each retreatment round as a one-off decrement, for the proportion of Kinpeygo patients who are eligible to receive retreatment (i.e., residing in CKD stages 1 to 3b). The assumption of applying the utility decrement associated with AEs in the first model cycle of each retreatment round was considered reasonable as patients who experienced multiple AEs would be expected to discontinue treatment and therefore not incur ongoing AEs.

The disutility and duration assumptions applied for each AE are presented in Table 43.

Table 43 Overview of adverse event rates duration and disutilities

	Disutility	Standard error	Duration (days)	Source disutility	Source duration
Acne	0.000	0.000	7.000	Assumption	Assumption
Cushingoid	0.156	0.040	7.000	Sullivan et al. (2011)	Assumption
Dyspepsia	0.044	0.007	7.000	Sullivan et al. (2011)	Assumption
Face oedema	0.156	0.030	7.000	Assumed same as cushingoid	Assumption
Hypertension	0.046	0.004	7.000	Sullivan et al. (2011)	Assumption
Oedema peripheral	0.156	0.030	7.000	Assumed same as cushingoid	Assumption
Weight increase	0.000	0.000	7.000	Assumption	Assumption
White blood cell count increased	0.001	0.020	7.000	Sullivan et al. (2011)	Assumption
Neutrophil count increased	0.000	0.000	7.000	Assumption	Assumption
Pulmonary embolism	0.018	0.002	30.438	NICE. Venous thromboembolic diseases: Diagnosis, management, and thrombophilia testing: Guidance. 2020.	Assumption
Renal impairment	0.060	0.006	30.438	Sullivan et al. (2006)	Assumption
Coronavirus infection	0.000	0.000	30.438	Assumption	Assumption
Pneumonia	0.000	0.000	30.438	Assumption	Assumption
Acute kidney injury	0.110	0.021	30.438	Sullivan et al. (2011)	Assumption
Hypertension - severe	0.046	0.004	30.438	Sullivan et al. (2011)	Assumption

Abbreviations: CKD, chronic kidney disease. Standard error calculated as (1-mean)/(1.96*2)

Age-adjusted general-population utilities

The HSUVs have been age-adjusted as according to DMC guidelines, for patients ≥18 years old and according to Table 1 in the Methods Guide appendix.[136]

11. Resource use and associated costs

11.1 Medicine costs - intervention and comparator

The costs for the medicines included in the model are presented in Table 44. These costs are presented in pharmacy purchase prices (*Apotekernes indkøbspris, AIP*), as per DMC guidelines.[137] If several pack sizes were available for the same strength, the cheapest pack was chosen. In the base case analysis, the relevant comparator to Kinpeygo was considered to be corticosteroids, represented by a regimen of oral prednisolone, informed by the Danish treatment guidelines [68] (based on doses from the TESTING trial [57]), which were confirmed by a Danish clinical expert.[12] Furthermore, both intervention and treatment arms were assumed to receive SoC additionally.

SoC was comprised of angiotensin-converting enzyme inhibitors (ACEis) and angiotensin receptor blockers (ARBs), as per Danish guidelines described on Section 3.3. The cost for SoC was calculated based on the average cost of the different ACEis and ARBs. For each SoC treatment, the number of tablets required per day was calculated by dividing the maximum daily dose by the tablet size. This was multiplied by the cost per tablet (calculated as the pack price divided by the number of tablets per pack) to determine the cost per day. The cost per month per SoC treatment was calculated by multiplying the cost per day by the model cycle length (30.4375 days). The inclusion of dapagliflozin in the SoC mix was tested in scenario analyses.

In the health economic model, all included medicines were administered orally in the exact prescribed dose, hence waste and vial sharing were not included as these were not considered relevant for the present analysis. Furthermore, the dose and dosing frequency of the medicine included in the analysis were retrieved from the respective SmPCs.

Regarding treatment duration, patients on the Kinpeygo arm were treated for nine months, as per SmPC [72]. Also in line with the SmPC, when treatment with Kinpeygo was discontinued, the dose was reduced to 8 mg once daily for two weeks of therapy.[72] Hence, the analysis also applied a dose reduction for two weeks after nine months of treatment. Also per SmPC, a treatment tapering period of 4 mg once daily for an additional 2 weeks following the end of the 9-month course and two weeks of reduced therapy was included in the base case analysis.[72] Prior to nine months, the number of patients that continue treatment each month was informed by the time to treatment discontinuation (TTD) data from Part B full analysis set of the NefIgArd Nef-301 study.[104] Patients on the corticosteroids arm were treated continuously, as per Danish treatment guidelines.[68]

Furthermore, in the base case analysis, the patients in the Kinpeygo arm could receive two rounds of treatment (first round followed by one retreatment round). The proportion of retreatment-eligible patients was assumed to be 65.44%. This proportion was calculated by multiplying the proportion of patients still on treatment at the end of their initial treatment period (87.25%) by the proportion of patients who are assumed to undergo retreatment (75%). The latter proportion was informed by international clinical expert opinion.[105] Hence, 65.44% of patients received the 9-month cost of Kinpeygo treatment twice, as well as the costs associated with a reduced and tapering dosing period.

Table 44 Medicine costs used in the model

Medicine	Dose	Relative dose intensity	Frequency	Vial sharing	Pharmacy purchase price
Intervention					
Kinpeygo	16 mg	NA	Once daily, orally	NA	[redacted]
Comparator					
Prednisolone	0.5 mg/kg/day [69]	NA	Once daily, orally[69]	NA	DKK 38.42
Standard of care		NA			

Medicine	Dose	Relative dose intensity	Frequency	Vial sharing	Pharmacy purchase price
Captopril 12.5 mg	150 mg	NA	Daily, orally	NA	DKK 199.00
Captopril 25 mg		NA		NA	DKK 35.32
Captopril 50 mg		NA		NA	DKK 191.00
Lisinopril 10 mg/Hydrochlorothiazide 12.5 mg	40 mg	NA	Daily, orally	NA	DKK 104.00
Lisinopril 10 mg		NA		NA	DKK 85.50
Lisinopril 20 mg /Hydrochlorothiazide 12.5 mg		NA		NA	DKK 80.00
Lisinopril 20 mg		NA		NA	DKK 107.70
Lisinopril 5 mg		NA		NA	DKK 76.40
Ramipril 1.25 mg	10 mg	NA	Daily, orally	NA	DKK 86.50
Ramipril 10 mg		NA		NA	DKK 16.00
Ramipril 2.5 mg		NA		NA	DKK 30.00
Ramipril 5 mg		NA		NA	DKK 11.00
Irbesartan 150 mg /Hydrochlorothiazide 12.5 mg	300 mg	NA	Daily, orally	NA	DKK 62.98
Irbesartan 150 mg		NA		NA	DKK 34.00
Irbesartan 300 mg /Hydrochlorothiazide 12.5 mg		NA		NA	DKK 54.89
Irbesartan 300 mg /Hydrochlorothiazide 25 mg		NA		NA	DKK 58.60
Irbesartan 300 mg		NA		NA	DKK 61.00
Irbesartan 75 mg		NA		NA	DKK 47.61
Losartan 100 mg	150 mg	NA	Daily, orally	NA	DKK 28.00

Note: Prices were updated on 4th March 2024. Abbreviations: NA, Not applicable. Source: Medicinpriser [138].

11.2 Medicine costs – co-administration

Not applicable.

11.3 Administration costs

In the health economic model, all included medicines are administered orally, hence no administration costs were included in the present analysis. This section is considered as not applicable.

Table 45 Administration costs used in the model

Administration type	Frequency	Unit cost [DKK]	DRG code	Reference
Not applicable				

11.4 Disease management costs

The disease management costs included in the health economic model were the costs for: hospital care, primary care, dialysis, transplant, and end of life. A cycle cost for medical resource use (MRU) was assumed for each health state in the health economic model. A description of how the cycle costs for each MRU were calculated is provided below. Table 46 summarises the unit costs and respective frequencies used in the health economic model.

11.4.1 Hospital care resource use and costs

Hospital care costs were calculated for the different CKD stages 1 to 5 and sourced from Eriksson et al. (2017), a study exploring the annual direct and indirect costs of patients with autosomal dominant polycystic kidney disease (ADPKD) by severity of the disease (i.e., chronic kidney disease [CKD] stages 1–3; CKD stages 4–5; transplant recipients; and maintenance dialysis patients).[110] The study reported, among others, the cost of hospitalization, outpatient care visits and surgical procedures from 2014. The costs were inflated to 2023 using the Danish consumer price index without energy.[139] The use of this study was considered appropriate by a Danish clinical expert.[12] The Danish clinical expert considered ADPKD an appropriate proxy to IgAN, since patients with IgAN have similar resource use to patients with ADPKD, possibly even higher resource use since IgAN frequently occurs in a younger population than ADPKD.[12]

11.4.2 Primary care resource use and costs

Primary care costs included in the health economic analysis were comprised of costs for general practitioner (GP) appointments and blood tests. The cost of a GP appointment was sourced from the DMC [140], with the cost of blood tests obtained from the Danish Medical Association (*Læger.dk*) [141, 142]. The model assumed GP appointments and blood tests occurred twice a year for CKD stages 1 to 3b (2.2 times a year) and quarterly (3.8 times) for CKD 4 and CKD 5. These frequencies were informed by Eriksson et al. (2017) study and validated by a Danish clinical expert as relevant to the Danish setting.[12, 110]

11.4.3 Dialysis resource use and costs

MRU unit costs for dialysis were sourced from the Sundhedsdatastyrelsen [143], and the Danish Medical Association (*Læger.dk*) [141, 142]. Patients in the dialysis health state are assumed to receive either haemodialysis (79.8%) or peritoneal dialysis (20.2%), based on the proportions reported in the *Dansk Nefrologisk Selskabs Landsregister (DNSL)* annual report from 2022.[144] Patients receiving haemodialysis were then further distributed by the modalities: hospital haemodialysis (92.4%) and home haemodialysis (7.6%), sourced from the DNSL's *Visionsrapport 2020 for dansk nefrologi.*[111] Hence, the total cost for dialysis was calculated as weighted average of the costs for haemodialysis and peritoneal dialysis, plus the cost of hospitalisation due to dialysis.

In the health economic model, patients receiving dialysis accrued the costs of nephrologist outpatient appointments, blood tests and hospitalisations. In the base case analysis, nephrology appointments and blood tests were assumed to occur approximately once a month (15.2 times a year), with approximately two (1.8) hospitalisations per year. The presented frequencies were validated by a Danish clinical expert.[12]

11.4.4 Transplant resource use and costs

MRU cost assumptions for the transplant health state were split into procedural and maintenance costs. Procedural costs included pre-assessment, transplant procedure, and post-transplant assessment and were applied upon transition to the transplant health state. For patients remaining in the transplant health state, a per cycle maintenance cost was applied, comprising equal costs to patients with CKD stage 3b, with additional nephrologist outpatient appointments, blood tests and immunosuppressive therapy. Following transplant, patients are expected to receive immunosuppressive maintenance therapy, as recommended in NICE TA481.[145] The guidance in TA481 suggests that in practice, patients may require a combination of immunosuppressive therapy. However, as this is considered on a case-by-case basis, the health economic model used a conservative assumption that immunosuppressive therapy is received in the form of tacrolimus monotherapy only. As such, immunosuppressive therapy was assumed to apply for all patients following transplant and comprised of tacrolimus administered at 0.25 mg/kg (the average of 0.2 and 0.3 mg/kg as described in TA481) daily in the health economic model. This estimate was considered appropriate to use in the Danish setting.

In the base case analysis, post-transplant maintenance costs were comprised of nephrology appointments and blood tests, and these were assumed to occur once every month. This was validated by a Danish clinical expert as relevant to the Danish setting.[12] Hospitalisations were also considered for transplant patients. The unit cost for hospitalisation was sourced from Eriksson et al. (2017) [110], and inflated to 2023, using the Danish consumer price index without energy [139]. Hospitalisations were assumed to occur approximately once annually (0.6 times a year), which was validated by Danish clinical expert opinion.[12]

Table 46 Disease management costs used in the model

Activity	Frequency	Unit cost [DKK]	DRG code	Reference
Hospital care				
Hospital care – CKD 1	NA	DKK 14,704.47	NA	Eriksson et al. (2017) [110] Validated by a Danish clinical expert [12]
Hospital care – CKD 2	NA	DKK 14,704.47	NA	
Hospital care – CKD 3a	NA	DKK 14,704.47	NA	
Hospital care – CKD 3b	NA	DKK 14,704.47	NA	
Hospital care – CKD 4	NA	DKK 33,656.36.	NA	Eriksson et al. (2017) [110] Validated by a Danish clinical expert [12]
Hospital care – CKD 5	NA	DKK 33,656.36	NA	
Primary care				
Primary care – CKD1	2.2 times a year (twice a year)	DKK 229.03	Konsultation (DKK 153.61) + Blod (DKK 22.02) + Blodtagning fra blodåre pr. Forsendelse (DKK 53.40)	Cost sources: DMC (2023) [140] Laeger (2023) [141, 142] Frequency source: Eriksson et al. (2017) [110] Validated by a Danish clinical expert [12]
Primary care – CKD2	2.2 times a year (twice a year)	DKK 229.03		
Primary care – CKD3a	2.2 times a year (twice a year)	DKK 229.03		
Primary care – CKD3b	2.2 times a year (twice a year)	DKK 229.03		
Primary care – CKD4	3.8 times a year (quarterly)	DKK 229.03		

Activity	Frequency	Unit cost [DKK]	DRG code	Reference
Primary care – CKD5	3.8 times a year (quarterly)	DKK 229.03		
Dialysis				
Haemodialysis				
Hospital haemodialysis	3 times a week	DKK 3,034.00	11PR10 "Dialyse, øvrige"	Cost source: Sundhedsdatastyrelsen (2024) [143] Frequency source: Danish Society of Nephrology (DNSL 2020) [111]
Home haemodialysis	4 - 7 times a week	DKK 1,517.00	Assumption: half of hospital haemodialysis cost, 11PR10 "Dialyse, øvrige"	Cost source: Sundhedsdatastyrelsen (2024) [143] Frequency source: DNSL (2020) [111]
Nephrologist visits	15.2 times a year (every 3-4 weeks)	DKK 1,550.00	11MA98 "MDC11 1-dagsgruppe, pat. mindst 7 år"	Cost source: Sundhedsdatastyrelsen (2024) [143] Frequency source: Eriksson et al. (2017) [110] Validated by a Danish clinical expert [12]
Blood tests	15.2 times a year (every 3-4 weeks)	DKK 75.42	Blod (DKK 22.02) + Blodtagning fra blodåre pr. Forsendelse (DKK 53.40)	Cost source: Laeger (2023) [141, 142] Frequency source: Assumption Validated by a Danish clinical expert [12]
Peritoneal dialysis				
Peritoneal dialysis	Daily	DKK 4,899.00	11PR09 "Peritonealdialyse"	Cost source: Sundhedsdatastyrelsen (2024) [143] Frequency source: Assumption
Nephrologist visits	15.2 times a year (every 3-4 weeks)	DKK 1,550.00	11MA98 "MDC11 1-dagsgruppe, pat. mindst 7 år"	Sundhedsdatastyrelsen (2024) [143] Frequency source: Eriksson et al. (2017) [110] Validated by a Danish clinical expert [12]
Blood tests	15.2 times a year (every 3-4 weeks)	DKK 75.42	Blod (DKK 22.02) + Blodtagning fra blodåre pr. Forsendelse (DKK 53.40)	Cost source: Laeger (2023) [141, 142] Frequency source: Assumption Validated by a Danish clinical expert [12]
Hospitalisation	1.8 times per year (twice a year)	DKK 33,260.15	NA	Eriksson et al. (2017) [110] Validated by a Danish clinical expert [12]
Transplant				

Activity	Frequency	Unit cost [DKK]	DRG code	Reference
Pre-assessment	Once (per patient)	DKK 153.61	Konsultation (assumption of one GP visit)	Cost source: DMC (2023) [140] Frequency source: Assumption
Procedure cost	Once (per patient)	DKK 306,221.50	11MP02 "Nyretransplantation" & 11MP01 "Nyretransplantation, kompliceret" (average)	Cost source: Sundhedsdatastyrelsen (2024) [143]
Post-transplant assessment	Once (per patient)	DKK 1,550.00	11MA98 "MDC11 1-dagsgruppe, pat. mindst 7 år"	Cost source: Sundhedsdatastyrelsen (2024) [143] Frequency source: Assumption
Maintenance post-transplant				
Nephrologist visits	11.6 times a year (once a month)	DKK 1,550.00	11MA98 "MDC11 1-dagsgruppe, pat. mindst 7 år"	Cost source: Sundhedsdatastyrelsen (2024) [143] Frequency source: Eriksson et al. (2017) [110]
Blood tests	11.6 times a year (once a month)	DKK 75.42	Konsultation (DKK 153.61) + Blod (DKK 22.02) + Blodtagning fra blodåre pr. Forsendelse (DKK 53.40)	Cost source: Laeger (2023) [141, 142] Frequency source: Assumption Validated by a Danish clinical expert [12]
Immunosuppressive therapy				
Tacrolimus	Daily	DKK 504.40	NA	Cost source: Medicinpriser (2024) [146] Frequency source: NICE guidance - TA481 [145]
Hospitalisation				
Hospitalisation	0.6 times a year (once a year)	DKK 46,764.86	NA	Eriksson et al. (2017) [110]

Note: Where not stated otherwise, cost and frequency sources were the same. Abbreviations: CKD, Chronic kidney disease; DRG, Diagnosis-related groups.

11.5 Costs associated with management of adverse events (AE)

The costs associated with the management of AEs included in the health economic model are presented in Table 47. The respective frequencies are presented in Section 9.1.4.

AEs were included as one-off costs in the first cycle of the model for each treatment arm. This simplification was to avoid double counting the cost of AEs and assumes that patients who experience multiple AEs will discontinue treatment and stop incurring costs associated with the treatment of AEs.

The one-off cost was calculated as the weighted average of the AEs from a specific treatment arm (unit costs for AEs multiplied by their respective frequencies). The cost of AE resolution for patients undergoing retreatment was applied in the first cycle of each retreatment round for those at risk of incurring an AE.

Table 47 Cost associated with management of adverse events

	DRG code	Unit cost/DRG tariff	Reference
Acne	Assumption	DKK 0.00	Assumption
Cryptococcal meningitis	01MA03 "Infektion i nervesystemet ekskl. virus meningitis"	DKK 72,892.00	Sundhedsdatastyrelsen (2024) [143]
Cushingoid	10MA98 "MDC10 1-dagsgruppe, pat. mindst 7 år"	DKK 1,847.00	Sundhedsdatastyrelsen (2024) [143]
Diabetes mellitus	10MA03 "Diabetes Mellitus"	DKK 37,913.00	Sundhedsdatastyrelsen (2024) [143]
Dyspepsia	Konsultation (assumption of one GP visit)	DKK 153.61	DMC (2023) [140]
Dyspnea	Konsultation (assumption of one GP visit)	DKK 153.61	DMC (2023) [140]
Face oedema	Assumption	DKK 0.00	Assumption
Gastrointestinal bleeding requiring hospitalization	06MA05 & 06MA07, average "Blødning fra mave-tarmkanal, pat. mindst 18 år, m. kompl. bidiag." (DKK 42,983) & "Blødning fra mave-tarmkanal, pat. mindst 18 år, u. kompl. bidiag." (DKK 27,312)	DKK 35,147.50	Sundhedsdatastyrelsen (2024) [143]
Gastrointestinal disorder	06MA14 "Andre sygdomme i fordøjelsesorganerne, pat. mindst 18 år"	DKK 28,499.00	Sundhedsdatastyrelsen (2024) [143]
Hematologic disorder	16MA10 & 16MA98, average "Øvrige sygdomme i blod og bloddannende organer " (DKK 27,121) & "MDC16 1-dagsgruppe, pat. mindst 7 år" (DKK 2,111)	DKK 14,616.00	Sundhedsdatastyrelsen (2024) [143]
Headache	Paracetamol "Orifarm" 500 mg 20 st pack size	DKK 13.41	Medicinpriser (2024) [147]
Herpes zoster	18MA05 & 18MA06 & 18MA08, average "Virussygdomme, pat. mindst 18 år, m. kompl. faktorer " (DKK 41,092) & "Virussygdomme, pat. mindst 18 år, u. kompl. Faktorer" (DKK 29,083) & "Andre infektioner eller parasitære sygdomme" (DKK 46,094)	DKK 38,756.33	Sundhedsdatastyrelsen (2024) [143]
Hirsutism	Assumption	DKK 0.00	Assumption
Hypertension	05MA11 "Hypertension"	DKK 18,261.00	Sundhedsdatastyrelsen (2024) [143]
Impaired glucose tolerance	10MA98 "MDC10 1-dagsgruppe, pat. mindst 7 år"	DKK 1,847.00	Sundhedsdatastyrelsen (2024) [143]
Knee empyema	08MA98, "MDC08 1-dagsgruppe, pat. mindst 7 år”	DKK 1,626.00	Sundhedsdatastyrelsen (2024) [143]
Macrocytic anemia	16MA10 & 16MA98, average "Øvrige sygdomme i blod og bloddannende organer " (DKK 27,121) & "MDC16 1-dagsgruppe, pat. mindst 7 år" (DKK 2,111)	DKK 14,616.00	Sundhedsdatastyrelsen (2024) [143]
Mood swings	Assumption	DKK 0.00	Assumption
Multiple skin infection	09MA03 & 09MA04, average "Lettere eller moderat hudsygdom, u. kompl. bidiag. " (DKK 20,231) & "Infektioner i hud og underhud, pat. mindst 18 år" (DKK 34,816)	DKK 27,523.50	Sundhedsdatastyrelsen (2024) [143]
Nocardia infection	18MA08 "Andre infektioner eller parasitære sygdomme"	DKK 46,094.00	Sundhedsdatastyrelsen (2024) [143]

	DRG code	Unit cost/DRG tariff	Reference
Oedema peripheral	Assumption	DKK 0.00	Assumption
Osteonecrosis	08MA19 & 08MA98 & 08MA17, average "Andre sygdomme i muskel-skeletsystemet og bindevæv " (DKK 43,533) & "MDC08 1-dagsgruppe, pat. mindst 7 år" DKK 1,626) & "Øvrige sygdomme i knogler og led" (DKK 2,058)	DKK 15,739.00	Sundhedsdatastyrelsen (2024) [143]
Other infection	18MA08 "Andre infektioner eller parasitære sygdomme"	DKK 46,094.00	Sundhedsdatastyrelsen (2024) [143]
Perianal abscess	06MA14 "Andre sygdomme i fordøjelsesorganerne, pat. mindst 18 år"	DKK 28,499.00	Sundhedsdatastyrelsen (2024) [143]
Pleuritis	04MA13 & 04MA14, avergage "Lungebetændelse og pleuritis, pat. mindst 60 år " (DKK 43,907) & "Lungebetændelse og pleuritis, pat. 18-59 år" (DKK 35,426)	DKK 39,666.50	Sundhedsdatastyrelsen (2024) [143]
Pneumocystis jirovecii pneumonia	DRG: 04MA13 & 04MA14, average "Lungebetændelse og pleuritis, pat. mindst 60 år " (DKK 43,907) & "Lungebetændelse og pleuritis, pat. 18-59 år" (DKK 35,426)	DKK 39,666.50	Sundhedsdatastyrelsen (2024) [143]
Pneumogenic sepsis	18MA01 "Sepsis"	DKK 50,299.00	Sundhedsdatastyrelsen (2024) [143]
Pulmonary embolism	04MA04 "Lungeemboli"	DKK 33,516.00	Sundhedsdatastyrelsen (2024) [143]
Renal impairment	11MA10 "Andre sygdomme, mistanke om sygdom, eller symptomer fra nyrer eller urinveje, pat. mindst 16 år"	DKK 18,333.00	Sundhedsdatastyrelsen (2024) [143]
Scrotal tumor	12MA01 & 12MA02, average "Ondartede sygdomme på mandlige kønsorganer" (DKK 40,702) & "Andre sygdomme, mistanke om sygdom, eller symptomer fra mandlige kønsorganer" (DKK 23,946)	DKK 32,324.00	Sundhedsdatastyrelsen (2024) [143]
Sigma-diverticulitis	06MA14 "Andre sygdomme i fordøjelsesorganerne, pat. mindst 18 år"	DKK 28,499.00	Sundhedsdatastyrelsen (2024) [143]
Transaminase + creatinine increase	07MA98 & 11MA98, average "MDC11 1-dagsgruppe, pat. mindst 7 år " (DKK 1,947 and DKK 1,550)	DKK 1,748.50	Sundhedsdatastyrelsen (2024) [143]
Tuberculosis with bacterial infection	04MA03 "Tuberkulose uden operation"	DKK 88,350.00	Sundhedsdatastyrelsen (2024) [143]
Upper respiratory tract infection	04MA06 "Infektioner og betændelse i luftveje, pat. 0-64 år"	DKK 60,209.00	Sundhedsdatastyrelsen (2024) [143]
Urinary tract infection	11MA98 "MDC11 1-dagsgruppe, pat. mindst 7 år"	DKK 1,550.00	Sundhedsdatastyrelsen (2024) [143]
Weight increase	Assumption	DKK 0.00	Assumption
Coronavirus infection	18MA05 & 18MA06, average "Virussygdomme, pat. mindst 18 år, m. kompl. faktorer " (DKK 41,092) & "Virussygdomme, pat. mindst 18 år, u. kompl. Faktorer" (DKK 29,083)	DKK 35,087.50	Sundhedsdatastyrelsen (2024) [143]
Pneumonia	04MA13 & 04MA14, avergage "Lungebetændelse og pleuritis, pat. mindst 60 år " (DKK 43,907) & "Lungebetændelse og pleuritis, pat. 18-59 år" (DKK 35,426)	DKK 39,666.50	Sundhedsdatastyrelsen (2024) [143]

	DRG code	Unit cost/DRG tariff	Reference
Acute kidney injury	11MA01 "Akutte medicinske nyresygdomme uden dialyse og uden plasmaferese"	DKK 49,298.00	Sundhedsdatastyrelsen (2024) [143]
Hypertension - severe	05MA11 & 05MA13, average "Hypertension" (DKK 18,261) & "Andre kredsløbsdiagnoser" (DKK 93,283)	DKK 55,772.00	Sundhedsdatastyrelsen (2024) [143]
White blood cell count increased	16MA10 & 16MA98, average "Øvrige sygdomme i blod og bloddannende organer " (DKK 27,121) & "MDC16 1-dagsgruppe, pat. mindst 7 år" (DKK 2,111)	DKK 14,616.00	Sundhedsdatastyrelsen (2024) [143]
Neutrophil count increased	16MA10 & 16MA98, average "Øvrige sygdomme i blod og bloddannende organer " (DKK 27,121) & "MDC16 1-dagsgruppe, pat. mindst 7 år" (DKK 2,111)	DKK 14,616.00	Sundhedsdatastyrelsen (2024) [143]
Acute myocardinal infarction	05MA01 & 05MA02, average "Akut myokardieinfarkt med ST-segment elevation" (DKK 22,387) & "Akut koronarsyndrom uden ST-segment elevation" (DKK 12,733)	DKK 17,560.00	Sundhedsdatastyrelsen (2024) [143]
Cardiac failure	05MA04 "Hjertesvigt og shock"	DKK 39,083.00	Sundhedsdatastyrelsen (2024) [143]
Ischaemic stroke	01SP01 & 01MP12, average "Sammedagspakke: Blodprop i hjernen, udredning" (DKK 6,661) & "Trombolysebehandling af akut apopleksi" (DKK 34,619)	DKK 20,640.00	Sundhedsdatastyrelsen (2024) [143]

11.6 Subsequent treatment costs

Not applicable.

Table 48 Medicine costs of subsequent treatments

Medicine	Strength	Package size	Pharmacy purchase price [DKK]	Relative dose intensity	Average duration of treatment
Not applicable					

11.7 Patient costs

The costs incurred by patients as a consequence of the medicine treatment (transport costs and time spent) were included in the base case analysis. Similarly to the disease management costs (or MRU costs), a cycle cost for each health state in the health economic model was calculated. The patient costs were obtained summing the cost for the patient time (calculated as the respective estimated time spent in a specific MRU, multiplied by the frequency of the MRU visit and the average hourly rate in Denmark) and a round trip cost (multiplied the frequency of MRU visit). The average hourly rate (DKK 203) and round trip cost (DKK 140) were sourced from *DMC's Værdisætning af enhedsomkostninger* (2023).[140] The patient time assumed per MRU included in the health economic analysis is presented in Table 49. The exclusion of patient costs was tested in scenario analyses.

Table 49 Patient costs used in the model

Activity	Time spent [hours]
Hospitalisations dialysis	24.00
Nephrologist visit haemodialysis	1.29
Nephrologist visit peritoneal dialysis	1.29
Haemodialysis hospital	5.29
Haemodialysis home	4.33
Peritoneal dialysis	0 (assumption)
CKD 1 (hospital care)	1.29
CKD 2 (hospital care)	1.29
CKD 3a (hospital care)	1.29
CKD 3b (hospital care)	1.29
CKD 4 (hospital care)	1.29
CKD 5 (hospital care)	1.29
CKD 1 (primary care)	1.29
CKD 2 (primary care)	1.29
CKD 3a (primary care)	1.29
CKD 3b (primary care)	1.29
CKD 4 (primary care)	1.29
CKD 5 (primary care)	1.29
Pre-assessment	1.29
Procedure cost	3.00
Post-transplant assessment	1.29
Nephrologist visits (maintenance transplant)	1.29
Hospitalisations transplant	132.00

Abbreviations: CKD, Chronic kidney disease.

11.8 Other costs (end of life cost)

The end of life cost was sourced from Sundhedsdatastyrelsen (2024) and is presented in Table 50.[143] This cost was included as a per patient cost and was applied upon transition to the death state to all patients. This cost has been validated by a Danish clinical expert, which considered the use of a 10-day cost as a conservative estimate.[12] This is because the end of life cost varies from patient to patient, for example patients in ESRD can have a short palliative care (less than a week), whereas patients with CKD 5 not having dialysis have a much longer palliative care (2-6 months).[12]

Table 50 End of life cost used in the model

Activity	Frequency	Unit cost [DKK]	DRG code	Reference
End of life	Cost per patient	DKK 45,110.00	26MP45 "Specialiseret Palliativ indsats, Stor" (daily cost), multiplied by 10.	Sundhedsdatastyrelsen (2024) [143]

12. Results

12.1 Base case overview

An overview of the base case is presented in Table 51.

Table 51 Base case overview

Feature	Description
Comparator	Corticosteroids
Type of model	Markov model
Time horizon	58 years (life time)
Treatment line	2nd line. Subsequent treatment lines not included.
Measurement and valuation of health effects	Health-related quality of life measured with EQ-5D-5L in Cooper et al. 2020 study [8]). Utilities were age-adjusted according to the health state utilities values for the Danish general population [136].
Costs included	Drug acquisition costs Drug administration costs Adverse event costs Monitoring costs (includes disease management and end of life costs) Patient costs
Dosage of medicine	16 mg once daily for 9 months Dose reduction: 8 mg once daily for 2 weeks Dose tapering: 4 mg once daily for 2 weeks (after dose reduction period)
Average time on treatment	[redacted]
Parametric function for PFS	Not applicable
Parametric function for OS	Not applicable
Inclusion of waste	Not applicable
Average time in model health state Health state 1 Health state 2 Health state 3 Death	There is no variation in treatment duration between health states. Please refer to "Average time on treatment".

12.1.1 Base case results

The base case results are presented in Table 52.

Table 52 Base case results, discounted estimates

	Kinpeygo	Corticosteroids	Difference
Medicine costs	[redacted]	[redacted]	[redacted]
Medicine costs – co-administration	[redacted]	[redacted]	[redacted]
Administration	[redacted]	[redacted]	[redacted]
Disease management costs	[redacted]	[redacted]	[redacted]
Costs associated with management of adverse events	[redacted]	[redacted]	[redacted]
Subsequent treatment costs	[redacted]	[redacted]	[redacted]
Patient costs	[redacted]	[redacted]	[redacted]
End of life costs	[redacted]	[redacted]	[redacted]

	Kinpeygo	Corticosteroids	Difference
Total costs	[redacted]	[redacted]	[redacted]
Life years gained (CKD 1)	[redacted]	[redacted]	[redacted]
Life years gained (CKD 2)	[redacted]	[redacted]	[redacted]
Life years gained (CKD 3a)	[redacted]	[redacted]	[redacted]
Life years gained (CKD 3b)	[redacted]	[redacted]	[redacted]
Life years gained (CKD 4)	[redacted]	[redacted]	[redacted]
Life years gained (CKD 5)	[redacted]	[redacted]	[redacted]
Life years gained (Dialysis)	[redacted]	[redacted]	[redacted]
Life years gained (Transplant)	[redacted]	[redacted]	[redacted]
Total life years	[redacted]	[redacted]	[redacted]
QALYs (CKD 1)	[redacted]	[redacted]	[redacted]
QALYs (CKD 2)	[redacted]	[redacted]	[redacted]
QALYs (CKD 3a)	[redacted]	[redacted]	[redacted]
QALYs (CKD 3b)	[redacted]	[redacted]	[redacted]
QALYs (CKD 4)	[redacted]	[redacted]	[redacted]
QALYs (CKD 5)	[redacted]	[redacted]	[redacted]
QALYs (Dialysis)	[redacted]	[redacted]	[redacted]
QALYs (Transplant)	[redacted]	[redacted]	[redacted]
QALYs (adverse reactions)	[redacted]	[redacted]	[redacted]
Total QALYs	[redacted]	[redacted]	[redacted]
Incremental costs per life year gained		[redacted]	
Incremental cost per QALY gained (ICER)		[redacted]	

12.2 Sensitivity analyses

Uncertainty in the model parameters was assessed in deterministic sensitivity analyses, scenario analyses and probabilistic sensitivity analyses.

12.2.1 Deterministic sensitivity analyses

Deterministic sensitivity analysis (DSA) is designed to identify uncertainty of parameters included in the model. The DSA was programmed to identify the main parameters and assumptions which have the greatest impact on results. Upper and lower values of model inputs (e.g., resource use, unit costs, utilities) were sourced from relevant literature in the first instance. For those parameters with no published standard errors or confidence interval, the base case value used in the model was varied by ±10%.

The results from the DSA analyses are presented in Table 53. These results are only presented for the ten parameters with highest impact on the ICER. The DSA revealed that the parameters with biggest impact were [redacted]. The tornado diagram is presented in Figure 15.

Table 53 One-way sensitivity analyses results

	Lower value	Upper value
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

	Lower value	Upper value
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

Figure 15 Tornado diagram

[redacted]

Scenario analyses

A range of scenarios were tested and are presented in Table 49 in Appendix L. The results of the scenario analyses for Kinpeygo versus corticosteroids are presented in Table 54. [redacted]

Table 54 Scenario analyses results

Scenario analysis	Incremental costs (DKK) (Kinpeygo vs corticosteroids)	Incremental QALYs	ICER (DKK/QALY)
Time horizon of 10 years	[redacted]	[redacted]	[redacted]
Time horizon of 20 years	[redacted]	[redacted]	[redacted]
Time horizon of 30 years	[redacted]	[redacted]	[redacted]
Time horizon of 40 years	[redacted]	[redacted]	[redacted]
Time horizon of 50 years	[redacted]	[redacted]	[redacted]
Distribution of CKD stage at baseline: UK RaDaR data (ACEi and ARB patients)	[redacted]	[redacted]	[redacted]

Distribution of CKD stage at baseline: UK RaDaR - apportioned to exclude CKD 4	[redacted]	[redacted]	[redacted]
Risk of ESRD: UK RADAR data - ACEi and ARB patients	[redacted]	[redacted]	[redacted]
UK RADAR data - All patients study parametric extrapolation: Exponential	[redacted]	[redacted]	[redacted]
UK RADAR data - All patients study parametric extrapolation: Generalised gamma	[redacted]	[redacted]	[redacted]
UK RADAR data - All patients study parametric extrapolation: Gompertz	[redacted]	[redacted]	[redacted]
UK RADAR data - All patients study parametric extrapolation: Log-logistic	[redacted]	[redacted]	[redacted]
UK RADAR data - All patients study parametric extrapolation: Log-normal	[redacted]	[redacted]	[redacted]
UK RADAR data - All patients study parametric extrapolation: Weibull	[redacted]	[redacted]	[redacted]
Assume no SoC acquisition costs	[redacted]	[redacted]	[redacted]
NefIgArd Part B FAS	[redacted]	[redacted]	[redacted]
Assume no treatment effect after: 1.5 years	[redacted]	[redacted]	[redacted]
Assume no treatment effect after: 2 years	[redacted]	[redacted]	[redacted]
Assume no treatment effect after: 2.5 years	[redacted]	[redacted]	[redacted]
Assume no treatment effect after: 5 years	[redacted]	[redacted]	[redacted]
Assume treatment effect continues over entire time horizon	[redacted]	[redacted]	[redacted]
Mortality source: Greene et al. (2019)	[redacted]	[redacted]	[redacted]
Mortality source: Hastings et al. (2018)	[redacted]	[redacted]	[redacted]
CKD stage utility source: Gorodetskaya et al. (2005)	[redacted]	[redacted]	[redacted]
Disable age-adjusted utilities	[redacted]	[redacted]	[redacted]

Exclude dose reduction (8mg in final 2 weeks of therapy)	[redacted]	[redacted]	[redacted]
Exclude tapering period (4mg for 2 weeks)	[redacted]	[redacted]	[redacted]
Treatment stopping approach: Follow TTD curve	[redacted]	[redacted]	[redacted]
Exclude patient costs	[redacted]	[redacted]	[redacted]
Allow Kinpeygo retreatment - Yes: Total number of rounds - 3	[redacted]	[redacted]	[redacted]
Allow Kinpeygo retreatment - Yes: Total number of rounds - 4	[redacted]	[redacted]	[redacted]
Allow Kinpeygo retreatment - Yes: Total number of rounds - 5	[redacted]	[redacted]	[redacted]
Allow Kinpeygo retreatment - Yes: Total number of rounds - 6	[redacted]	[redacted]	[redacted]
Allow Kinpeygo retreatment - No	[redacted]	[redacted]	[redacted]
Treatment effect in subsequent treatments - [redacted]	[redacted]	[redacted]	[redacted]
Same utility value for CKD 1 – 3b health states	[redacted]	[redacted]	[redacted]
Same utility value for CKD 1 – 4 health states	[redacted]	[redacted]	[redacted]
Include relative dose intensity	[redacted]	[redacted]	[redacted]
Patients eligible for retreatment - [redacted]	[redacted]	[redacted]	[redacted]
Patients eligible for retreatment - [redacted]	[redacted]	[redacted]	[redacted]
Time between retreatment cycles - [redacted] months	[redacted]	[redacted]	[redacted]
Time between retreatment cycles - [redacted] months	[redacted]	[redacted]	[redacted]
Time between retreatment cycles - [redacted] months	[redacted]	[redacted]	[redacted]
Monthly transition probability from CKD 5 to dialysis - [redacted]	[redacted]	[redacted]	[redacted]
Exclusion of dapagliflozin as a cost component of SoC	[redacted]	[redacted]	[redacted]

Abbreviations: ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blockers; CKD, chronic kidney disease; CSR, clinical study report; ESRD, end-stage renal disease; ICER, incremental cost-effectiveness ratio;

QALYs, quality-adjusted life years; SoC, standard of care; TRF, targeted-release formulation; TTD, time to discontinuation; UK RaDaR, United Kingdom National Registry of Rare Kidney Diseases

12.2.2 Probabilistic sensitivity analyses

A probabilistic sensitivity analysis (PSA) was performed by assigning probability distributions to certain variables in the model and repeatedly sampling values from these distributions to capture the overall uncertainty in model parameters and the resulting uncertainty in model results. For this PSA, 1,000 simulations were performed.

Different probability distributions were selected depending on the parameter:

- **Probabilities, proportions, and utilities** range from 0 to 1, and were therefore sampled from Beta distributions;
- **Costs, doses, and resource use** parameters take positive values and are likely to be right skewed, they were therefore sampled from Gamma distributions;
- **Relative risks and ratios** have an additive relationship on the log scale and were therefore sampled from log-normal distributions;
- **Distribution across the CKD health states** at baseline are correlated with each other as they must always sum to 1 and must be sampled together. Therefore, they were sampled from Dirichlet distribution.

The cost-effectiveness plane is presented in Figure 16. The ICER scatterplot shows the cost-effectiveness pairs estimated in each PSA iteration, in terms of incremental costs (y-axis) and incremental QALYs (x-axis). The placement and distribution of these points is reflective of the intervention arm relative to the comparator arm, and the level of uncertainty surrounding the point estimates. The majority of points is located in the northeast quadrant, meaning Kinpeygo was more costly but also more effective (i.e., produced more QALYs) as compared to corticosteroids.

Figure 16 Cost-effectiveness plane

[redacted]

The cost-effectiveness acceptability curve, presented in Figure 17, illustrates the likelihood of each treatment being considered the most cost-effective treatment option, based on a range of willingness-to-pay (DKK/QALY) thresholds. At a willingness-to-pay of approximately DKK 750,000, Kinpeygo has [redacted] chance of being the cost-effective treatment option. The convergence plot can be found in the PSA sheet in the health economic model.

Figure 17 Cost-effectiveness acceptability curve

[redacted]

13. Budget impact analysis

This budget impact analysis describes how budgets will be affected over a five-year period if Kinpeygo is introduced in Denmark.

13.1.1 Number of patients (including assumptions of market share)

The expected number of patients eligible for treatment with Kinpeygo has been described in detail in Section 3.2. Hence, in this budget impact analysis, the prevalent population was assumed to be approximately 380 patients and the incident population was assumed to be approximately 24 patients.

If Kinpeygo is recommended, it was assumed that in the first year (2024), Kinpeygo would have a market share of [redacted] Contrarily, if Kinpeygo is not recommended, it was assumed that corticosteroids would have a market share of 100% during the entire five-year period.

In this analysis, retreatment was allowed for [redacted] of the patients. Retreatment was only allowed once per patient, and it was assumed to occur two years after the first treatment with Kinpeygo. This meant that in any given second year of treatment, no patients incurred treatment costs with Kinpeygo (as the first treatment period fit within the first and second years). In any given third year, the patients undergoing retreatment were added to the number of new patients in that year. This was considered appropriate as these patients were expected to incur the costs of a new treatment round of Kinpeygo, as well as all the costs/cost-savings of the other medical resource use (associated with receiving treatment). Patients who were not retreated incurred the expected costs for any given year. The patient numbers adjusted for market share expected to be treated with Kinpeygo are presented in Table 55.

This approach was only applied to treatment costs. Concerning other medical resource use (except treatment costs), all patients (adjusted for market share) incurred costs every year. As described previously, if the patient was retreated in any given year 3, it would incur the same costs of patients in year 1. Patients who were not retreated incurred the expected costs for any given year. The number of patients adjusted for market share incurring other MRU costs than treatment costs can be found in the BIM sheet.

Finally, in the world with Kinpeygo scenario, an assumption was made that patients treated with corticosteroids in year 1 would remain on corticosteroids for the whole five-year period.

Table 55 Number of new patients expected to be treated over the next five-year period if the medicine is introduced (adjusted for market share)

	2024	2025	2026	2027	2028
			Recommendation		
Kinpeygo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Corticosteroids	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
			Non-recommendation		
Kinpeygo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Corticosteroids	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

13.1.2 Budget impact

The obtained budget impact is presented in Table 56. In 2028 (year 5), the introduction of Kinpeygo is expected to have a budget impact of [redacted].

Table 56 Expected budget impact of recommending the medicine for the indication

	2024	2025	2026	2027	2028
The medicine under consideration is recommended	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
The medicine under consideration is NOT recommended	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Budget impact of the recommendation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

14. List of experts

The following clinical experts was consulted in during this application submission:

- Nicholas Carlson, MD PhD BA. Staff specialist, Postdoc. Department of Nephrology, Copenhagen University Hospital Rigshospitalet[12]
- Per Ramløv Ivarsen, MD, PhD, Consultant, Clinical Professor of Nephrology, Aarhus University Hospital, Aarhus, Denmark[64]

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Appendix A. Main characteristics of studies included

A.1 NefIgArd Phase III trial – Part A and B

Table 57. Main characteristic of studies included

Trial name: NefIgArd Phase III trial		**NCT number: NCT03643965**
Objective	To evaluate the efficacy, safety and tolerability of Kinpeygo 16 mg/day in patients with primary IgAN at risk of progressing to ESRD, despite maximum tolerated RAS blockade	
Publications – title, author, journal, year	Barratt J, Lafayette RA, Kristensen CM*, et al*. Results from part A of the multi-center, double-blind, randomized, placebo-controlled NefIgArd trial, which evaluated targeted-release formulation of budesonide for the treatment of primary immunoglobulin A nephropathy. *Kidney International*. 2023;103:391–402.	
Study type and design	Phase 3, randomized, 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. Part A and B is completed.	
Sample size (n)	Part A: 199 Part B: 364	
Main inclusion criteria	≥18 years with biopsy-confirmed primary IgAN, eGFR ≥35 and ≤90 mL/min per 1.73 m2, proteinuria ≥1 g/day or UPCR ≥0.8 g/g.	
Main exclusion criteria	Systemic diseases that may cause mesangial IgA deposition. Patients who have undergone a kidney transplant. Patients with acute or chronic infectious disease including hepatitis, tuberculosis, human immunodeficiency virus (HIV), and chronic urinary tract infections. Patients with liver cirrhosis, as assessed by the Investigator. Patients with a diagnosis of type 1 or type 2 diabetes mellitus which is poorly controlled. Patients with history of unstable angina, class III or IV congestive heart failure, and/or clinically significant arrhythmia, as judged by the Investigator; Patients with unacceptable blood pressure control defined as a blood pressure consistently above national guidelines for proteinuric renal disease, as assessed by the Investigator Patients with diagnosed malignancy within the past 5 years.	
Intervention	Part A: Optimised RASi therapy plus Kinpeygo 16 mg/day or placebo (1:1 randomisation stratified by baseline proteinuria, baseline eGFR and geographic region). 97 patients assigned to Kinpeygo.	

Trial name: NefIgArd Phase III trial	NCT number: NCT03643965
	Part B: Optimised RASi therapy (maximally tolerated doses) was continued but patients did not receive Kinpeygo. 180 patients assigned to Kinpeygo.
Comparator(s)	Part A: placebo, 102 patients. Part B: Placebo, 179 patients.
Follow-up time	Part A: 3 months Part B: 12 months
Is the study used in the health economic model?	Part A: Yes Part B: Yes
Primary, secondary and exploratory endpoints	**Part A Endpoints included in this application:** The primary objective of Part A was to assess the effect of Kinpeygo 16 mg treatment on urine protein to creatinine ratio (UPCR) over 9 months compared to placebo. Primary outcomes: Ratio of UPCR at 9 months compared with baseline. Secondary outcomes: • Ratio of eGFR at 9 and 12 months compared with baseline; • ratio of UACR at 9 months compared with baseline; • supportive analyses of the above endpoints at time points up to 12 months; • 1-year eGFR slope; safety variables. **Part B Endpoints included in this application:** The primary objective of Part B was 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. Primary outcomes: AUC-based endpoint of eGFR calculated as a time-weighted average of eGFR recordings observed at each time point over 2 years (analysis performed when the last patient randomised completed Visit 17b). Secondary endpoints: 2-year eGFR slope; time to 30% reduction from baseline in eGFR; ratio of UPCR, UACR, and eGFR compared with baseline averaged over time points between 12 and 24 months **Other endpoints:** Secondary outcomes: • time to rescue medication; • proportion of patients without microhaematuria in at least two time points; • proportion of patients receiving rescue treatment; • SF-36 at 9 and 24 months; • exploratory analyses on blood and urine; • safety variables

Trial name: NefIgArd Phase III trial	NCT number: NCT03643965
Method of analysis	The Part B SAS included all patients who received at least one dose of study drug (and includes the 29 patients mentioned above, but excludes five patients who were randomised and included in the Part B FAS but did not receive any blinded study treatment).11 The Part B Per Protocol Set included all patients in the Part B FAS for whom no protocol deviations occurred during the study that were considered to have the potential to impact the efficacy evaluation.1,11
Subgroup analyses	Patients with baseline UPCR ≥1.5 g/g. See Section A.1.7.3.
Other relevant information	*N/A*

A.1.1 Trial design

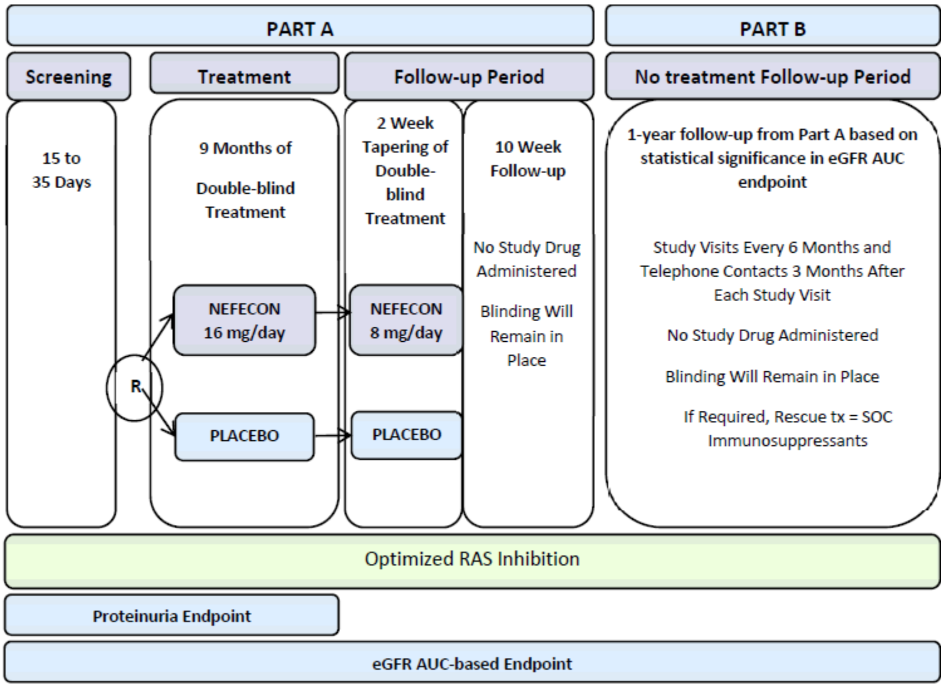
NefIgArd was a multinational, randomised, double-blind, placebo-controlled, multicentre clinical trial (EudraCT: 2017-004902-16; NCT03643965) with a two-part design (see Table 11).[5, 104] The aim was to evaluate the efficacy, safety, and tolerability of oral Kinpeygo 16 mg/day compared with placebo in patients with primary IgAN treated with optimised RAS inhibition therapy.[104] NefIgArd was conducted across 132 hospital-based clinical sites in 20 countries (see Table 11).[104] A placebo comparator was selected due to the lack of approved treatments for patients with IgAN at risk of progressing to ESRD.[11]

Part A of the trial included 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).[11, 92] The data cut-off (DCO) date for Part A was 5 October 2020.[92]

Part B consisted of a blinded, 12-month observational follow-up period, during which no study drugs were administered, followed by a final visit for replicate eGFR sampling at 14 to 35 days after the 24-month visit.[11, 104] Each patient randomised to the NefIgArd trial was followed for a total of 25 months after the first dose of study drug (Kinpeygo or placebo), or, if a patient did not receive any study drug, for 25 months after randomisation.[11] The DCO date for Part B was 6 February 2023.[5]

The planned number of patients was 200 for the Part A efficacy analysis and 360 for the Part B efficacy analysis.[11] The Part A DCO was scheduled to occur once the first 201 randomised patients had had the opportunity to complete their 9-month visit.[11] Part B analysis was conducted when the last randomised patient had the opportunity to complete Visit 17b, which could occur up to 35 days after Visit 17a (the 24-month visit).[11] Patients who completed Parts A and B of this trial were eligible to enter the Phase IIIb open-label extension trial, NefIgArd-OLE (Section A.3).

Figure 18. NefIgArd Phase III trial design



Abbreviations: AUC, area under the curve; eGFR, estimated glomerular filtration rate; RAS, renin-angiotensin system; SoC, standard of care; tx, treatment
Source: DOF (NEF-301 Part B CSR)[5]; Lafayette *et al*, 2023;[104]

A.1.2 Trial populations

Table 58 shows the key inclusion and exclusion criteria. To avoid confounding the comparison with placebo, patients received a stable dose of RAS inhibition for 3 months prior to randomisation and throughout both parts of the trial.[104] Investigators ensured that patients were informed at screening of potentially beneficial lifestyle choices, including weight normalisation, smoking cessation, physical activity, and dietary options (low salt and low protein).[11]

Table 58. Key inclusion and exclusion criteria in the NefIgArd Phase III trial

Key inclusion criteria	Key exclusion criteria
• ≥18 years of age • Diagnosed IgAN with biopsy verification within past 10 years • Receiving a stable* dose of RAS inhibitor therapy (ACEI and/or ARB) at the maximum allowed dose or MTD according to the 2012 KDIGO guideline for 3 months prior to randomisation (target SBP<125 mmHg and DBP <75 mmHg recommended)	• Other causes of mesangial IgA deposition, other glomerulopathies, nephrotic syndrome • Recipients of a kidney transplant • Acute/chronic/latent infectious disease, chronic UTI, liver cirrhosis, a history of unstable angina, class III or IV congestive heart failure, clinically significant arrhythmia, unacceptable blood pressure control, poorly controlled type 1 or type 2 DM, liver cirrhosis, diagnosed malignancy within past 5 years, osteoporosis in medium-/high-risk category, glaucoma, cataracts, GI disorders that could interfere with release of study drug • Hypersensitivity to budesonide, previous severe adverse reactions to steroids

• Proteinuria ≥1 g/day or UPCR ≥0.8 g/g (≥90 mg/mmol) in two consecutive measurements • eGFR (using CKD-EPI formula) ≥35 and ≤90 mL/min/1.73 m^2	• Treated with any systemic GCSs within the 3 months before randomisation or treated with any systemic GCSs within the 12 months before randomisation except for a maximum of three periods of 2 weeks with the equivalent of ≤0.5 mg/kg/day prednisolone for non-IgAN indications • Treated with immunosuppressive medications within the 12 months before randomisation • Taking potent inhibitors of cytochrome P450 3A4 • Pregnant, breastfeeding, or unwilling to use highly-effective contraception (women of childbearing potential) • Life expectancy <5 years • Current or prior (within the past 2 years) alcohol or drug abuse, other medical or social reasons for exclusion at the discretion of the Investigator

*A stable dose was defined as doses within 25% of the dose at randomisation; patients on a stable dose of RAS inhibitor therapy (ACEIs and/or ARBs) below the maximum allowed dose or MTD according to the 2012 KDIGO guideline were permitted if an attempt to reach the maximum allowed dose or MTD had been performed or if such attempt was deemed unsafe for the patient by the Investigator
Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CKD-EPI, chronic kidney disease epidemiology collaboration equation; DBP, diastolic blood pressure; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; GCS, glucocorticosteroid; GI, gastrointestinal; IgA, immunoglobulin A; IgAN, immunoglobulin A nephropathy, KDIGO, Kidney Disease: Improving Global Outcomes; MTD, maximum tolerated dose, RAS, renin-angiotensin system; SBP, systolic blood pressure; UPCR, urine protein-to-creatinine ratio; UTI, urinary tract infection
Source: Lafayette *et al*, 2023, Supplementary Appendix[93]

A.1.3 Randomisation and study treatment

Patients were randomised 1:1 to receive Kinpeygo 16 mg/day (four 4 mg capsules once daily) or placebo (four matching capsules once daily) administered orally for 9 months during the treatment period (Part A).[104] 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). After completing 9 months of study treatment, the daily dose of study drug was reduced from four capsules once daily (Kinpeygo 16 mg or placebo) to two capsules once daily (Kinpeygo 8 mg or placebo) for 2 weeks to prevent adrenal insufficiency (tapering period in Part A).[11, 104]

A.1.4 Endpoints

Table 59 and Table 60 show the primary, secondary and supportive efficacy endpoints for Parts A and B of the NefIgArd trial. These efficacy endpoints are also presented in Section 3.7.

Table 59. NefIgArd Phase III trial Part A efficacy endpoints

Endpoint	Measurement
Primary	
Ratio of UPCR at 9 months following the first dose of study drug compared with baseline	UPCR based on 24-hour urine collections
Secondary	
Ratio of eGFR at 9 and 12 months compared with baseline	Calculated using the CKD-EPI formula

Ratio of UACR at 9 months compared with baseline	-
Supportive/exploratory analyses	
Analyses of the above endpoints after 3, 6, 9, and 12 months	-
1-year eGFR slope	-

Abbreviations: CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; eGFR, estimated glomerular filtration rate; UACR, urine albumin-to-creatinine ratio; UPCR, urine protein-to-creatinine ratio
Source: DOF (NEF-301 CSR)[11]; Barratt *et al*, 2023[92]

Table 60. NefIgArd Phase III trial Part B efficacy endpoints

Endpoint	Measurement
Primary	
AUC-eGFR	Time-weighted average of eGFR recordings observed at each time point over 2 years, with eGFR (CKD-EPI) calculated by a central laboratory at each timepoint. The eGFR at baseline and 2 years was repeated to provide a second value obtained within 14 to 35 days (eGFR recorded was the geometric mean of the two assessments) Each timepoint was weighted in proportion to the time elapsed since the previous recording. Therefore, recordings made at 18 and 24 months received twice as much weight as those made at 3, 6, 9, and 12 months. The weights totalled 1 so that the treatment effect could be interpreted as the average effect over 2 years. Robust regression was used to prevent outlying data having undue influence on the results. A multiple imputation procedure was used to handle missing data. Data were log-transformed before analysis
Secondary	
Composite endpoint of time from randomisation to confirmed 30% reduction in eGFR or confirmed kidney failure	Composite endpoint of time from randomisation to confirmed 30% reduction in eGFR (CKD-EPI formula; confirmed by two values over ≥4 weeks) or confirmed kidney failure (defined as dialysis for ≥1 month, kidney transplantation, sustained [≥1 month] eGFR <15 mL/min per 1.73 m^2, or kidney-related death)
Time from the first dose of study drug until receiving rescue medication	Analysed using a Cox Regression Model
UPCR, UACR, and eGFR (CKD-EPI) ratio compared with baseline	Average over time points between 12 and 24 months, inclusive, following the first dose of study drug
Proportion of patients without microhaematuria	In at least two of the following time points: 12, 18, and 24 months following the first dose of study drug (N.B.: a patient was defined without microhaematuria if the urine dipstick returned a result of negative or trace)
Proportion of patients receiving rescue treatment	This was secondary endpoint but was not subject to formal statistical analysis
Quality of life assessment	SF-36 at 9 and 24 months

Supportive/exploratory analyses	
2-year eGFR slope	Primary supportive analysis of 2-year eGFR total slope using a random coefficients analysis was planned prior to unblinding Part A; however, this analysis method underestimates the magnitude of the Kinpeygo treatment effect. Therefore 2-year total slope was estimated as half of the between-arm difference in mean change from baseline to 2 years derived from a robust regression analysis of the multiply imputed values of log-transformed eGFR at 2 years used in the primary endpoint calculation. An analysis of 2-year eGFR total slope using a linear spline mixed-effects analysis, with a fixed knot at 3 months, was also pre-specified prior to unblinding the full study to provide a more accurate estimate of the magnitude of the 2-year eGFR total slope
Exploratory biomarker analyses on blood and urine	-

Abbreviations: AUC, area under the curve; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; eGFR, estimated glomerular filtration rate; SF-36, Short form 36; UACR, urine albumin-to-creatinine ratio; UPCR, urine protein-to-creatinine ratio
Source: Lafayette *et al*, 2023, Supplementary Appendix;[93] DOF (NEF-301 Part B CSR)[5]

A.1.5 Determination of sample size

It was estimated that 200 patients in Part A 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 with placebo.[11] Inclusion of 360 patients followed for 2 years in Part B was estimated to have 90% power to detect a statistically significant difference in eGFR at 2 years, using a 2-sided alpha of 5% if the true effect of Kinpeygo is 2.24 mL/min/1.73 m^2.[104]

A.1.6 Analysis population

Part A

The Part A full analysis set (FAS), which included all patients who had received at least one dose of study drug, provides an evaluation of efficacy and safety in a population of patients who have all had the opportunity to receive the full 9-month treatment regimen.[11] The safety analysis set (SAS), which included all randomised patients who had received at least one dose of study drug as of the DCO, was presented for completeness.[11] In all efficacy analyses (Part A and Part B), any data impacted by rescue medication will be excluded.[11]

The per protocol set includes all data from patients in the FAS for whom no protocol deviations occurred during the study period that were considered to have the potential to impact the efficacy evaluation.[11] The Part A Per Protocol Set was determined through blinded review prior to Part A database lock.

The pre-defined subgroups for the Part A primary endpoint and eGFR at 9 months were:[11]

- 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 m^2 or ≥60 mL/min/1.73 m^2)

- Dose of RAS inhibitor therapy (angiotensin-converting enzyme inhibitors [ACEIs] and/or angiotensin receptor blockers [ARBs]) with patients split into three groups: <50%, ≥50% to <80% and ≥80% of the maximum allowed dose.

Subgroup analyses of eGFR according to weight (<85 kg or ≥85 kg) were added *post hoc*.[11]

Part B

The Part B FAS included all randomly assigned patients (apart from two patients who were prospectively excluded due to being incorrectly randomised [and were also excluded from the Part A FAS] and 29 patients recruited for regulatory requirements in China after enrolment of the planned 360 patients was complete).[5, 104] The Part B SAS included all patients who received at least one dose of study drug (and includes the 29 patients mentioned above, but excludes five patients who were randomised and included in the Part B FAS but did not receive any blinded study treatment).[5] The Part B Per Protocol Set included all patients in the Part B FAS for whom no protocol deviations occurred during the study that were considered to have the potential to impact the efficacy evaluation.[5, 104]

Predefined subgroup analyses for the Part B primary endpoint were done in populations defined by key patient characteristics and clinical variables (age, sex, race, region, baseline proteinuria, baseline eGFR, dose of RAS inhibitor therapy, and baseline UPCR).[104]

A.1.7 Patient characteristics

A.1.7.1 Part A

At Part A DCO, the Part A FAS included data from 199 patients out of the first 201 patients randomised (two patients randomised in error discontinued the trial and were not included in the FAS).[11]

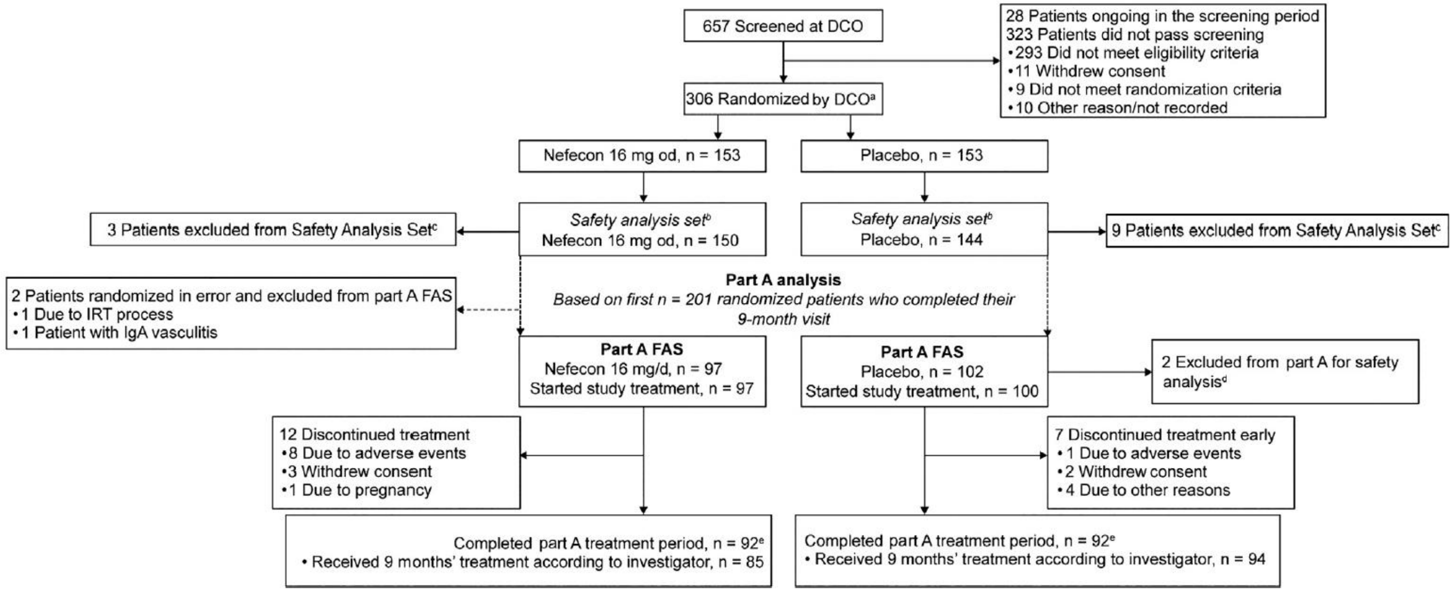
The NefIgArd Phase III trial FAS included data from 199 patients out of the first 201 patients randomised, regardless of whether the patient received a study drug (two patients randomised in error discontinued the trial and were not included in the FAS).[92] There were 97 patients in the Kinpeygo 16 mg group and 102 patients in the placebo group (see Figure 19).[11] The SAS included all 294 randomised patients who had received at least one dose of study drug as of the DCO, including data from patients who had not yet completed the 9-month treatment phase.[92]

Baseline patient demographics, disease and treatment characteristics (see Table 12) were balanced across the groups and as expected for a high risk IgAN population, with similar medical history, concomitant medication and background RAS inhibitor use in Kinpeygo and placebo groups.[92]In the Part A FAS, the ratio of males (67.8%) to females (32.2%) (approximately 2:1) was consistent with that expected for a predominantly Caucasian (85.9%) IgAN patient population.[92] Approximately 12% of patients in the Part A FAS and 17% of patients in the SAS were of Asian racial origin. No Black or African American patients had been enrolled at the time of DCO in the Part A FAS or SAS.[11, 92] Median age was 44 years (range 23 to 73 years) in the Part A FAS.[92]

Baseline disease characteristics were consistent between the analysis sets and as expected for patients with IgAN considered to be at risk of progressing to ESRD.[11] There were no clinically-relevant differences in medical history across treatment groups, although a higher percentage of patients in the Kinpeygo 16 mg group had a medical history of DM compared with the placebo group (9.3% versus 1.0% in the Part A FAS).[92] There were no clinically-relevant differences in concomitant medication use across treatment groups and their use was as expected considering the comorbidities present in the patients population.[11]

Background RAS inhibitor therapy was similar across treatment groups.[92] Although there were some small imbalances in the percentages of patients on ACEIs or ARBs between treatment groups, overall RAS inhibition was similar, with the majority of patients receiving at least 50% of the maximum allowed dose. Prior glucocorticosteroid (GCS) or immunosuppressive use (for any disease) was reported in less than 10% of patients.[92]

Figure 19. NefIgArd patient disposition as of Part A data cutoff (updated figure from primary publication for Part A)



[a]The DCO for the Part A analysis was scheduled to occur once the first 201 patients randomised had the opportunity to complete their 9-month visit. The dataset extracted from the database and cleaned for analysis included all safety data from 294 patients dosed by the time of the DCO date of October 5, 2020, and all efficacy data up to and including the 12-month visit from all patients randomized at the DCO date. Part A database lock occurred on October 28, 2020. Part A (FAS) included data from 199 patients among the first 201 patients randomised, regardless of whether the patient received study drug (2 patients incorrectly randomised were excluded). The DCO was predefined to be based on the first 201 patients because the 200th and 201st patient were randomised on the same day; [b]Safety analysis set included all patients who had received at least 1 dose of study drug as of the DCO (n ¼ 294) and, therefore, includes data from patients who have not yet completed the 9-month treatment phase; [c]The number of patients randomised before the DCO but who had not yet started treatment at the time of DCO. Five patients (2 of whom were included in the Part A FAS) are not expected to be dosed because of withdrawal of consent. The remaining 7 patients were randomised close to the DCO and had not yet been dosed by the time of the DCO; [d]Two patients were excluded from the Part A FAS for safety analyses as they were randomised to placebo but did not receive any study treatment, discontinued from the study, and did not provide any follow-up data; [e]Completed Part A treatment period was defined as the patient has at least 1 valid urine protein-to-creatinine ratio value available in the 9-month visit window (days 229–319)

Abbreviations: DCO; data cutoff; FAS; full analysis set; IRT, interactive response technology; od, once daily

Source: Barratt *et al*, 2023[92]

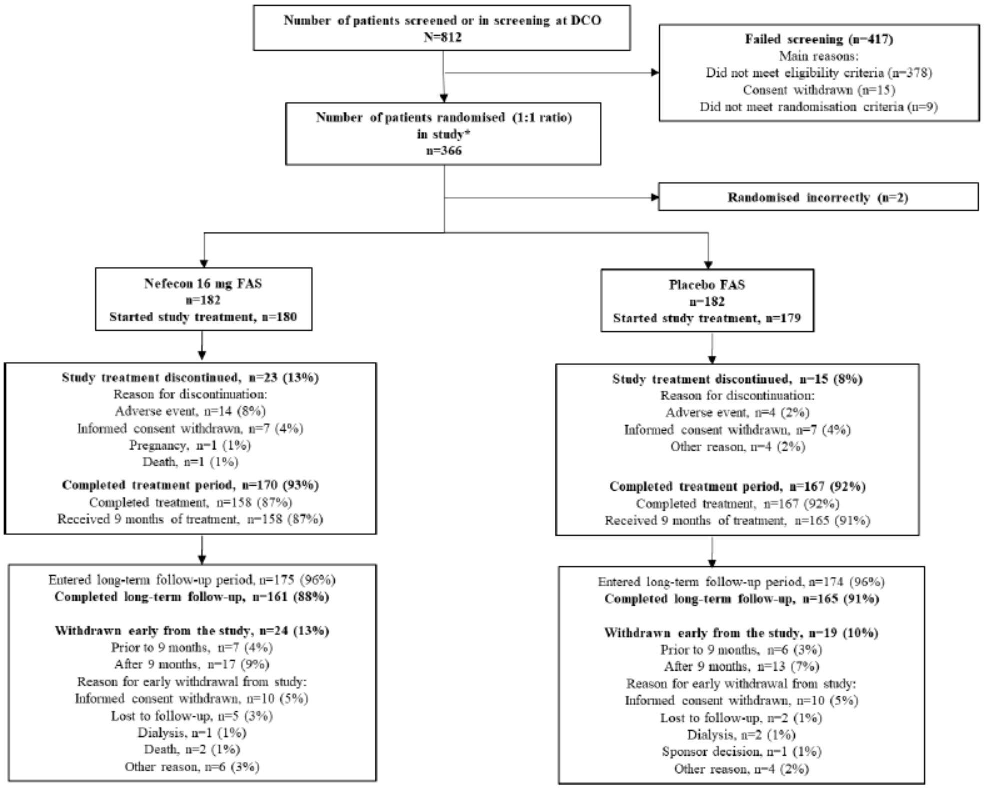
A.1.7.2 Part B

Patients were recruited to the NefIgArd trial between 5 September 2018 and 20 January 2021, with the final follow-up visit (last-patient last-visit) on 6 February 2023.[104] The NefIgArd Phase III Part B FAS comprised 364 patients (182 per treatment group) (see Figure 20). Of these, 359 patients (180 assigned to Kinpeygo and 179 to placebo) received at least one dose of study treatment; five patients (two assigned to Kinpeygo and three to placebo) did not start masked study treatment).[104]

Patient demographics and baseline characteristics were balanced across the treatment groups and were representative of the intended primary IgA nephropathy population. In the Part A FAS, the ratio of males (66%) to females (34%) (approximately 2:1) was consistent with that expected for a predominantly Caucasian (76%) IgAN patient population.[5] Median age was 43 years (range 20 to 73 years), with just over half of all patients less than 45 years of age.[5] The SAS and Part B FAS were generally consistent with respect to demographic characteristics, although the SAS had a slightly higher proportion of Asian patients compared with the Part B FAS (29% vs. 23%) due to the additional patients enrolled in China after recruitment to the global study was completed.[5] No Black or African American patients were enrolled in the trial, most likely because IgAN is less prevalent in these populations.[104]

Patients in the FAS had clinically significant proteinuria (median UPCR 1.26 g/g [IQR 0.89–1.75], median total urine protein 2.23 g/24 h [1.58–3.21]), despite optimised RAS treatment, and mild to moderate kidney dysfunction at baseline according to the CKD nomenclature used by KDIGO 2021 guidelines[29] (median eGFR 55.49 mL/min per 1.73 m² [45.93–69.84]); the majority also had microhaematuria.[104] The median time from IgA nephropathy biopsy diagnosis to study entry was 2.5 years (0.6–6.8). BP was well controlled at study entry and approximately 80% of patients were receiving at least 50% of the maximum allowable dose of RAS inhibitor therapy, with most patients receiving either an ACEi or an ARB. A few patients (<5%) were receiving combined ACEi and ARB therapy. The Kinpeygo group had more patients with diabetes (9% vs. 4%) and pre-diabetes (39% vs. 27%) than the placebo group.[104]

Figure 20. NefIgArd patient disposition as of the Part B data cut-off



*A further n=29 patients in China were randomised for Chinese regulatory requirements; however, this occurred after global recruitment had ended and so they were not included in the study analysis

Definitions: 'Completed treatment period' was defined as the patient has at least one valid UPCR value available in the 9-month visit window (Day 229 to Day 319); 'Completed treatment' is the number recorded by the investigator. The patient is considered to have received 9 months of treatment if the date of last dose (excluding doses received in the tapering period) – date of first dose + 1 ≥255.; The patient is defined as having entered the 'long-term follow-up period' if they attended at least one study visit or had any AE recorded that is more than 14 days after the last dose of study treatment (including tapering); 'Completion of long-term follow-up' is defined as the patient has at least one valid eGFR value within the 24-month visit window (Day 640 to Day 821)

In addition to the main reasons for withdrawal recorded on the eCRF, the Covid-19 situation also contributed to the discontinuation of study treatment in three Kinpeygo-treated patients (two patient decisions and one death from Covid-19). All three of these patients also discontinued the study (one due to other reasons with the Covid-19 situation also a contributing factor, one due to participant decision not Covid-related, and the other was the patient who died of Covid-19)

Abbreviations: AE, adverse event; Covid-19, Coronavirus Disease 2019; DCO, data cut-off (6 Feb 2023); eCRF, electronic case report form; eGFR, estimated glomerular filtration rate; FAS, full analysis set; UPCR, urine protein-to-creatinine ratio

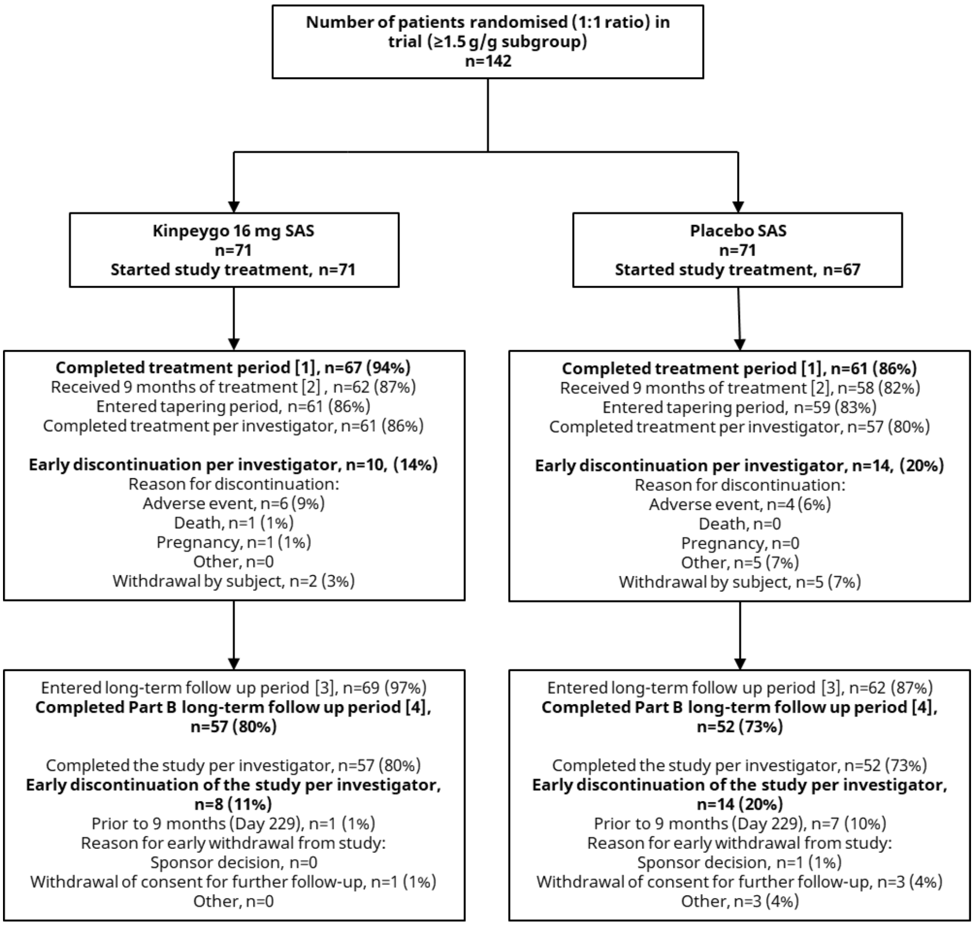
Source: Lafayette *et al*, 2023, Supplementary Appendix[93]

A.1.7.3 Part B – Baseline UPCR ≥1.5 g/g subgroup population

In total, the Part B ≥1.5 g/g subgroup FAS comprised 129 patients (65 patients in the Kinpeygo treatment arm and 64 patients in the placebo arm) and the SAS comprised 142 patients (71 assigned to each arm).[17] Of patients included in the SAS, 138 patients (71 assigned to Kinpeygo and 67 assigned to placebo received at least one dose of study treatment (see Figure 21).[17]

As for the full population, patient demographics and characteristics at baseline were balanced across treatment groups (Table 12). Just over half of patients in the FAS were male in both arms (54.3%), and median age was 42 years (range 21 to 68 years).[17] Patients had clinically significant baseline proteinuria (median UPCR 2.05 g/g [IQR 1.71 to 2.63], median total urine protein 3.68 g/24 h [2.76–4.80]), which as would be expected was greater than that observed in the total population.[17] Median time from IgA nephropathy biopsy diagnosis to trial entry was 3.0 years (0.7 to 8.1).[17]

Figure 21. NefIgArd patient disposition as of the Part B data cut-off | Baseline UPCR ≥1.5 g/g subgroup



[1] Completed treatment period defined as the patient has at least one valid urine UPCR value available in the 9-month visit window (Day 229 to Day 319); [2] The patient is considered to have received 9 months of treatment if date of last dose (excluding doses received in the tapering period) – date of first dose + 1 ≥255; [3] The patient is defined as entered the long-term follow up period if attended at least one study visit or had any AE recorded that is more than 14 days after the last dose of study treatment (including tapering); [4] Completion of Part B is defined as the patient has at least one valid eGFR value within the 24-month visit window (Day 640 to Day 821)
Abbreviations: AE, adverse event; eGFR, estimated glomerular filtration rate; SAS, safety analysis set; UPCR, urine protein–creatinine ratio
Source: DOF (NEF-301 Part B additional tables and figures)[17]

A.2 NefIgAN Phase IIb trial

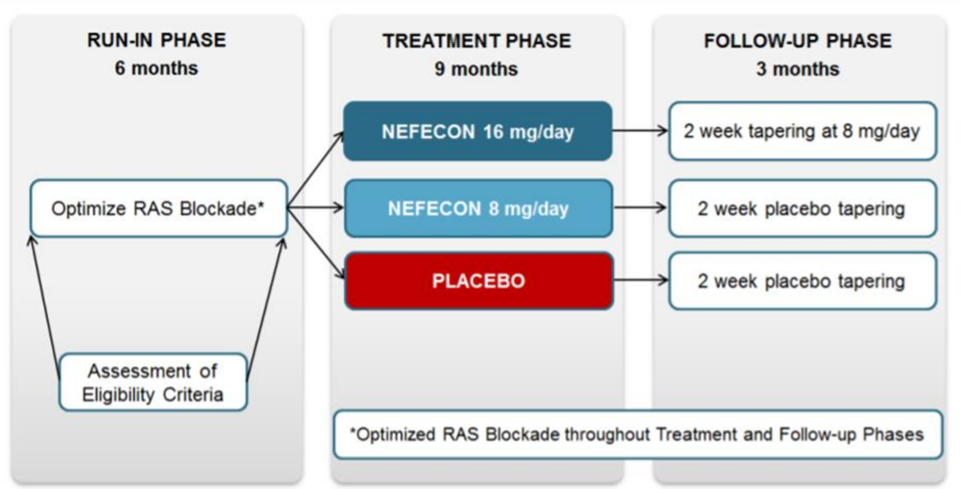
Trial name: NefIgAN Phase IIb trial [59]	NCT number: NCT01738035
Objective	To evaluate the safety and efficacy of two doses of Kinpeygo in patients with IgAN at risk of progression to ESRD despite optimised RAS blockade.
Publications – title, author, journal, year	Fellstrom BC, Barratt J, Cook H, *et al*. Targeted-release budesonide versus placebo in patients with IgA nephropathy (NEFIGAN): a double-blind, randomised, placebo-controlled phase 2b trial. *Lancet*. 2017;389(10084):2117-2127[59]
Study type and design	A Multicentre, Interventional Treatment, Randomized, Double-Blind, Placebo Controlled Study to Evaluate the Efficacy and Safety of Two Different Doses of Nefecon in Primary IgA Nephropathy Patients at Risk of End-stage Renal Disease
Sample size (n)	150
Main inclusion criteria	≥18 years biopsy-confirmed primary IgAN, eGFR ≥45 mL/min per 1.73 m^2, and UPCR >0.5 g/g or urine protein ≥0.75 g/24-h
Main exclusion criteria	
Intervention	Optimised RASi therapy plus Kinpeygo 16 mg/day or Kinpeygo 8 mg/day or placebo (1:1:1 randomisation stratified by baseline UPCR)
Comparator(s)	Placebo
Follow-up time	3 months follow-up
Is the study used in the health economic model?	No. Information on this study is included in the submission document to show the efficacy of two different doses of Kinpeygo.
Primary, secondary and exploratory endpoints	Primary otucome: Mean change from baseline in UPCR over the 9-month treatment phase. Secondary outcomes: Mean changes from baseline in UPCR, eGFR, 24-h urine protein excretion, UACR, and 24-h urine albumin excretion - assessed at various timepoints, presence/absence of microhaematuria.
Method of analysis	
Subgroup analyses	
Other relevant information	

A.2.1 Trial design

Nefigan (NEF-202; NCT01738035) was a randomised, placebo-controlled, double-blind, multicentre trial, aiming to evaluate the safety and efficacy of two different doses of Kinpeygo (8 mg/day and 16 mg/day) in patients with IgAN who were at risk of progression to ESRD due to persistent proteinuria despite optimised RAS blockade therapy (see Figure 22).[59] An overview is provided in Table 11.

Nefigan had a 6-month run-in phase, a 9-month treatment phase, and a 3-month follow-up phase.[59] During run-in, RAS blockade was optimised by up-titrating ACEIs and ARBs to a maximum recommended dose or maximum tolerated dose (in keeping with established clinical practice), to a target blood pressure <130/80 mm Hg, UPCR <0.5 g/g, and urine protein <0.75 g/day. At the end of run-in, patients with persistent proteinuria (UPCR, >0.5 g/g or proteinuria, ≥0.75 g/day) despite optimised RAS blockade, eGFR ≥45 mL/min/1.73 m^2 and blood pressure ≤160/100 mm Hg were eligible for randomisation to treatment (see Figure 22).[114]

Figure 22. Nefigan Phase IIb clinical trial design



Abbreviations: RAS, renin-angiotensin system
Source: Fellström *et al*, 2017[59]; DOF (NEF-202 CSR)[114]

A.2.2 Trial populations

Following run-in, 150 patients were randomised to receive study medication; see Table 61 for key inclusion and exclusion criteria.

Table 61. Key inclusion and exclusion criteria in Nefigan Phase IIb trial

Key inclusion criteria	Key exclusion criteria
• Female or male patients ≥18 years • Biopsy-verified IgAN • Urine protein ≥0.75 g/day or UPCR ≥0.5 g/g (56.5 mg/mmol)	• Secondary forms of IgAN, as defined by the treating physician • Crescent formation in ≥50% of glomeruli assessed on renal biopsy • Recipients of a kidney transplant

• eGFR ≥45 mL/min/1.73 m^2 • Patients on a maximum recommended or MTD of ACEIs and/or ARBs for 3 months • BP ≤160/100 mm Hg	• Severe GI disorders or other disorders which may modify the effect of the study drug • Patients with recent history of treatment with immunosuppressive agents, or systemic corticosteroid drugs • Patients with severe liver disease, diabetes, uncontrolled CVD, acute/chronic infectious diseases, current/recent malignancy

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BP, blood pressure; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; GI, gastrointestinal; mm Hg, millimetres of mercury; MTD, maximum tolerated dose; UPCR, urine protein-to-creatinine ratio

Source: Fellström *et al*, 2017[59]

A.2.3 Randomisation and study treatment

Patients were randomised 1:1:1: to receive Kinpeygo 16 mg/day, Kinpeygo 8 mg/day, or matched placebo.[59]

A.2.4 Endpoints

The primary endpoint was the mean reduction in UPCR at 9 months compared with baseline UPCR values (mean reduction measured as a ratio of UPCR at 9 months compared with baseline).[59] Other efficacy endpoints are shown in Table 62.

Table 62. Secondary and tertiary endpoints of Nefigan Phase IIb trial

Type	Endpoint
Secondary	• Mean change in urine protein, 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, eGFR (CKD-EPI), eGFR (MDRD) and creatinine clearance from baseline at 9 months
Tertiary	• Achieving defined reductions (≥30%, ≥40%, ≥50%) in UPCR, urine protein, UACR and urine albumin at Month 9 compared with 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

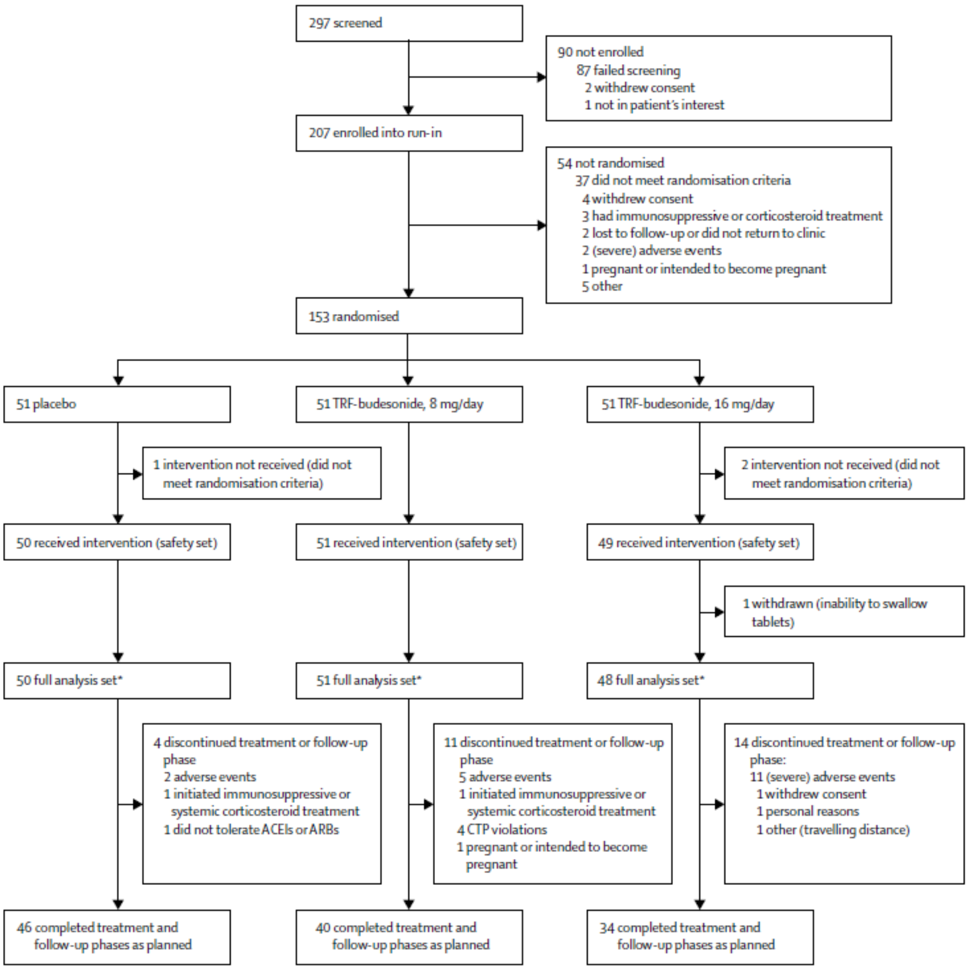
Abbreviations: CKD-EPI, chronic kidney disease epidemiology collaboration equation; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; MDRD, modification of diet in renal disease; UACR, urine albumin-to-creatinine ratio; UPCR, urine protein creatinine ratio

Source: DOF (NEF-202 CSR)[114]

A.2.5 Patient characteristics

The SAS included all 150 patients randomised to receive a study drug, and the FAS was defined as all randomised patients who took at least one dose of the study medication and had at least one post-dose efficacy measurement (see Figure 23).[59] The FAS comprised 149 patients, as one patient was withdrawn from the analysis due to an inability to swallow tablets.[59]

Figure 23. Patient disposition in Nefigan Phase IIb trial



*Full analysis set corresponds with the modified intention-to-treat analysis set
Abbreviations: ACEI, angiotensin-converting-enzyme inhibitors; ARBs, angiotensin receptor blockers; CTP, clinical trial protocol
Source: Fellström *et al*, 2017[59]

The baseline patient characteristics of the FAS (N=149) are summarised in Table 12. Treatment groups had similar demographic and baseline characteristics, with all patients using RAS blockade therapy.[59] Almost all the patients were aged between 18 and 65 years apart from two (aged 69 and 82 years).[114] There were more males than females in the FAS (70.5% versus 29.5%), but this was similar in all treatment groups and consistent with the expected distribution of males and females (2:1) in an IgAN patient population. There were small variations between the treatment groups for mean eGFR CKD-EPI (creatinine) at baseline: being highest in the Kinpeygo 16 mg/day (83.84 mL/min/1.73 m^2) group and lowest in the Kinpeygo 8 mg/day (74.08 mL/min/1.73 m^2) group, but this was not considered to have an effect on the interpretation of the efficacy or safety results, as the efficacy and most of the safety analyses were adjusted for baseline.[114]

A.3 NefIgArd-OLE open-label extension trial

The NefIgArd-OLE open-label extension is an ongoing Phase IIIb, multicentre, open-label, single-arm extension trial to evaluate the efficacy and safety of Kinpeygo 16 mg/day treatment in patients with IgAN who have completed the Phase III NefIgArd trial.[113] All patients will receive Kinpeygo 16 mg/day for 9 months (including those who received Kinpeygo) and were previously treatment naïve to Kinpeygo), as well a stable dose of RAS inhibitor therapy. The Kinpeygo dose may be reduced if clinically-relevant AEs develop that the Investigator considers related to the trial drug and that mandate dose reduction. The trial design is summarised in Table 63, and trial completion is due in May 2024.[113]

Table 63. Overview of NefIgArd-OLE trial

Characteristic	NefIgArd-OLE
Trial details	• Open-label extension trial in patients who completed Phase III trial NefIgArd • Estimated enrolment, 250 patients • One 9-month treatment period; follow-up visit at 12 months after the first dose
Intervention	• Kinpeygo 16 mg orally once daily for 9 months
Key inclusion criteria	• Completed Study Nef-301 • Completed Visit 17b in Study Nef-301 within 3 months before Study Visit 3 • On a stable dose of RASi therapy at the maximum allowed dose or maximum tolerated dose • 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 (proteinuria ≥1 g/day or UPCR ≥0.8 g/g) • eGFR ≥30 mL/min per 1.73 m^2 using the CKD-EPI formula
Key exclusion criteria	• Had a dose reduction to Nefecon 8 mg/day in Study Nef-301 • Systemic diseases that may cause mesangial IgA deposition • Patients who have undergone a kidney transplant • Patients with presence of other glomerulopathies or nephrotic syndrome • Patients with acute, chronic, or latent infectious disease; liver cirrhosis; poorly controlled Type 1 or type 2 diabetes mellitus; history of unstable angina, class III or IV congestive heart failure, and/or clinically significant arrhythmia, unacceptable blood pressure control; diagnosed malignancy within the past 5 years; known osteoporosis in the medium- or high-risk category; known glaucoma, known cataract(s), and/or history of cataract surgery, unless the surgery was performed on both eyes • Gastrointestinal disorders that may interfere with the effects or release of the study drug • Hypersensitivity to budesonide or any component of the study drug formulation • Patients who have received rescue therapy with systemic immunosuppressants, including GCSs, during Study Nef-301 • Patients who have been treated with any systemic GCSs within the 3 months before screening • Patients who have been treated with any systemic GCSs within the 12 months before screening except for a maximum of 3 periods of 2 weeks with the equivalent of ≤0.5 mg/kg/day prednisolone for non-IgAN indications

		• Patients taking potent inhibitors of cytochrome P450 3A4 (CYP3A4) • Current or prior (within the past 2 years) alcohol or drug abuse
Primary endpoints		• Ratio of eGFR at 9 months compared with baseline, calculated using the CKD-EPI formula • Ratio of UPCR at 9 months compared with baseline • Incidence of TEAEs from enrolment up to 12 months
Secondary endpoint		• Ratio of UACR at 9 months compared with baseline • SF-36 QoL assessment at 12 months compared with baseline • Proportion of patients with microhaematuria at 9 months compared with baseline • Proportion of patients receiving rescue treatment and time to receiving rescue treatment • Proportion of patients on dialysis, undergoing kidney transplantation, or with eGFR <15 mL/min per 1.73 m^2 • Cortisol suppression at 9 and 12 months, compared with baseline

Abbreviations: CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; eGFR, estimated glomerular filtration rate; GCS, glucocorticoid; IgA, immunoglobulin A; KDIGO, Kidney Disease: Improving Global Outcomes; OLE, open-label extension; QoL, quality of life; RASi, renin-angiotensin system inhibitor; SF-36, Short Form-36; TEAE, treatment-emergent adverse event; UACR, urine albumin-to-creatinine ratio; UPCR, urine protein-to-creatinine ratio
Source: clinicaltrials.gov[113]

A.4 STOP-IgAN trial

A.4.1 Study design

A prospective, open-label, randomized, controlled clinical trial with a two-group, parallel, group-sequential design was conducted.[148] The protocol is available at NEJM.org. All the authors collected the data and vouch for the completeness and accuracy of the data and analyses and for the fidelity of the study to the protocol. The decision to submit the manuscript for publication was made by all the authors.

During a 6-month run-in phase, all the patients received comprehensive supportive care that included blockers of the renin–angiotensin system to lower blood pressure to a target below 125/75 mm Hg. If proteinuria remained above the target of 0.75 g per day of urinary protein excretion despite blood-pressure control, the dose of renin–angiotensin system blocker was increased to the maximum approved daily dose or to the highest dose at which the patient did not have unacceptable side effects. Patients received dietary counseling and were advised to quit smoking and to avoid nonsteroidal antiinflammatory drugs and other nephrotoxins. Total cholesterol levels were lowered to less than 200 mg per deciliter (5.2 mmol per liter) with the use of statins, if necessary.

High-risk patients who had persistent proteinuria with urinary protein excretion of at least 0.75 g per day, but lower than 3.5 g per day, at the end of the run-in phase entered the 3-year study phase and were randomly assigned to continue supportive care alone (supportive-care group) or to receive supportive care with the addition of immunosuppressive therapy (immunosuppression group). Participants whose proteinuria dropped below 0.75 g of urinary protein excretion per day at the end of the run-in phase did not undergo randomization; if proteinuria exceeded the threshold of 0.75 g of urinary protein excretion per day in these patients despite supportive care during the randomization phase of the trial, the patients were eligible for randomization. At the end of the run-in phase, patients who had a urinary protein excretion rate above 3.5 g per day, an eGFR lower than 30 ml per minute per 1.73 m^2, or a decrease in the eGFR of more than 30% from the start of the run-in phase were not randomly assigned (dropout criteria).

Patients randomly assigned to the immunosuppression group who had an eGFR of at least 60 ml per minute per 1.73 m^2 received glucocorticoid monotherapy for 6 months (methylprednisolone, administered intravenously at a dose of 1 g per day for 3 days at the start of months 1, 3, and 5; and oral prednisolone at a dose of 0.5 mg per kilogram per 48 hours on the other days).[149, 150] On the basis of the literature available in 2007, patients with an eGFR between 30 and 59 ml per minute per 1.73 m^2 received cyclophosphamide at a dose of 1.5 mg per kilogram per day for 3 months, followed by azathioprine at a dose of 1.5 mg per kilogram per day during months 4 through 36, plus oral prednisolone at a dose of 40 mg per day, tapered to 10 mg per day, over the first 3 months of the study, 10 mg per day during months 4 through 6, and 7.5 mg per day during months 7 through 36.[151] All drugs were administered as part of general medical care and were not donated specifically for the trial.

The run-in phase included visits at weeks 0, 4, 8, 16, 20, 23, and 24. At week 24 (defined as baseline), eligible patients underwent randomization, and study visits occurred at 2 weeks after randomization, once a month thereafter for 3 months, and then once every 3 months until month 36. GFR was estimated with the use of the Chronic Kidney Disease Epidemiology Collaboration Creatinine Equation (www.kidney.org/professionals/KDOQI/gfr_calculator. opens in new tab).

The level of proteinuria was quantified according to 24-hour urine collections and was expressed as grams per day of urinary protein excretion during the run-in phase, as in most randomized, controlled trials; however, during the randomized, controlled trial phase, we switched to using the protein-to-creatinine ratio (with both protein and creatinine measured in grams), given the greater accuracy of this approach.[152] Data that determined primary end points (i.e., eGFR and proteinuria) were confirmed by repeated measurements after a 2-week interval, and the mean value of all the measurements was used in the analysis. Patients provided three home measurements of blood pressure before each visit. The mean of these measurements was recorded. If home measurements were not provided (which was the case for <20% of the patients at each single visit), office measurements were recorded.

A.4.2 Study population

From February 2008 through October 2011, we screened 379 patients with IgA nephropathy at 32 nephrology centers in Germany. A total of 42 patients were excluded because of patient or physician decision, incomplete data, or other reasons, and 337 patients were enrolled in the run-in phase. The key inclusion criteria were primary IgA nephropathy confirmed on biopsy; an age of 18 to 70 years; and a proteinuria level above 0.75 g per day of urinary protein excretion plus arterial hypertension (defined by the use of antihypertensive medication or by an ambulatory blood pressure ≥140/90 mm Hg), impaired renal function (defined as an eGFR <90 ml per minute per 1.73 m2), or both. Major exclusion criteria were an eGFR lower than 30 ml per minute per 1.73 m2, secondary and rapidly progressive, crescentic IgA nephropathy, other chronic renal diseases, and any prior immunosuppressive therapy. Written informed consent was obtained from all participants. The study was approved by the ethics committee at each participating center.

A.4.3 Study endpoints

The two primary end points in hierarchical order were full clinical remission (defined as proteinuria with a protein-to-creatinine ratio of <0.2 and stable renal function with a decrease in the eGFR of <5 ml per minute per 1.73 m^2 from the baseline eGFR at the end of the 3-year trial phase) and a decrease in the eGFR of at least 15 ml per minute per 1.73 m2 from the baseline eGFR. Secondary end points were the absolute decrease in the eGFR, a decrease in the eGFR of at least 30 ml per minute per 1.73 m^2 from the baseline eGFR, the need for dialysis (onset of end-stage renal disease), the mean annual change in the slope of the reciprocal of serum creatinine concentration, proteinuria at 12 and 36 months, and disappearance of microhematuria as determined by means of a dipstick or urinary sediment test.

A.4.4 Statistical analyses

We calculated that a sample of 74 patients per group (including a 10% dropout adaptation) would give the study 80% power, at a two-sided significance level of 5%, to detect rates of full clinical remission (the first primary end point) of 5% in the supportive-care group and 25% in the immunosuppression group (with these rates assumed on the basis of prior randomized, controlled trials).[150, 151] We used a chi-square test with continuity correction and adjustment for two interim analyses (after one third and two thirds of the cohort had completed the trial) [153].

Randomization codes that were used to assign patients in a 1:1 ratio were generated by means of covariate adaptive randomization with respect to factors that had the potential to modify the treatment effect (i.e., eGFR and proteinuria).[148, 154] Data are presented as means and standard deviations for continuous variables and as counts, percentages, and odds ratios with 95% confidence intervals for categorical variables. The full-analysis set was used for the primary analyses, with patients with missing data considered to have treatment failure.[155] A logistic-regression model that included two stratification factors (baseline eGFR and baseline proteinuria) was fitted to the data of the two primary end points. The individual significance level of the two end points was set to 5% according to the hierarchical order; the significance level was corrected for the group sequential design to 0.0005 at the first interim analysis, 0.0141 at the second interim analysis, and 0.0451 at the final analysis.[153, 156] Various sensitivity analyses were performed with the use of an available-case analysis set, multiple-imputation techniques to account for missing observations, and a permutation test.

Secondary end points were analyzed on the basis of available cases with the use of multivariate models that included two stratification factors (baseline eGFR and baseline proteinuria). Additional details regarding the analyses of the secondary end points are provided in the trial statistical analysis plan (available with the protocol at NEJM.org). Adverse events were analyzed by means of Fisher's exact test, except for the total number of events of infection and serious adverse events of infection, for which the Wilcoxon signed-rank test was used to determine significance levels.

Appendix B. Efficacy results per study

B.1 Results per study

B.1.1 NefIgArd Part B

Results from Part B of the NefIgArd trial demonstrate the 2-year efficacy and durability of Kinpeygo treatment effect, and support filing for full regulatory approval for the entire trial population. Note that Part B is an interim readout and not an extra study to the Part A. Part B includes the same patients as in Part A + an additional 160 patients, and has a longer follow-up. Part B is therefore the main results for which this assessment is based, but the Part A data is also included in Appendix for transparency.

Following completion of part B of the trial, NefIgArd met its 2-year primary endpoint, demonstrating that 9 months of treatment with Kinpeygo* provided a statistically significant and clinically relevant reduction in eGFR decline, and the treatment benefit was maintained during the 15-month of observational follow-up; over 2 years, [redacted].[104]

The eGFR benefit accrued by the end of 9 months of treatment with Kinpeygo* was maintained during the 15 months of observational follow-up.[104]

- At 9 months, Kinpeygo* significantly improved the mean absolute change in eGFR from baseline with a difference versus placebo of [redacted], providing a treatment effect of [redacted].[5, 104]
- The absolute difference in eGFR between Kinpeygo* and placebo continued to numerically improve up to 24 months to [redacted], providing a treatment effect of [redacted].[5, 104]

The beneficial eGFR treatment effect was achieved irrespective of UPCR baseline.[104]

B.1.1.1 Results table - Full population

Table 64. Results of NefIgArd Phase III NEF-301 – Part B (NCT:03643965) – full population

Results of NefIgArd NEF-301 (Part B; NCT: 03643965) - full population												
				Estimated absolute difference in effect			Estimated relative difference in effect				Description of methods used for estimation	References
Outcome	Study arm	N	Result (95 % CI)	Absolute change (SEM), g/g	95% CI	*P* value	Relative change (95% CI)†	Geo, LS mean†	95% CI	*P* value*		
[redacted]	Kinpeygo 16 mg/day		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted] See Section 3.7.1	Lafayette *et al*, 2023;[104] DOF (NEF-301 Part B CSR)[5]
	Placebo		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted] See Section 3.7.1	Lafayette *et al*, 2023;[104] DOF (NEF-301 Part B CSR)[5]
[redacted]	Kinpeygo 16 mg/day		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted] See Section 3.7.1	Lafayette *et al*, 2023;[104] DOF (NEF-301 Part B CSR)[5]
	Placebo		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted] See Section 3.7.1	Lafayette *et al*, 2023;[104] DOF (NEF-301 Part B CSR)[5]

Results of NefIgArd NEF-301 (Part B; NCT: 03643965) - full population													
				Estimated absolute difference in effect			Estimated relative difference in effect				Description of methods used for estimation		References
Outcome	Study arm	N	Result (95 % CI)	Absolute change (SEM), g/g	95% CI	*P* value	Relative change (95% CI)†	Geo, LS mean†	95% CI	*P* value*			
[redacted]	Kinpeygo 16 mg/day		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		See Section 3.7.1	Lafayette *et al*, 2023;[104] DOF (NEF-301 Part B CSR)[5]
	Placebo		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	See Section 3.7.1	Lafayette *et al*, 2023;[104] DOF (NEF-301 Part B CSR)[5]
Supportive analyses of 2-year eGFR total slope - Primary supportive random coefficients analysis†	Kinpeygo 16 mg/day*	182	–3.55	1.82	0.50-3.13	0.0035	N/A	N/A	N/A	N/A	N/A	See Section 3.7.1	Lafayette *et al*, 2023, Supplementary Appendix[93]
	Placebo*	182	–5.37				N/A	N/A	N/A	N/A	N/A	See Section 3.7.1	Lafayette *et al*, 2023, Supplementary Appendix[93]

Results of NefIgArd NEF-301 (Part B; NCT: 03643965) - full population												
				Estimated absolute difference in effect			Estimated relative difference in effect				Description of methods used for estimation	References
Outcome	Study arm	N	Result (95 % CI)	Absolute change (SEM), g/g	95% CI	*P* value	Relative change (95% CI)†	Geo, LS mean†	95% CI	*P* value*		
Supportive analyses of 2-year eGFR total slope - Robust regression analysis of multiply imputed 2-year eGFR values‡	Kinpeygo 16 mg/day*	182	−3.06	2.95	1.67-4.58	<0.0001	N/A	N/A	N/A	N/A	See Section 3.7.1	Lafayette *et al*, 2023, Supplementary Appendix[93]
	Placebo*	182	−6.00				N/A	N/A	N/A	N/A	See Section 3.7.1	Lafayette *et al*, 2023, Supplementary Appendix[93]
Supportive analyses of 2-year eGFR total slope - Linear spline mixed-effects model†	Kinpeygo 16 mg/day*	182	−2.65	2.78	1.39-4.17	<0.0001	N/A	N/A	N/A	N/A	See Section 3.7.1	Lafayette *et al*, 2023, Supplementary Appendix[93]
	Placebo*	182	−5.44				N/A	N/A	N/A	N/A	See Section 3.7.1	Lafayette *et al*, 2023, Supplementary Appendix[93]

Results of NefIgArd NEF-301 (Part B; NCT: 03643965) - full population													
				Estimated absolute difference in effect			Estimated relative difference in effect				Description of methods used for estimation		References
Outcome	Study arm	N	Result (95 % CI)	Absolute change (SEM), g/g	95% CI	*P* value	Relative change (95% CI)†	Geo, LS mean†	95% CI	*P* value*			
Composite endpoint of time from randomisation to confirmed 30% eGFR reduction or kidney failure, overall and by UPCR subgroup -Number (%) of patients with confirmed 30 % eGFR reduction or kidney failure** (Part B FAS)	Kinpeygo 16 mg/day	182	21 (12%)		N/A		N/A	N/A	N/A	N/A		See Section 3.7.1	Lafayette *et al*, 2023[104]
	Placebo	182	39 (21%)		N/A	N/A	N/A	N/A	N/A	N/A	N/A	See Section 3.7.1	Lafayette *et al*, 2023[104]
Composite endpoint of time from	Kinpeygo 8mg/day		N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	See Section 3.7.1	Lafayette *et al*, 2023[104]

Results of NefIgArd NEF-301 (Part B; NCT: 03643965) - full population													
				Estimated absolute difference in effect			Estimated relative difference in effect				Description of methods used for estimation		References
Outcome	**Study arm**	**N**	**Result (95 % CI)**	**Absolute change (SEM), g/g**	**95% CI**	***P* value**	**Relative change (95% CI)†**	**Geo, LS mean†**	**95% CI**	***P* value***			
randomisation to confirmed 30% eGFR reduction or kidney failure, overall and by UPCR subgroup -HR (95% CI) (Part B FAS	Kinpeygo 16 mg/day vs placebo		N/A	N/A	N/A	N/A	0.45	N/A	0.26 to 0.75	N/A	N/A	See Section 3.7.1	Lafayette *et al*, 2023[104]
Ratio of time-averaged UPCR between 12 and 24 months compared with baseline - % reduction from baseline	Kinpeygo 16 mg/day	172	40.3%	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	See Section 3.7.1	Lafayette *et al*, 2023[104]
	Placebo	173	-1.0%	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	See Section 3.7.1	Lafayette *et al*, 2023[104]
Ratio of time-averaged UPCR between 12 and 24 months	Kinpeygo 16mg/day vs placebo		N/A	N/A	N/A	N/A	40.9%		31.9 to 48.7%	<0.0001		See Section 3.7.1	Lafayette *et al*, 2023[104]

Results of NefIgArd NEF-301 (Part B; NCT: 03643965) - full population												
				Estimated absolute difference in effect			**Estimated relative difference in effect**				**Description of methods used for estimation**	**References**
Outcome	**Study arm**	**N**	**Result (95 % CI)**	**Absolute change (SEM), g/g**	**95% CI**	***P* value**	**Relative change (95% CI)†**	**Geo, LS mean†**	**95% CI**	***P* value***		
compared with baseline - % reduction vs placebo												
Ratio of time-averaged UACR between 12 and 24 months compared with baseline - % reduction from baseline	Kinpeygo 16 mg/day		48.2%	N/A	N/A	N/A	N/A	N/A	N/A	N/A	See Section 3.7.1 and Table 67	Lafayette *et al*, 2023[104]
	Placebo		3.7%	N/A	N/A	N/A	N/A	N/A	N/A	N/A	See Section 3.7.1 and Table 67	Lafayette *et al*, 2023[104]
Ratio of time-averaged UPCR between 12 and 24 months	Kinpeygo 16mg/day vs placebo		N/A	N/A	N/A	N/A	46.3%		36.5–54.5%	0.0001	See Section 3.7.1	Lafayette *et al*, 2023[104]

Results of NefIgArd NEF-301 (Part B; NCT: 03643965) - full population													
				Estimated absolute difference in effect			Estimated relative difference in effect				Description of methods used for estimation	References
Outcome	Study arm	N	Result (95 % CI)	Absolute change (SEM), g/g	95% CI	*P* value	Relative change (95% CI)†	Geo, LS mean†	95% CI	*P* value*		
compared with baseline - % reduction vs placebo												
Microhaematuria reduction over 24 months	Kinpeygo 16 mg/day	158	53 (34)	N/A	N/A	N/A	N/A	N/A	N/A	N/A		Lafayette et al, 2023[104]; Lafayette *et al*, 2023, Supplementary Appendix[93]
- Patients without microhaematuria at baseline[†], n (%)	Placebo	152	49 (32)	N/A	N/A	N/A	N/A	N/A	N/A	N/A		
Microhaematuria reduction over 24 months	Kinpeygo 16 mg/day	158	94 (59)	N/A	N/A	N/A	N/A	N/A	N/A	N/A		Lafayette et al, 2023[104]; Lafayette *et al*, 2023, Supplementary Appendix[93]
- Patients without microhaematuria during the observational	Placebo	152	59 (39)	N/A	N/A	N/A	N/A	N/A	N/A	N/A		

Results of NefIgArd NEF-301 (Part B; NCT: 03643965) - full population												
				Estimated absolute difference in effect			Estimated relative difference in effect				Description of methods used for estimation	References
Outcome	Study arm	N	Result (95 % CI)	Absolute change (SEM), g/g	95% CI	*P* value	Relative change (95% CI)†	Geo, LS mean†	95% CI	*P* value*		
follow-up period‡, n (%)												
Microhaematuria reduction over 24 months - OR§ (95% CI) Kinpeygo 16 mg/day vs. placebo	Kinpeygo 16 mg/day vs placebo						2.5		1.6 to 4.1	0.0001		Lafayette et al, 2023[104]; Lafayette *et al*, 2023, Supplementary Appendix[93]

*Treatment in addition to RAS inhibition; the primary endpoint was calculated as a time-weighted average of log-eGFR baseline ratio of measurements at each post-baseline visit compared to baseline for Month 3, 6, 9, 12, 18, and 24, respectively, where recordings made at 18 and 24 months received twice as much weight as those made at 3, 6, 9, and 12 months. Data included at baseline and 24 months are the log of the geometric mean of the 2 replicate values recorded at each time point, respectively. All patients in the Part B FAS are included in the robust regression analysis, with data multiply imputed, either implicitly or explicitly, prior to analysis. Mean changes in eGFR averaged over the 2-year period of treatment and observation were derived directly from the robust regression analysis performed on the log scale. Mean change from baseline = baseline geometric mean for the total across both treatment arms × (geometric LS mean of ratio of time-weighted average over 2 years compared to baseline for each treatment arm – 1); **Excluding data observed after receiving rescue medication; †Data not log-transformed prior to analysis. Actual time measurements were included in the model as a continuous variable and any unscheduled values were included in the model at the actual time they were recorded. The average of the two baseline eGFR values recorded per patient was included and assigned a time value of 0. The two repeat measurements at month 24 were included as separate observations, using the actual time measurements. After exclusion of data impacted by rescue medication, no missing data were imputed; ‡Analysis based on multiply imputed log-transformed eGFR values at 2 years. Mean changes were annualised (i.e., divided by 2) to provide the change from baseline per year in each treatment arm and the difference between Kinpeygo and placebo in 2-year eGFR slope per year; eGFR was calculated by the central laboratory using the CKD-EPI formula. Abbreviations: AUC, area under the curve; CI, confidence interval; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; eGFR, estimated glomerular filtration rate; FAS, full analysis set; LS, least squares; RAS, renin-angiotensin system, UACR, urine albumin-to-creatinine ratio; UPCR, urine protein-to-creatinine ratio

Source: Lafayette *et al*, 2023;[104] DOF (NEF-301 Part B CSR)[5], Supplementary Appendix[93]

B.1.1.2 Results table - UPCR ≥1.5 g/g subgroup (relevant for this assessment)

Table 65. Results of NefIgArd Phase III NEF-301 – Part B (NCT:03643965) – UPCR ≥1.5 g/g subgroup

Results of NefIgArd NEF-301 (Part B; NCT: 03643965) UPCR ≥1.5 g/g subgroup													
					Estimated absolute difference in effect			Estimated relative difference in effect				Description of methods used for estimation	References
Outcome		Study arm	N	Result (95 % CI)	Absolute change (SEM), g/g	95% CI	*P* value	Relative change (95% CI)†	Geo, LS mean†	95% CI	*P* value*		
[redacted]	[redacted]	Kinpeygo 16 mg/day	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	See Section 3.7.1	DOF (NEF-301 Part B additional tables and figures)[17]
		Placebo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	See Section 3.7.1	
	[redacted]	Kinpeygo 16 mg/day			[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	See Section 3.7.1	

Results of NefIgArd NEF-301 (Part B; NCT: 03643965) UPCR ≥1.5 g/g subgroup													
					Estimated absolute difference in effect			Estimated relative difference in effect				Description of methods used for estimation	References
Outcome		Study arm	N	Result (95 % CI)	Absolute change (SEM), g/g	95% CI	*P* value	Relative change (95% CI)†	Geo, LS mean†	95% CI	*P* value*		
	[redacted]	vs placebo		N/A	N/A	N/A	N/A	N/A				See Section 3.7.1	
	[redacted]	Kinpeygo 16 mg/day	[redacted]		[redacted]	[redacted]		[redacted]	[redacted]	[redacted]	[redacted]	See Section 3.7.1	DOF (NEF-301 Part B additional tables and figures)[17]
		Placebo	[redacted]		[redacted]	[redacted]			[redacted]	[redacted]	[redacted]	See Section 3.7.1	
[redacted]		Kinpeygo 16 mg/day*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	See Section 3.7.1	DOF (NEF-301 Part B additional tables and figures)[17]
		Placebo*	[redacted]	[redacted]				[redacted]	[redacted]	[redacted]	[redacted]	See Section 3.7.1	

Results of NefIgArd NEF-301 (Part B; NCT: 03643965) UPCR ≥1.5 g/g subgroup												
				Estimated absolute difference in effect			Estimated relative difference in effect				Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (95 % CI)**	**Absolute change (SEM), g/g**	**95% CI**	***P* value**	**Relative change (95% CI)†**	**Geo, LS mean†**	**95% CI**	***P* value***		
Composite endpoint of time from randomisation to confirmed 30% eGFR reduction or kidney failure, overall and by UPCR subgroup	Kinpeygo 16 mg/day	65	12 (18%)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	See Section 3.7.1	Lafayette *et al*, 2023[104]
-Number (%) of patients with confirmed 30 % eGFR reduction or kidney failure**	Placebo	64	23 (36%)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	See Section 3.7.1	Lafayette *et al*, 2023[104]

Results of NefIgArd NEF-301 (Part B; NCT: 03643965) UPCR ≥1.5 g/g subgroup												
				Estimated absolute difference in effect			Estimated relative difference in effect				Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (95 % CI)**	**Absolute change (SEM), g/g**	**95% CI**	***P* value**	**Relative change (95% CI)†**	**Geo, LS mean†**	**95% CI**	***P* value***		
(Part B FAS)												
Composite endpoint of time from randomisation to confirmed 30% eGFR reduction or kidney failure, overall and by UPCR subgroup -HR (95% CI) (Part B FAS				N/A	N/A	N/A	N/A	N/A	N/A	N/A	See Section 3.7.1	Lafayette *et al*, 2023[104]
	Kinpeygo 16 mg/day vs placebo		0.42 (0.21 to 0.83)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	See Section 3.7.1	Lafayette *et al*, 2023[104]

[redacted]

*Treatment in addition to RAS inhibition

[redacted]

[redacted]

Abbreviations: AUC, area under the curve; CI, confidence interval; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; eGFR, estimated glomerular filtration rate; FAS, full analysis set; LS, least squares; RAS, renin-angiotensin system; UPCR, urine protein-to-creatinine ratio
Source: DOF (NEF-301 Part B additional tables and figures)[17]

B.1.1.3 Additional information – full trial population

The first three sub sections (B.1.1.3.1 to B.1.1.4.1.1) shows additional results information for the full trial population, and sections B.1.1.2 to B.1.1.5.1 show information for the population relevant for this assessment, i.e., patients with UPCR ≥1.5 g/g.

B.1.1.3.1 Primary outcome: AUC-eGFR (time weighted average of eGFR over 2 years)

The primary efficacy endpoint of time-weighted average of eGFR over 2 years (see Figure 24) was met for the full trial (Part B analysis).[104] The time-weighted average of eGFR over 2 years showed a statistically significant [redacted] treatment benefit with Kinpeygo 16 mg/day versus placebo [redacted], Table 66. Over 2 years, eGFR was on average 5.05 mL/min/1.73 m^2 higher (95% CI 3.24 to 7.38) with Kinpeygo compared with placebo ($p<0.0001$).[5] The time-weighted average change reported with Kinpeygo was –2.47 mL/min per 1.73 m^2 (95% CI –3.88 to –1.02) and reported with placebo was –7.52 mL/min per 1.73 m^2 (95% CI –8.83 to –6.18).[104]

Data impacted by rescue medication were excluded from the primary analysis of eGFR over 2 years. Results of supplementary analyses that included all data recorded after the use of rescue medication or prohibited immunosuppressive medications and other sensitivity analyses were consistent with the primary analysis.[104]

The 2-year eGFR treatment effects were highly consistent across all evaluated subgroups (see Figure 24). For the primary timeweighted average of eGFR over 2 years, all numerical differences observed across subgroups were consistent with that expected due to random variability, with all interaction tests non-significant ($p>0.10$, including baseline levels of UPCR assessed on a continuous scale [$p=0.8769$]). An additional analysis of the time-weighted average of eGFR over 2 years by region indicated there was no meaningful variation between the main geographical regions.[93]

Kinpeygo treatment did not change the amount of creatinine excreted in the urine compared with placebo, indicating no evidence of a sarcopenic (muscle wasting) effect.[104]

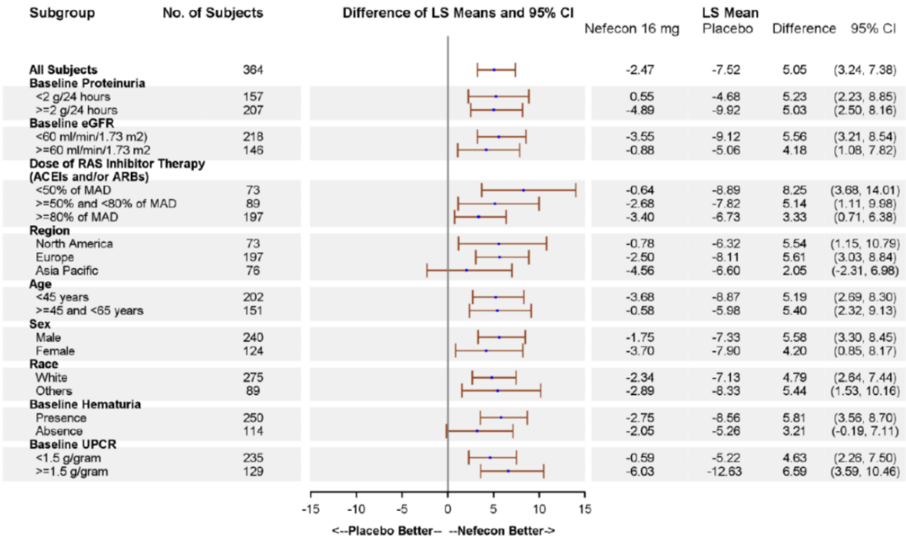
Table 66. Analysis of eGFR time weighted average of eGFR over 2 years in NefIgArd (Part B FAS)

	Kinpeygo 16 mg/day* n=182	Placebo* n=182
Ratio of geometric LS mean time weighted average of eGFR over 2 years (95% CI)	[redacted]	[redacted]
Mean change from baseline in eGFR averaged over 2 years (mL/min/1.73 m^2) (95% CI)	−2.47 (−3.88 to −1.02)	−7.52 (−8.83 to −6.18)
Kinpeygo vs. placebo		
Ratio of geometric LS means (95% CI)	[redacted]	
Average difference in eGFR over 2 years (mL/min/1.73 m^2) (95% CI)	5.05 (3.24 to 7.38)	
p value	p<0.0001	

*Treatment in addition to RAS inhibition; the primary endpoint was calculated as a time-weighted average of log-eGFR baseline ratio of measurements at each post-baseline visit compared to baseline for Month 3, 6, 9, 12, 18, and 24, respectively, where recordings made at 18 and 24 months received twice as much weight as those made at 3, 6, 9, and 12 months. Data included at baseline and 24 months are the log of the geometric mean of the 2 replicate values recorded at each time point, respectively. All patients in the Part B FAS are included in the robust regression analysis, with data multiply imputed, either implicitly or explicitly, prior to analysis. Mean changes in eGFR averaged over the 2-year period of treatment and observation were derived directly from the robust regression analysis performed on the log scale. Mean change from baseline = baseline geometric mean for the total across both treatment arms × (geometric LS mean of ratio of time-weighted average over 2 years compared to baseline for each treatment arm – 1)

Abbreviations: AUC, area under the curve; CI, confidence interval; eGFR, estimated glomerular filtration rate; FAS, full analysis set; LS, least squares; RAS, renin-angiotensin system
Source: Lafayette *et al*, 2023;[104] DOF (NEF-301 Part B CSR)[5]

Figure 24. Subgroups summary of time-weighted average of eGFR over 2 years using robust regression analysis (Part B FAS)



Interaction p values were 0.7133 for baseline proteinuria, 0.4760 for baseline eGFR, 0.3293 for dose of RAS inhibitor therapy, 0.6924 for region, 0.7386 for age, 0.8918 for sex, 0.5278 for race, 0.3743 for baseline haematuria, and 0.3586 for baseline UPCR (<1.5 g/g vs ≥1.5 g/g). Baseline haematuria was analysed *post hoc*
Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II type I receptor blocker; CI, confidence interval; eGFR, estimated glomerular filtration rate; LS, least squares; MAD, maximum allowable dose; RAS, renin-angiotensin system; UPCR, urine protein-creatinine ratio
Source: Lafayette *et al*, 2023, Supplementary Appendix[93]

B.1.1.4 Additional information - UPCR ≥ 1.5 g/g subgroup (relevant for this assessment)

B.1.1.4.1 Secondary outcomes and supportive analysis

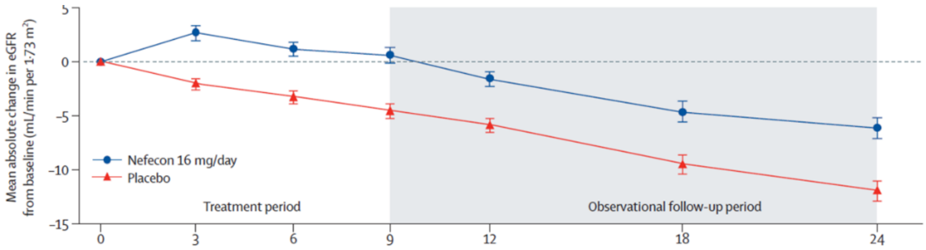
B.1.1.4.1.1 Mean absolute change in eGFR from baseline

As shown in Figure 25, the eGFR benefit accrued by the end of 9 months of treatment with Kinpeygo was maintained during the 15 months of observational follow-up.[104]

At 9 months, Kinpeygo significantly improved the mean absolute change in eGFR from baseline with a difference versus placebo of 5.21 mL/min/1.73 m^2 (95% CI 3.35 to 7.58); (Kinpeygo: 0.66, 95% CI –0.80 to 2.15; versus placebo: −4.56, 95% CI –5.86 to –3.22), providing a treatment effect of [redacted].[5, 104]

The absolute difference in eGFR between Kinpeygo and placebo continued to numerically improve up to 24 months to 5.89 mL/min/1.73 m^2 (95% CI 3.35 to 9.15); (Kinpeygo: −6.11, 95% CI: –8.04 to –4.11, versus placebo: −12.00, 95% CI: –13.76 to –10.15), providing a treatment effect of [redacted].[5, 104]

Figure 25. Mean absolute change in eGFR from baseline to 24 months (Part B FAS)



	0	3	6	9	12	18	24
Nefecon, n	182	171	167	167	153	155	149
Placebo, n	182	178	171	164	161	150	146
Mean absolute change (95% CI) from baseline, mL/min per 1·73 m²							
Nefecon 16 mg/day		2·76 (1·62 to 3·93)	1·22 (−0·08 to 2·54)	0·66 (−0·80 to 2·15)	−1·52 (−2·96 to −0·03)	−4·59 (−6·46 to −2·66)	−6·11 (−8·04 to −4·11)
Placebo		−2·04 (−3·07 to −0·98)	−3·28 (−4·48 to −2·04)	−4·56 (−5·86 to −3·22)	−5·85 (−7·16 to −4·51)	−9·50 (−11·21 to −7·72)	−12·00 (−13·76 to −10·15)
Mean absolute difference (95% CI), mL/min per 1·73 m²							
Nefecon 16 mg/day vs placebo		4·80 (3·32 to 6·70)	4·49 (2·79 to 6·61)	5·21 (3·35 to 7·58)	4·33 (2·44 to 6·66)	4·90 (2·43 to 7·96)	5·89 (3·35 to 9·15)

Estimated geometric mean % change (and SE) was calculated from a mixed-effects model for repeated measures of log-transformed post-baseline to baseline ratios at 3, 6, 9, 12, 18, and 24 months. Data included at baseline and 24 months are the log of the geometric mean of the two replicate values recorded at each timepoint, respectively. The corresponding percentage % and CI was derived from (1 – ratio of geometric LSM) × 100; eGFR was calculated by the central laboratory with the Chronic Kidney Disease Epidemiology Collaboration formula
Abbreviations: eGFR, estimated glomerular filtration rate; FAS, full analysis set
Source: Lafayette *et al*, 2023[104]

B.1.1.5 Secondary outcomes and supportive analysis UPCR ≥1.5 g/g subgroup

B.1.1.5.1 Mean absolute change in eGFR from baseline for the baseline UPCR ≥1.5 g/g subgroup

As shown in Figure 26, the eGFR benefit accrued by the end of 9 months of treatment with Kinpeygo was maintained during the 15 months of observational follow-up.[17]

At 9 months, Kinpeygo significantly improved the mean absolute change in eGFR from baseline with a difference versus placebo of [redacted].[17]

The absolute difference in eGFR between Kinpeygo and placebo continued to numerically improve up to 24 months to [redacted].[5]

Figure 26. Mean absolute change in eGFR from baseline to 24 months (Part B FAS – baseline UPCR ≥1.5 g/g subgroup)

[redacted]

[redacted]

B.1.2 NefIgArd Part A

Table 67 summarises additional definitions for efficacy endpoints. The main results per study are presented in Table 68.

Table 67 Additional definitions for efficacy outcome measures

Outcome measure	Time point*	Definition	How was the measure investigated/method of data collection
UACR [Included NefIgArd Part A + B]	Part A: 9 and 12 months Part B: 12 and 24 months	Part A: 1. Ratio of UACR at 9 months compared with baseline; supportive analyses of the above endpoints at time points up to 12 months Part B: 2. Ratio of UACR compared with baseline averaged over time points between 12 and 24 months **Definition of UACR** Reducing proteinuria (assessed by measuring proteinuria over 24 hour, UPCR, and/or UACR) slows the progression of CKD and is accepted as a surrogate endpoint for improved outcomes in IgAN by KDIGO and the FDA.[24, 29, 37] UPCR and UACR measured from early morning samples are accepted as simple measurements of proteinuria.[37]	1. Average over time points between 12 and 24 months, inclusive, following the first dose of study drug The secondary endpoints that assess time-averaged parameters (UPCR and UACR) between 12 and 24 months were log-transformed prior to analysis and were analyzed using a MMRM model with separate visit terms for 3, 6, 9, 12, 18, and 24 months. The visits at 12, 18, and 24 months were given equal weight to obtain the geometric mean treatment effect averaged over these time points.
Time to receiving rescue medication in days [NefIgArd Part B]		Time from the first dose of study drug until receiving rescue medication. Time from the first dose of study drug until receiving rescue medication (not counting visit-level exclusions).	Analysed using a Cox Regression Model, included terms for treatment, log-baseline UPCR, log-baseline eGFR, and geographic region as defined in the stratification variable. The HR was estimated together with the associated 95% CI and p-value, with the CI estimated using a profile-likelihood approach and the p-values from a likelihood-ratio test. The Efron approach to tie-

Outcome measure	Time point*	Definition	How was the measure investigated/method of data collection
			handling was used. In addition, the proportion of patients who received rescue medication by Months 9, 12, 18, and 24 was summarized.
Quality of life assessment [NefIgArd Part B]	Part B: 9 and 24 months	SF-36 at 9 and 24 months. There are 36 questions in the SF-36 v2 survey, each of which are grouped into 1 of 8 subscales: physical functioning, role limitations due to physical health, bodily pain, general health perceptions, vitality, social functioning, role limitations due to emotional problems, and mental health.	The mean re-coded score for each of the 8 subscales, overall physical and mental health scores, was summarized by treatment group at baseline and 9, 18, and 24 months.

* Time point for data collection used in analysis (follow up time for time-to-event measures)
Abbreviations: AUC, area under the curve, CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; eGFR, estimated glomerular filtration rate; UACR, urine albumin-to-creatinine ratio; UPCR, urine protein-to-creatinine ratio
Source: DOF (NEF-301 CSR)[11]; Barratt *et al*, 2023[92], Lafayette *et al*, 2023, Supplementary Appendix;[93] DOF (NEF-301 Part B CSR)[5]

Table 68. Results of NefIgArd Phase III NEF-301 – Part A (NCT:03643965)

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

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[redacted]

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[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

B.1.2.1 Efficacy results: NefIgArd Phase III trial (Part A)

NefIgArd is a multinational, randomised, double-blind, placebo-controlled, multicentre clinical trial (EudraCT: 2017-004902-16; NCT03643965) with a two-part design.[9, 11] The aim is to evaluate the efficacy, safety, and tolerability of oral Kinpeygo 16 mg/day compared with placebo in patients with primary IgAN treated with optimised RAS inhibition therapy.[9, 11] NefIgArd is being conducted across 155 nephrology clinics in 20 countries.[9] A placebo comparator was selected due to the lack of approved treatments for patients with IgAN at risk of progressing to ESRD.[11] Part A of the trial included 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).[11] The data cut-off (DCO) date for Part A was 5 October 2020.[11] A full description of the trial design is included in Appendix A, and an overview is provided in Table 11.

Regarding patients discontinuing treatment, in the Part A FAS, 9 (9.3%) patients in the Kinpeygo 16 mg group and 1 (1.0%) patient in the placebo group discontinued study treatment due to a TEAE (up until 14 days after the last dose of study treatment.[92] [redacted][157] See more information in Appendix E, Sections E.1.2.4 and E.1.2.7.3.

B.1.2.2 Kinpeygo efficacy in baseline UPCR ≥1.5 g/g subgroup

[redacted]

B.1.2.2.1 Improvement in proteinuria levels in baseline UPCR ≥1.5 g/g subgroup

[redacted]

Table 69. Analysis of the UPCR (g/g) at 9 months compared with baseline in baseline UPCR ≥1.5 g/g subgroup in NefIgArd Part A (FAS)

[redacted]

[redacted]

Table 70. Analysis of UPCR (g/g) at 3, 6, 9, and 12 months compared with baseline using MMRM for baseline UPCR ≥1.5 g/g subgroup in NefIgArd (Part A FAS)

[redacted]

Figure 27. Percentage change in UPCR (g/g) from baseline in baseline UPCR ≥1.5 g/g subgroup in NefIgArd (Part A FAS)*

[redacted]

B.1.2.2.2 Ratio of eGFR at 9 and 12 months compared with baseline in baseline UPCR ≥1.5 g/g subgroup

[redacted]

[redacted]

Table 71. Analysis of the ratio of eGFR (mL/min/1.73 m2) at 9 months compared with baseline in the baseline UPCR ≥1.5 g/g subgroup in NefIgArd (Part A FAS)

[redacted]

Table 72. Analysis of the ratio of eGFR (CKD-EPI) (mL/min/1.73 m2) at 3, 6, 9, and 12 months compared with baseline using robust regression in the baseline UPCR ≥1.5 g/g subgroup in NefIgArd (Part A FAS)

[redacted]

Figure 28. Percentage Change in eGFR (CKD-EPI) (mL/min/1.73 m2) from baseline in the baseline UPCR ≥1.5 g/g subgroup in NefIgArd (Part A FAS)*

[redacted]

B.1.2.3 Primary outcome: Change in UPCR

The primary efficacy endpoint was met at DCO for the Part A analysis (5 October 2020).[11] After 9 months of treatment, the ratio of UPCR compared with baseline was 0.69 for patients treated with Kinpeygo 16 mg/day and 0.95 for those who received placebo (see Table 73). As discussed in Section 3.1.3, proteinuria reduction is associated with lower risk of kidney function loss, progression to ESRD and mortality, and improved HRQoL in patients with IgAN or CKD.[24, 37, 43, 44, 158, 159]

Table 73. Analysis of the UPCR (g/g) at 9 months compared with baseline in NefIgArd Part A (full analysis set [FAS])

	Kinpeygo 16 mg/day* 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 with baseline (95% CI)	0.69 (0.61 to 0.79)	0.95 (0.83 to 1.08)
Corresponding % reduction (95% CI)	31% (21% to 39%)	5% (-8% to 17%)
Kinpeygo vs. placebo		
Ratio of geometric LS mean UPCR at 9 months (95% CI)	0.73 (0.61 to 0.88)	
Corresponding % reduction (95% CI)	27% (12% to 39%)	
p value	0.0003	

*Treatment in addition to RAS inhibition
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; RAS, renin-angiotensin system; UPCR, urine protein-to-creatinine ratio
Source: DOF (NEF-301 CSR)[11]

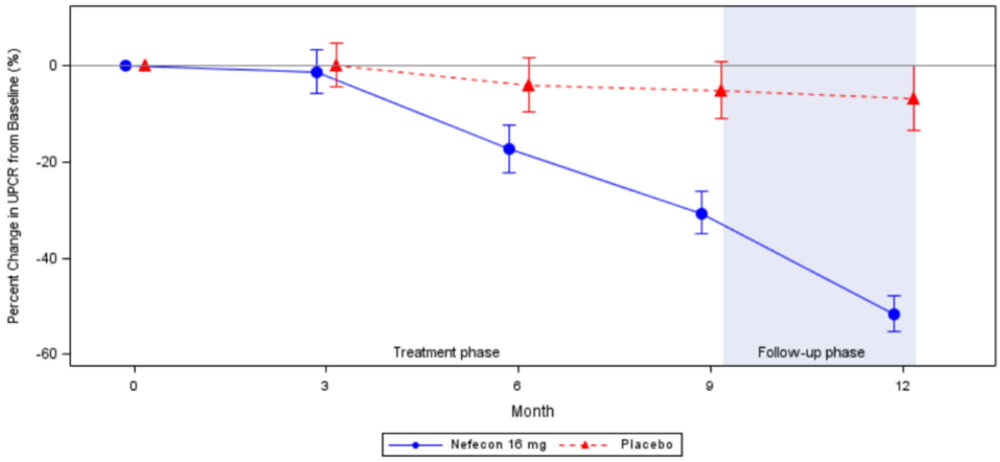
A reduction of UPCR from baseline with Kinpeygo 16 mg/day was seen at all timepoints (Table 74 and Figure 29).[11] After 3 and 6 months of treatment, UPCR was 1% (p=0.413) and 14% (p=0.398) lower, respectively for Kinpeygo 16 mg/day compared with placebo. At the 12-month timepoint (after 3 months of observational follow-up following the 9-month treatment period), UPCR was 48% lower with Kinpeygo 16 mg/day compared with placebo (p<0.0001).[11]

Table 74. Analysis of UPCR (g/g) at 3, 6, 9, and 12 months compared with baseline using MMRM in NefIgArd (Part A FAS)

Timepoint (n, n)	Comparison of Kinpeygo 16 mg/day vs. placebo* Ratio of geometric LS means (95% CI); p value	Corresponding % change (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%)

*Treatment in addition to RAS inhibition
Note: n=number of patients in each treatment group (Kinpeygo 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; RAS, renin-angiotensin system; UPCR, urine protein-to-creatinine ratio
Source: DOF (NEF-301 CSR)[11]

Figure 29. Percentage change in UPCR (g/g) from baseline in NefIgArd (Part A FAS)*



*Treatment in addition to RAS inhibition
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 two consecutive measurements prior to randomisation
FAS, full analysis set; LS, least squares; MMRM, mixed-effects model for repeated measures; RAS, renin-angiotensin system; UPCR, urine protein-to-creatinine ratio Source: DOF (NEF-301 CSR)[11]

The UPCR treatment effect was generally consistent across pre-defined subgroups (based on age, gender, region, baseline proteinuria, baseline eGFR and RAS inhibitor dose), indicating no differential treatment effect on UPCR at 9 months for any baseline characteristic.[11] An additional mixed-effects model for repeated measures analysis of UPCR at 9 months by region indicated there was no meaningful variation between the main geographical regions; the empirical shrinkage estimates were very consistent with the overall treatment effect from the primary analysis (the ratio of geometric least squares [LS] means for North America, South America, Europe, and Asia Pacific were 0.74, 0.74, 0.72, and 0.73, respectively).[11]

B.1.2.4 Secondary outcomes and supportive analysis

Results for other proteinuria endpoints provided supportive evidence for the efficacy of Kinpeygo 16 mg/day plus optimised RAS blockade.[11]

B.1.2.4.1 UACR at 9 and 12 months compared with baseline (secondary outcome and supportive analysis)

Consistent with the primary endpoint, after 9 months of treatment, patients treated with Kinpeygo 16 mg per day showed a statistically significant and clinically-relevant 31% reduction in UACR compared with placebo (95% CI 14% to 45%; p=0.0005). UACR at 9 months was reduced from baseline by 36% in patients treated with Kinpeygo 16 mg/day compared with 7% in patients treated with placebo. After 3 months of observational follow-up, a 54% reduction in UACR with Kinpeygo 16 mg was observed at 1 year compared with placebo (p<0.0001).

B.1.2.4.2 Ratio of eGFR at 9 and 12 months compared with baseline (secondary outcome)

After 9 months of treatment, a statistically significant and clinically-relevant benefit on eGFR was observed with Kinpeygo 16 mg/day compared with placebo (Table 75). Patients who received Kinpeygo 16 mg/day maintained kidney function during 9 months of treatment (0% eGFR change from baseline: 0.17 mL/min/1.73 m^2 decrease), whereas patients receiving placebo experienced a 7% deterioration in eGFR (4.04 mL/min/1.73 m^2 decrease versus baseline; p=0.0014).[11] The eGFR treatment effect continued for 3 months after stopping Kinpeygo, with a 7% eGFR treatment benefit (p=0.0106) versus placebo observed in patients who had received Kinpeygo 16 mg/day at 12.[11]

Table 75. Analysis of the ratio of eGFR (mL/min/1.73 m2) at 9 months compared with baseline in NefIgArd (Part A FAS)

	Kinpeygo 16 mg/day* 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 with baseline (95% CI)	1.00 (0.96 to 1.03)	0.93 (0.90 to 0.96)
Corresponding % change (95% CI)	0% (-4% to 3%)	-7% (-10% to -4%)
Kinpeygo vs. placebo		
Ratio of geometric LS mean eGFR at 9 months (95% CI)	1.07 (1.03 to 1.13)	
Corresponding % change (95% CI)	7% (3% to 13%)	
p value	0.0014	
Difference in absolute change (mL/min/1.73 m2)	3.87	

*Treatment in addition to RAS inhibition
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 m2 and subtracting from the baseline value of 55.69 mL/min/1.73 m2, 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; eGFR, estimated glomerular filtration rate; FAS, full analysis set; LS, least squares; RAS, renin-angiotensin system
Source: DOF (NEF-301 CSR)[11]

B.1.2.4.3 Decline in eGFR at 1-year eGFR (total slope; supportive analysis)

The decline in eGFR after 1 year was measured by the eGFR slope.[160] eGFR slope, with sufficient sample size and duration of measurement is a viable surrogate measurement for CKD progression.[91] A supportive analysis of 1-year eGFR total slope for the Part A FAS shows an improvement in slope of 3.37 mL/min/1.73 m^2 per year with Kinpeygo 16 mg/day compared with placebo (95% CI 0.49 to 6.25; p=0.0111).[11] This corresponds to a 1-year eGFR slope of -1.26 mL/min/1.73 m^2 per year in the Kinpeygo 16 mg/day group and of -4.63 mL/min/1.73 m^2 in the placebo group.[11] Therefore, the observed effect with Kinpeygo could be indicative of reduced risk of future progression to ESRD.

B.1.3 NefIgAN

B.1.3.1 Results table

Table 76. Results of NefIgAN Phase IIb trial NEF-202 (NCT: 01738035)

Results of NefIgAN NEF-202 (NCT01738035)												
				Estimated absolute difference in effect			Estimated relative difference in effect				Description of methods used for estimation	References
Outcome	Study arm	N	Result (SEM), g/g	Absolute change (SEM), g/g	95% CI	*P* value	Relative change (95% CI)†	Geo, LS mean†	95% CI	*P* value*		
UPCR absolute change from baseline at 9 months NefIgAN (FAS)	Kinpeygo 8mg/day		−0.187 (0.1042)	−0.212 (0.1408)	N/A	N/A	N/A	0.763	0.577, 1.009	0.0290	N/A	Fellström *et al*, 2017[59]
	Kinpeygo 16 mg/day		−0.237 (0.1092)	−0.262 (0.1448)	N/A	N/A	N/A	0.707	0.531, 0.942	0.0092	N/A	Fellström *et al*, 2017[59]
	Placebo		0.024 (0.1009)	N/A	N/A	N/A	N/A	N/A	N/A	Ref	N/A	Fellström *et al*, 2017[59]

Results of NefIgAN NEF-202 (NCT01738035)												
				Estimated absolute difference in effect			**Estimated relative difference in effect**				**Description of methods used for estimation**	**References**
Outcome	**Study arm**	**N**	**Result (SEM), g/g**	**Absolute change (SEM), g/g**	**95% CI**	***P* value**	**Relative change (95% CI)†**	**Geo, LS mean†**	**95% CI**	***P* value***		
24hr urine protein excretion – 9 months versus placebo	Kinpeygo 8mg/day		N/A	N/A	N/A	N/A	N/A	0.795	0.612, 1.033	0.0425	N/A	Fellström *et al*, 2017[59]
	Kinpeygo 16 mg/day		N/A	N/A	N/A	N/A	N/A	0.693	0.529, 0.907	0.0040	N/A	Fellström *et al*, 2017[59]
24hr urine protein excretion – 12 months versus placebo	Kinpeygo 8mg/day		N/A	N/A	N/A	N/A	N/A	0.764	0.613, 0.952	0.0085	N/A	Fellström *et al*, 2017[59]
	Kinpeygo 16 mg/day		N/A	N/A	N/A	N/A	N/A	0.619	0.492, 0.780	0.0000	N/A	Fellström *et al*, 2017[59]
UACR – 9 months	Kinpeygo 8mg/day		N/A	N/A	N/A	N/A	N/A	0.817	0.614, 1.087	0.0818	N/A	Fellström *et al*, 2017[59]

Results of NefIgAN NEF-202 (NCT01738035)													
				Estimated absolute difference in effect			Estimated relative difference in effect				Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (SEM), g/g**	**Absolute change (SEM), g/g**	**95% CI**	***P* value**	**Relative change (95% CI)†**	**Geo, LS mean†**	**95% CI**	***P* value***		
versus placebo	Kinpeygo 16 mg/day		N/A	N/A	N/A	N/A	N/A	0.676	0.502, 0.911	0.0053	N/A	Fellström *et al*, 2017[59]
UACR – 12 months versus placebo	Kinpeygo 8mg/day		N/A	N/A	N/A	N/A	N/A	0.72	0.556, 0.934	0.0068	N/A	Fellström *et al*, 2017[59]
	Kinpeygo 16 mg/day		N/A	N/A	N/A	N/A	N/A	0.622	0.473, 0.818	0.0004	N/A	Fellström *et al*, 2017[59]
24hr albumin excretion – 9 months versus placebo	Kinpeygo 8mg/day		N/A	N/A	N/A	N/A	N/A	0.798	0.596, 1.069	0.0646	N/A	Fellström *et al*, 2017[59]
	Kinpeygo 16 mg/day		N/A	N/A	N/A	N/A	N/A	0.656	0.484, 0.889	0.0035	N/A	Fellström *et al*, 2017[59]

Results of NefIgAN NEF-202 (NCT01738035)													
				Estimated absolute difference in effect			Estimated relative difference in effect				Description of methods used for estimation	References
Outcome	Study arm	N	Result (SEM), g/g	Absolute change (SEM), g/g	95% CI	*P* value	Relative change (95% CI)†	Geo, LS mean†	95% CI	*P* value*		
24hr albumin excretion – 12 months versus placebo	Kinpeygo 8mg/day		N/A	N/A	N/A	N/A	N/A	0.716	0.550, 0.932	0.0067	N/A	Fellström *et al*, 2017[59]
	Kinpeygo 16 mg/day		N/A	N/A	N/A	N/A	N/A	0.569	0.432, 0.751	0.000	N/A	Fellström *et al*, 2017[59]
eGFR mean % (and relative %) change at 9 months for Kinpeygo versus placebo	Kinpeygo 8 mg/day		N/A	−0.9	N/A	N/A	1.10 (1.02, 1.18)	1.099	1.021, 1.184	0.0064	N/A	Fellström *et al*, 2017[59]
	Kinpeygo 16 mg/day		N/A	0.6	N/A	N/A	1.12 (1.03, 1.205)	1.116	1.034, 1.205	0.0026	N/A	Fellström *et al*, 2017[59]
	Placebo		N/A	−9.8	N/A	N/A	N/A	N/A	N/A	Ref	N/A	Fellström *et al*, 2017[59]

Results of NefIgAN NEF-202 (NCT01738035)												
				Estimated absolute difference in effect			Estimated relative difference in effect				Description of methods used for estimation	References
Outcome	Study arm	N	Result (SEM), g/g	Absolute change (SEM), g/g	95% CI	*P* value	Relative change (95% CI)†	Geo, LS mean†	95% CI	*P* value*		
eGFR mean % (and relative %) change at 9 months for Kinpeygo versus placebo	Kinpeygo 8 mg/day		N/A	Not reported	N/A	N/A	Not reported	1.032	0.941, 1.133	0.2508	N/A	Fellström *et al*, 2017[59]
	Kinpeygo 16 mg/day		N/A	0.7	N/A	N/A	1.11 (1.01, 1.225)	1.114	1.013, 1.225	0.0134	N/A	Fellström *et al*, 2017[59]
	Placebo		N/A	−10.9	N/A	N/A	N/A	N/A		Ref	N/A	Fellström *et al*, 2017[59]

*Treatment in addition to RAS inhibition
†Geo LS mean and p value calculated versus placebo
Abbreviations: CI, confidence interval; FAS; full analysis set; eGFR, estimated glomerular filtration rate; Geo., geometric; LS, least square; N/A, not applicable; N/E, not estimated; RAS, renin-angiotensin system; Ref, reference; SEM, standard error of the LS means; UACR, urine albumin creatinine ratio; UPCR, urine protein creatinine ratio
Source: Fellström *et al*, 2017[59]

B.1.4 STOP-IgAN trial

B.1.4.1 Results table

Table 77. Results of STOP-IgAN (NCT00554502)

Results of STOP-IgAN NCT00554502													
					Estimated absolute difference in effect			Estimated relative difference in effect				Description of methods used for estimation	References
Outcome		Study arm	N	Result (95 % CI)	Absolute change	95% CI	*P* value	Odds ratio	Relative change	95% CI	*P* value*		
Full clinical remission at the end of the 3-year trial phase (protein-to-creatinine ratio <0.2 [with both protein and creatinine measured in grams] and a decrease in the estimated glomerular filtration rate [eGFR] of <5 ml per minute per 1.73 m2 of body-	Percentage of patients, %	Immunosuppressives* + SoC	82	17%	N/A	N/A	N/A	4.82	N/A	1.43-16.30	0.01	N/A	Rauen et al. 2015 [6]
		SoC	80	5%	N/A	N/A	N/A		N/A			N/A	
	Percentage of patients eGFR≥60 mL/min/1.73 m2 subgroup	Immunosuppressives* + SoC	82	5.5%	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	Rauen te al. 2018 [7]
		SoC	80	20.0%	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	
	Percentage of patients eGFR<60 mL/min/1.73 m2 subgroup	Immunosuppressives* + SoC	82	3.8%	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	Rauen te al. 2018 [7]
		SoC	80	11.1%	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	

Results of STOP-IgAN NCT00554502													
					Estimated absolute difference in effect			Estimated relative difference in effect				Description of methods used for estimation	References
Outcome		**Study arm**	**N**	**Result (95 % CI)**	**Absolute change**	**95% CI**	***P* value**	**Odds ratio**	**Relative change**	**95% CI**	***P* value***		
surface area from baseline).													
eGFR decrease of at least 15 mL/min/1.73 m²	Percentage of patients, %	Immunosuppressives* + SoC	82	28%	N/A	N/A	N/A	0.86	N/A	0.44 to 1.81	0.75	N/A	Rauen et al. 2015 [6]
		SoC	80	26%	N/A	N/A	N/A		N/A			N/A	
10-year follow-up (median 7.4 years), eGFR loss of >40% from baseline, progression to ESRD or death	Percentage of patients, %	Immunosuppressives* + SoC		45.5%	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	Rauen et al. 2020[77]
		SoC		50%	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	
	Hazard ratio (HR)	Immunosuppressives* + SoC vs. SoC		1.20	N/A	N/A	N/A	N/A	N/A	0.75 to 1.95	0.45	N/A	
Absolute eGFR change at 36		Immunosuppressives* + SoC	72	-4.2 ± 14.1	N/A	N/A	N/A	Not determined	N/A	N/A	0.32	N/A	Rauen et al. 2015 [6]

Results of STOP-IgAN NCT00554502													
				Estimated absolute difference in effect			**Estimated relative difference in effect**				**Description of methods used for estimation**	**References**
Outcome	**Study arm**	**N**	**Result (95 % CI)**	**Absolute change**	**95% CI**	***P* value**	**Odds ratio**	**Relative change**	**95% CI**	***P* value***		
months – ml/min/1.73m^2	SoC	71	-4.7 ± 12.3	N/A	N/A	N/A	Not determined	N/A	N/A		N/A	
Mean annual change in the slope of the reciprocal of serum creatinine concentration – mg/dL	Immunosuppressives* + SoC	74	-0.01 ± 0.06	N/A	N/A	N/A	Not determined	N/A	N/A	0.60	N/A	Rauen et al. 2015 [6]
	SoC	77	-0.02 ± 0.06	N/A	N/A	N/A	Not determined	N/A	N/A		N/A	
Mean annual change in the slope of the reciprocal of serum creatinine concentration – mg/dL – <u>12 months</u>	Immunosuppressives* + SoC	59	0.57 ± 0.53	N/A	N/A	N/A	Not determined	N/A	N/A	0.01	N/A	Rauen et al. 2015 [6]
	SoC	67	0.80 ± 0.67	N/A	N/A	N/A	Not determined	N/A	N/A		N/A	

Results of STOP-IgAN NCT00554502												
				Estimated absolute difference in effect			**Estimated relative difference in effect**				**Description of methods used for estimation**	**References**
Outcome	**Study arm**	**N**	**Result (95 % CI)**	**Absolute change**	**95% CI**	***P* value**	**Odds ratio**	**Relative change**	**95% CI**	***P* value***		
Mean annual change in the slope of the reciprocal of serum creatinine concentration – mg/dL – 36 months	Immunosuppressives* + SoC	59	0.76 ± 0.90	N/A	N/A	N/A	Not determined	N/A	N/A	0.66		Rauen et al. 2015 [6]
	SoC	64	0.85 ± 0.66	N/A	N/A	N/A	Not determined	N/A	N/A			
eGFR decrease ≥ 30ml/min/1.73m^2	Immunosuppressives* + SoC	78	10 (13)	N/A	N/A	N/A	1.45	N/A	0.51-4.10	0.49		Rauen et al. 2015 [6]
	SoC	76	7 (9)	N/A	N/A	N/A		N/A				
Onset of end-stage renal disease	Immunosuppressives* + SoC	78	6 (8)	N/A	N/A	N/A	0.97	N/A	0.29-3.22	0.96		Rauen et al. 2015 [6]
	SoC	76	6 (8)	N/A	N/A	N/A		N/A				

Results of STOP-IgAN NCT00554502												
				Estimated absolute difference in effect			Estimated relative difference in effect				Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (95 % CI)**	**Absolute change**	**95% CI**	***P* value**	**Odds ratio**	**Relative change**	**95% CI**	***P* value***		
Disappearance of microhematura	Immunosuppressives* + SoC	57†	24 (42)	N/A	N/A	N/A	3.73	N/A	1.52-9.14	0.004		Rauen et al. 2015 [6]
	SoC	55†	9 (16)	N/A	N/A	N/A		N/A				

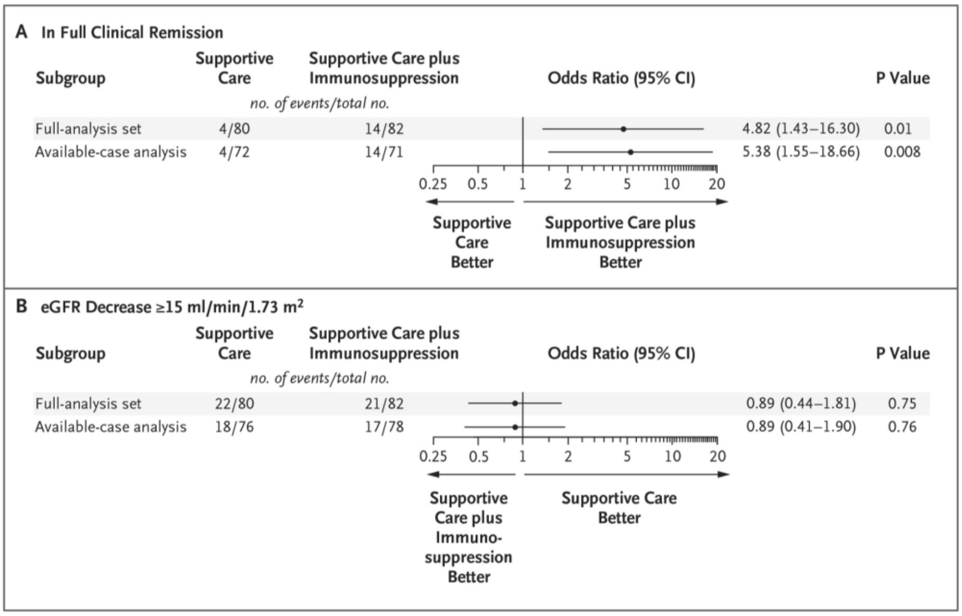
*Patients randomly assigned to the immunosuppression group who had an eGFR ≥60 mL/min/1.73 m^2 received glucocorticoid monotherapy for 6 months (intravenous [IV] methylprednisolone 1 g/day for three days at the start of months 1, 3, and 5, and oral prednisolone 0.5 mg/kg/48 hours on the other days). Patients with an eGFR 30–59 mL/min/1.73 m^2 received cyclophosphamide 1.5 mg/kg/day for three months, followed by azathioprine 1.5 mg/kg/day during months 4–36, plus oral prednisolone 40 mg/day, tapered to 10 mg/day, over the first three months of the study, 10 mg/day during months 4–6, and 7.5 mg/day during months 7–36)[77]

†A total of 67 patients in the supportive care (SoC) group and 74 patients in the immunosuppression group had microhematuria at baseline.

Abbreviations: CI, confidence interval; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; HR, hazard ratio; OR, odds ratio

B.1.4.1.1 Primary outcome: Decrease in the eGFR of at least 15 ml per minute per 1.73 m2 from the baseline eGFR

Figure 30. Primary End Points



Panel A shows the first primary end point: full clinical remission at the end of the 3-year trial phase (protein-to-creatinine ratio <0.2 [with both protein and creatinine measured in grams] and a decrease in the estimated glomerular filtration rate [eGFR] of <5 ml per minute per 1.73 m2 of body-surface area from baseline). Panel B shows the second primary end point: a decrease in the eGFR of at least 15 ml per minute per 1.73 m2 during the trial phase. A subgroup analysis was performed for both end points with the use of a full-analysis set and an available-case analysis set. In the full-analysis set, missing values in all events in all patients who underwent randomization were substituted by the worst clinical case (i.e., no clinical remission and decrease in the eGFR of at least 15 ml per minute per 1.73 m2); in the available-case analysis set, only documented events among patients with available data were included in the analysis.

B.1.4.1.2 Secondary outcomes

No significant differences were observed between the supportive-care group and the immunosuppression group at the end of the trial phase with respect to the mean absolute change in eGFR, the mean annual change in the slope of the reciprocal of serum creatinine concentration, the number of patients with a decrease in the eGFR of at least 30 ml per minute per 1.73 m^2, and the number of patients with the onset of end-stage renal disease (**Table 2**).

Twelve months after randomization, patients in the immunosuppression group had a significantly lower mean proteinuria level than did those in the supportive-care group (**Table 2**). At month 36, the difference was no longer significant. Microhematuria, as assessed by means of a urine dipstick or sediment test, was noted in 87% of the patients at baseline (67 in the supportive-care group and 74 in the immunosuppression group). Among these patients, microhematuria was no longer present in 9 in the supportive-care group and in 24 in the immunosuppression group at the end of the study (P=0.004). In the immunosuppression group, more patients receiving glucocorticoid monotherapy than those receiving combination immunosuppressive therapy had remission of proteinuria, hematuria, or both.

Figure 31. Secondary End Points on the Basis of the Analysis of Available Cases at the End of the Trial Phase

Secondary End Point	Supportive Care (N=80)		Supportive Care plus Immunosuppression (N=82)		Odds Ratio (95% CI)	P Value
	Patients with Available Data	End-Point Value	Patients with Available Data	End-Point Value		
	no.	*mean ±SD or no. (%)*	*no.*	*mean ±SD or no. (%)*		
Absolute eGFR change at 36 mo — ml/min/1.73 m^2	71	−4.7±12.3	72	−4.2±14.1	Not determined	0.32
Mean annual change in the slope of the reciprocal of serum creatinine concentration — mg/dl	77	−0.02±0.06	74	−0.01±0.06	Not determined	0.60
At 12 mo	67	0.80±0.67	59	0.57±0.53	Not determined	0.01
At 36 mo	64	0.85±0.66	59	0.76±0.90	Not determined	0.66
eGFR decrease ≥30 ml/min/1.73 m^2	76	7 (9)	78	10 (13)	1.45 (0.51–4.10)	0.49
Onset of end-stage renal disease	76	6 (8)	78	6 (8)	0.97 (0.29–3.22)	0.96
Disappearance of microhematuria	55†	9 (16)	57†	24 (42)	3.73 (1.52–9.14)	0.004

*To convert the values for serum creatinine to micromoles per liter, multiply by 88.4
†A total of 67 patients in the supportive-care group and 74 patients in the immunosuppression group had microhematuria at baseline

Appendix C. Comparative analysis of efficacy

Table 78. Comparative analysis of studies comparing Kinpeygo to corticosteroids (incl. prednisolone) for patients with primary IgAN in adults at risk of rapid disease progression with a UPCR ≥1.5 g/g

Outcome		Absolute difference in effect			Relative difference in effect			Method used for quantitative synthesis	Result used in the health economic analysis?
	Studies included in the analysis	Difference	CI	P value	Difference	CI	P value		
MD in CFB to 24 months in eGFR (RE model)	Barratt 2022 [161] Rauen 2015 [123]	N/A	N/A	N/A	6.21	-1.49, 13.77	N/A	The outcomes is presented as relative treatment effects. Relative effects are represented by the treatment difference, i.e. mean difference (MD) in CFB to 24 months between each comparator. Uncertainty is represented by 95% CrI, which are presented alongside the estimated treatment effects.	Yes

Abbreviations: CFB, change from baseline; CrI, credible interval; CS, corticosteroid; IST, immunosuppressive therapy; MD, mean difference; RE, random-effects; TRF, targeted-release formulation

Notes: NMA results are presented as the median and 95% CrI; results are interpreted as the MD between the therapy in the respective row versus the therapy in the respective column; bold denotes statistical significance at 5% level; green shading represents an improved treatment-effect (MD>0 for eGFR) for the comparator in the row versus the therapy in the respective column; orange shading represents a worse treatment-effect (MD<0 for eGFR) for the comparator in the row versus the therapy in the respective column. Studies included in the network are as follows: NefIgArd and STOP-IgAN.
*Posterior probability that Kinpeygo is superior to comparator (MD>0 for eGFR).

C.1 Indirect treatment comparison

Table 79. Statistical methods overview in the ITC

Statistics methods overview	
Overview of data	A total of 51 individual publications, representing 41 unique studies were identified for inclusion in the SLR (completed in March 2023). To serve as a reliable comparator to Kinpeygo and be reflective of current clinical practice, patients were required to be receiving appropriate RAS inhibitor regimen. In the NefIgArd trial, optimised supportive care required that patients receive the maximum tolerated or maximum allowed (country-specific) dose of an angiotensin-converting enzyme inhibitor (ACEI) and/or an angiotensin receptor blocker (ARB) for at least 3 months prior to randomisation. Therefore, priority studies were defined as those where patients were receiving supportive care with RAS inhibitor(s) (ACEI and/or ARB) prior study commencement for any time period. A total of 12 publications, representing eight unique studies, fulfilled this criteria for prioritisation. Only STOP-IgAN[6] was considered relevant to Danish practice, because this comprised a population generalizable to Denmark and patients were treated with prednisolone. TESTING [57, 79] and Li 2022 [34], by contrast, comprised a primarily Asian population and used methylprednisolone, so they were not considered relevant to Danish clinical practice and thus not included in the ITC.
Treatment regimens and comparator	Corticosteroids (prednisolone) Clinicians confirmed that first-line treatment of IgAN in Denmark comprises blood pressure management by prescription of maximally tolerated dose of RAS blockers and lifestyle modifications, consistent with the KDIGO guidelines.[29, 64] Therefore, the control arm in all studies in the ITC had to include: placebo in addition to blood pressure management by prescription of maximally tolerated dose of RAS blockers and lifestyle modifications.
Populations	The analyses were informed by a cohort from Part B of the NefIgArd trial who had a baseline UPCR of ≥1.5 g/g (which is the indicated population).[115] However, the ITT population from all comparator studies was evaluated in all networks in the absence of results reported for UPCR ≥1.5 g/g subgroup. It is important to note that no studies except NefIgArd reported data for this subpopulation and therefore there are no study populations homogenous to the NefIgArd trial.
Outcomes	eGFR. Consistent with the analyses conducted using data related to the CFB to 12 months, ITC analyses are limited to changes in renal function as measured by **eGFR** and are informed by data related to the CFB to 24 months.
Statistical model	**Bayesian NMA** See Section 7.1.2. **Population-adjusted indirect comparison - MAIC** As a supplementary approach to evidence synthesis, a form of population-adjusted indirect comparisons has been explored. Specifically, MAIC analyses have

	been conducted for the efficacy outcome (eGFR), using individual patient data (IPD) from Part B of the NefIgArd trial. (i.e. patients with baseline UPCR ≥ 1.5 g/g). Methodology adopted for the MAIC is in line with the approach outlined by Phillippo 2018 and is consistent with recommendations in the NICE guidance published by the DSU in TSD.[162, 163]
Presentation of results	For each analysis, a network diagram (with study labels) is presented as well as a forest plot showing treatment effects of Kinpeygo versus each comparator, supplemented with a table of all pairwise treatment comparisons (represented by the median and 95% credible interval [CrI] from the posterior distribution). **NMA** • Relative effects are represented by the treatment difference, i.e. mean difference (MD) in CFB to 24 months between each comparator. Relative treatment effects are presented as well as the probability of superiority of Kinpeygo. • The probability of superiority of Kinpeygo has also been estimated from the NMA, and is based on the probability of the MD between Kinpeygo versus each comparator being less than zero (for analysis of UPCR) or greater than zero (for analysis of eGFR), which has been calculated using the posterior distribution (i.e. 10,000 CODA samples). **MAIC** • Baseline characteristics are reported for the NefIgArd trial as well as each comparator study under investigation, including STOP-IgAN. • A summary of the population characteristics (represented by the mean or percentage for each factor) are presented for both unadjusted (unweighted) and weighted NefIgArd trial data. • Relative effects are represented by the treatment difference, i.e. MD in CFB to 24 months between Kinpeygo and each comparator under investigation. A comparison analogous to a Bucher approach has been performed to estimate the treatment-effects, which are presented using both unadjusted (unweighted) and weighted NefIgArd trial data. • An assessment of the MAIC performance has been included, by reporting the effective sample size (ESS) after weighting (the ESS is the number of independent non-weighted individuals that would be required to give an estimate with the same precision as the weighted sample estimate), as well as exploring the distributions of the weights (through the use of histograms) to help identify any outliers after matching.[162]

C.1.1 Statistical methods

C.1.1.1 Overview of data

Studies

A total of 51 individual publications, representing 41 unique studies were identified for inclusion in the SLR (completed in March 2023). To serve as a reliable comparator to Kinpeygo and be reflective of current clinical practice, patients were required to be receiving appropriate RAS inhibitor regimen. In the NefIgArd trial, optimised supportive care required that patients receive the maximum tolerated or maximum allowed (country-specific) dose of an angiotensin-converting enzyme inhibitor (ACEI) and/or an angiotensin receptor blocker (ARB) for at least 3 months prior to randomisation. Therefore, priority studies were defined as those where patients were receiving supportive care with RAS inhibitor(s) (ACEI and/or ARB) prior study commencement for any time period. A total of 12 publications, representing eight unique studies, fulfilled this criteria for prioritisation. Note: these eight studies were evaluated in the ITC feasibility assessment and were discussed with UK clinicians to understand suitability for an ITC relevant to UK clinical practice. The results from the ITC is deemed to be relevant also for the Danish clinical practice, since it is similar between the countries.[79, 123, 164-166]

A network could be constructed using data from studies relevant to UK clinical practice, however, there were observed differences between studies in regard to baseline characteristics. Differences in key baseline characteristics across studies may introduce heterogeneity into the evidence base and may undermine the robustness of an NMA (which relies on the assumption of homogeneity); NMA relies on the underlying assumption that included studies are sufficiently homogenous in terms of the included participants.[167]

Treatment regimens and treatment setting

Kinpeygo was evaluated in two studies – NefIgArd (phase 3 trial comparing Kinpeygo versus placebo) and NefIgAN (Fellström 2017) (three-arm phase 2b trial also comparing Kinpeygo at two different doses versus placebo), however, the phase 2b study only reported data until 12 months post-baseline.[92] For the purposes of the NMA, only data for the higher dose (Kinpeygo 16 mg/day) were evaluated and were based on the subgroup of patients with baseline UPCR ≥1.5 g/g, in line with the marketing authorisation (MA) and indicated dose.[115]

Clinicians confirmed that first-line treatment of IgAN in Denmark comprises blood pressure management by prescription of maximally tolerated dose of RAS blockers and lifestyle modifications, consistent with the KDIGO guidelines.[168] Therefore, the control arm in all studies in the ITC had to include: placebo in addition to blood pressure management by prescription of maximally tolerated dose of RAS blockers and lifestyle modifications.

DAPA-CKD was considered relevant to the UK treatment pathway, despite uncertainties whether RASI dosage was proactively maximised.[169] This is because SGLT-2 inhibitors are expected to become part of best supportive care for IgAN as a first-line therapy [170].

Only STOP-IgAN was considered relevant to Danish practice, because this comprised a population generalisable to Denmark and patients were treated with prednisolone. TESTING and Li 2022, by contrast, comprised a primarily Asian population and used methylprednisolone, so were not considered relevant to Danish clinical practice. Additionally, Li 2022 did not report sufficient efficacy data to inform an ITC analysis. There was also insufficient efficacy data on CFB for relevant clinical endpoints reported by Roy-Chaudhary 2022 to include this study in an ITC analysis (data were only available at 9 months of follow-up).

Populations

Consistent with the target population relevant for this reimbursement application of Kinpeygo, the analyses were informed by a cohort from Part B of the NefIgArd trial who had a baseline UPCR of ≥1.5 g/g (which is the indicated population).[115] However, the ITT population from all comparator studies was evaluated in all networks in the absence of results reported for UPCR ≥1.5 g/g subgroup. It is important to note that no studies except NefIgArd reported data for this subpopulation and therefore there are no study populations homogenous to the NefIgArd trial. This is a limitation of the analyses as baseline proteinuria is a predictor of patient outcomes, and further, analysis of differing trial populations may undermine the robustness of the NMA.

C.1.1.2 Outcomes

eGFR

This outcome was measured as the CFB to 24 months; a connected network was available, comprising three studies.[115, 118, 123]

NefIgArd reported data in regard to mean CFB to 24 months, along with a corresponding 95% confidence interval (CI) from which the standard error (SE) was deduced. [115] STOP-IgAN reported baseline data in tabular format, however, 24-month follow-up data were reported in graphical format; CFB was calculated as the difference between the 24-month follow-up and baseline measurements.[123] The SE of the CFB estimate was calculated using baseline SE (SE_B) and the final (24-month) SE (SE_F) estimates in the following formula:

$$SE(CFB) = \sqrt{SE_B^2 + SE_F^2 - 2\rho SE_B SE_F}$$

where ρ is the correlation coefficient between baseline and 24-month values.

The correlation coefficient estimated to be 0.87 (based on the average of the values across Kinpeygo and placebo arms in the ITT population of Part A of the NefIgArd trial). This correlation coefficient estimate was used for the STOP-IgAN study, which was required to provide an estimate of the SE of the CFB using baseline and 24-month values. Furthermore, 24-month data were only reported graphically, therefore, these data were estimated using digitisation software (GetData Graph Digitizer v2.26).[171] A further assumption was required in order to estimate the SE of the CFB; no information was reported regarding the sample sizes of each individual treatment arm at 24 months and therefore, it has been assumed that the sample sizes for each arm were equivalent to the number of patients evaluated at baseline. Note: all data included in the NMA, including data extracted and digitised from graphical figures are reported in the SLR report.

C.1.1.3 Statistical model

Network meta-analysis

A Bayesian NMA approach was adopted for synthesis of the evidence base, which is a method that combines observed study data with prior beliefs (represented in the form of distributions) to estimate a posterior distribution, upon which inferences can be made.

Both random-effects (RE) and fixed-effect (FE) models were fitted to the data to estimate relative treatment-effects between Kinpeygo and relevant comparators. Results from the RE models are presented in the main body of the report; these models are considered to be more conservative and appropriate in the presence of observed heterogeneity in the network. Furthermore, findings from the ITC feasibility assessment identified several observed differences between studies, meaning that between-study heterogeneity is likely to be present in the evidence base. The approach adopted for synthesis was based on a model structure reported in the NICE guidance published by the Decision Support Unit (DSU) Technical Support Document (TSD).[119] Independent NMA were conducted for each outcome.

An arm-based treatment-effect model using a Normal likelihood with identity link function was fitted to the data, evaluating the mean CFB in eGFR along with the associated SE.

In the RE NMA, an informative prior distribution based on using Turner's prior was used, with an adjustment made for analysis of outcomes measured on a continuous scale, using recommendations published by Ren 2018.[120, 121] Specifically, Turner's prior based on internal/external structure-related outcomes was explored, truncated with upper bound 0.345, with an adjustment of $(\sigma\sqrt{3})/\pi$ applied to the prior distribution, where σ is estimate of an individual level standard deviation (SD) from one trial, in line with recommendations published by Ren 2018.[120] The trial selected to provide an estimate of the SD was the study which evaluated the largest number of patients included in the network for each outcome (UPCR: NefIgArd; eGFR: DAPA-CKD). Note: this informative prior distribution has been explored due to the limited size of the evidence base for both outcomes. Bayesian statistical software, WinBUGS (v1.4.3) – a Markov chain Monte Carlo (MCMC) simulation-based software, was adopted for all analyses.[122] For each analysis, 50,000 initial samples were discarded as burn-in and 10,000 samples were retained to inform summary parameter estimates. A thinning interval of 10 was utilised to mitigate the issue of autocorrelation.

For each analysis, a network diagram (with study labels) is presented as well as a forest plot showing treatment effects of Kinpeygo versus each comparator, supplemented with a table of all pairwise treatment comparisons (represented by the median and 95% credible interval [CrI] from the posterior distribution).

Matching-adjusted indirect comparisons (MAIC)

As a supplementary approach to evidence synthesis, a form of population-adjusted indirect comparisons has been explored. Specifically, MAIC analyses have been conducted for both efficacy outcomes (eGFR), using individual patient data (IPD) from Part B of the NefIgArd trial.

Methodology adopted for the MAIC is in line with the approach outlined by Phillippo 2018 and is consistent with recommendations in the NICE guidance published by the DSU in TSD 18 [162, 163]. Patients from the index trial (i.e. Part B of the NefIgArd trial with a baseline UPCR of ≥1.5 g/g) were weighted in order to match aggregate-level baseline characteristics from each comparator study under investigation.

Anchored MAIC analyses were performed using data from the placebo arm from the NefIgArd trial as the common comparator arm; individual MAIC analyses have been performed against each comparator study. Matching to two different sets of prognostic factors (PF) and treatment-effect modifiers (TEM) has been explored in order to assess the uncertainty around the ITC estimates as well as assessing the impact of weighting patients in the NefIgArd trial prior to conducting an ITC analysis; the factors selected were identified through clinical input. A comparison analogous to a Bucher approach has been performed using both unadjusted (unweighted) and weighted data to estimate the treatment-effect (represented by the MD in CFB to 24 months in eGFR and associated 95% CrI between Kinpeygo and each comparator of interest. Results from the MAIC analyses are included in Section C.1.2.2.

Presentation of results

See Table 79 in Section 7.1.2.

C.1.1.4 Summary of reported data included in the NMA

Table 80 presents a summary of the available data for UPCR and eGFR for the trials included in the NMA.

Table 80. Summary of unique trials reporting data for at least one outcome of interest (informed by 24-month data)

Study	Trial name /trial number	Interventions	UPCR	eGFR
Barratt 2022	NefIgArd; NCT03643965	Kinpeygo (16 mg/day) Placebo	✓	✓

[161]				
Rauen 2015 [123]	STOP-IgAN; NCT00554502	Immunosuppression therapy (plus glucocorticoid*) Placebo	✓	✓

✓	Data reported without limitations	✓	Data available but associated with limitations (e.g. graphical data requiring digitisation)

Abbreviations: eGFR, estimated glomerular filtration rate; TRF, targeted-release formulation; UPCR, urine protein/creatinine ratio.
*Patients who had an eGFR of ≥60 ml per minute per 1.73 m^2 received glucocorticoid monotherapy for 6 months (methylprednisolone administered intravenously at a dose of 1 g per day for 3 days at the start of months 1, 3, and 5; and oral prednisolone at a dose of 0.5 mg per kilogram per 48 hours on the other days).

Reported data

A summary of the data included in the NMA for eGFR are presented in Table 81, respectively.

Table 81. Summary of reported data included in the NMA for CFB to 24 months in eGFR

Study	Arm	Baseline		24 months		CFB
		N	Mean (SD)	N	Mean (SD)	Mean [95% CI]
NefIgArd (ad-hoc analysis tables*)	Kinpeygo 16 mg/day Placebo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Rauen 2015 (STOP-IgAN)[123]	CS or IST Control	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

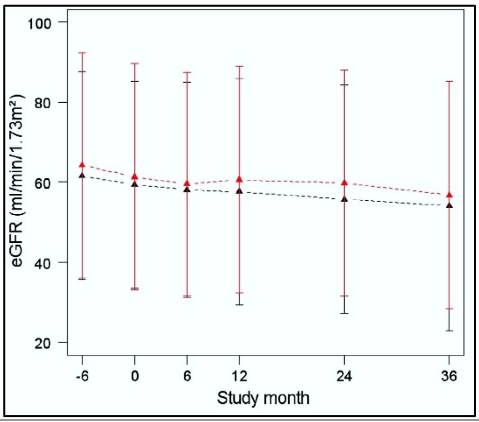
Abbreviations: CFB, change from baseline; CS, corticosteroid; DAPA, dapagliflozin; eGFR, estimated glomerular filtration rate; IST, immunosuppressive therapy; N, number of patients; NMA, network meta-analysis; SD, standard deviation; SE, standard error; UPCR, urine protein-creatinine ratio.
Notes: (-) Data not reported; *Data reported for patients with baseline UPCR ≥1.5 g/g.

Graphical data

Where outcomes of interest were reported within publication figures but not reported numerically within the publication or associated appendices, data were estimated using the digitisation software. A summary of the graphical data that was digitised prior to inclusion in the NMA is presented in Table 82.

Table 82. Summary of graphical data requiring digitisation for eGFR

Study	Outcome	Data	Source within paper	Figure

STOP-IgAN[123]	eGFR	24 months: Mean (SD) • CS or IST: 59.83 (28.24) • Control: 55.79 (28.55)	Figure S1b	

Abbreviations: CFB, change from baseline; CS, corticosteroid; eGFR, estimated glomerular filtration rate; IST, immunosuppressive therapy; SD, standard deviation; SE, standard error.

C.1.2 Matching-adjusted indirect comparisons

C.1.2.1 Methods

As a supplementary approach to evidence synthesis, a form of population-adjusted indirect comparisons has been explored. Specifically, MAIC analyses have been conducted for both efficacy outcomes under investigation (i.e. UPCR and eGFR), using a subgroup of IPD from Part B of the phase 3 NefIgArd trial (i.e. patients with baseline UPCR ≥ 1.5 g/g).[115]

Methodology adopted for the MAIC is in line with the approach outlined by Phillippo 2018 and is consistent with recommendations in the NICE guidance published by the DSU in TSD 18.[162, 163] MAIC analyses have been performed to provide a comparison of outcomes between Kinpeygo versus CS or IST (STOP-IgAN) and DAPA (DAPA-CKD).[115, 118, 123]

Patients from the index trial (NefIgArd) have been weighted in order to match published aggregate-level data from each comparator study under investigation.[115] Matching to two different sets of PF and TEM has been explored in order to assess the uncertainty around the ITC estimates as well as assessing the impact of weighting patients in the NefIgArd trial prior to conducting an ITC analysis. The full list of factors (which has been defined using clinical feedback) is summarised in Table 83. Note: all factors were reported in the NefIgArd trial data.[115]

Table 83. Summary of PF and TEM selected for inclusion in the MAIC

Factor	Units/categories	Priority factor	Categorisation of factor	Factor reported in comparator study STOP-IgAN
Age	Years	No	Continuous	ü
Gender	Male versus female	No	Dichotomous	ü
Race	**White/Caucasian versus Asian/Other***	**Yes**	**Dichotomous**	û
BMI	kg/m^2	No	Continuous	ü
SBP	**mm Hg**	**Yes**	**Continuous**	ü
DBP	mm Hg	No	Continuous	ü
Protein uria	**g/day**	**Yes**	**Continuous**	ü

UACR	g/g	No	Continuous	û
eGFR	ml/min per 1.73m²	No	Continuous	ü

Abbreviations: BMI, body mass index; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; g/g, ; kg, kilogram; MAIC, matching-adjusted indirect comparison; mm Hg, millimetre of mercury; N, number of patients; PF, prognostic factor; SBP, systolic blood pressure; TEM, treatment-effect modifier; UACR, urine albumin-creatinine ratio. Notes: factors considered priority and most influential PF and/or TEM are included in the reduced set of factors; *Other race also includes black patients.

Not every factor was reported by each comparator study; therefore matching has been performed using the subset of factors from the list which were reported in each study. Consistent with the approach adopted in the NMA, the NefIgArd trial population utilised in the MAIC is informed by the subpopulation of patients with baseline UPCR ≥1.5 g/g, however, a dataset based on using imputation methods (to overcome missing data) has been used in the MAIC analysis; therefore, the sample size of 129 patients has been used in the MAIC analysis (Kinpeygo: n=65; placebo: n=64). Specifically, the dataset used to inform the MAIC analysis contains the UPCR ratio to baseline and eGFR CFB to 24 months, both of which have been calculated based on imputed values. Note: UPCR ratio to baseline was converted to CFB to 24 months to align with the format of these data in the STOP-IgAN trial.

Anchored comparisons were conducted; independent analyses were performed to compare NefIgArd trial data with each comparator study of interest for eGFR outcomes, each time weighting NefIgArd to the relevant comparator trial population. A weighted treatment-effect was estimated within the NefIgArd trial and this was then compared to the comparator study treatment-effect, using an approach analogous to a Bucher comparison to estimate the MD in CFB to 24 months and corresponding 95% CrI between Kinpeygo and each comparator of interest. Note: for all MAIC analyses, weighting has been performed using the full set of factors as well as the reduced set of factors (based on those considered priority factors). For comparison purposes, results from the unadjusted (i.e. unweighted) NefIgArd data are also presented.

C.1.2.2 Results

A summary of baseline characteristics is presented in Table 84, including prior to- and after weighting NefIgArd trial data to match the aggregate-level baseline characteristics in the STOP-IgAN study.[123] Two factors (baseline UPCR and proteinuria) were not included in the matching process due to no or little overlap between the STOP-IgAN and NefIgArd study populations; mean UPCR was equal to 1.05 g/g in the STOP-IgAN study, whereas all patients in the NefIgArd trial had baseline UPCR greater than 1.5 g/g. [redacted] Therefore, due to the lack of overlap between study populations for these two factors and the expected substantial reduction in ESS (as well as unstable weights), these factors could not be included in the MAIC. Note: matching has been performed based on the full and reduced sets of PF and TEM from the list reported in Section C.1.2.1 (which were reported in the STOP-IgAN trial).

Table 84. Summary of baseline characteristics before and after weighting (NefIgArd and STOP-IgAN)

Factor	STOP-IgAN	NefIgArd – Unadjusted	NefIgArd – Weighted (full set of factors)	NefIgArd – Weighted (reduced set of factors)
Number of patients	**n=162***	[redacted]	[redacted]	[redacted]
Arm	**CS or IST**	[redacted]	[redacted]	[redacted]

Age (years)		[redacted]	[redacted]	[redacted]
Mean	44.3			
Gender, %		[redacted]	[redacted]	[redacted]
Male	78.4			
BMI, kg/m²		[redacted]	[redacted]	[redacted]
Mean	27.8			
SBP, mm Hg		[redacted]	[redacted]	[redacted]
Mean	125.5			
DBP, mm Hg		[redacted]	[redacted]	[redacted]
Mean	77.5			
eGFR, mL/min per 1.73m² Mean	59.3	[redacted]	[redacted]	[redacted]

Abbreviations: BMI, body mass index; CS, corticosteroid; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; ESS, effective sample size; IST, immunosuppressive therapy; mL/min, millilitres per minute; mm Hg, millimetre of mercury; N, number of patients; SBP, systolic blood pressure; TRF, targeted release formulation.
(-) factor not included in matching.
*Comparator population based on pooled arms from the STOP-IgAN trial; [redacted]

[redacted]

Figure 32. Summary of weights obtained from matching process (NefIgArd versus STOP-IgAN) – full set of factors (L) and reduced set of factors (R)

[redacted]

[redacted]

[redacted]

[redacted]

C.1.2.2.1 Change from baseline in eGFR to 24 months

The results from the MAIC using weights from the matching process are presented in Table 85; weights have been estimated from two sets of factors – a full set of factors and a reduced set of factors. For comparison purposes, results from an unweighted analysis are also presented. Results from the **unadjusted analyses for Kinpeygo versus CS or IST are consistent with those obtained in the NMA** (based on the FE model), **favouring Kinpeygo over CS or IST** (unweighted [redacted]

[redacted]

Table 85. MAIC results – MD in CFB to 24 months in eGFR, prior to and after weighting (NefIgArd versus STOP-IgAN)

[redacted]	[redacted]	[redacted]		[redacted]		[redacted]
		[redacted]	[redacted]	[redacted]	[redacted]	
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

C.1.2.2.2 Summary

The MAIC analyses presented in C.1.2.2 show that for the comparison with STOP-IgAN (using both the full and reduced set of factors) there are no extreme weights and all ESS values are at least 50% of the original sample size.

A comparison between Kinpeygo and CS or IST was possible to assess CFB to 24 months in eGFR. Prior to weighting, there were imbalances in study populations; there was a lower percentage of male patients in the NefIgArd trial compared to the STOP-IgaN trial [redacted] and mean eGFR was lower in the NefIgArd trial [redacted]. For CFB to 24 months in eGFR, both prior to- and after weighting [redacted] Results are largely unchanged when evaluating the two different sets of factors and conclusions remain the same. [redacted]

When assessing study populations, there were notable imbalances between study populations. After matching, baseline characteristics are similar, however, three important factors (baseline UPCR, proteinuria and UACR) could not be included in the MAIC due to lack of overlap in study populations. [redacted]

C.1.3 Differences in ldefinitions of outcomes between studies

Population-adjusted indirect comparison - MAIC

When assessing study populations, there were notable imbalances between study populations. After matching, baseline characteristics are similar, however, three important factors (baseline UPCR, proteinuria and UACR) could not be included in the MAIC due to lack of overlap in study populations. [redacted] Therefore, despite attempting to balance study populations, there is likely to be residual confounding present due to important observed differences between NefIgArd and the STOP-IgAN trials.

C.1.4 Summary from NMA and MAIC

Despite these methodological limitations, indirect comparisons numerically favoured TRF-budesonide over CS or IST in both NMA and MAIC analyses (based on data from the STOP-IgAN).

In the NMA, the differences numerically favored Kinpeygo versus CS or IST when comparing eGFR. A summary of results from the NMA for eGFR are presented in Table 16.

For the MAIC, for analysis of UPCR using data from the STOP-IgAN trial, conclusions from the MAIC analysis are unchanged compared to those obtained from the NMA, [redacted]. For analysis of eGFR using data from the STOP-IgAN trial, [redacted]. In the MAIC analyses based on matching on the full list of factors, [redacted]

Appendix D. Extrapolation

D.1 Extrapolation of risk of CKD 5 (eGFR <15 mL/min/1.73m2)

All available information regarding extrapolations can be found in Section 8, hence no additional information will be added to this section.

D.1.1 Data input

See Section 8.

D.1.2 Model

See Section 8.

D.1.3 Proportional hazards

See Section 8.

D.1.4 Evaluation of statistical fit (AIC and BIC)

See Section 8.

D.1.5 Evaluation of visual fit

See Section 8

D.1.6 Evaluation of hazard functions

N/A

D.1.7 Validation and discussion of extrapolated curves

See Section 8

D.1.8 Adjustment of background mortality

See Section 8

D.1.9 Adjustment for treatment switching/cross-over

N/A

D.1.10 Waning effect

N/A

D.1.11 Cure-point

N/A

Appendix E. Adverse events (incl. serious adverse events)

E.1.1 Comparison of key safety results from NefIgArd and NefIgAN

Table 86. Overview of key safety results from NefIgArd (Part A and B FAS) and NefIgAN (SAS), during treatment

[redacted]	[redacted]		[redacted]		[redacted]	
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]						
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]						
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]						
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

Table 87. Overview of key safety results from NefIgArd (Part A and B SAS) for patients with baseline UPCR ≥ 1.5 g/g, during treatment

[redacted]	[redacted]		[redacted]	
	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]			[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]			[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

[redacted]

E.1.2 NefIgArd Part A

Information about treatment exposure, treatment emergent adverse events (TEAEs), serious adverse events (AEs), discontinuations, deaths and changes in laboratory parameters or vital signs were recorded. An overview of all the safety results is provided in the following E.1.2.

In Part A, the safety analysis set (SAS), included all randomised patients who had received at least one dose of study drug as of the DCO, was presented for completeness.[11] The Part B SAS included all patients who received at least one dose of study drug (and includes the 29 patients mentioned above, but excludes five patients who were randomised and included in the Part B FAS but did not receive any blinded study treatment).[5] The per protocol set includes all data from patients in the FAS for whom no protocol deviations occurred during the study period that were considered to have the potential to impact the efficacy evaluation.[11] The Part A Per Protocol Set was determined through blinded review prior to Part A database lock.

Table 88. Overview of key efficacy safety results from NefIgArd (Part A FAS)

AEs, n(%)	NefIgArd NEF-301 (Phase III) Part A FAS	
	Kinpeygo 16 mg*	Placebo*
Overview of AEs		
Any TEAE	84 (86.6)	73 (73.0)
Any AESI	[redacted]	[redacted]
Any study treatment-related TEAE	[redacted]	[redacted]
Serious TEAEs	11 (11.3)	5 (5.0)
Discontinuations/deaths		
TEAEs leading to discontinuations	[redacted]	[redacted]
AEs leading to death	[redacted]	[redacted]
Most commonly reported corticosteroid-related AEs		
[redacted]	[redacted]	[redacted]
[redacted]		
[redacted]	[redacted]	[redacted]

*Treatment in addition to RAS inhibition
AE, adverse event; AESI, adverse event of special interest; FAS, full analysis set; NR, not reported; RAS, renin-angiotensin system; SAS, safety analysis set; TEAE, treatment-emergent adverse event
Source: DOF (NEF-301 CSR)[11]

[redacted]

In the Part A FAS, 84 (86.6%) patients in the Kinpeygo 16 mg group and 73 (73.0%) patients in the placebo group reported treatment-emergent adverse events (TEAEs), up until 14 days after the last dose of study treatment. [11] The majority of AEs reported by patients who received Kinpeygo 16 mg/day were mild to moderate (4.1% patients in the Kinpeygo group and 1.0% patients in the placebo group experienced a severe TEAE) and were in-line with the known safety profile of an oral budesonide product.[11] In the Part A FAS, the most commonly reported TEAEs with a >5% greater incidence in the Kinpeygo 16 mg/day group compared with the placebo group were [redacted][11]

[redacted]

E.1.2.1 Treatment exposure

All patients included in the Part A FAS had the opportunity to receive 9 months of treatment. Overall exposure was similar in both treatment groups (Table 89).[11] The median percentage of maximum intended dose received was [redacted] across the 9-month treatment period (Part A FAS). The lower quartile for percentage of maximum intended dose received was [redacted] in the Kinpeygo group (Part A FAS), which reflects a low discontinuation rate and high compliance.[11]

Table 89. Study drug exposure in SAS and Part A FAS in NefIgArd

	[redacted]		[redacted]	
	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]				
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]				
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

E.1.2.2 Overview of TEAEs

In the Part A FAS, [redacted] patients in the Kinpeygo 16 mg group and [redacted] patients in the placebo group reported treatment-emergent adverse events (TEAEs), up until 14 days after the last dose of study treatment.[11] The TEAE incidence rates were [redacted] patients in the Kinpeygo 16 mg group and [redacted] patients in the placebo group reported AEs.[11]

The majority of TEAEs were of mild or moderate severity (Table 90).[11] In the Part A FAS, [redacted] patients in the Kinpeygo 16 mg group and [redacted] patient in the placebo group experienced an AE graded severe. Of all AEs reported in the Kinpeygo 16 mg group, [redacted] were graded severe.[11]

The frequencies of TEAEs in the Part A FAS considered to be possibly study treatment-related by the Investigator were higher in the Kinpeygo 16 mg/day group compared with the placebo group ([redacted]; Table 91).[11]

In the Part A FAS, the most commonly reported TEAEs with a >5% greater incidence in the Kinpeygo 16 mg/day group compared with the placebo group were [redacted] (Table 91).[11] [redacted].[11]

Notably, there was no increased incidence of infections with Kinpeygo 16 mg/day ([redacted] in the Part A FAS) versus placebo ([redacted])[11], as has been seen with systemic corticosteroid use.[6, 57, 79] Furthermore, there were [redacted] reported with Kinpeygo treatment.

Table 90. Overview of AEs in SAS and Part A FAS in NefIgArd

Adverse events, n (%)	SAS*		Part A FAS*	
	Kinpeygo 16 mg [redacted]	Placebo [redacted]	Kinpeygo 16 mg n=97	Placebo n=100
Any TEAE	[redacted]	[redacted]	84 (86.6)	73 (73.0)
Maximum severity of TEAEs				

Mild	[redacted]	[redacted]	49 (50.5)	46 (46.0)
Moderate	[redacted]	[redacted]	31 (32.0)	26 (26.0)
Severe	[redacted]	[redacted]	[redacted]	[redacted]
Maximum severity of study treatment-related AEs				
Mild	[redacted]	[redacted]	[redacted]	[redacted]
Moderate	[redacted]	[redacted]	[redacted]	[redacted]
Severe	[redacted]	[redacted]	[redacted]	[redacted]
Any AESI	[redacted]	[redacted]	[redacted]	[redacted]
Any SAE	[redacted]	[redacted]	[redacted]	[redacted]
Any study treatment-related TEAE	[redacted]	[redacted]	[redacted]	[redacted]
Any study treatment-related TESAE	[redacted]	[redacted]	[redacted]	[redacted]
Any AE leading to death	[redacted]	[redacted]	[redacted]	[redacted]
Any TEAE leading to discontinuation of study treatment	[redacted]	[redacted]	[redacted]	[redacted]

*Treatment in addition to RAS inhibition

TEAEs were defined as AEs that occurred for the first time after dosing with study treatment or existed before but worsened in severity or relationship to study treatment after dosing. Study treatment-related TEAEs were those assessed by the Investigator to have a reasonable possibility that the event may have been caused by the study treatment. If the relationship was missing, then it was considered as study treatment-related. AEs that started >14 days after the last dose of study treatment were excluded from the summary. The last dose was defined as the last dose the patient received, including the tapering period, regardless of the duration of treatment

AE, adverse event; AESI, adverse event of special interest; FAS, full analysis set; RAS, renin-angiotensin system; SAE, serious adverse event; SAS, safety analysis set; TEAE, treatment-emergent adverse event; TESAE, treatment-emergent serious adverse event

Source: DOF (NEF-301 CSR)[11]

Table 91. Summary of TEAEs (occurring in >5% of patients in either treatment group) by preferred terms in SAS and Part A FAS in NefIgArd

[redacted]	[redacted]		[redacted]	
	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

E.1.2.3 Serious AEs

In the Part A FAS, 16 patients reported 21 TESAEs: 11 (11.3%) patients in the Kinpeygo 16 mg/day group and 5 (5.0%) patients in the placebo group.[11]

[redacted]

E.1.2.4 Discontinuations and deaths

[redacted]

Table 92. Summary of TEAEs leading to study treatment discontinuation by preferred term in SAS and Part A FAS in NefIgArd

[redacted]	[redacted]		[redacted]	
	[redacted]	[redacted]	[redacted]	[redacted]
[redacted] [redacted] [redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

E.1.2.5 Glucocorticosteroid-related TEAEs and AEs of special interest

[redacted]

Table 93. Summary of glucocorticosteroid-related TEAEs in SAS and Part A FAS in NefIgArd

[redacted]	[redacted]		[redacted]	
	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

Table 94. Summary of AESIs in SAS in NefIgArd

[redacted]	[redacted]		[redacted]	
	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

E.1.2.6 Changes in laboratory parameters or vital signs

[redacted]

[redacted]

E.1.2.7 Kinpeygo safety in baseline UPCR ≥1.5 g/g subgroup

E.1.2.7.1 Overview of TEAEs in UPCR ≥1.5 g/g subgroup

[redacted]

Table 95. Overview of AEs in SAS and Part A FAS in NefIgArd for the subgroup of patients with baseline UPCR ≥1.5 g/g

[redacted]	[redacted]		[redacted]	
	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]			[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]			[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	

[redacted]

Table 96. Summary of TEAEs (occurring in ≥5% of patients in either treatment group) by preferred terms in SAS in NefIgArd for the subgroup of patients with baseline UPCR ≥1.5 g/g

[redacted]		[redacted]	
		[redacted]	[redacted]
[redacted]		[redacted]	[redacted]
[redacted]		[redacted]	[redacted]
[redacted]		[redacted]	[redacted]
[redacted]		[redacted]	[redacted]
[redacted]		[redacted]	[redacted]
[redacted]		[redacted]	[redacted]
[redacted]		[redacted]	[redacted]
[redacted]		[redacted]	[redacted]
[redacted]		[redacted]	[redacted]
[redacted]		[redacted]	[redacted]
[redacted]		[redacted]	[redacted]
[redacted]		[redacted]	[redacted]
[redacted]		[redacted]	[redacted]
[redacted]		[redacted]	[redacted]
[redacted]		[redacted]	[redacted]
[redacted]		[redacted]	[redacted]
[redacted]		[redacted]	[redacted]

[redacted]

E.1.2.7.2 Serious AEs in UPCR ≥1.5 g/g subgroup

[redacted].[157]

E.1.2.7.3 Discontinuations and deaths in UPCR ≥1.5 g/g subgroup

[redacted]

E.1.3 NefIgArd Part B

E.1.3.1 Treatment exposure

[redacted]

Table 97. Study drug exposure in SAS and Part B FAS in NefIgArd

		[redacted]		[redacted]	
	[redacted]		[redacted]	[redacted]	[redacted]
[redacted]					
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
[redacted]					

[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]				
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]				
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]				
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]				
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

E.1.3.2 Overview of TEAEs

The majority of AEs reported by patients who received Kinpeygo 16 mg/day* were mild to moderate and were in-line with the known safety profile of an oral budesonide product.[104]

- 5% patients in the Kinpeygo group and 2% patients in the placebo group experienced a severe TEAE during the 9-month treatment period. One serious TEAE in each group was considered to be treatment-related
- 9% patients in the Kinpeygo group and 5% patients in the placebo group experienced a severe TEAE during the 15-month off-treatment observation period.

Importantly, the rate of serious infections – which occur frequently during treatment with systemic corticosteroids – was low during treatment with Kinpeygo 16 mg/day*.[104]

- 5 (3%) patients in the Kinpeygo group and 2 (1%) in the placebo group had serious TEAEs related to infection, of these 3 versus 1 required hospitalisation. One serious TEAE in each group was considered to be treatment-related

- In the STOP-IgAN trial, 8 of 82 [10%] of patients receiving immunosuppression experienced serious TEAEs related to infection, and one patient died of sepsis during the 3-year trial[6]

Overall incidence of infections during treatment was similar between treatment groups[104]

- 35% patients in the Kinpeygo group vs. 31% patients in the placebo group reported infection-related TEAEs.

An overview of the AEs during treatment in SAS and Part B FAS is presented in Table 98.

**Kinpeygo 16 mg/day in addition to optimised RAS blockade vs. placebo in addition to optimised RAS blockade (FAS)*

Table 98. Overview of AEs during treatment in SAS and Part B FAS in NefIgArd

Adverse events, n (%)	SAS*		Part B FAS*	
	Kinpeygo 16 mg [redacted]	Placebo [redacted]	Kinpeygo 16 mg n=182	Placebo n=182
Any TEAE	[redacted]	[redacted]	159 (87.4)	125 (68.7)
Maximum severity of TEAEs				
Mild	[redacted]	[redacted]	93 (51.1)	75 (41.2)
Moderate	[redacted]	[redacted]	57 (31.3)	46 (25.3)
Severe	[redacted]	[redacted]	9 (4.9)	4 (2.2)
Any study treatment-related TEAE†	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]				
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Any SAE	[redacted]	[redacted]	18 (9.9)	11 (6.0)
Any TESAE	[redacted]	[redacted]	18 (9.9)	9 (4.9)
Any study treatment-related TESAE	[redacted]	[redacted]	4 (2.2)	4 (2.2)
Any AE leading to death	[redacted]	[redacted]	1 (0.5)	0 (0.0)
Any TEAE leading to discontinuation of study treatment	[redacted]	[redacted]	17 (9.3)	3 (1.6)
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

*Treatment in addition to RAS inhibition; TEAEs were defined as AEs that occurred for the first time after dosing with study treatment or existed before but worsened in severity or relationship to study treatment after dosing. AEs that started >14 days after the last dose of study treatment were excluded from the summary. The last dose was defined as the last dose the patient received, including the tapering period, regardless of the duration of treatment; †A reasonable possibility that the event may have been caused by the study treatment, as assessed by the Investigator. If relationship was missing, then it was considered as study treatment-related
Abbreviations: AE, adverse event; AESI, adverse event of special interest; FAS, full analysis set; RAS, renin-angiotensin system; SAE, serious adverse event; SAS, safety analysis set; TEAE, treatment-emergent adverse event; TEAESI, treatment-emergent serious adverse event of special interest; TESAE, treatment-emergent serious adverse event
Source: DOF (NEF-301 Part B CSR)[5]; Lafayette et al, 2023[104]

Table 99. Overview of AEs during follow-up in SAS and Part B FAS in NefIgArd

	SAS*	Part B FAS*

Adverse events, n (%)	Kinpeygo 16 mg [redacted]	Placebo [redacted]	Kinpeygo 16 mg n=182	Placebo n=182
Number of patients who had a study visit during follow-up period	[redacted]	[redacted]	175	174
Any TEAE	[redacted]	[redacted]	127 (72.6)	124 (71.3)
Maximum severity of TEAEs				
Mild	[redacted]	[redacted]	62 (35.4)	73 (42.0)
Moderate	[redacted]	[redacted]	49 (28.0)	43 (24.7)
Severe	[redacted]	[redacted]	16 (9.1)	8 (4.6)
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]				
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Any TESAE	[redacted]	[redacted]	14 (8.0)	14 (8.0)
Any treatment-related TEAE	[redacted]	[redacted]	0 (0.0)	1 (0.6)
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

*Treatment in addition to RAS inhibition; TEAEs were defined as AEs that occurred for the first time after dosing with study treatment or existed before but worsened in severity or relationship to study treatment after dosing. The last dose was defined as the last dose the patient received, including the tapering period, regardless of the duration of treatment; † [redacted]

Abbreviations: AE, adverse event; AESI, adverse event of special interest; FAS, full analysis set; RAS, renin-angiotensin system; SAE, serious adverse event; SAS, safety analysis set; TEAE, treatment-emergent adverse event; [redacted]; TESAE, treatment-emergent serious adverse event

Source: DOF (NEF-301 Part B CSR)[5]; Lafayette et al, 2023[104]

Table 100. Summary of TEAEs (occurring in ≥5% of patients in either treatment group) by preferred terms in SAS and Part B FAS in NefIgArd

[redacted]	[redacted]		[redacted]	
	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
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[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

Table 101. Summary of TEAEs during follow-up (occurring in ≥5% of patients in the Kinpeygo 16 mg/day treatment group) in the Part B FAS in NefIgArd

Adverse events, n (%)	Kinpeygo 16 mg/day* n=182	Placebo* n=182
Number of patients who had a study visit during the follow-up	175	174
Patients with any TEAE that started >14 days after the last dose**	127 (73)	124 (71)
SARS-CoV-2 infection	26 (15)	30 (17)
Peripheral oedema	14 (8)	10 (6)
Gout	11 (6)	8 (5)
Hypertension	10 (6)	12 (7)

TEAEs were defined as AEs that occurred for the first time after dosing with study drug or existed before but worsened in severity or relationship to study drug after dosing. AEs that started or worsened during follow up more than 14 days after completion of the tapering period are included. Any previously reported TEAE had to be reported at a higher severity during follow-up to be counted as a new AE in the follow-up period; *Treatment in addition to RAS inhibition; **The last dose was defined as the last dose the patient received, including the tapering period, regardless of the duration of treatment

Abbreviations: AE, adverse event; FAS, full analysis set; RAS, renin-angiotensin system; TEAE, treatment-emergent adverse event

Source: Lafayette et al, 2023, Supplementary Appendix[93]

E.1.3.3 Glucocorticosteroid-related TEAEs and AEs of special interest

[redacted]

[redacted]

Table 102. Summary of glucocorticosteroid-related TEAEs during treatment in SAS and Part B FAS in NefIgArd

[redacted]		[redacted]		[redacted]					
		[redacted]		[redacted]		[redacted]		[redacted]	
[redacted]		[redacted]		[redacted]		[redacted]		[redacted]	
[redacted]		[redacted]		[redacted]		[redacted]		[redacted]	
[redacted]		[redacted]		[redacted]		[redacted]		[redacted]	
[redacted]		[redacted]		[redacted]		[redacted]		[redacted]	
[redacted]		[redacted]		[redacted]		[redacted]		[redacted]	
[redacted]		[redacted]		[redacted]		[redacted]		[redacted]	
[redacted]		[redacted]		[redacted]		[redacted]		[redacted]	
[redacted]		[redacted]		[redacted]		[redacted]		[redacted]	
[redacted]		[redacted]		[redacted]		[redacted]		[redacted]	

[redacted]

Table 103. Summary of AESIs reported during treatment (SAS)

[redacted]		[redacted]		[redacted]	
[redacted]		[redacted]		[redacted]	
[redacted]		[redacted]		[redacted]	
[redacted]		[redacted]		[redacted]	
[redacted]		[redacted]		[redacted]	
[redacted]		[redacted]		[redacted]	
[redacted]		[redacted]		[redacted]	
[redacted]		[redacted]		[redacted]	
[redacted]		[redacted]		[redacted]	
[redacted]		[redacted]		[redacted]	
[redacted]		[redacted]		[redacted]	
[redacted]		[redacted]		[redacted]	

[redacted]

Table 104. Summary of AESIs reported during follow-up (SAS)

[redacted]		[redacted]		[redacted]	
[redacted]		[redacted]		[redacted]	
[redacted]		[redacted]		[redacted]	

[redacted]

[redacted]

E.1.3.4 Changes in laboratory parameters or vital signs

There were no clinically-relevant changes in median values of any chemistry, haematology, or urinalysis parameters observed over time between Kinpeygo 16 mg/day and placebo, apart from:[11, 104]

- 24-hour urine cortisol excretion, which decreased during Kinpeygo treatment with reversibility seen at the 3-month follow-up
- HbA1c, where there was a tendency for a minor and reversible increase from baseline in HbA1c values to be observed in Kinpeygo-treated patients who were diabetic or pre-diabetic at baseline.

[redacted].[11] Systemic GCS treatment can be associated with increased blood pressure and significant weight gain.[6, 29] In NefIgArd, no clinically relevant differences in bodyweight or blood pressure measurements were observed between the treatment groups throughout the trial.[104]

E.1.3.5Discontinuations and deaths

In the FAS, discontinuations due to TEAEs occurred in 17 (9%) of 182 patients in the Kinpeygo group and three (2%) of 182 in the placebo group (FAS) (Table 102).[104] [redacted].[5]

One death due to SARS-CoV-2 infection was reported during Kinpeygo treatment in a patient with several risk factors for COVID-19 mortality, and another patient treated with Kinpeygo died from a cerebral haemorrhage 10.5 months after their last dose.[104] Neither death was considered to be related to study treatment. No TEAEs leading to death were reported in the placebo group.[104]

E.1.3.6Kinpeygo safety in baseline UPCR ≥1.5 g/g subgroup

The safety results for the baseline UPCR ≥1.5 g/g subgroup were consistent with those observed for the full NefIgArd trial population[17]

Table 105 and Table 106 provide an overview of AEs during treatment and follow-up for the baseline UPCR ≥1.5 g/g subgroup. In the Part B SAS, [redacted] of patients in the UPCR ≥1.5 g/g subgroup who received experienced TEAEs during Kinpeygo treatment,[17] compared with 88.7% in the full SAS population.[104] During Kinpeygo treatment, the percentage of patients experiencing mild, moderate and severe TEAEs were similar in the UPCR ≥1.5 g/g subgroup ([redacted])[17] compared with the full SAS population (52.8%, 31.3% and 4.6%, respectively).[104]. TEAEs of special interest occurred in [redacted] of patients in the UPCR ≥1.5 g/g subgroup during Kinpeygo treatment,[17] compared with 4.6% in the full SAS population.[104]

The majority of TEAEs were of mild with only 5% and 2% of patients in the Kinpeygo and placebo groups, respectively, experiencing severe TEAE (see Table 98 for the full population).[104]

Table 105. Overview of AEs during treatment in SAS in NefIgArd - baseline UPCR ≥1.5 g/g subgroup

[redacted]			[redacted]		
		[redacted]		[redacted]	
[redacted]		[redacted]		[redacted]	
[redacted]					
[redacted]		[redacted]		[redacted]	
[redacted]		[redacted]		[redacted]	
[redacted]		[redacted]		[redacted]	
[redacted]		[redacted]		[redacted]	
[redacted]					
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[redacted]		[redacted]		[redacted]	
[redacted]		[redacted]		[redacted]	
[redacted]		[redacted]		[redacted]	
[redacted]		[redacted]		[redacted]	
[redacted]		[redacted]		[redacted]	
[redacted]		[redacted]		[redacted]	
[redacted]		[redacted]		[redacted]	
[redacted]		[redacted]		[redacted]	
[redacted]		[redacted]		[redacted]	

Table 106. Overview of AEs >14 days after the last dose in SAS in NefIgArd - baseline UPCR ≥1.5 g/g subgroup

[redacted]			[redacted]		
		[redacted]		[redacted]	
[redacted]		[redacted]		[redacted]	
[redacted]		[redacted]		[redacted]	
[redacted]					
[redacted]		[redacted]		[redacted]	

[redacted]

[redacted]

E.1.4 NefIgAN

The safety results from the NefIgArd Phase III trial were consistent with those from the NefigAN Phase IIb trial (see Table 107 for a high-level overview of key safety results).

Table 107. Overview of key safety results from Nefigan Phase IIb trial (SAS)

AEs, n (%)	Nefigan NEF-202 (Phase IIb)	
	SAS	
	Kinpeygo 16 mg*	Placebo*
Overview of AEs		
Any TEAE	43 (88)	42 (84)
Any AESI	NR	NR
Any study treatment-related TEAE	11 (22.4)	2 (4.0)
Serious TEAEs	7 (14.3)	3 (6.0)
Discontinuations/deaths		
TEAEs leading to discontinuations	11 (22.4)	2 (4.0)
AEs leading to death	0 (0.0)	0 (0.0)
Most commonly reported corticosteroid-related AEs		
Peripheral oedema/ ankle swelling	10 (20.4)	4 (8.0)
Acne	9 (18.4)	1 (2.0)

*Treatment in addition to RAS inhibition
AE, adverse event; AESI, adverse event of special interest; FAS, full analysis set; NR, not reported; RAS, renin-angiotensin system; SAS, safety analysis set; TEAE, treatment-emergent adverse event
Source: Fellström *et al*, 2017[59]; DOF (NEF-202 CSR)[172]

E.1.4.1 Extent of exposure

The SAS included all 150 randomised patients, and the extent of exposure was similar between the Kinpeygo and placebo groups (Table 108).[59]

Table 108. Study drug exposure in NefIgAN

Overall exposure (days)	Kinpeygo 16 mg* n=49	Kinpeygo 8 mg* n=51	Placebo* n=50
Median	274	271	274
IQR	259 to 280	169 to 277	267 to 281

*Treatment in addition to RAS inhibition
IQR, interquartile range; RAS, renin-angiotensin system
Source: Fellström *et al*, 2017[59]

E.1.4.2 Overview of adverse events

The total incidence of TEAEs was similar across treatment groups (Table 109).[59] The most frequently reported AE, nasopharyngitis, was reported by similar percentages of patients in each group.[59]

The incidence of GI-related AEs was similar in Kinpeygo-treated and placebo-treated patients during treatment (Kinpeygo 16 mg/day, 36.7%; placebo, 28.0%).[59]

Table 109. TEAEs reported by ≥5% of all patients by preferred term in NefigAN (SAS)

Adverse events, n (%)	Kinpeygo 16 mg* n=49	Kinpeygo 8 mg* n=51	Placebo* n=50
Any AE	43 (88)	48 (94)	42 (84)
Nasopharyngitis	10 (20)	8 (16)	10 (20)
Acne†	9 (18)	8 (16)	3 (6)
Joint swelling	9 (18)	8 (16)	2 (4)
Cushingoid†	8 (16)	5 (10)	3 (6)
Insomnia	8 (16)	6 (12)	2 (4)
Diarrhoea	5 (10)	1 (2)	7 (14)
Dyspepsia§	7 (14)	2 (4)	4 (8)
Headache	6 (12)	3 (6)	3 (60)
Alopecia†	4 (8)	5 (8)	2 (4)
Back pain	3 (6)	6 (12)	1 (2)
Mood swings†	5 (10)	3 (6)	2 (4)
Oedema peripheral	6 (12)	2 (4)	2 (4)
Blood creatine phosphokinase increased	3 (6)	3 (6)	3 (6)
Hirsutism†	5 (10)	3 (6)	1 (2)
Hypertension	5 (10)	3 (6)	1 (2)
Muscle spasms	2 (4)	5 (10)	2 (4)
Abdominal pain§	3 (6)	4 (8)	1 (2)
Nausea	3 (6)	4 (8)	1 (2)
Upper respiratory tract infection	3 (6)	2 (4)	3 (6)

*Treatment in addition to RAS inhibition
†Corticosteroid-related adverse events solicited by questionnaire at every visit
§Gastrointestinal-related adverse events solicited by questionnaire at every visit
AE, adverse event; RAS, renin-angiotensin system; SAS, safety analysis set; TEAE, treatment-emergent adverse event
Source: Fellström *et al*, 2017[59]

E.1.4.3 Serious AEs

Eleven patients reported a total of 13 serious TEAEs (seven patients in Kinpeygo 16 mg group, one patient in Kinpeygo 8 mg group, and three patients in placebo group).[59] In the Kinpeygo 16 mg group, patients reported aggravated condition, deep vein thrombosis, menorrhagia, proteinuria, appendicitis, aortic dissection, and nephrotic syndrome. In the Kinpeygo, 8 mg group, patients reported aggravated condition, and in the placebo group, patients reported proteinuria, aggravated condition, and sciatica.[59]

Two serious AEs were considered possibly associated with Kinpeygo by the Investigators (who were masked to trial medication): deep vein thrombosis (Kinpeygo 16 mg group) and unexplained worsening of renal function, reported during follow-up after tapering from 16 mg/day to 8 mg/day.[59] Another two serious AEs, reported in the placebo-treated group, were considered possibly associated with trial medication: both were cases of increased proteinuria, one of which presented with a decline in renal function.[59]

E.1.4.4 Discontinuations and deaths

Eighteen patients experienced AEs that led to discontinuation of treatment (11 in the Kinpeygo 16 mg group, five in the Kinpeygo 8 mg group, two in the placebo group).[59] Most patients who discontinued in the Kinpeygo groups experienced corticosteroid-related AEs.[59]

No participants died and none progressed to ESRD. Fourteen patients (three patients who received Kinpeygo 16 mg, four who received Kinpeygo 8 mg, and seven who received placebo) reported AEs associated with worsening of renal function, or received high-dose systemic corticosteroid therapy, or both.[59]

E.1.4.5 Corticosteroid-related AEs

Solicited corticosteroid-related AEs were more frequently reported by Kinpeygo-treated patients; these were generally reversible after treatment was stopped (Table 110).[59]

Table 110. Summary of solicited corticosteroid-related AEs in Nefigan (SAS)

Adverse events, n (%)	Phase	Kinpeygo 16 mg* n=49	Kinpeygo 8 mg* n=51	Placebo* n=50
Any corticosteroid-related AE	Run-in	10 (20.4)	6 (11.8)	10 (20.0)
	Treatment	20 (40.8)	20 (39.2)	11 (22.0)
	Follow-up	14 (28.6)	12 (23.5)	10 (20.0)
Moon face	Run-in	0 (0.0)	1 (2.0)	0 (0.0)
	Treatment	8 (16.3)	5 (9.8)	0 (0.0)
	Follow-up	4 (8.2)	3 (5.9)	3 (6.0)
Acne	Run-in	3 (6.1)	3 (5.9)	0 (0.0)
	Treatment	9 (18.4)	7 (13.7)	1 (2.0)
	Follow-up	4 (8.2)	6 (11.8)	2 (4.0)
Swelling of ankles	Run-in	7 (14.3)	0 (0.0)	1 (2.0)
	Treatment	10 (20.4)	6 (11.8)	4 (8.0)
	Follow-up	8 (16.3)	2 (3.9)	0 (0.0)
Bruising easily	Run-in	0 (0.0)	0 (0.0)	0 (0.0)
	Treatment	5 (10.2)	4 (7.8)	0 (0.0)
	Follow-up	1 (2.0)	1 (2.0)	0 (0.0)
Hirsutism	Run-in	1 (2.0)	0 (0.0)	2 (4.0)
	Treatment	5 (10.2)	3 (5.9)	1 (2.0)
	Follow-up	2 (4.1)	2 (3.9)	2 (4.0)
Buffalo hump	Run-in	0 (0.0)	0 (0.0)	0 (0.0)
	Treatment	3 (6.1)	1 (2.0)	0 (0.0)
	Follow-up	3 (6.1)	2 (3.9)	0 (0.0)
Purple skin	Run-in	0 (0.0)	0 (0.0)	0 (0.0)
	Treatment	0 (0.0)	1 (2.0)	0 (0.0)
	Follow-up	1 (2.0)	2 (3.9)	0 (0.0)

Striae	Run-in	3 (6.1)	1 (2.0)	5 (10.0)
	Treatment	4 (8.2)	1 (2.0)	4 (8.0)
	Follow-up	4 (8.2)	3 (5.9)	3 (6.0)
Hair loss	Run-in	1 (2.0)	0 (0.0)	1 (2.0)
	Treatment	1 (2.0)	1 (2.0))	2 (4.0)
	Follow-up	4 (8.2)	3 (5.9)	0 (0.0)
Mood swing	Run-in	2 (4.1)	0 (0.0)	0 (0.0)
	Treatment	4 (8.2)	4 (7.8)	2 (4.0)
	Follow-up	2 (4.1)	0 (0.0)	3 (3.6)
Depression	Run-in	1 (2.0)	0 (0.0)	0 (0.0)
	Treatment	2 (4.1)	2 (3.9)	0 (0.0)
	Follow-up	1 (2.0)	0 (0.0)	0 (0.0)
Insomnia	Run-in	1 (2.0)	3 (5.9)	4 (8.0)
	Treatment	7 (14.3)	7 (13.7)	4 (8.0)
	Follow-up	2 (4.1)	4 (7.8)	3 (6.0)

*Treatment in addition to RAS inhibition
AE, adverse event; RAS, renin-angiotensin system; SAS, safety analysis set
Source: Fellström *et al*, 2017[59]

E.1.4.6 Changes in laboratory parameters and vital signs

Bodyweight, blood pressure, and glycated haemoglobin (HbA1c) values did not significantly change from baseline in either Kinpeygo group compared with placebo at the end of treatment (Table 111) [59]. Two patients receiving Kinpeygo, both with a BMI of 36 kg/m² at baseline, had increases of HbA1c into the diabetic range (≥48 mmol/mol) at the end of treatment or during follow-up.[59]

There were no other clinically-relevant changes in clinical chemistry variables in any treatment group.[59]

Table 111. Change from baseline in selected patient safety variables at the end of treatment in Nefigan (SAS)

Variable (mean change from baseline, SD)	End of treatment*			End of follow-up*		
	Kinpeygo 16 mg n=49	Kinpeygo 8 mg n=51	Placebo n=50	Kinpeygo 16 mg n=49	Kinpeygo 8 mg n=51	Placebo n=50
Systolic blood pressure (mmHg)	4.7 (16.02)	1.5 (13.55)	-1.0 (13.83)	0.6 (13.36)	1.0 (10.26)	-1.2 (12.1)
Diastolic blood pressure (mmHg)	2.7 (9.89)	-0.6 (10.70)	1.9 (10.02)	0.2 (8.94)	-0.8 (9.64)	0.3 (9.47)
Body weight (kg)	0.2 (3.82)	1.0 (2.4.)	1.5 (3.32)	0.4 (3.24)	1.0 (2.7)	1.1 (3.34)
HbA1c (mmol/mol)	1.1 (2.33)†	-0.1 (3.24)	0.5 (2.36)	0.4 (3.58)	-0.1 (3.24)	0.5 (3.20)

*Treatment in addition to RAS inhibition
†Mean HbA1c was statistically significantly higher in the Kinpeygo 16 mg/day group when compared with the 8 mg/day group at the end of treatment (p=0·0252). This was the only comparison that was statistically significant
HbA1c, glycosylated haemoglobin A1; RAS, renin-angiotensin system; SAS, safety analysis set; SD, standard deviation
Source: Fellström *et al*, 2017[59]

Appendix F. Health-related quality of life

Not applicable, no specific domains need to be highlighted, all available information is presented in Section 10.3.

Appendix G. Probabilistic sensitivity analyses

The parameters tested in the PSA are presented in Table 112.

Table 112. Overview of parameters in the PSA

Input parameter	Point estimate	Lower bound	Upper bound	Probability distribution
Age (years)	[redacted]	[redacted]	[redacted]	Normal
Proportion female	[redacted]	[redacted]	[redacted]	Beta
Average weight	[redacted]	[redacted]	[redacted]	Normal
Baseline patient distribution: CKD 1	[redacted]	[redacted]	[redacted]	Dirichlet
Patient distribution: CKD 2	[redacted]	[redacted]	[redacted]	Dirichlet
Patient distribution: CKD 3a	[redacted]	[redacted]	[redacted]	Dirichlet
Patient distribution: CKD 3b	[redacted]	[redacted]	[redacted]	Dirichlet
UK RaDaR distribution: CKD 1	[redacted]	[redacted]	[redacted]	Dirichlet
UK RaDaR distribution: CKD 2	[redacted]	[redacted]	[redacted]	Dirichlet
UK RaDaR distribution: CKD 3a	[redacted]	[redacted]	[redacted]	Dirichlet
UK RaDaR distribution: CKD 3b	[redacted]	[redacted]	[redacted]	Dirichlet
Proportion haemodialysis	[redacted]	[redacted]	[redacted]	Beta
HR: Kinpeygo vs. SoC - Applied to risk of CKD 5	[redacted]	[redacted]	[redacted]	Log normal
Proportion of eligible patients that receive retreatment	[redacted]	[redacted]	[redacted]	Normal
Include Corticosteroids / immunosuppressive therapy	[redacted]	[redacted]	[redacted]	Fixed
SMR: CKD 1	[redacted]	[redacted]	[redacted]	Log normal
SMR: CKD 2	[redacted]	[redacted]	[redacted]	Log normal
SMR: CKD 3a	[redacted]	[redacted]	[redacted]	Log normal
SMR: CKD 3b	[redacted]	[redacted]	[redacted]	Log normal
SMR: CKD 4	[redacted]	[redacted]	[redacted]	Log normal
SMR: CKD 5	[redacted]	[redacted]	[redacted]	Log normal
SMR: Dialysis	[redacted]	[redacted]	[redacted]	Log normal
SMR: Post-transplant	[redacted]	[redacted]	[redacted]	Log normal
Kinpeygo cost per pack	[redacted]	[redacted]	[redacted]	Fixed
SoC monthly treatment cost	[redacted]	[redacted]	[redacted]	Normal

SoC monthly administration cost	[redacted]	[redacted]	[redacted]	Normal
Dapagliflozin monthly treatment cost	[redacted]	[redacted]	[redacted]	Normal
Dapagliflozin monthly administration cost	[redacted]	[redacted]	[redacted]	Normal
Oral prednisolone - dose description	[redacted]	[redacted]	[redacted]	Fixed
Oral prednisolone - Total duration	[redacted]	[redacted]	[redacted]	Fixed
Oral prednisolone - Admin cost per dose	[redacted]	[redacted]	[redacted]	Fixed
Oral prednisolone - Pack price	[redacted]	[redacted]	[redacted]	Normal
Oral prednisolone - Size	[redacted]	[redacted]	[redacted]	Fixed
Oral prednisolone - Pack size	[redacted]	[redacted]	[redacted]	Fixed
Annual hospital care cost - CKD 1	[redacted]	[redacted]	[redacted]	Normal
Annual hospital care cost - CKD 2	[redacted]	[redacted]	[redacted]	Normal
Annual hospital care cost - CKD 3a	[redacted]	[redacted]	[redacted]	Normal
Annual hospital care cost - CKD 3b	[redacted]	[redacted]	[redacted]	Normal
Annual hospital care cost - CKD 4	[redacted]	[redacted]	[redacted]	Normal
GP appointment	[redacted]	[redacted]	[redacted]	Normal
Blood tests	[redacted]	[redacted]	[redacted]	Normal
Primary care frequency per year - CKD 1	[redacted]	[redacted]	[redacted]	Normal
Primary care frequency per year - CKD 2	[redacted]	[redacted]	[redacted]	Normal
Primary care frequency per year - CKD 3	[redacted]	[redacted]	[redacted]	Normal
Primary care frequency per year - CKD 4	[redacted]	[redacted]	[redacted]	Normal
Primary care frequency per year - CKD 5	[redacted]	[redacted]	[redacted]	Normal
Hospital haemodialysis unit cost	[redacted]	[redacted]	[redacted]	Normal
Satellite haemodialysis unit cost	[redacted]	[redacted]	[redacted]	Normal
Home haemodialysis unit cost	[redacted]	[redacted]	[redacted]	Normal
Nephrologist visits unit cost	[redacted]	[redacted]	[redacted]	Normal
Blood tests unit cost	[redacted]	[redacted]	[redacted]	Normal

Haemodialysis transport unit cost	[redacted]	[redacted]	[redacted]	Normal
Hospital haemodialysis frequency description	[redacted]	[redacted]	[redacted]	Fixed
Satellite haemodialysis frequency description	[redacted]	[redacted]	[redacted]	Fixed
Home haemodialysis frequency description	[redacted]	[redacted]	[redacted]	Fixed
Nephrologist visits frequency description	[redacted]	[redacted]	[redacted]	Fixed
Blood tests frequency description	[redacted]	[redacted]	[redacted]	Fixed
Haemodialysis transport frequency description	[redacted]	[redacted]	[redacted]	Fixed
Hospital haemodialysis frequency per year	[redacted]	[redacted]	[redacted]	Fixed
Satellite haemodialysis frequency per year	[redacted]	[redacted]	[redacted]	Fixed
Home haemodialysis frequency per year	[redacted]	[redacted]	[redacted]	Fixed
Nephrologist visits frequency per year	[redacted]	[redacted]	[redacted]	Fixed
Blood tests frequency per year	[redacted]	[redacted]	[redacted]	Fixed
Haemodialysis transport frequency per year	[redacted]	[redacted]	[redacted]	Fixed
Peritoneal dialysis unit cost	[redacted]	[redacted]	[redacted]	Fixed
Nephrologist visits unit cost	[redacted]	[redacted]	[redacted]	Fixed
Blood tests unit cost	[redacted]	[redacted]	[redacted]	Fixed
Peritoneal dialysis frequency description	[redacted]	[redacted]	[redacted]	Fixed
Nephrologist visits frequency description	[redacted]	[redacted]	[redacted]	Fixed
Blood tests frequency description	[redacted]	[redacted]	[redacted]	Fixed
Peritoneal dialysis frequency per year	[redacted]	[redacted]	[redacted]	Fixed
Nephrologist visits frequency year	[redacted]	[redacted]	[redacted]	Normal
Blood tests frequency year	[redacted]	[redacted]	[redacted]	Normal
Nephrologist visits unit cost	[redacted]	[redacted]	[redacted]	Normal
Blood tests unit cost	[redacted]	[redacted]	[redacted]	Normal
Nephrologist visits frequency description	[redacted]	[redacted]	[redacted]	Fixed
Blood tests frequency description	[redacted]	[redacted]	[redacted]	Fixed
Nephrologist visits frequency per year	[redacted]	[redacted]	[redacted]	Normal

Blood tests frequency per year	[redacted]	[redacted]	[redacted]	Normal
Tacrolimus Cost per pack	[redacted]	[redacted]	[redacted]	Fixed
Tacrolimus Size (mg)	[redacted]	[redacted]	[redacted]	Fixed
Tacrolimus Pack size	[redacted]	[redacted]	[redacted]	Fixed
Tacrolimus Dose description	[redacted]	[redacted]	[redacted]	Fixed
Tacrolimus Annual freq	[redacted]	[redacted]	[redacted]	Fixed
Hospitalisation unit cost	[redacted]	[redacted]	[redacted]	Fixed
Hospitalisation frequency description	[redacted]	[redacted]	[redacted]	Fixed
Hospitalisation frequency per year	[redacted]	[redacted]	[redacted]	Fixed
Terminal care unit cost	[redacted]	[redacted]	[redacted]	Normal
Cryptococcal meningitis	[redacted]	[redacted]	[redacted]	Normal
Cushingoid	[redacted]	[redacted]	[redacted]	Normal
Diabetes mellitus	[redacted]	[redacted]	[redacted]	Normal
Dyspepsia	[redacted]	[redacted]	[redacted]	Normal
Dyspnea	[redacted]	[redacted]	[redacted]	Normal
Gastrointestinal bleeding requiring hospitalization	[redacted]	[redacted]	[redacted]	Normal
Gastrointestinal disorder	[redacted]	[redacted]	[redacted]	Normal
Hematologic disorder	[redacted]	[redacted]	[redacted]	Normal
Headache	[redacted]	[redacted]	[redacted]	Normal
Herpes zoster	[redacted]	[redacted]	[redacted]	Normal
Hypertension	[redacted]	[redacted]	[redacted]	Normal
Impaired glucose tolerance	[redacted]	[redacted]	[redacted]	Normal
Knee empyema	[redacted]	[redacted]	[redacted]	Normal
Macrocytic anemia	[redacted]	[redacted]	[redacted]	Normal
Multiple skin infection	[redacted]	[redacted]	[redacted]	Normal
Nocardia infection	[redacted]	[redacted]	[redacted]	Normal
Osteonecrosis	[redacted]	[redacted]	[redacted]	Normal
Other infection	[redacted]	[redacted]	[redacted]	Normal
Perianal abscess	[redacted]	[redacted]	[redacted]	Normal
Pleuritis	[redacted]	[redacted]	[redacted]	Normal
Pneumocystis jirovecii pneumonia	[redacted]	[redacted]	[redacted]	Normal
Pneumogenic sepsis	[redacted]	[redacted]	[redacted]	Normal
Pulmonary embolism	[redacted]	[redacted]	[redacted]	Normal
Renal impairment	[redacted]	[redacted]	[redacted]	Normal
Scrotal tumor	[redacted]	[redacted]	[redacted]	Normal
Sigma-diverticulitis	[redacted]	[redacted]	[redacted]	Normal
Transaminase + creatinine increase	[redacted]	[redacted]	[redacted]	Normal
Tuberculosis with bacterial infection	[redacted]	[redacted]	[redacted]	Normal

Upper respiratory tract infection	[redacted]	[redacted]	[redacted]	Normal
Urinary tract infection	[redacted]	[redacted]	[redacted]	Normal
Coronavirus infection	[redacted]	[redacted]	[redacted]	Normal
Pneumonia	[redacted]	[redacted]	[redacted]	Normal
Acute kidney injury	[redacted]	[redacted]	[redacted]	Normal
Hypertension - severe	[redacted]	[redacted]	[redacted]	Normal
White blood cell count increased	[redacted]	[redacted]	[redacted]	Normal
Neutrophil count increased	[redacted]	[redacted]	[redacted]	Normal
Acute myocardinal infarction	[redacted]	[redacted]	[redacted]	Normal
Cardiac failure	[redacted]	[redacted]	[redacted]	Normal
Ischaemic stroke	[redacted]	[redacted]	[redacted]	Normal
Patient time - Hospitalisations dialysis	[redacted]	[redacted]	[redacted]	Fixed
Patient time - Nephrologist visit haemodialysis	[redacted]	[redacted]	[redacted]	Fixed
Patient time - Nephrologist visit peritonealdialysis	[redacted]	[redacted]	[redacted]	Fixed
Patient time - Haemodialysis hospital	[redacted]	[redacted]	[redacted]	Fixed
Patient time - Haemodialysis home	[redacted]	[redacted]	[redacted]	Fixed
Patient time - Peritoneal dialysis	[redacted]	[redacted]	[redacted]	Fixed
Patient time - CKD 1	[redacted]	[redacted]	[redacted]	Fixed
Patient time - CKD 2	[redacted]	[redacted]	[redacted]	Fixed
Patient time - CKD 3a	[redacted]	[redacted]	[redacted]	Fixed
Patient time - CKD 3b	[redacted]	[redacted]	[redacted]	Fixed
Patient time - CKD 4	[redacted]	[redacted]	[redacted]	Fixed
Patient time - CKD 5	[redacted]	[redacted]	[redacted]	Fixed
Patient time - CKD 1 (primary care)	[redacted]	[redacted]	[redacted]	Fixed
Patient time - CKD 2 (primary care)	[redacted]	[redacted]	[redacted]	Fixed
Patient time - CKD 3a (primary care)	[redacted]	[redacted]	[redacted]	Fixed
Patient time - CKD 3b (primary care)	[redacted]	[redacted]	[redacted]	Fixed
Patient time - CKD 4 (primary care)	[redacted]	[redacted]	[redacted]	Fixed
Patient time - CKD 5 (primary care)	[redacted]	[redacted]	[redacted]	Fixed
Patient time - Pre-assessment	[redacted]	[redacted]	[redacted]	Fixed
Patient time - Procedure cost	[redacted]	[redacted]	[redacted]	Fixed
Patient time - Post-transplant assessment	[redacted]	[redacted]	[redacted]	Fixed

Patient time - Nephrologist visits (maintenance transplant)	[redacted]	[redacted]	[redacted]	Fixed
Patient time - Hospitalisations transplant	[redacted]	[redacted]	[redacted]	Fixed
Patient time (hourly)	[redacted]	[redacted]	[redacted]	Fixed
Transport cost (round trip)	[redacted]	[redacted]	[redacted]	Fixed
Transportation time	[redacted]	[redacted]	[redacted]	Fixed
Cooper et al. 2020 - Utility: CKD 1	[redacted]	[redacted]	[redacted]	Beta
Cooper et al. 2020 - Utility: CKD 2	[redacted]	[redacted]	[redacted]	Beta
Cooper et al. 2020 - Utility: CKD 3a	[redacted]	[redacted]	[redacted]	Beta
Cooper et al. 2020 - Utility: CKD 3b	[redacted]	[redacted]	[redacted]	Beta
Cooper et al. 2020 - Utility: CKD 4	[redacted]	[redacted]	[redacted]	Beta
Cooper et al. 2020 - Utility: CKD 5	[redacted]	[redacted]	[redacted]	Beta
Gorodestskaya et al. 2020 - Utility: CKD 1	[redacted]	[redacted]	[redacted]	Beta
Gorodestskaya et al. 2020 - Utility: CKD 2	[redacted]	[redacted]	[redacted]	Beta
Gorodestskaya et al. 2020 - Utility: CKD 3a	[redacted]	[redacted]	[redacted]	Beta
Gorodestskaya et al. 2020 - Utility: CKD 3b	[redacted]	[redacted]	[redacted]	Beta
Gorodestskaya et al. 2020 - Utility: CKD 4	[redacted]	[redacted]	[redacted]	Beta
Gorodestskaya et al. 2020 - Utility: CKD 5	[redacted]	[redacted]	[redacted]	Beta
Utility: Haemodialysis	[redacted]	[redacted]	[redacted]	Beta
Utility: Peritoneal dialysis	[redacted]	[redacted]	[redacted]	Beta
Utility: Post-transplant	[redacted]	[redacted]	[redacted]	Beta
Acne disutility	[redacted]	[redacted]	[redacted]	Beta
Cryptococcal meningitis disutility	[redacted]	[redacted]	[redacted]	Beta
Cushingoid disutility	[redacted]	[redacted]	[redacted]	Beta
Diabetes mellitus disutility	[redacted]	[redacted]	[redacted]	Beta
Dyspepsia disutility	[redacted]	[redacted]	[redacted]	Beta
Dyspnea disutility	[redacted]	[redacted]	[redacted]	Beta
Face oedema disutility	[redacted]	[redacted]	[redacted]	Beta
Gastrointestinal bleeding requiring hospitalization disutility	[redacted]	[redacted]	[redacted]	Beta
Gastrointestinal disorder disutility	[redacted]	[redacted]	[redacted]	Beta

Hematologic disorder disutility	[redacted]	[redacted]	[redacted]	Beta
Headache disutility	[redacted]	[redacted]	[redacted]	Beta
Herpes zoster disutility	[redacted]	[redacted]	[redacted]	Beta
Hirsutism disutility	[redacted]	[redacted]	[redacted]	Beta
Hypertension disutility	[redacted]	[redacted]	[redacted]	Beta
Impaired glucose tolerance disutility	[redacted]	[redacted]	[redacted]	Beta
Knee empyema disutility	[redacted]	[redacted]	[redacted]	Beta
Macrocytic anemia disutility	[redacted]	[redacted]	[redacted]	Beta
Mood swings disutility	[redacted]	[redacted]	[redacted]	Beta
Multiple skin infection disutility	[redacted]	[redacted]	[redacted]	Beta
Nocardia infection disutility	[redacted]	[redacted]	[redacted]	Beta
Oedema peripheral disutility	[redacted]	[redacted]	[redacted]	Beta
Osteonecrosis disutility	[redacted]	[redacted]	[redacted]	Beta
Other infection disutility	[redacted]	[redacted]	[redacted]	Beta
Perianal abscess disutility	[redacted]	[redacted]	[redacted]	Beta
Pleuritis disutility	[redacted]	[redacted]	[redacted]	Beta
Pneumocystis jirovecii pneumonia disutility	[redacted]	[redacted]	[redacted]	Beta
Pneumogenic sepsis disutility	[redacted]	[redacted]	[redacted]	Beta
Pulmonary embolism disutility	[redacted]	[redacted]	[redacted]	Beta
Renal impairment disutility	[redacted]	[redacted]	[redacted]	Beta
Scrotal tumor disutility	[redacted]	[redacted]	[redacted]	Beta
Sigma-diverticulitis disutility	[redacted]	[redacted]	[redacted]	Beta
Transaminase + creatinine increase disutility	[redacted]	[redacted]	[redacted]	Beta
Tuberculosis with bacterial infection disutility	[redacted]	[redacted]	[redacted]	Beta
Upper respiratory tract infection disutility	[redacted]	[redacted]	[redacted]	Beta
Urinary tract infection disutility	[redacted]	[redacted]	[redacted]	Beta
Weight increase disutility	[redacted]	[redacted]	[redacted]	Beta
Coronavirus infection disutility	[redacted]	[redacted]	[redacted]	Beta
Pneumonia disutility	[redacted]	[redacted]	[redacted]	Beta

Acute kidney injury disutility	[redacted]	[redacted]	[redacted]	Beta
Hypertension - severe disutility	[redacted]	[redacted]	[redacted]	Beta
White blood cell count increased disutility	[redacted]	[redacted]	[redacted]	Beta
Neutrophil count increased disutility	[redacted]	[redacted]	[redacted]	Beta
Acute myocardinal infarction disutility	[redacted]	[redacted]	[redacted]	Beta
Cardiac failure disutility	[redacted]	[redacted]	[redacted]	Beta
Ischaemic stroke disutility	[redacted]	[redacted]	[redacted]	Beta
Acne duration (days)	[redacted]	[redacted]	[redacted]	Normal
Cryptococcal meningitis duration (days)	[redacted]	[redacted]	[redacted]	Normal
Cushingoid duration (days)	[redacted]	[redacted]	[redacted]	Normal
Diabetes mellitus duration (days)	[redacted]	[redacted]	[redacted]	Normal
Dyspepsia duration (days)	[redacted]	[redacted]	[redacted]	Normal
Dyspnea duration (days)	[redacted]	[redacted]	[redacted]	Normal
Face oedema duration (days)	[redacted]	[redacted]	[redacted]	Normal
Gastrointestinal bleeding requiring hospitalization duration (days)	[redacted]	[redacted]	[redacted]	Normal
Gastrointestinal disorder duration (days)	[redacted]	[redacted]	[redacted]	Normal
Hematologic disorder duration (days)	[redacted]	[redacted]	[redacted]	Normal
Headache duration (days)	[redacted]	[redacted]	[redacted]	Normal
Herpes zoster duration (days)	[redacted]	[redacted]	[redacted]	Normal
Hirsutism duration (days)	[redacted]	[redacted]	[redacted]	Normal
Hypertension duration (days)	[redacted]	[redacted]	[redacted]	Normal
Impaired glucose tolerance duration (days)	[redacted]	[redacted]	[redacted]	Normal
Knee empyema duration (days)	[redacted]	[redacted]	[redacted]	Normal
Macrocytic anemia duration (days)	[redacted]	[redacted]	[redacted]	Normal
Mood swings duration (days)	[redacted]	[redacted]	[redacted]	Normal

Multiple skin infection duration (days)	[redacted]	[redacted]	[redacted]	Normal
Nocardia infection duration (days)	[redacted]	[redacted]	[redacted]	Normal
Oedema peripheral duration (days)	[redacted]	[redacted]	[redacted]	Normal
Osteonecrosis duration (days)	[redacted]	[redacted]	[redacted]	Normal
Other infection duration (days)	[redacted]	[redacted]	[redacted]	Normal
Perianal abscess duration (days)	[redacted]	[redacted]	[redacted]	Normal
Pleuritis duration (days)	[redacted]	[redacted]	[redacted]	Normal
Pneumocystis jirovecii pneumonia duration (days)	[redacted]	[redacted]	[redacted]	Normal
Pneumogenic sepsis duration (days)	[redacted]	[redacted]	[redacted]	Normal
Pulmonary embolism duration (days)	[redacted]	[redacted]	[redacted]	Normal
Renal impairment duration (days)	[redacted]	[redacted]	[redacted]	Normal
Scrotal tumor duration (days)	[redacted]	[redacted]	[redacted]	Normal
Sigma-diverticulitis duration (days)	[redacted]	[redacted]	[redacted]	Normal
Transaminase + creatinine increase duration (days)	[redacted]	[redacted]	[redacted]	Normal
Tuberculosis with bacterial infection duration (days)	[redacted]	[redacted]	[redacted]	Normal
Upper respiratory tract infection duration (days)	[redacted]	[redacted]	[redacted]	Normal
Urinary tract infection duration (days)	[redacted]	[redacted]	[redacted]	Normal
Weight increase duration (days)	[redacted]	[redacted]	[redacted]	Normal
Coronavirus infection duration (days)	[redacted]	[redacted]	[redacted]	Normal
Pneumonia duration (days)	[redacted]	[redacted]	[redacted]	Normal
Acute kidney injury duration (days)	[redacted]	[redacted]	[redacted]	Normal
Hypertension - severe duration (days)	[redacted]	[redacted]	[redacted]	Normal
White blood cell count increased duration (days)	[redacted]	[redacted]	[redacted]	Normal
Neutrophil count increased duration (days)	[redacted]	[redacted]	[redacted]	Normal

Acute myocardinal infarction duration (days)	[redacted]	[redacted]	[redacted]	Normal
Cardiac failure duration (days)	[redacted]	[redacted]	[redacted]	Normal
Ischaemic stroke duration (days)	[redacted]	[redacted]	[redacted]	Normal
Transition: CKD 5 to Dialysis	[redacted]	[redacted]	[redacted]	Beta
Transition: CKD 5 to Transplant	[redacted]	[redacted]	[redacted]	Beta
Transition: Dialysis to Transplant	[redacted]	[redacted]	[redacted]	Beta
Transition: Transplant to Dialysis	[redacted]	[redacted]	[redacted]	Beta
Control: (Progressed disease)Variance covariance matrix - Intercept	[redacted]	[redacted]	[redacted]	Fixed
Control: (Progressed disease)Variance covariance matrix - Baseline UPCR	[redacted]	[redacted]	[redacted]	Fixed
Control: (Progressed disease)Variance covariance matrix - Kinpeygo	[redacted]	[redacted]	[redacted]	Fixed
Control: (Progressed disease)Variance covariance matrix - CKD 1	[redacted]	[redacted]	[redacted]	Fixed
Control: (Progressed disease)Variance covariance matrix - CKD 2	[redacted]	[redacted]	[redacted]	Fixed
Control: (Progressed disease)Variance covariance matrix - CKD 3a	[redacted]	[redacted]	[redacted]	Fixed
Control: (Progressed disease)Variance covariance matrix - Intercept	[redacted]	[redacted]	[redacted]	Fixed
Control: (Progressed disease)Variance covariance matrix - Baseline UPCR	[redacted]	[redacted]	[redacted]	Fixed
Control: (Progressed disease)Variance covariance matrix - CKD 1	[redacted]	[redacted]	[redacted]	Fixed
Control: (Progressed disease)Variance	[redacted]	[redacted]	[redacted]	Fixed

covariance matrix - CKD 2				
Control: (Progressed disease)Variance covariance matrix - CKD 3a	[redacted]	[redacted]	[redacted]	Fixed
Control: Exponential: Rate	[redacted]	[redacted]	[redacted]	Fixed
Control: Generalised gamma: mu	[redacted]	[redacted]	[redacted]	Fixed
Control: Generalised gamma: sigma	[redacted]	[redacted]	[redacted]	Fixed
Control: Generalised gamma: Q	[redacted]	[redacted]	[redacted]	Fixed
Control: Gompertz: shape	[redacted]	[redacted]	[redacted]	Fixed
Control: Gompertz: rate	[redacted]	[redacted]	[redacted]	Fixed
Control: Log-Logistic: shape	[redacted]	[redacted]	[redacted]	Fixed
Control: Log-Logistic: scale	[redacted]	[redacted]	[redacted]	Fixed
Control: Log-Normal: meanLog	[redacted]	[redacted]	[redacted]	Fixed
Control: Log-Normal: sdLog	[redacted]	[redacted]	[redacted]	Fixed
Control: Weibull: shape	[redacted]	[redacted]	[redacted]	Fixed
Control: Weibull: scale	[redacted]	[redacted]	[redacted]	Fixed
Control: Gamma: shape	[redacted]	[redacted]	[redacted]	Fixed
Control: Gamma: rate	[redacted]	[redacted]	[redacted]	Fixed
Kinpeygo: Acne	[redacted]	[redacted]	[redacted]	Normal
Kinpeygo: Cryptococcal meningitis	[redacted]	[redacted]	[redacted]	Normal
Kinpeygo: Cushingoid	[redacted]	[redacted]	[redacted]	Normal
Kinpeygo: Diabetes mellitus	[redacted]	[redacted]	[redacted]	Normal
Kinpeygo: Dyspepsia	[redacted]	[redacted]	[redacted]	Normal
Kinpeygo: Dyspnea	[redacted]	[redacted]	[redacted]	Normal
Kinpeygo: Face oedema	[redacted]	[redacted]	[redacted]	Normal
Kinpeygo: Gastrointestinal bleeding requiring hospitalization	[redacted]	[redacted]	[redacted]	Normal
Kinpeygo: Gastrointestinal disorder	[redacted]	[redacted]	[redacted]	Normal
Kinpeygo: Hematologic disorder	[redacted]	[redacted]	[redacted]	Normal
Kinpeygo: Headache	[redacted]	[redacted]	[redacted]	Normal

Kinpeygo: Herpes zoster	[redacted]	[redacted]	[redacted]	Normal
Kinpeygo: Hirsutism	[redacted]	[redacted]	[redacted]	Normal
Kinpeygo: Hypertension	[redacted]	[redacted]	[redacted]	Normal
Kinpeygo: Impaired glucose tolerance	[redacted]	[redacted]	[redacted]	Normal
Kinpeygo: Knee empyema	[redacted]	[redacted]	[redacted]	Normal
Kinpeygo: Macrocytic anemia	[redacted]	[redacted]	[redacted]	Normal
Kinpeygo: Mood swings	[redacted]	[redacted]	[redacted]	Normal
Kinpeygo: Multiple skin infection	[redacted]	[redacted]	[redacted]	Normal
Kinpeygo: Nocardia infection	[redacted]	[redacted]	[redacted]	Normal
Kinpeygo: Oedema peripheral	[redacted]	[redacted]	[redacted]	Normal
Kinpeygo: Osteonecrosis	[redacted]	[redacted]	[redacted]	Normal
Kinpeygo: Other infection	[redacted]	[redacted]	[redacted]	Normal
Kinpeygo: Perianal abscess	[redacted]	[redacted]	[redacted]	Normal
Kinpeygo: Pleuritis	[redacted]	[redacted]	[redacted]	Normal
Kinpeygo: Pneumocystis jirovecii pneumonia	[redacted]	[redacted]	[redacted]	Normal
Kinpeygo: Pneumogenic sepsis	[redacted]	[redacted]	[redacted]	Normal
Kinpeygo: Pulmonary embolism	[redacted]	[redacted]	[redacted]	Normal
Kinpeygo: Renal impairment	[redacted]	[redacted]	[redacted]	Normal
Kinpeygo: Scrotal tumor	[redacted]	[redacted]	[redacted]	Normal
Kinpeygo: Sigma-diverticulitis	[redacted]	[redacted]	[redacted]	Normal
Kinpeygo: Transaminase + creatinine increase	[redacted]	[redacted]	[redacted]	Normal
Kinpeygo: Tuberculosis with bacterial infection	[redacted]	[redacted]	[redacted]	Normal
Kinpeygo: Upper respiratory tract infection	[redacted]	[redacted]	[redacted]	Normal
Kinpeygo: Urinary tract infection	[redacted]	[redacted]	[redacted]	Normal
Kinpeygo: Weight increase	[redacted]	[redacted]	[redacted]	Normal
Kinpeygo: Coronavirus infection	[redacted]	[redacted]	[redacted]	Normal

Kinpeygo: Pneumonia	[redacted]	[redacted]	[redacted]	Normal
Kinpeygo: Acute kidney injury	[redacted]	[redacted]	[redacted]	Normal
Kinpeygo: Hypertension - severe	[redacted]	[redacted]	[redacted]	Normal
Kinpeygo: White blood cell count increased	[redacted]	[redacted]	[redacted]	Normal
Kinpeygo: Neutrophil count increased	[redacted]	[redacted]	[redacted]	Normal
Kinpeygo: Acute myocardinal infarction	[redacted]	[redacted]	[redacted]	Normal
Kinpeygo: Cardiac failure	[redacted]	[redacted]	[redacted]	Normal
Kinpeygo: Ischaemic stroke	[redacted]	[redacted]	[redacted]	Normal
SoC: Acne	[redacted]	[redacted]	[redacted]	Normal
SoC: Cryptococcal meningitis	[redacted]	[redacted]	[redacted]	Normal
SoC: Cushingoid	[redacted]	[redacted]	[redacted]	Normal
SoC: Diabetes mellitus	[redacted]	[redacted]	[redacted]	Normal
SoC: Dyspepsia	[redacted]	[redacted]	[redacted]	Normal
SoC: Dyspnea	[redacted]	[redacted]	[redacted]	Normal
SoC: Face oedema	[redacted]	[redacted]	[redacted]	Normal
SoC: Gastrointestinal bleeding requiring hospitalization	[redacted]	[redacted]	[redacted]	Normal
SoC: Gastrointestinal disorder	[redacted]	[redacted]	[redacted]	Normal
SoC: Hematologic disorder	[redacted]	[redacted]	[redacted]	Normal
SoC: Headache	[redacted]	[redacted]	[redacted]	Normal
SoC: Herpes zoster	[redacted]	[redacted]	[redacted]	Normal
SoC: Hirsutism	[redacted]	[redacted]	[redacted]	Normal
SoC: Hypertension	[redacted]	[redacted]	[redacted]	Normal
SoC: Impaired glucose tolerance	[redacted]	[redacted]	[redacted]	Normal
SoC: Knee empyema	[redacted]	[redacted]	[redacted]	Normal
SoC: Macrocytic anemia	[redacted]	[redacted]	[redacted]	Normal
SoC: Mood swings	[redacted]	[redacted]	[redacted]	Normal
SoC: Multiple skin infection	[redacted]	[redacted]	[redacted]	Normal
SoC: Nocardia infection	[redacted]	[redacted]	[redacted]	Normal
SoC: Oedema peripheral	[redacted]	[redacted]	[redacted]	Normal
SoC: Osteonecrosis	[redacted]	[redacted]	[redacted]	Normal
SoC: Other infection	[redacted]	[redacted]	[redacted]	Normal
SoC: Perianal abscess	[redacted]	[redacted]	[redacted]	Normal
SoC: Pleuritis	[redacted]	[redacted]	[redacted]	Normal
SoC: Pneumocystis jirovecii pneumonia	[redacted]	[redacted]	[redacted]	Normal
SoC: Pneumogenic sepsis	[redacted]	[redacted]	[redacted]	Normal

SoC: Pulmonary embolism	[redacted]	[redacted]	[redacted]	Normal
SoC: Renal impairment	[redacted]	[redacted]	[redacted]	Normal
SoC: Scrotal tumor	[redacted]	[redacted]	[redacted]	Normal
SoC: Sigma-diverticulitis	[redacted]	[redacted]	[redacted]	Normal
SoC: Transaminase + creatinine increase	[redacted]	[redacted]	[redacted]	Normal
SoC: Tuberculosis with bacterial infection	[redacted]	[redacted]	[redacted]	Normal
SoC: Upper respiratory tract infection	[redacted]	[redacted]	[redacted]	Normal
SoC: Urinary tract infection	[redacted]	[redacted]	[redacted]	Normal
SoC: Weight increase	[redacted]	[redacted]	[redacted]	Normal
SoC: Coronavirus infection	[redacted]	[redacted]	[redacted]	Normal
SoC: Pneumonia	[redacted]	[redacted]	[redacted]	Normal
SoC: Acute kidney injury	[redacted]	[redacted]	[redacted]	Normal
SoC: Hypertension - severe	[redacted]	[redacted]	[redacted]	Normal
SoC: White blood cell count increased	[redacted]	[redacted]	[redacted]	Normal
SoC: Neutrophil count increased	[redacted]	[redacted]	[redacted]	Normal
SoC: Acute myocardinal infarction	[redacted]	[redacted]	[redacted]	Normal
SoC: Cardiac failure	[redacted]	[redacted]	[redacted]	Normal
SoC: Ischaemic stroke	[redacted]	[redacted]	[redacted]	Normal
Corticosteroids: Acne	[redacted]	[redacted]	[redacted]	Normal
Corticosteroids: Cryptococcal meningitis	[redacted]	[redacted]	[redacted]	Normal
Corticosteroids: Cushingoid	[redacted]	[redacted]	[redacted]	Normal
Corticosteroids: Diabetes mellitus	[redacted]	[redacted]	[redacted]	Normal
Corticosteroids: Dyspepsia	[redacted]	[redacted]	[redacted]	Normal
Corticosteroids: Dyspnea	[redacted]	[redacted]	[redacted]	Normal
Corticosteroids: Face oedema	[redacted]	[redacted]	[redacted]	Normal
Corticosteroids: Gastrointestinal bleeding requiring hospitalization	[redacted]	[redacted]	[redacted]	Normal
Corticosteroids: Gastrointestinal disorder	[redacted]	[redacted]	[redacted]	Normal
Corticosteroids: Hematologic disorder	[redacted]	[redacted]	[redacted]	Normal

Corticosteroids: Headache	[redacted]	[redacted]	[redacted]	Normal
Corticosteroids: Herpes zoster	[redacted]	[redacted]	[redacted]	Normal
Corticosteroids: Hirsutism	[redacted]	[redacted]	[redacted]	Normal
Corticosteroids: Hypertension	[redacted]	[redacted]	[redacted]	Normal
Corticosteroids: Impaired glucose tolerance	[redacted]	[redacted]	[redacted]	Normal
Corticosteroids: Knee empyema	[redacted]	[redacted]	[redacted]	Normal
Corticosteroids: Macrocytic anemia	[redacted]	[redacted]	[redacted]	Normal
Corticosteroids: Mood swings	[redacted]	[redacted]	[redacted]	Normal
Corticosteroids: Multiple skin infection	[redacted]	[redacted]	[redacted]	Normal
Corticosteroids: Nocardia infection	[redacted]	[redacted]	[redacted]	Normal
Corticosteroids: Oedema peripheral	[redacted]	[redacted]	[redacted]	Normal
Corticosteroids: Osteonecrosis	[redacted]	[redacted]	[redacted]	Normal
Corticosteroids: Other infection	[redacted]	[redacted]	[redacted]	Normal
Corticosteroids: Perianal abscess	[redacted]	[redacted]	[redacted]	Normal
Corticosteroids: Pleuritis	[redacted]	[redacted]	[redacted]	Normal
Corticosteroids: Pneumocystis jirovecii pneumonia	[redacted]	[redacted]	[redacted]	Normal
Corticosteroids: Pneumogenic sepsis	[redacted]	[redacted]	[redacted]	Normal
Corticosteroids: Pulmonary embolism	[redacted]	[redacted]	[redacted]	Normal
Corticosteroids: Renal impairment	[redacted]	[redacted]	[redacted]	Normal
Corticosteroids: Scrotal tumor	[redacted]	[redacted]	[redacted]	Normal
Corticosteroids: Sigma-diverticulitis	[redacted]	[redacted]	[redacted]	Normal
Corticosteroids: Transaminase + creatinine increase	[redacted]	[redacted]	[redacted]	Normal
Corticosteroids: Tuberculosis with bacterial infection	[redacted]	[redacted]	[redacted]	Normal
Corticosteroids: Upper respiratory tract infection	[redacted]	[redacted]	[redacted]	Normal

Corticosteroids: Urinary tract infection	[redacted]	[redacted]	[redacted]	Normal
Corticosteroids: Weight increase	[redacted]	[redacted]	[redacted]	Normal
Corticosteroids: Coronavirus infection	[redacted]	[redacted]	[redacted]	Normal
Corticosteroids: Pneumonia	[redacted]	[redacted]	[redacted]	Normal
Corticosteroids: Acute kidney injury	[redacted]	[redacted]	[redacted]	Normal
Corticosteroids: Hypertension - severe	[redacted]	[redacted]	[redacted]	Normal
Corticosteroids: White blood cell count increased	[redacted]	[redacted]	[redacted]	Normal
Corticosteroids: Neutrophil count increased	[redacted]	[redacted]	[redacted]	Normal
Corticosteroids: Acute myocardial infarction	[redacted]	[redacted]	[redacted]	Normal
Corticosteroids: Cardiac failure	[redacted]	[redacted]	[redacted]	Normal
Corticosteroids: Ischaemic stroke	[redacted]	[redacted]	[redacted]	Normal

Appendix H. Literature searches for the clinical assessment

H.1 Efficacy and safety of the intervention and comparator(s)

The objective of the systematic literature review (SLR) was to assess the efficacy, safety and HRQoL outcomes in patients with primary IgAN treated with TRF-budesonide in comparison to established management. This section

Summary of methods (more information presented in Sections H.1.1 to H.1.5)
The following sources were searched on 3rd November 2022: Embase, MEDLINE (including Epub Ahead of Print, In-Process & other Non-Indexed Citations, Daily), and Evidence-Based Medicine (EBM) Reviews (incorporating American College of Physicians [ACP] Journal Club, Cochrane Central Register of Controlled Trials [CENTRAL], Cochrane Database of Systematic Reviews, Cochrane Clinical Answers, Cochrane Methodology Register, Database of Abstracts of Reviews of Effects [DARE], health technology assessment (HTA) database, National Health Service Economic Evaluation Database [NHS EED]). Review authors conducted supplementary searches of conference proceedings not covered in Embase, reference lists of included publications, websites of HTA global bodies, the US National Institutes of Health (NIH) registry & results database (https://clinicaltrials.gov) and the World Health Organization International Clinical Trials Registry Platform (WHO ICTRP) (http://apps.who.int/trialsearch/) to identify relevant evidence.

The population of interest was people with primary IgAN. Studies reporting efficacy, safety or HRQoL outcomes for TRF-budesonide, or relevant established treatments, including ACEIs, ARBs, diuretics, dietary and lifestyle modifications, sodium-glucose co-transporter-2 (SGLT-2) inhibitors, systemic glucocorticoids or cyclophosphamide. Outcome measures included change from baseline in urine protein creatinine ratio (UPCR), renal function as measured by estimated glomerular filtration rate (eGFR), disease progression (incidence of dialysis and/or transplant post treatment), mortality rate, survival rates, adverse effects of treatment, and HRQoL measures.

Screening of records for inclusion or exclusion in the review (both at title/abstract and full publication review) was conducted by two independent analysts. Any disputes were resolved by consensus or through the intervention of a third analyst, when necessary. The final list of included studies for extraction was agreed with Britannia Pharmaceuticals Ltd. Data extraction was conducted by one reviewer and checked independently by a second analyst; any disputes were resolved by consensus or by a third reviewer, when necessary. Quality (risk of bias; ROB) assessments of full publications were conducted using the 8-domain tool recommended by the National Institute for Health and Care Excellence (NICE) [173]. Results were described narratively.

The review followed the published systematic review methods of the Cochrane Collaboration [174] and the Centre for Reviews and Dissemination (CRD) (York, UK) [175], to reduce the risk of bias and error. The review was documented in accordance with the reporting recommendations outlined in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [176], including PRISMA-S for the study search strategies [177], see

Figure 33. The eligibility criteria for the clinical assessment are outlined in Table 119.

The electronic databases presented in Table 113 were searched via the Ovid® platform (http://ovidsp.ovid.com/) using the proposed search strategies detailed in Table 126.

Table 113 Bibliographic databases included in the literature search

Database	Platform	Relevant period for the search	Date of search completion
Embase	Ovid	1974 to present	15.11.2022
Medline Incorporating: • MEDLINE Epub Ahead of Print • MEDLINE In-Process & Other Non-Indexed Citations • MEDLINE Daily	Ovid	1946 to present	15.11.2022
EBM Reviews Incorporating: • American College of Physicians (ACP) Journal Club • Cochrane Central Register of Controlled Trials (CENTRAL) • Cochrane Database of Systematic Reviews • Cochrane Clinical Answers • Cochrane Methodology Register • Database of Abstracts of Reviews of Effects (DARE) (1991–2015) • HTA database (2001–2016) • National Health Service Economic Evaluation Database (NHS EED) (1995–2015)	Ovid	• DARE: 1991–2015 • HTA database: 2001–2016 • NHS EED: 1995–2015	15.11.2022
EconLit	Ovid	1886 to present	15.11.2022

Note: Bibliographic details for NHS EED, DARE are only published in EBM Reviews up until March 2015 when the databases ceased. The HTA database is published in EBM reviews up to the end of 2016, potentially relevant articles published post-2016 for the HTA database were identified via The International Network of Agencies for Health Technology Assessment (INAHTA) database website (https://database.inahta.org/).
Abbreviations:

Table 114 Other sources included in the literature search

Source name	Location/source	Search strategy	Date of search
Reference lists	The reference lists of eligible studies (primary studies and relevant systematic reviews) were screened to identify any further relevant		15.11.2022

Source name	Location/source	Search strategy	Date of search
	publications that were not identified as part of the database searches.		
National Institute for Health and Care Excellence (NICE)	https://www.nice.org.uk/	Electronic search	15.11.2022
Scottish Medicines Consortium (SMC)	https://www.scottishmedicines.org.uk/	Electronic search	15.11.2022
Canadian Agency for Drugs and Technologies in Health (CADTH), including the pan-Canadian Oncology Drugs Review (pCODR)	https://www.cadth.ca/	Electronic search	15.11.2022
Pharmaceutical Benefits Scheme (PBS)	https://www.pbs.gov.au/pbs/home	Electronic search	15.11.2022
Agencia Española de Medicamentos y Productos Sanitarios (AEMPS)	https://www.aemps.gob.es/	Electronic search	15.11.2022
Agenzia Italiana del Farmaco (AIFA)	https://www.aifa.gov.it/	Electronic search	15.11.2022
Haute Autorité de Santé (HAS)	https://www.has-sante.fr/	Electronic search	15.11.2022
Institute for Quality and Efficiency in Health Care (IQWiG)	https://www.iqwig.de/	Electronic search	15.11.2022
Institute for Clinical and Economic Review (ICER)	https://icer-review.org/	Electronic search	15.11.2022
US Food and Drug Administration (FDA)	https://www.fda.gov/	Electronic search	15.11.2022
European Medicines Agency (EMA)	https://www.ema.europa.eu/en	Electronic search	15.11.2022
Finnish Coordinating Centre for Heath Technology Assessment (FinCCHTA)	https://oys.fi/fincchta/	Electronic search	15.11.2022
DEFACTUM Social & Health Services and Labour Market	http://www.defactum.net	Electronic search	15.11.2022
Norwegian Institute of Public Health (NIPH)	http://www.fhi.no	Electronic search	15.11.2022

Source name	Location/source	Search strategy	Date of search
Swedish Agency for Health Technology Assessment and Assessment of Social Services [Statens beredning för medicinsk och social utvärdering] (SBU)	https://www.sbu.se/en/	Electronic search	15.11.2022
Dental and Pharmaceutical Benefits Agency [Tandvårds- och läkemedelsförmånsverket] (TLV)	https://www.tlv.se/	Electronic search	15.11.2022
US National Institutes of Health (NIH) registry & results database	https://clinicaltrials.gov	Electronic search	15.11.2022
World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP)	http://apps.who.int/trialsearch/	Electronic search	15.11.2022
EuroQoL website	https://euroqol.org/	Electronic search	15.11.2022
University of Sheffield's ScHARRHUD database	https://www.scharrhud.org/	Electronic search	15.11.2022
CEA Registr	http://healtheconomicsdev.tuftsmedicalcenter.org/cear2/search/search.aspx	Electronic search	15.11.2022
RePEc website (EconPapers)	https://econpapers.repec.org/	Electronic search	15.11.2022
International Network of Agencies for Health Technology Assessment (INAHTA)	https://database.inahta.org/	Electronic search	15.11.2022
National Institute for Health Research (NIHR)	https://www.nihr.ac.uk/	Electronic search	15.11.2022
European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCEPP)	https://www.encepp.eu/	Electronic search	15.11.2022

The conferences listed in Table 115 were searched (last 3 years' availability).

Table 115 Conference material included in the literature search

Conference	Source of abstracts	Search strategy	Words/terms searched	Date of search
American Society of Nephrology (ASN)†	https://www.asn-online.org/	Electronic search	See Table 128	15.11.2022
European Renal Association (ERA)	https://www.era-online.org/	Electronic search	See Table 128	15.11.2022
International IgA Nephropathy Network (IIGANN) International Symposium on IgA Nephropathy†	https://www.iigann2021.com/	Electronic search	See Table 128	15.11.2022
National Kidney Foundation†	https://www.kidney.org/	Electronic search	See Table 128	15.11.2022
International Society of Nephrology (ISN) World Congress of Nephrology (WCN)†	https://www.theisn.org/in-action/events/world-congress-of-nephrology/	Electronic search	See Table 128	15.11.2022

Conference abstracts and proceedings were identified in a two-stage approach. The main Embase® search strategy included conference abstracts and proceedings. †Named conference proceedings that were not indexed in Embase® were manually searched online.

H.1.1 Search strategies

[redacted].

Table 116 of search strategy table for Embase (Ovid): 1974 to 2022 November 02: searched 3.11.22

[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

Table 117 of search strategy table for Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations, Daily and Versions: 1946 to November 02, 2022: searched 3.11.22

[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
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[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

Table 118 of search strategy table for EBM Reviews (Ovid) - Cochrane Methodology Register 3rd Quarter 2012, Database of Abstracts of Reviews of Effects 1st Quarter 2016, Health Technology Assessment 4th Quarter 2016, NHS Economic Evaluation Database 1st Quarter 2016, ACP Journal Club 1991 to October 2022, Cochrane Central Register of Controlled Trials September 2022, Cochrane Database of Systematic Reviews 2005 to November 2, 2022, Cochrane Clinical Answers October 2022: searched 3.11.22

[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

H.1.2 Systematic selection of studies

[redacted]

Table 119. Inclusion and exclusion criteria used for assessment of studies

[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	○ [redacted] ○ [redacted] ○ [redacted] ○ [redacted] ○ [redacted] ○ [redacted] ○ [redacted] ○ [redacted]	[redacted]
[redacted]	[redacted] [redacted]	[redacted]
[redacted]	[redacted]: ○ [redacted] ○ [redacted] ○ [redacted] ○ [redacted] ○ [redacted] [redacted] ○ [redacted] ○ [redacted] ○ [redacted] ○ [redacted] ○ [redacted]	[redacted]

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- [redacted]
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[redacted]	○ [redacted] ○ [redacted]	[redacted]
[redacted]	○ [redacted] ○ [redacted] ○ [redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

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[redacted]

Figure 33. PRISMA flow diagram for the clinical SLR

[redacted]

[redacted]

[redacted]

[redacted]

[redacted] The studies (n=33) included in the SLR but considered non-priority studies are presented in Table 121.

Table 120. Overview of study design for studies included in the analyses

[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]						

[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]						
[redacted]						

[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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			[redacted]			

[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
			[redacted]			

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[redacted]						
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[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		[redacted]				

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[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		[redacted]				

[redacted]

Table 121. Summary of treatment regimens for non-priority studies (n=33)

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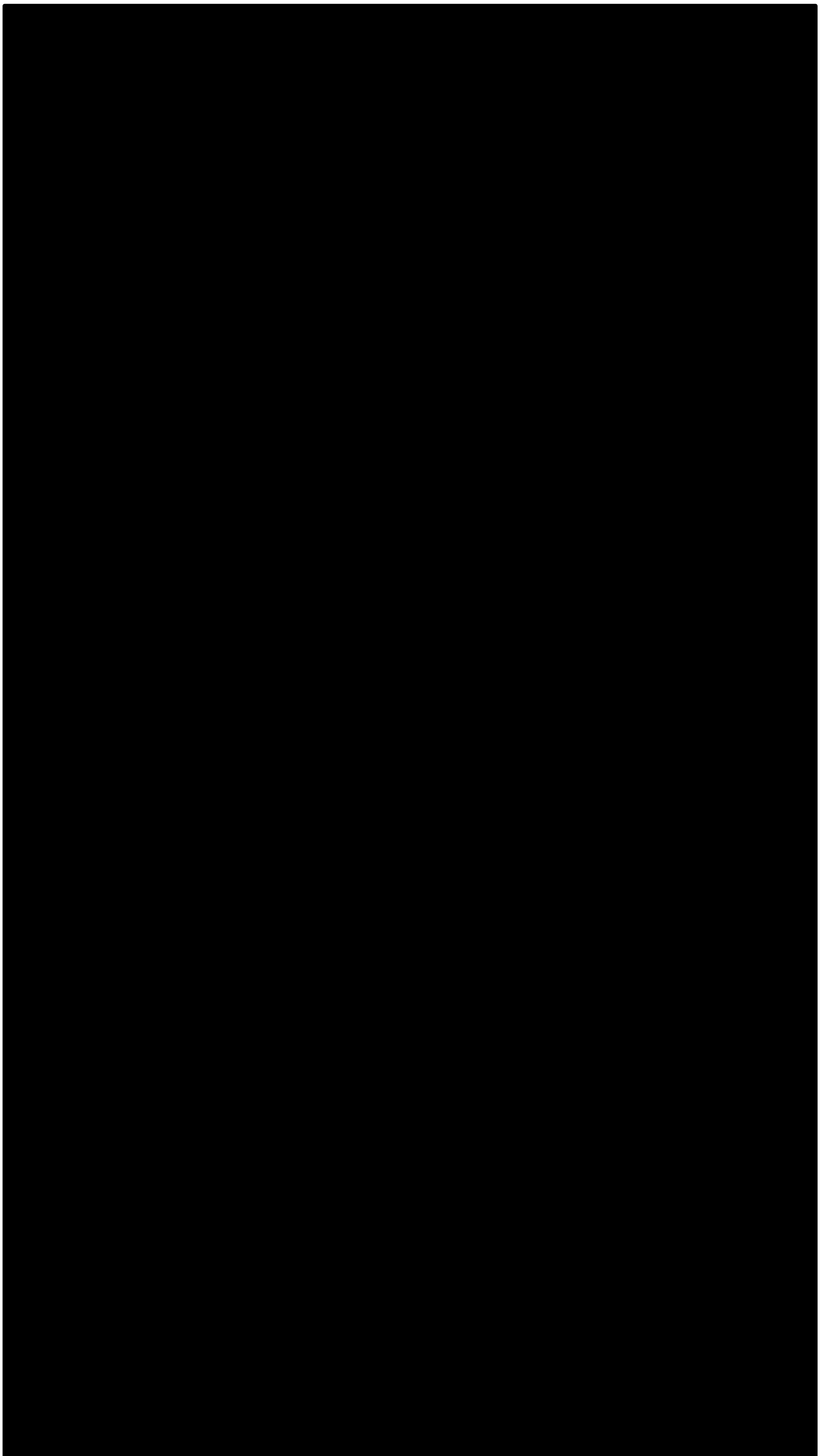
H.1.3 Results

[redacted]

[redacted]

[redacted]



H.1.4 Quality assessment

[redacted]

[redacted]

H.1.5 Unpublished data

Not applicable.

Appendix I. Literature searches for health-related quality of life

I.1 Health-related quality-of-life search

A systematic literature review (SLR) was performed to address the following research question: What health-related quality of life (HRQoL) and heath state utility value (HSUV) outcomes are associated with patients with primary IgAN. Information on the included databases and other sources for which the SLR is based, are the same as those presented in Appendix H, for the clinical assessment.

No UK or Danish-specific EQ-5D studies were identified in the economic systematic literature review (SLR) for patients with IgAN, see Section 10.

Table 122 Bibliographic databases included in the literature search

Database	Platform/source	Relevant period for the search	Date of search completion
See Table 122 in Appendix H			

Table 123 Other sources included in the literature search

Source name	Location/source	Search strategy	Date of search
See Table 123 in Appendix H			

Table 124 Conference material included in the literature search

Conference	Source of abstracts	Search strategy	Words/terms searched	Date of search
See Table 124 in Appendix H				

I.1.1 Search strategies

The SLR for QoL/HSUV was based on the inclusion and exclusion criteria outlined in Table 125.

Table 125. Inclusion and exclusion criteria used for QoL/HSUV SLR

[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	
[redacted]	[redacted]	
[redacted]	[redacted]	

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Table 126 Search strategy for Embase (Ovid): 1974 to 2022 November 14: searched 15.11.22

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Table 127. Search strategy for Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations, Daily and Versions: 1946 to November 14, 2022: searched 15.11.22

[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
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Table 128. EBM Reviews (Ovid): Cochrane Methodology Register 3rd Quarter 2012, Database of Abstracts of Reviews of Effects 1st Quarter 2016, Health Technology Assessment 4th Quarter 2016, NHS Economic Evaluation Database 1st Quarter 2016, ACP Journal Club 1991 to

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I.1.1.1 Results

[redacted]

Table 129.Summary of results for studies reporting mean utility data for patients with IgAN (n=4)

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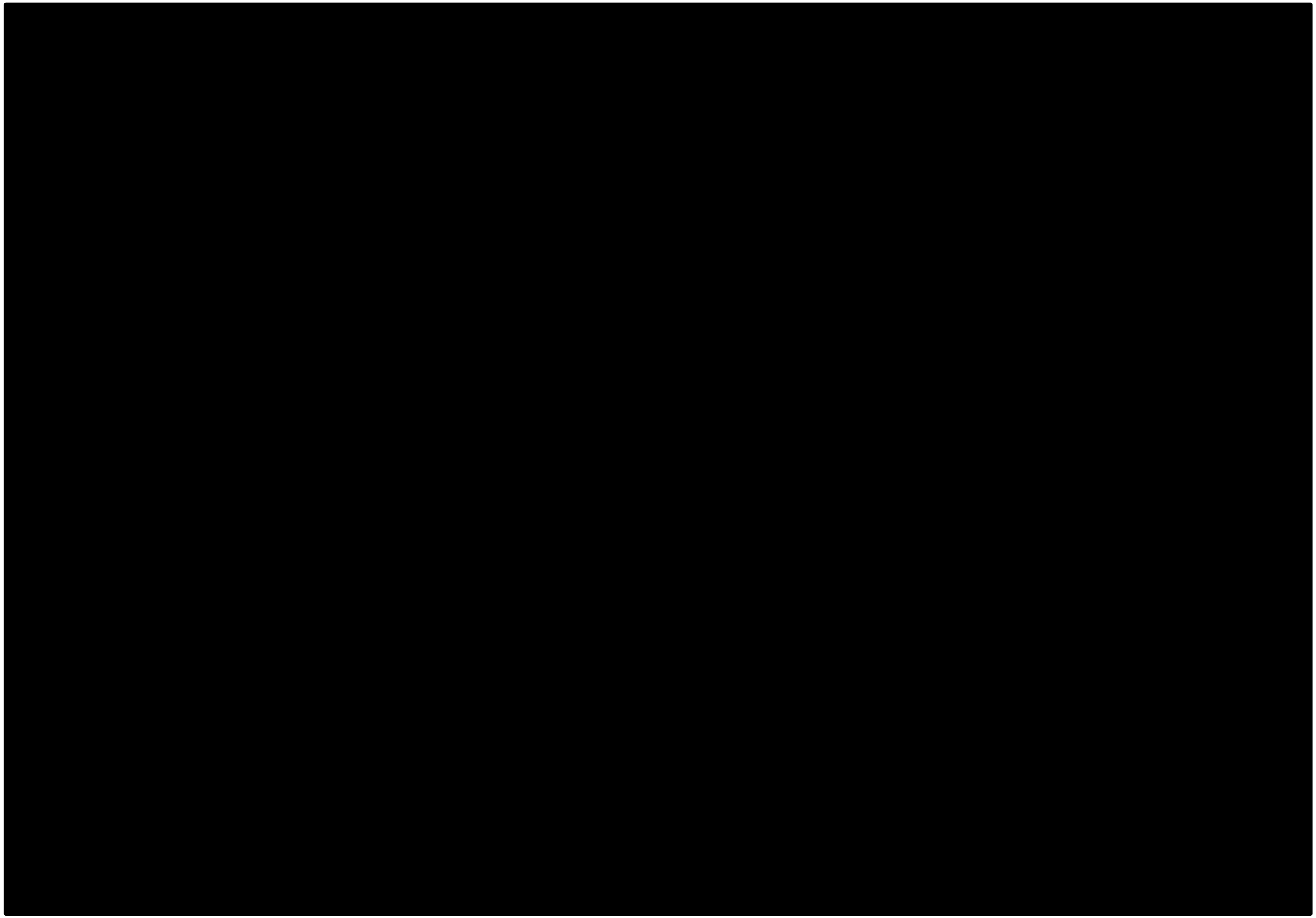
[redacted]						



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I.1.1.1.1 Identification of studies

[redacted]

[redacted]

None of the studies met the requirements for use as HTA reference case.

Figure 34. PRISMA flow diagram for QoL/HSUV SLR

[redacted]

Table 130. Summary of included QoL/HSUV studies (n=6)

[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]				

I.1.2 Quality assessment and generalizability of estimates

No UK or Danish-specific EQ-5D studies were identified in the search for patients with IgAN and does not form the basis of the health economic analysis, an assessment of their generalizability to the Danish population is not applicable.

I.1.3 Unpublished data

Not applicable.

Appendix J. Literature searches for input to the health economic model

J.1 External literature for input to the health economic model

An economic systematic literature review (SLR) conducted at initial model development did not identify any UK (nor Danish) cost-effectiveness analyses for IgAN. Therefore, it was necessary to develop a de novo economic model to determine the cost-effectiveness of Kinpeygo versus relevant comparators for the treatment of patients with IgAN at risk of rapid disease progression with a UPCR ≥1.5 g/g.

J.1.1 Systematic search for the health economic model

Not applicable.

Table 131 Sources included in the search

Database	Platform/source	Relevant period for the search	Date of search completion
Embase	N/A	N/A	N/A
Medline	N/A	N/A	N/A
CENTRAL	N/A	N/A	N/A

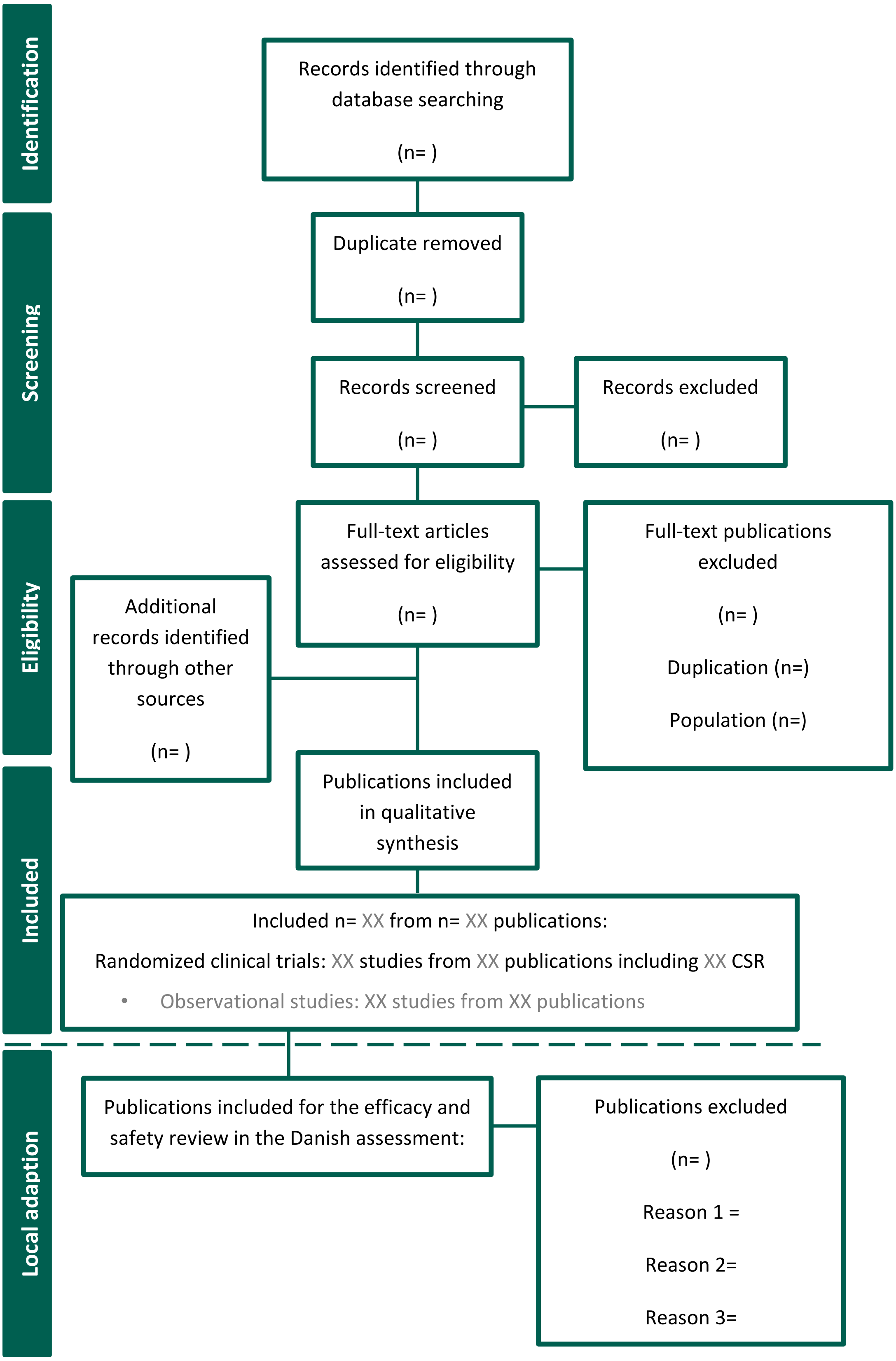
J.1.2 Targeted literature search for mortality and utilities

A targeted literature review was undertaken to find the studies UK RaDaR [16] and Cooper *et al.* 2020.[8] The UK RaDaR study that was used to source the risk of death from the health states CKD 5, dialysis and transplant and the Cooper *et al.* 2020 study used for utilities were found in a targeted literature review. For more information on the studies, see Sections 8.4 and 10.3, respectively.

Table 132 Sources included in the targeted literature search

Source name/ database	Location/source	Search strategy	Date of search
NR	NR	NR	NR

Example of PRISMA diagram. The diagram is editable and may be used for recording the records flow for the literature searches and for the adaptation of existing SLRs (not reported)



Appendix K. Additional information on the medical condition

K.1.1 Risk factors for progression to ESRD

Table 133 shows the clinical outcomes based on the total follow-up time for patients from the UK RaDaR IgAN cohort. See more information in Section 3.1.3.

Table 133. Clinical outcomes based on total follow-up time*-averaged proteinuria for patients from the UK RaDaR IgAN cohort

Total time-averaged proteinuria category	Overall	<0.44 g/g	0.44 to <0.88 g/g	0.88 to <1.76 g/g	≥1.76 g/g
10-yr survival rate, estimate (95% CI)	n=887	n=215[b]	n=175[b]	n=251	n=246
	0.46 (0.41 to 0.51)	0.78 (0.68 to 0.85)[b]	0.69 (0.56 to 0.79)[b]	0.40 (0.31 to 0.48)	0.15 (0.09 to 0.22)
Adjusted kidney failure risk (10-yr), Cox regression, HR (95% Wald CL)	N/A	Reference	1.07 (0.64 to 1.79)[b]	2.73 (1.78 to 4.16)	7.66 (5.09 to 11.52)

*Median follow-up 4.5 years; Q1, Q3: 2.5, 6.8
Abbreviations: CI, confidence interval; HR, hazard ratio; CL, confidence limit; NA, not available; IQR, interquartile range; UK RaDaR, United Kingdom National Registry of Rare Kidney Diseases
Source: Pitcher *et al*. 2023[16]

Appendix L. Scenario analyses

The scenario analyses performed and respective justification are presented in Table 134.

Table 134 Scenario analyses

Variable	Base case	Scenario analysis	Justification
Time horizon	58 years	10 years	To explore the impact of alternative time horizons on the model results
		20 years	
		30 years	
		40 years	
		50 years	
Distribution of patients across CKD states at baseline	Part A NefIgArd Nef-301 trial subgroup data for UPCR ≥1.5 g/g	UK RaDaR data	To assess the impact of using real world data has compared to clinical trial data has when informing baseline distribution across CKD stages.
		UK RaDaR data - apportioned to exclude CKD 4	
Parametric extrapolations to estimate time to CKD 5	Gamma	Exponential	To explore the uncertainty associated with parametric survival model fitted to extrapolate the risk of CKD 5 data
		Generalised gamma	
		Gompertz	
		Log-logistic	
		Log-normal	
		Weibull	
Risk of ESRD	UK RaDaR data - all patients	UK RaDaR data – ACEi and ARB patients	To explore uncertainty in the method for estimation of risk of CKD 5 in the SoC arm
		UK RADAR data - All patients (ESRD only)	
SoC acquisition costs	DKK 194	DKK 0	To assess the impact of SoC costs in the ICER
Inclusion of data from NefIgArd Part A FAS	Data from NefIgArd Part B informed the TRF-budesonide and SoC CKD 1 –	Data from NefIgArd Part A informed the TRF-budesonide and SoC CKD 1 – 4 transition matrices	To assess the impact early trial data has on the ICER. Inclusion of data from NefIgArd Part A FAS require the following

	4 transition matrices		assumptions due the lack of data due to the short follow-up: The trial provided 9-months of data to inform the transition probabilities. These transition probabilities were converted to monthly transitions and applied for 12 months TRF-budesonide is assumed to have a treatment effect for 1 year
Time point from where no treatment effect is assumed	1 year	1.5 year	To explore uncertainty in the timepoint at which TRF-budesonide no longer has a treatment effect
		2 years	
		2.5 years	
		5 years	
Mortality source	UK RaDaR data	Greene et al. 2019	To assess the impact of using various sources of mortality rates
		Hastings et al. 2018	
CKD stage utility source	Cooper et al. 2020	Gorodetskaya et al. 2005	To assess the impact of using different utility values to estimate the total QALYs in each arm
Age-adjusted utilities	Included	Excluded	To determine the impact age-adjusted utilities have on the ICER
TRF-budesonide dose reduction	Included	Excluded	To explore the impact excluding a reduce dose of 4 mg for the final two weeks of treatment has on the model results
TRF-budesonide treatment tapering period	Included	Excluded	To explore the impact the exclusion of a reduce dose of 4 mg for the two weeks after treatment discontinuation has on the model results
Treatment stopping approach	All patients stop treatment after 9 months	Use the TTD curve from the CSRs	To explore the impact using TTD curves has on the model results
Patient costs	Included	Excluded	To determine the impact excluding patient costs has on the model results

TRF-budesonide retreatment	2 rounds of treatment	3 rounds of treatment	To explore the uncertainty associated with retreating patients with TRF-budesonide
		4 rounds of treatment	
		5 rounds of treatment	
		6 rounds of treatment	
		No subsequent rounds of treatment	
Treatment effect in subsequent treatments	[redacted]	[redacted]	To determine the impact a lower efficacy in retreatment cycles has on the model results
Setting equivalent utility values	Utility values based on Cooper et al	Same utility values for CKD 1 – 3b health states (health states are assumed equivalent to the CKD 1 value)	As the SF-36 data is unavailable and unlikely to show differences in in QoL across health states CKD 1–4, additional scenario analyses assuming the utility values for CKD 1–4 and CKD 1–3b are equivalent have been assessed to explore the likely impact the SF-36 data would have had on the model results
		Same utility values for CKD 1 – 4 health states (health states are assumed equivalent to the CKD 1 value)	
Relative dose intensity	Excluded	Included	To determine the impact including relative dose intensity has on the model results
Proportion of CKD 1 – 3b patients eligible for retreatment	[redacted]	[redacted]	To explore the impact reducing the proportion of patients eligible for retreatment has on the model results
		[redacted]	
Time between retreatment cycles	[redacted]	[redacted]	To explore the impact increasing the time between retreatment cycles has on the model results
		[redacted]	
		[redacted]	
Monthly transition probability from CKD 5 to dialysis	[redacted]	[redacted]	The transitions from CKD 5 to dialysis and transplantation were sourced from a Danish clinical expert. The estimated monthly probability of patients

			in CKD 5 to dialysis is 85%. A scenario analysis was run to explore the impact decreasing the transition probability has on the ICER.
Inclusion of dapagliflozin as a cost component of SoC	The cost of dapagliflozin is excluded as part SoC's cost	The cost of dapagliflozin is included as part SoC's cost	To explore the impact including dapagliflozin from SoC has on the model outcomes.

Abbreviations: ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blockers; CKD, chronic kidney disease; CS, corticosteroids; CSR, clinical study report; ESRD, end-stage renal disease; ICER, incremental cost-effectiveness ratio; IS, immunosuppressant; QALYs, quality-adjusted life years; SoC, standard of care; TRF, targeted-release formulation; TTD, time to discontinuation; UK RaDaR, United Kingdom National Registry of Rare Kidney Diseases; UPCR, urine protein creatine ratio.

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