NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Targeted-release budesonide for treating primary IgA nephropathy (review of TA937) [ID6485]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Targeted-release budesonide for treating primary IgA nephropathy (review of TA937) [ID6485]

Contents:

The following documents are made available to stakeholders:

Access the **final scope and final stakeholder list** on the NICE website.

1. **Company submission** from Genus Pharmaceuticals:
   a. Full submission
   b. Summary of Information for Patients (SIP)

2. **Clarification questions and company responses**

3. **Patient group, professional group, and NHS organisation submission** from:
   a. Kidney Research UK
   b. The UK Kidney Association*
   c. The Renal Pharmacy Group (part of The UK Kidney Association)

4. **Expert personal perspectives** from:
   a. Dr Chee Kay Cheung, Consultant Nephrologist and Honorary Associate Professor – Clinical expert, nominated by The UK Kidney Association see 3b*
   b. Professor Jonathan Barratt, Professor of Renal Medicine – Clinical expert, nominated by Genus Pharmaceuticals Ltd
   c. Patient expert nominated by Kidney Research UK

5. **External Assessment Report** prepared by Southampton Health Technology Assessments Centre

6. **External Assessment Group response to factual accuracy check of EAR**

Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Targeted-release budesonide for treating primary IgA nephropathy (review of TA937) [ID 6485]

Company evidence submission

May 2025

File name	Version	Contains confidential information	Date
ID6485 budesonide company evidence submission 06Aug25	**2.0**	**Yes**	**26th August 2025**

Contents

Tables and figures

Abbreviations

ACE	Angiotensin converting enzyme
AE	Adverse event
AESI	Adverse event of special interest
ARB	Angiotensin II receptor blocker
CEM	Cost-effectiveness model
CI	Confidence interval
CKD	Chronic kidney disease
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CS	Corticosteroids
CSR	Clinical study report
CVD	Cardiovascular disease
DSA	Deterministic sensitivity analysis
eGFR	Estimated glomerular filtration rate
EAG	Evidence Assessment Group
EMA	European Medicines Agency
ESRD	End-stage renal disease
FAS	Full analysis set
Gd-IgA	Galactose-deficient immunoglobulin
HR	Hazard ratio
HRQoL	Health-related quality of life
HSUV	Health state utility value
HTA	Health technology assessment
ICER	Incremental cost-effectiveness ratio
IgA	Immunoglobulin A
IgAN	Immunoglobulin A nephropathy
IVRS	Interactive Voice Response System
KDIGO	Kidney Disease Improving Global Outcomes
KM	Kaplan-Meier
LS	Least squares
LYG	Life-years gained
MHRA	Medicines and Healthcare products regulatory Agency
MMRM	Mixed model for repeated measures
MRU	Medical resource use
NHB	Net health benefit
NHS	National Health Service
OLE	Open-label extension
ONS	Office for National Statistics

PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PSA	Probabilistic sensitivity analysis
PSS	Personal Social Services
PSSRU	Personal Social Services Research Unit
QALY	Quality-adjusted life year
QD	Once daily
QoL	Quality of life
RaDaR	National Registry of Rare Kidney Diseases
RAS	Renin-angiotensin system
RCT	Randomised controlled trial
RDI	Relative dose intensity
RR	Relative risk
RRT	Renal replacement therapy
SAE	Serious adverse event
SAS	Safety analysis set
SF-36	Short Form-36
SGLT-2	Sodium/glucose cotransporter 2
SLR	Systematic literature review
SmPC	Summary of product characteristics
SMR	Standardised mortality ratio
SoC	Standard of care
TEAE	Treatment-emergent adverse event
TESAE	Treatment-emergent serious adverse event
TRF	Targeted-release formulation
TSD	Technical support document
TTD	Time to treatment discontinuation
UACR	Urine albumin to creatinine ratio
UKRR	UK Renal Registry
UPCR	Urine protein to creatinine ratio
WTP	Willingness-to-pay

1 Decision problem, description of the technology and clinical care pathway

1.1 Decision problem

The submission covers the technology's full anticipated marketing authorisation for the treatment of adults with primary immunoglobulin A nephropathy (IgAN) with a urine protein excretion ≥1.0 g/day (or urine protein-to-creatinine ratio ≥0.8 g/g) (see Appendix A).

Table 1: The decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	Adults with primary IgA nephropathy with a urine protein-to-creatinine ratio of 0.8 g/gram or more	Adults with primary immunoglobulin A nephropathy (IgAN) with a urine protein excretion ≥1.0 g/day (or urine protein-to-creatinine ratio ≥0.8 g/g)	The population addressed in the company submission is aligned with the anticipated licensed indication for TRF-budesonide
Intervention	Targeted-release budesonide as an add-on to standard care	As per scope	
Comparator(s)	Individually optimised standard care without targeted-release budesonide: Standard care is defined as: • ACE inhibitors and ARBs at the maximum tolerated licensed doses, diuretics, and dietary and lifestyle modification, with or without: – SGLT2 inhibitors – Sparsentan (subject to NICE evaluation)	As per scope	
Outcomes	The outcome measures to be considered include: • proteinuria (for example, change from baseline in urine protein creatine ratio) • kidney function (eGFR) • disease progression (dialysis and/or transplant) • mortality • adverse effects of treatment • health-related quality of life	As per scope	
Subgroups to be considered	If the evidence allows the following subgroup will be considered:	Subgroup not included	The evidence for the clinical and cost effectiveness of TRF-budesonide for patients at risk of rapidly progressive IgA

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
	• People at risk of rapidly progressive IgA nephropathy (urine protein-to-creatinine ratio of 1.5g/gram or more)		nephropathy (urine protein-to-creatinine ratio of 1.5g/gram or more) has previously been presented and accepted by NICE in TA937. The population considered within the submission is aligned with the anticipated marketing authorisation for TRF-budesonide, which will cover all patients with primary IgAN and a urine protein excretion ≥1.0 g/day (or urine protein-to-creatinine ratio ≥0.8 g/g)

1.2 Description of the technology being evaluated

TRF-budesonide is the first and only approved treatment specifically designed to treat the underlying cause of IgAN. It has been formulated to release the active component, budesonide, in the distal ileum where there is a high concentration of Peyer's patches (a primary site of galactose-deficient immunoglobulin A [gd-IgA] production) (1). Here, its anti-inflammatory action provides a disease-modifying effect by decreasing the secretion of gd-IgAs, preventing downstream effects manifesting as kidney inflammation and loss of renal function (1-3). Details of the draft summary of product characteristics (SmPC) are provided in Appendix A. An overview of TRF-budesonide is provided in Table 2.

Table 2: Technology being evaluated

UK approved name and brand name	Generic name: TRF-budesonide Brand name: Kinpeygo®
Mechanism of action	TRF-budesonide is formulated to release its active component in the distal ileum, where it is expected to act on Peyer's patches—key sites of Gd-IgA1 production. By modulating mucosal B-cell activity, it reduces the formation of Gd-IgA1 and subsequent immune complex formation in the blood. This targeted effect is anticipated to lower glomerular immune complex deposition, thereby reducing kidney inflammation and slowing disease progression.
Marketing authorisation/CE mark status	A UK marketing authorisation application has been submitted via the International Recognition Procedure. Marketing authorisation is expected in July/August 2025.
Indications and any restriction(s) as described in the summary of product characteristics (SmPC)	The anticipated licensed indication is for the treatment of adults with primary immunoglobulin A nephropathy (IgAN) with a urine protein excretion ≥1.0 g/day (or urine protein-to-creatinine ratio ≥0.8 g/g)
Method of administration and dosage	The recommended dose is 16 mg (four 4 mg capsules) once daily in the morning, at least one hour before a meal, for 9 months. When treatment is to be discontinued, the dose should be reduced to 8 mg once daily for 2 weeks of therapy; the dose may be reduced to 4 mg once daily for an additional 2 weeks, at the discretion of the treating physician. Re-treatment may be considered at the discretion of the treating physician.
Additional tests or investigations	No additional tests/investigations needed.
List price and average cost of a course of treatment	£4,681.24 for 120 x 4 mg capsules The average cost of a course of treatment is £42,745.57 for 9-months of treatment (assuming 30.4375 days per month and no treatment waning or tapering)
Patient access scheme (if applicable)	A simple discount has been agreed with NHS England ([redacted])

1.3 Health condition and position of the technology in the treatment pathway

Disease overview

- IgAN is a progressive chronic kidney disease (CKD) which affects >12,000 people in England (4)
- The development of IgAN is induced by the accumulation of immunoglobulin A (IgA)-containing immune complexes in the kidney glomeruli that initiate a cascade of events causing inflammation and fibrosis which can lead to a decline in kidney function and CKD (3, 5-8)
- In the UK, the median age of diagnosis is around 40–45 years of age and the majority of patients progress to end stage renal disease (ESRD) within 10–15 years of diagnosis (9)
- Patients with IgAN are at high risk of comorbidities (10), and may experience a broad range of symptoms which can cause physical limitation and restrict daily activities (11-15)
- Patients with IgAN may also experience anxiety, depression, and fear of progression to ESRD (11, 13)
- Patients with IgAN face an average 10-year reduction in life expectancy and a mortality rate approximately twice that of the general population (16, 17)

Treatment pathway

- There is no cure for IgAN; Kidney Disease Improving Global Outcomes (KDIGO) draft guidelines state that the aim of treatment in patients with IgAN at risk of progressive loss of kidney function is to reduce the rate of kidney function loss to <1 mL/min per year (18)
- Draft KDIGO guidelines state that the aim of IgAN treatment should be to simultaneously prevent/reduce IgA immune complex formation and immune complex mediated glomerular injury and manage the consequences of existing IgAN-induced nephron loss (18)
- TRF-budesonide is currently the only approved treatment recommended in KDIGO guidelines which can treat the underlying cause of IgAN, reducing IgA

immune complex formation and delay progression to more advanced kidney disease (18)

- TRF-budesonide is recommended by NICE as an option for the treatment of primary IgAN when there is a risk of rapid disease progression in adults with a urine protein-creatinine ratio (UPCR) of ≥1.5 g/g as an add on to optimised standard of care which includes the highest tolerated licensed dose of RAS inhibitors (TA937) in line with the existing marketing authorisation (19)
- There are currently no NICE-recommended immune-mediated treatment options to delay disease progression for patients with IgAN who have UPCR <1.5 g/g
- This submission seeks to extend the NICE recommendation for TRF-budesonide for patients aged 18 years and older with primary IgAN with a urine protein excretion ≥1.0 g/day or UPCR ≥0.8 g/g, in line with the anticipated expanded marketing authorisation

1.3.1 Disease overview

Immunoglobulin A nephropathy (IgAN) is a progressive, chronic kidney disease that occurs when immunoglobulin A (IgA) antibody complexes deposit in the kidney, causing inflammation and fibrosis, which can lead to a decline in kidney function and may progress to end-stage renal disease (ESRD) (3, 8). The exact causes of IgAN are unknown, however genetic and environmental factors are thought to play a role in disease development (15). The median age at diagnosis in the UK is around 40–45 years of age (9).

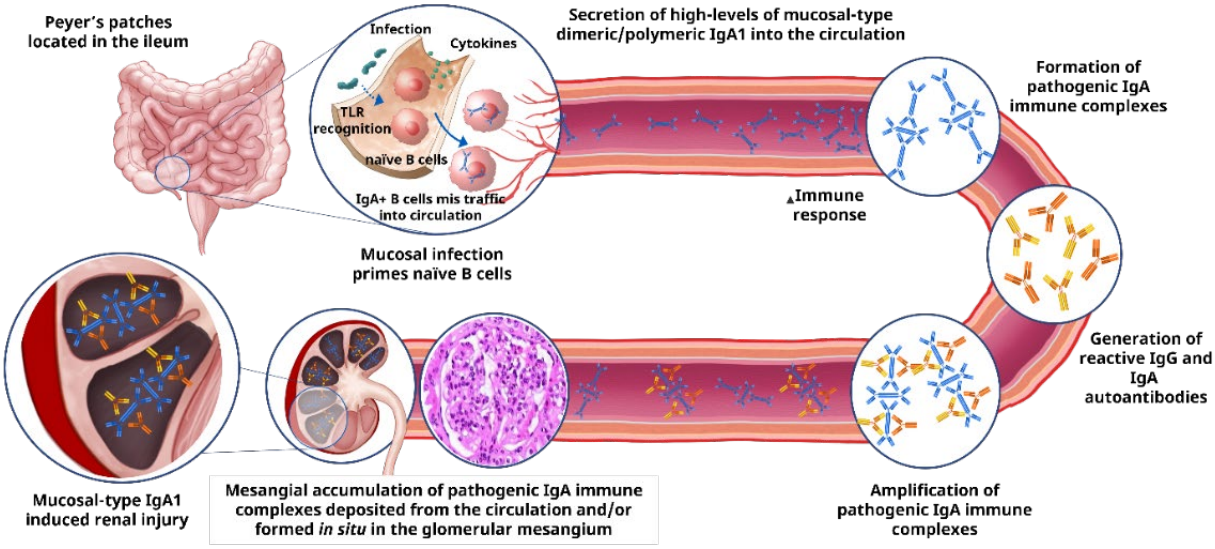
In line with the anticipated indication for TRF-budesonide, this submission focuses on primary IgAN with a urine protein excretion ≥1.0 g/day or UPCR ≥0.8 g/g.

1.3.1.1 Pathogenesis

The steps leading to in the development of IgAN have been described by the "four-hit" hypothesis (Figure 1):

1. Increased levels of circulating galactose-deficient immunoglobulin A (gd-IgA) which are produced by IgA1-producing cells, including those in the Peyer's patches at the distal ileum, a primary site of IgA production (1, 3, 20)
2. IgG and IgA autoantibodies are generated and directed against gd-IgAs (3, 20)
3. Autoantibodies and gd-IgAs form immune complexes (20)
4. IgA-containing immune complexes deposit in the glomerular mesangium and initiate inflammatory and fibrotic processes in the kidney which lead to renal injury (3, 20).

Figure 1: Pathophysiology of IgAN



Abbreviations: IgA, immunoglobulin A; IgAN, immunoglobulin A nephropathy; IgG, immunoglobulin G; TLR, Toll-Like Receptor.
Adapted from Boyd et al. 2012 (21).

1.3.1.2 Diagnosis

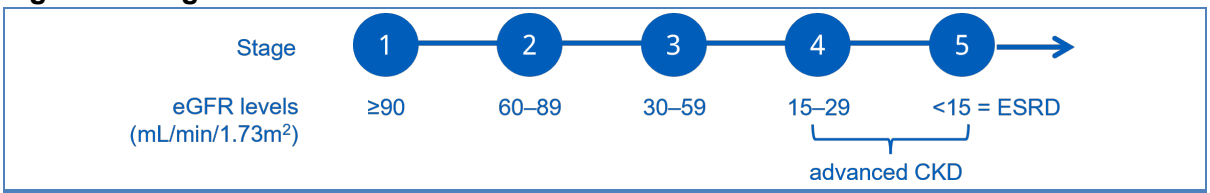
The first step towards a diagnosis of IgAN typically includes a urine test to check for a urine infection and to measure protein levels (22, 23). A blood test to measure serum creatinine can also be conducted to assess kidney function (22, 23). A

definitive diagnosis of IgAN requires a renal biopsy with immunofluorescence or immunoperoxidase to detect IgA deposition (3, 5, 24). As IgAN is often asymptomatic in the early stages, a substantial proportion of patients experience delayed diagnosis (median time from first clinical sign to diagnosis: 5.0 months; interquartile range [IQR]: 0.9–29.3) (25). Diagnosis is based on the MEST-C score, which includes five histological features (i.e. mesangial [M] and endocapillary [E] hypercellularity, segmental sclerosis [S], interstitial fibrosis/tubular atrophy [T], and crescents [C]) (5). There are no validated diagnostic serum or urine biomarkers for IgAN (5).

1.3.1.3 Disease course and risk factors for progression

IgAN causes a chronic decline in kidney function, the extent of which is defined based on estimated glomerular filtration rate (eGFR) levels (Figure 2) (3, 8, 26). Disease progression can lead to ESRD (CKD stage 5), where patients require renal replacement therapy (RRT) in the form of a kidney transplant or chronic dialysis (5, 15, 27, 28). Almost all patients are at risk of ESRD within their expected lifetime unless an eGFR rate loss ≤1 ml/min per 1.73 m^2 per year can be maintained from diagnosis (9).

Figure 2: Stages of CKD based on eGFR levels

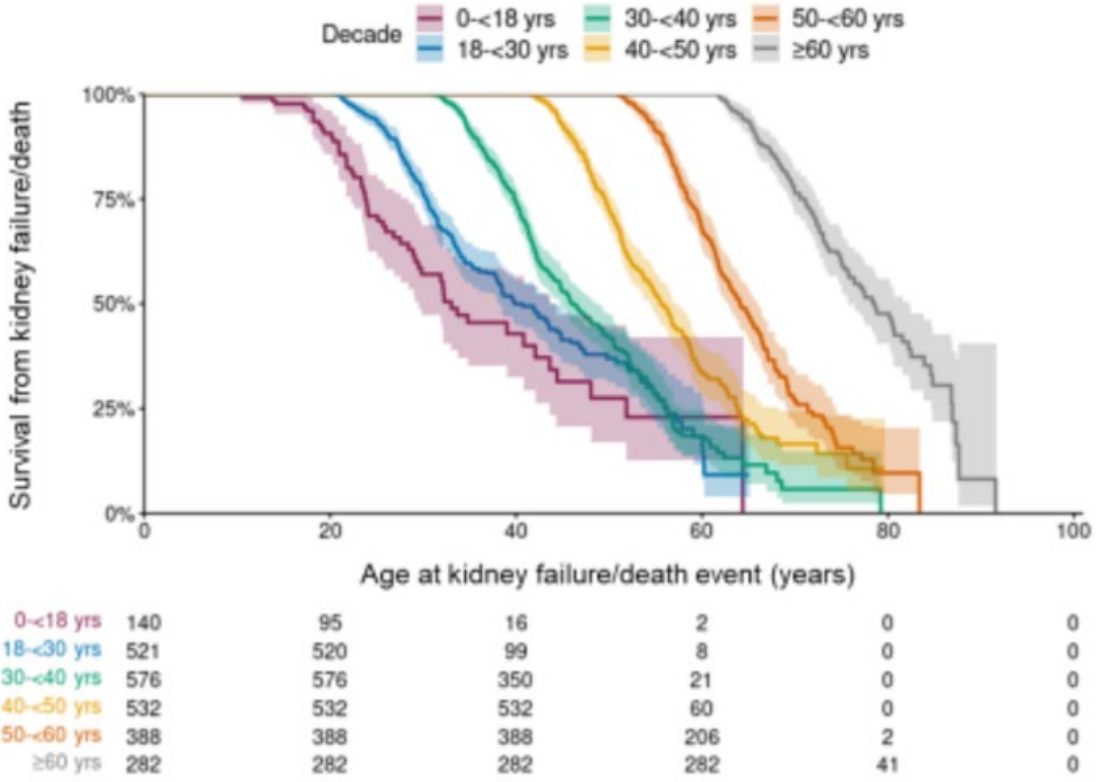


Stage	Description	eGFR levels (mL/min/1.73 m²)†
1	Kidney damage‡ with normal or increased eGFR	≥90
2	Kidney damage‡ with mildly decreased eGFR	60 to 89
3	Moderate decreased eGFR	30 to 59
4	Severe decreased eGFR	15 to 29
5	Kidney failure (ESRD)	<15 or dialysis

Abbreviations: CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease.
† 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
Source: Chronic kidney disease guidelines, 2004 (AJKD) (26).

People with IgAN typically progress to ESRD or death at a substantially earlier age than the overall CKD population, although disease course and rate of progression of IgAN are variable (9, 29). In a study of patients from the UK National Registry of Rare Kidney Diseases (RaDaR) IgAN cohort (2,299 adults, 140 children), 50% of patients reached ESRD or died during the study period (median [Q1, Q3] follow-up: 5.9 [3.0, 10.5] years) (9). The mean age at ESRD/death was 48 years and most patients progressed to ESRD within 10–15 years from diagnosis (Figure 3) (9). In contrast, the median age of kidney replacement therapy among the overall CKD population in the European Renal Association Registry age was 67.9 years (29).

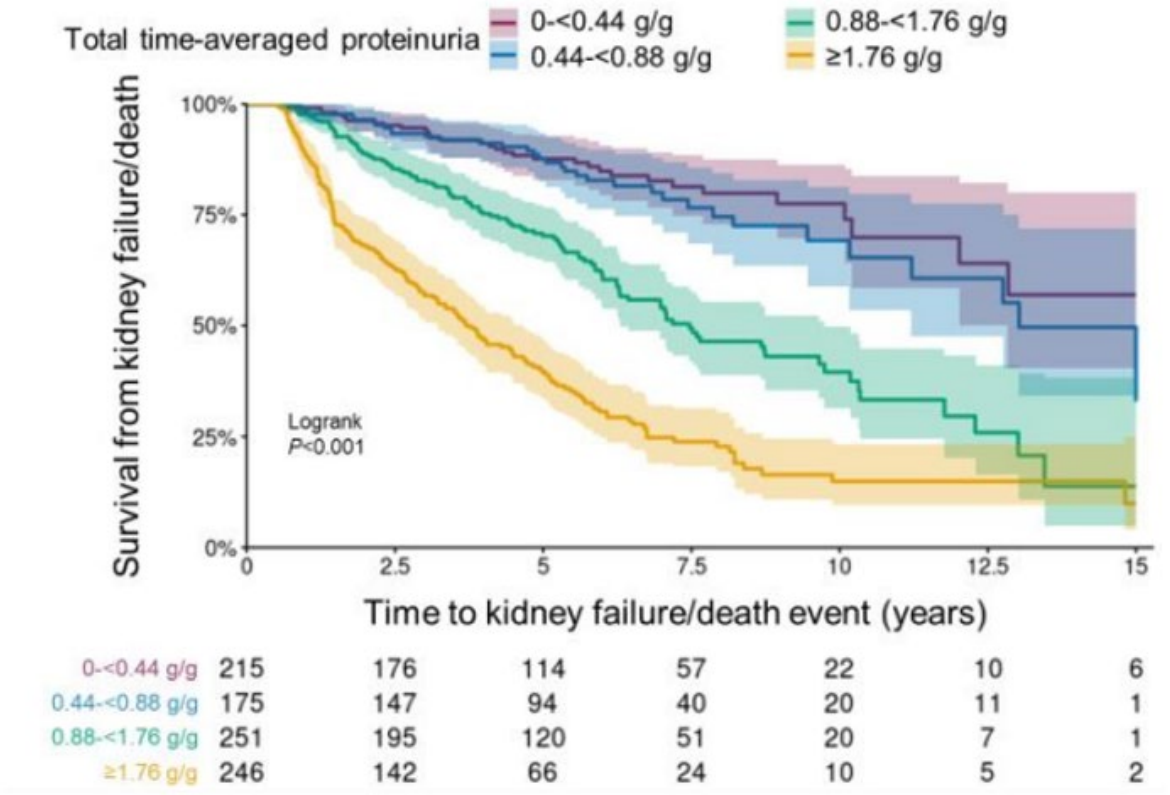
Figure 3: Kaplan-Meier survival curves (95% CI) of time to ESRD/death event based on age at diagnosis for patients from the UK RaDaR IgAN cohort



Abbreviations: CI, confidence interval; IgAN, immunoglobulin A nephropathy; UK RaDaR, United Kingdom National Registry of Rare Kidney Diseases.
Source: Pitcher et al. 2023 (9).

Proteinuria (high levels of protein in urine) is a key risk factor predicting loss of kidney function, progression to ESRD, and mortality, with consistent evidence demonstrating faster progression in patients with higher proteinuria (3, 8, 15). Kaplan-Meier survival analyses of the UK RaDaR IgAN cohort categorised by time-averaged proteinuria showed that patients with time-averaged proteinuria >0.88 g/g (>100 mg/mmol or approximately 1g/day) were likely to progress to ESRD or death more quickly than patients with time-averaged proteinuria <0.88g/g (Figure 4). Patients with low proteinuria of <0.88 g/g UPCR (n=390) had a median time to ESRD or death of >15 years (9).

Figure 4: Kaplan-Meier survival curves (95% CI) of time to ESRD/death event in the UK RaDaR IgAN cohort

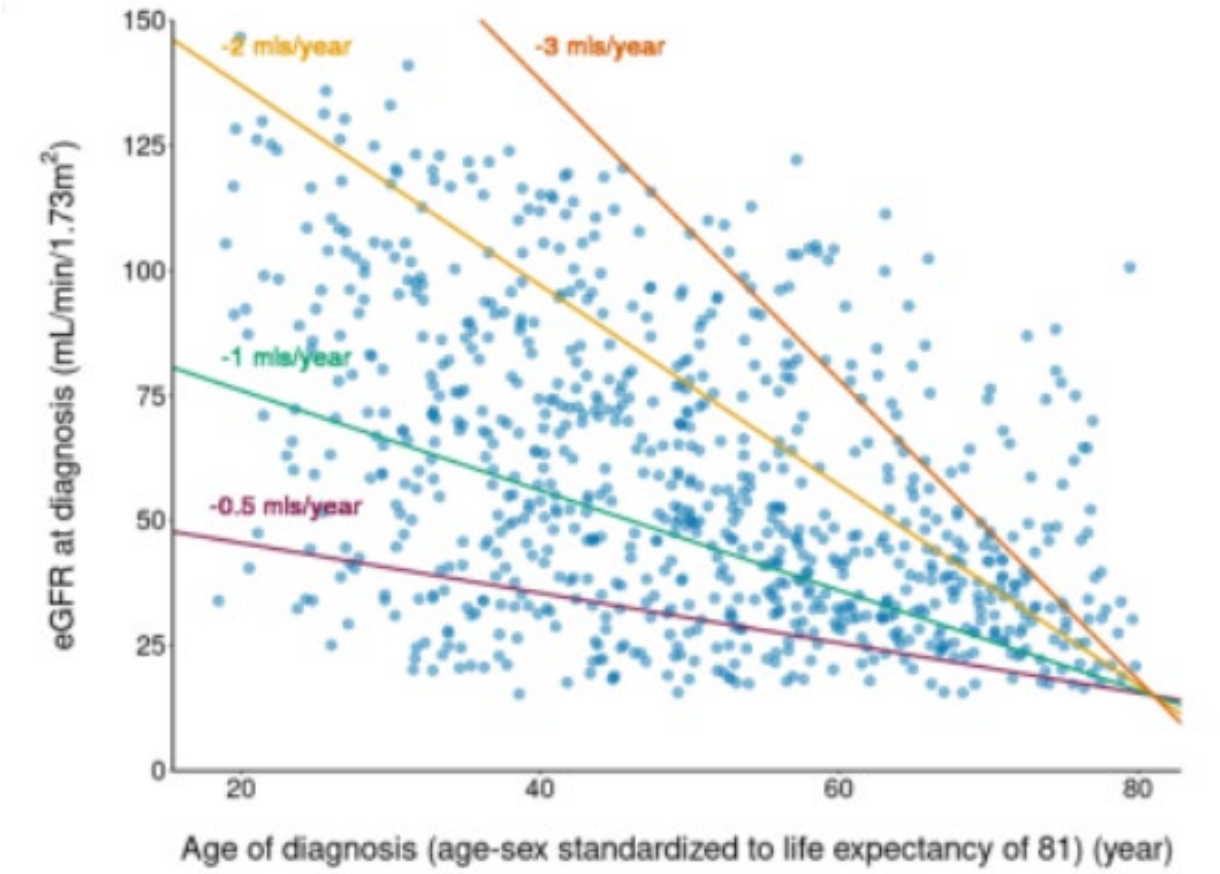


Abbreviations: CI, confidence interval; IgAN, immunoglobulin A nephropathy; UK RaDaR, United Kingdom National Registry of Rare Kidney Diseases.
Source: Pitcher et al. 2023 (9).

Low eGFR levels at renal biopsy and decreases in eGFR levels over time are also associated with an elevated risk of progression to ESRD and an increased risk of mortality in patients with IgAN (16, 30). In an assessment of the cumulative risk for progression to ESRD based on eGFR levels at biopsy in patients with IgAN, patients with low eGFR levels at renal biopsy (eGFR <30 mL/min/1.73 m^2) were 3.6 times more likely to die compared with an age-matched population (standardised mortality rate [SMR]: 3.6; 95% confidence interval [CI]: 2.6, 5.0) (16). Similarly, an international, retrospective, cohort study of patients with IgAN receiving treatment with RAS blockade and/or immunosuppressives reported a significant association between low eGFR levels at biopsy and a 5-year risk of 50% reduction in eGFR or ESRD (hazard ratio [HR]: 0.70; 95% CI: 0.67, 0.74; p<0.001) (30). The majority of people with IgAN in the UK RaDaR cohort were shown to be at risk of progression to ESRD in their expected lifetime, unless a rate of eGFR loss ≤1 ml/min/1.73 m^2/year could be maintained (9) (Figure 5). A decline in eGFR of 3 mL/min/1.73 m^2/year was

predicted to result in 100% of people diagnosed with IgAN before 40 years of age reaching ESRD within their predicted lifetime (9). A decline of as little as 1 mL/min/1.73 m^2/year would result in ~40% of people diagnosed with IgAN before 50 years of age reaching ESRD (9). This implies that a decline in eGFR of <1 mL/min/year is required to avoid risk of progression ESRD (9).

Figure 5: Scatter plot of eGFR at diagnosis against age at diagnosis for the UK RaDaR IgAN cohort



Abbreviations: eGFR, estimated glomerular filtration rate; IgAN, immunoglobulin A nephropathy; UK RaDaR, United Kingdom National Registry of Rare Kidney Diseases.
Reference lines showing rates of decline that reach eGFR=15 by age-sex standardized life expectancy of 81 years. Patients below a reference line will reach an eGFR of 15 mL/min/1.73m2 before 81 years at the reference line rate of loss of eGFR.
Source: Pitcher et al. 2023 (9).

Lifestyle factors, such as smoking and alcohol consumption, as well as male gender, an increased serum IgA/C3 ratio (a prognostic marker for IgAN diagnosis), and comorbidities that damage the kidneys, such as primary hypertension and diabetes mellitus, are also associated with progression in IgAN (31-34).

1.3.2 Epidemiology of IgAN

IgAN is an orphan disease and the most common form of glomerulonephritis (diseases which cause damage to the glomeruli, the filters in the kidney) with a worldwide annual incidence of at least 2.5 per 100,000 people (35). Rates of IgAN diagnosis vary widely between countries, likely due to differences in screening and biopsy practices (3, 15, 36), however the highest rates of IgAN are seen in East and Pacific Asian countries (15).

In England, IgAN is estimated to affect [redacted] people (prevalence of [redacted] per 10,000 people) (4), with an estimated annual incidence rate of approximately 0.99 per 100,000 people (37). UK RaDaR data estimates that [redacted] of these patients have UPCR ≥0.8 g/g. Based on these proportions, [redacted] people are estimated to be eligible for treatment with TRF-budesonide in England in 2025.

1.3.3 Disease burden

1.3.3.1 Clinical burden

The symptoms of IgAN at presentation commonly include haematuria (which may be visible in urine or not visible, and detected on urine testing), proteinuria (asymptomatic or manifesting as foamy urine or abnormal sediment), pain in the sides of the back (flank pain), swelling in the ankles, and high blood pressure (15, 24, 38). A broad range of other clinical manifestations may also present and can vary as IgAN progresses (3, 15). These can include progressive CKD and infections leading to acute care events, including hospitalisation or emergency department visits (3, 15, 39). Patients with IgAN may experience tiredness and fatigue which limit physical activity and result in low stamina (11).

Patients with IgAN who have advanced CKD have a high symptom burden as outlined in Table 3 and symptoms become more severe as the disease progresses (12, 27, 40). If left untreated, ESRD ultimately leads to death (27). Therefore, RRT is needed for people with ESRD, either in the form of chronic dialysis or kidney transplantation (12, 27). However, dialysis is associated with a debilitating emotional and physical burden (Section 1.3.3.2) as well as multiple unpleasant symptoms frequently reported to include fatigue, muscle weakness, itching, and sleep problems

(40-43). Kidney transplantation is associated with a risk of transplant failure, disease recurrence, iatrogenic infection, and the requirement for lifelong immunosuppressive therapy (44-47).

A high risk of certain comorbidities has also been reported for patients with IgAN, including cardiovascular disease (CVD) (see Section 1.3.3.1.1).

1.3.3.1.1 Cardiovascular risk in patients with IgAN

Proteinuria (5, 48, 49) and low eGFR (50) are risk factors for CVD, which is a leading cause of death in patients with IgAN (16, 51) and CKD (27). Patients with IgAN have been reported to have an 86% increased risk of future ischaemic heart disease compared with the general population (10). In a meta-analysis of cohort studies conducted to obtain a summary estimate of the association between measures of proteinuria and coronary risk, individuals with proteinuria were reported to have an approximately 50% greater risk of coronary heart disease compared with those without the condition: the relative risk (RR) was 1.47 (95% CI: 1.23, 1.74) (48). Similarly, in an international meta-analysis of 1,234,182 participants with CKD, the risk of cardiovascular mortality was approximately 2–3 times higher for patients with lower eGFR (eGFR 15 mL/min/1.73 m^2 vs eGFR 95 mL/min/1.73 m^2, HR: 2.66 [95% CI: 2.04, 3.46]; eGFR 45 mL/min/1.73 m^2 vs eGFR 95 mL/min/1.73 m^2, HR: 1.99 [95% CI: 1.73, 2.28]) (50).

Table 3: Symptoms/signs in patients with CKD and ESRD

Symptoms/signs in CKD	Symptoms/signs in ESRD
• Bone/joint pain • Muscle weakness • Diarrhoea • Anxiety • Trouble with memory • Abdominal pain • Depression	• Progressive uraemia • Volume overload • Mineral and bone disorders • Dry mouth • Sleep disturbance • Oedema • Anaemia • Electrolyte abnormalities • Acidaemia • Drowsiness • Poor concentration
Symptoms/signs experienced in both CKD and ESRD	
• Fatigue • Constipation • Restless leg syndrome • Pruritus (itching) • Dyspnoea (shortness of breath) • Pain • Muscle cramps • Lack of appetite • Sexual dysfunction	

Abbreviations: CKD, chronic kidney disease; ESRD, end-stage renal disease.
Source: Fletcher et al. 2022 (40); O'Connor 2012 (12); Voskamp et al. 2019 (52).

1.3.3.1.2 Life expectancy

Patients with IgAN face an average 10-year reduction in life expectancy and a mortality rate approximately twice that of the general population (16, 17). In a UK study of 797 patients with IgAN, 23% of patients died at a median follow-up of 6.3 years and the mortality risk was reported to be above the national average (53). Cardiovascular disease has been reported to be a leading cause of death in patients with IgAN (16, 51).

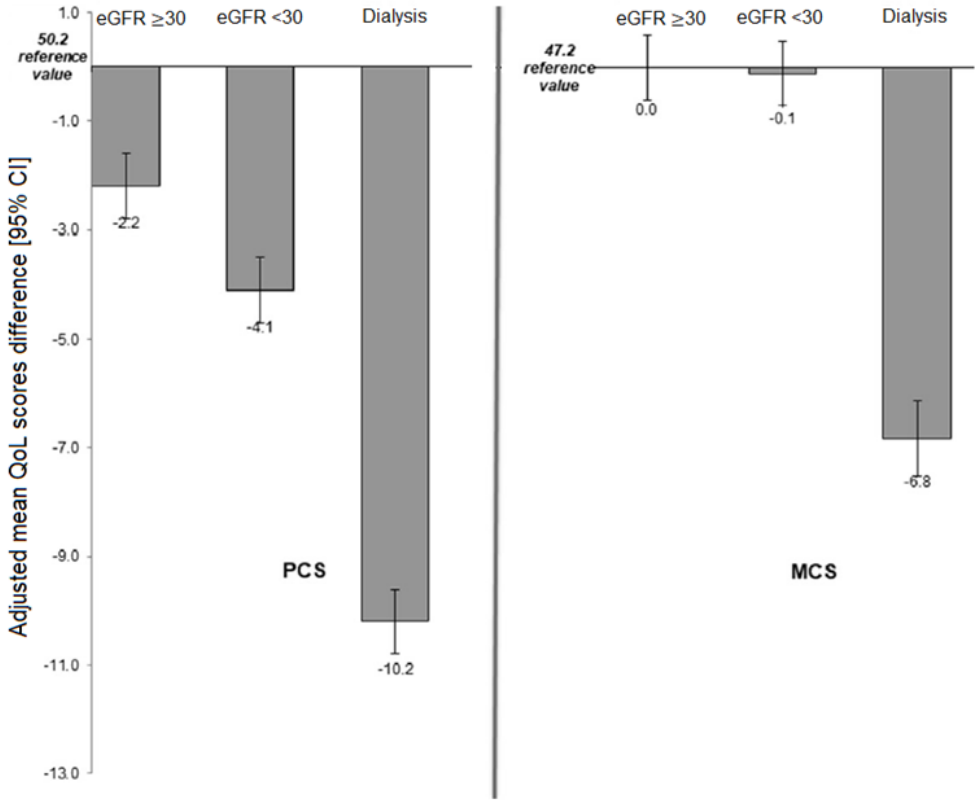
1.3.3.2 Humanistic burden

The symptoms and emotional burden of IgAN and its treatment can have a life-changing impact on patients' lives, causing physical limitations and restricting daily activities at all disease stages (11-13). Debilitating fatigue can prevent patients from achieving simple daily tasks and leading a normal life, while dietary restrictions, recommended in patients with IgAN, can also negatively affect quality of life and lifestyle (3, 5, 11, 54). Patients with IgAN suffer from anxiety, depression, and fear of progression to ESRD (11, 13).

The considerable physical and mental health burden of IgAN increases with disease progression, particularly when dialysis becomes necessary (13). A diagnosis of CKD often causes trauma and distress, with uncertainty about the future prompting

patients to re-evaluate their lives (55). Late-stage kidney disease is associated with worse health-related quality of life scores and perceived health scores compared with early-stage disease and healthy controls (40, 56-59). Dialysis itself has a substantial impact on patients ability to work, social life, and wellbeing, due to increased symptom burden and demanding dialysis schedules which entail lengthy treatment sessions (3–6 hours) multiple times a week (19, 26, 43, 60-62). As a result, dialysis is associated with lower health-related quality of life scores in both the physical and mental domains of patients with CKD compared with earlier stages of disease and with the general population (Figure 6) (56, 63, 64).

Figure 6: Differences in QoL scores between the general population, patients with CKD and patients with CKD on dialysis



Reference value represents the general population QoL. QoL adjusted for age, sex, education levels, diabetes, and obesity. A negative difference indicates lower QoL score.
Abbreviations: eGFR, estimated glomerular filtration rate; CI, confidence interval; MCS, mental component score; PCS, physical component score; QoL, quality of life.
Adapted from: Legrand et al. 2020 (56).

The impact of CKD on patients can place a substantial burden on caregivers, due to pressures relating to performing tasks, managing lifestyle restrictions, and the debilitating burden of dealing with the patients' emotional load (11, 55, 65). Carers of

patients with CKD can be impacted by depressive symptoms or anxiety, with some caregivers reporting battling an unrelenting and debilitating burden (55).

1.3.3.3 Healthcare burden

As the most common form of primary glomerulonephritis worldwide and a leading cause of ESRD in young people, IgAN significantly contributes to the global burden of CKD and ESRD (24, 66). However, limited published evidence of the economic and healthcare burden of IgAN is available (13); the majority of data available relates to the management of patients with CKD and ESRD.

CKD is a substantial burden for individuals, healthcare systems, and societies, with overall annual healthcare costs projected to reach up to £13.99 billion in the UK in 2025 (67-70). Costs increase substantially with progression of CKD, even at early stages (68, 71). Progression from stages 1–2 to stage 3 is associated with a 1.1–1.7 fold increase in costs, and from stage 3 to stages 4–5 with a 1.3–4.2 fold increase in costs (68). ESRD is the most expensive stage of CKD (68, 71). The largest direct cost drivers in CKD and ESRD are hospitalisation and medication costs (72-74). Indirect cost drivers include productivity loss and years lost due to absenteeism or presenteeism of patients and/or caregivers, and disability/sick leave (68, 72, 75).

Dialysis is associated with the highest cost burden in patients with ESRD, with a 9.4-fold increase in mean annual costs reported for patients receiving dialysis compared with patients who have CKD stages 4–5 without dialysis in a population-based cohort study of the Swedish national healthcare system (76). In an analysis of the costs of different dialysis modalities in one UK nation (Wales), the annual direct cost per patient ranged from £15,875 for continuous ambulatory peritoneal dialysis to £31,785 for National Health Service (NHS) unit-based haemodialysis (77). Cost drivers for dialysis relate to the procedure itself, hospitalisations, outpatient care, transportation, and drug costs (76, 78-82).

1.3.4 Clinical pathway of care

There is currently no cure for IgAN. Clinical experts have reported that in England, KDIGO guidelines (5) are widely used in the management of patients with IgAN. Draft KDIGO 2024 guidelines state that the aim of treatment for IgAN patients at risk

of progressive loss of kidney function (defined as proteinuria ≥0.5 g/d or equivalent) is to reduce the rate of kidney function loss to <1 mL/min per year (18). Draft KDIGO guidelines state that the aim of IgAN treatment should be to simultaneously manage the consequences of existing IgAN-induced nephron loss and prevent/reduce IgA immune complex formation and immune complex mediated glomerular injury (18). This dual approach to managing IgAN has also been recommended in other clinical commentaries, which highlight the need to prioritise the reduction of pathogenic forms of IgA when treating IgAN (83, 84).

IgAN patients at risk of progressive loss of kidney function currently receive established clinical management (standard of care [SoC]) to manage the consequences of IgAN-induced nephron loss including blood pressure management, maximally tolerated dose of angiotensin-converting enzyme inhibitor (ACEi)/angiotensin II type I receptor blocker (ARB) and lifestyle modification (18, 85). The sodium-glucose co-transporter-2 (SGLT-2) inhibitor dapagliflozin is also increasingly used as part of SoC in patients with IgAN (86) (see Figure 7).

Draft 2024 KDIGO guidelines recommend the use of TRF-budesonide for all patients with IgAN who are at risk of progressive kidney function loss to prevent/reduce IgA immune complex formation and immune complex mediated glomerular injury in conjunction with standard of care (18). TRF-budesonide is currently the only approved treatment which can address the underlying cause of IgAN (18) and increase the likelihood that patients can avoid or delay the need for kidney transplant or dialysis (18). NICE currently recommends TRF-budesonide for the treatment of primary IgAN when there is a risk of rapid disease progression in adults with a UPCR of ≥1.5 g/g as an add on to optimised standard of care which includes RAS inhibitors (19). This recommendation was based on the licensed indication for TRF-budesonide, granted by the MHRA in February 2023 for the treatment of primary IgAN in adults at risk of rapid disease progression with a UPCR ≥1.5 g/g (87) (Figure 7).

The KDIGO 2024 draft guideline states that systemic corticosteroids should only be considered in settings where TRF-budesonide is not available, and highlight that such treatments have no proven effects on levels of pathogenic forms of IgA or IgA

immune complexes (18). Furthermore, during the TA937 committee meeting, clinical experts advised that while systemic corticosteroids can be used to treat IgAN, they have an unfavourable risk-benefit profile and are not used by most nephrologists in the UK (19). In line with the NICE scope for this appraisal, systemic corticosteroids are not considered within this appraisal.

Sparsentan is a dual endothelin and angiotensin receptor antagonist which is currently subject to a NICE appraisal as an option for the treatment of IgA nephropathy (88). Clinical experts at the first committee meeting highlighted that sparsentan could replace traditional RAS inhibitor therapy as part of SoC for IgAN (88). At the time of this submission, final NICE guidance on the use of sparsentan for IgAN had not been published. Given that sparsentan has yet to receive a NICE recommendation and is not currently part of SoC in UK clinical practice, it was not included as part of standard of care in this submission.

1.3.4.1 Unmet need

Patients with IgAN with a UPCR of ≥0.8 g/g and <1.5 g/g currently have no NICE-recommended options to treat the underlying cause of the disease and delay kidney disease progression. Given that systemic corticosteroids are not approved for treatment of IgAN or used by most nephrologists in the UK due to their unfavourable risk-benefit profile (19), current treatment for these patients is standard of care, consisting of lifestyle and dietary changes as well as RAS inhibitors (ACEI or ARBs) and SGLT2i. There is therefore an unmet need for a treatment which can address the underlying cause of IgAN and reduce the rate of kidney function loss for all adult patients with IgAN and UPCR of ≥0.8 g/g.

1.3.4.2 Place in therapy of TRF-budesonide

As previously described, TRF-budesonide is currently the only approved treatment which can treat the underlying cause of IgAN (18) and delay progression to more advanced kidney disease. Draft KDIGO guidelines for the management of IgAN recommend the use of TRF-budesonide for all patients with IgAN who are at risk of progressive kidney function loss in conjunction with standard of care (18).

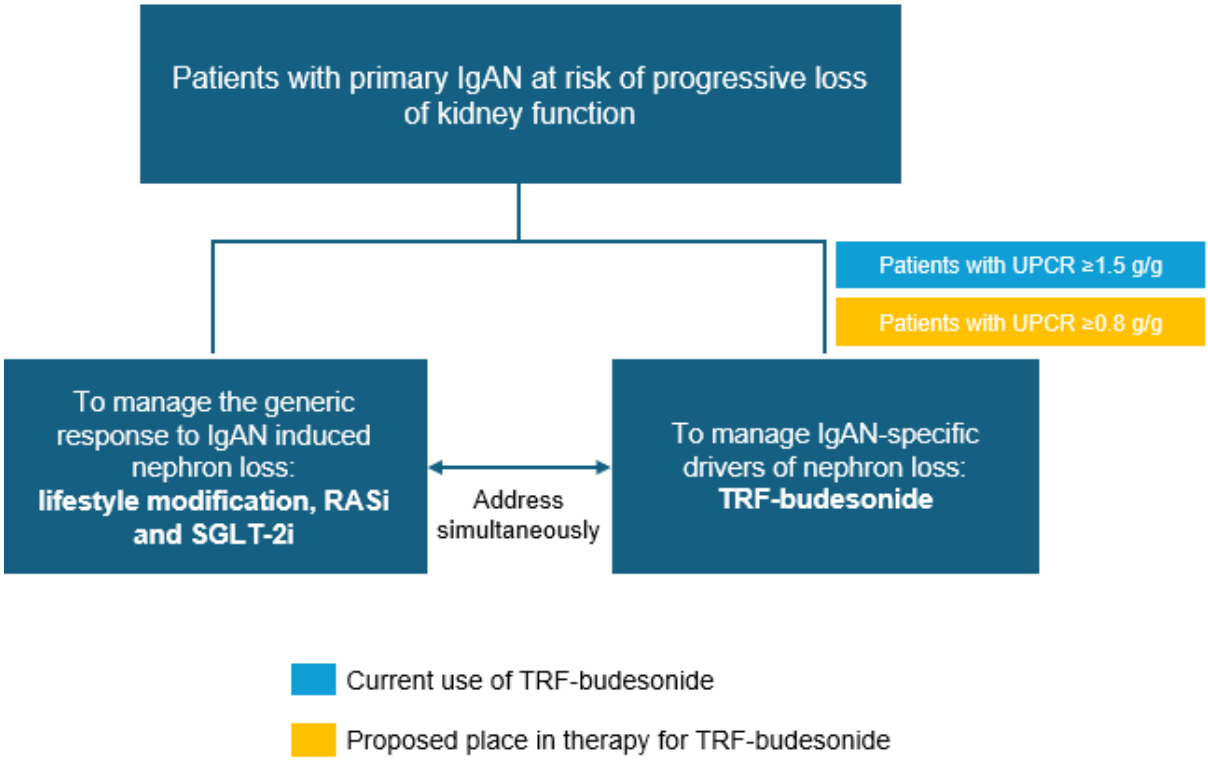
NICE already recommends TRF-budesonide for the treatment of primary IgAN in adults with a UPCR of 1.5 g/g or more, based on the MHRA marketing authorisation granted in February 2023 (TA937) (19). This submission seeks a recommendation to extend the use of TRF-budesonide for patients with IgAN and UPCR of ≥0.8 g/g in line with the anticipated expanded licensed indication and current draft KDIGO guideline recommendations (18).

Figure 7 presents an overview of the current clinical pathway of care in the UK based on NICE and draft KDIGO guidelines and shows the proposed additional positioning of TRF-budesonide.

1.4 Equality considerations

The use of TRF-budesonide is not expected to raise any equality issues.

Figure 7: Treatment pathway for IgAN



Abbreviations: IgAN, immunoglobulin A nephropathy; RASI, renin-angiotensin system inhibitor; SGLT-2i, sodium glucose cotransporter 2 inhibitor; TRF, targeted-release formulation; UPCR, urine protein-creatinine ratio.
Source: NICE 2023 (19); KGIGO 2024 (18).

2 Clinical effectiveness

Overview

- NefIgArd Nef-301 was a multinational, randomised, double-blind, placebo-controlled, multicentre clinical trial (NCT03643965) with a two-part design comparing oral TRF-budesonide 16 mg/day with placebo in patients with primary IgAN treated with optimised RAS inhibition therapy:
    - Part A evaluated the efficacy and safety of TRF-budesonide over 12 months (9 months of treatment and 3 months of follow up) from the first 201 participants randomised to the study
    - Part B included all patients randomised into the study and continued to evaluate the effect of TRF-budesonide on long-term renal function preservation over an additional 12 months of non-interventional follow-up (9 months of treatment and 15 months of follow up in total) and is the focus of this appraisal
- TRF-budesonide 16 mg/day resulted in a statistically significant preservation of kidney function, with a treatment benefit of 5.05 mL/min/1.73 m² (95% CI 3.24 to 7.38, p<0.0001) in time-weighted average eGFR over 2 years, corresponding to a 10% relative benefit versus placebo (ratio of least squares [LS] means 1.10, 95% CI 1.06 to 1.14).
- The eGFR benefit accrued by the end of 9 months of treatment was maintained during the 15-month observational follow-up, and the treatment effect was consistent across all evaluated subgroups
- The primary supportive analysis of eGFR total slope demonstrated a treatment benefit of 1.82 mL/min/1.73 m² per year (95% CI [0.50–3.13]; p=0.0035) for TRF-budesonide versus placebo, exceeding thresholds predictive of long-term clinical benefits (89, 90)
- The time from randomisation to the composite endpoint of confirmed 30% reduction in eGFR or kidney failure was significantly delayed, with a 55% risk reduction for TRF-budesonide versus placebo (HR 0.45; 95% CI 0.26 to 0.75; p=0.0014)
- The significant reduction in UPCR observed after 9 months of TRF-budesonide treatment was maintained throughout the 15-month observational follow-up

period, with a maximum reduction of 49.7% at 12 months; at 24 months, UPCR reduction was 30%, similar to the effect at 9 months

- TRF-budesonide was well-tolerated, with a safety profile consistent with that expected for a locally acting oral budesonide product
- Nef-301 OLE was an open-label extension (OLE) of NefIgArd Nef-301 (NCT04541043) which included patients with persistent proteinuria ≥1 g/day or UPCR ≥0.8 g/gram and eGFR ≥30 mL/min per 1.73 m^2 after completion of NefIgArd Nef-301 Part B; all patients in Nef-301 OLE were treated with TRF-budesonide for 9 months
- In Nef-301 a similar treatment benefit in both eGFR and UPCR was observed after 9 months of treatment with TRF-budesonide regardless of whether patients received TRF-budesonide or placebo in the Phase 3 NefIgArd-Nef 301 study:
    - The absolute change from baseline in eGFR was -1.28 mL/min/1.73m^2 in patients who had previously received TRF-budesonide in NefIgArd Nef-301 and -1.53 mL/min/1.73m^2 in patients who received placebo in NefIgArd Nef-301
    - UPCR was reduced by 33% from baseline in patients who had previously received TRF-budesonide in NefIgArd Nef-301 and by 31% in patients who received placebo in NefIgArd Nef-301

2.1 Identification and selection of relevant studies

A systematic literature review (SLR) was conducted to identify relevant clinical data assessing the clinical effectiveness and safety of treatments, including TRF-budesonide and relevant comparators for primary IgAN.

An overview of the methodology, including search strategy, Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram, list of included studies and list of excluded studies at full paper review is provided in Appendix B. The SLR was originally conducted in November 2022 and updated in January 2025. In total, 65 publications and one previous health technology assessment (HTA) submission were included in the SLR; of these, five publications

provided relevant clinical evidence for TRF-budesonide in patients with IgAN (2, 90-93).

2.2 List of relevant clinical effectiveness evidence

A summary of studies which report on the clinical evidence for TRF-budesonide is presented in Table 4. In addition to the publications identified in the SLR, clinical study reports for the relevant trials are also included.

Table 4: Clinical effectiveness evidence

Study	NefIgArd Nef-301 (NCT03643965)				Nef-301 OLE (NCT04541043)		Nefigan Nef-202 (NCT01738035)	
	Part A		Part B					
Primary sources	Part A CSR (94), Part B CSR (95), Barratt et al. 2023 (91), Lafayette et al. 2023 (90), Barratt et al. 2024 (92)				CSR (96), Lafayette et al. 2024 (93), clinicaltrials.gov, 2025 (97)		CSR (98), Fellström et al. 2017 (2)	
Study design	Phase 3, double-blind, RCT				Phase 3b open-label, single-arm, extension trial with active treatment in patients who completed the NefIgArd phase 3 trial		Phase 2b, double-blind, RCT	
	Part A evaluated the efficacy and safety of TRF-budesonide		Part B evaluated TRF-budesonide for longer term renal function preservation					
Population	• ≥18 years with biopsy-confirmed primary IgAN • eGFR ≥35 and ≤90 mL/min per 1.73 m^2 • Proteinuria ≥1 g/day or UPCR ≥0.8 g/g				• Patients who completed the NefIgArd phase 3 trial with proteinuria ≥1 g/day or UPCR ≥0.8 g/g: and eGFR ≥30 mL/min/1.73m^2		• ≥18 years biopsy-confirmed primary IgAN • eGFR ≥45 mL/min per 1·73 m^2 • UPCR >0.5 g/g or urine protein ≥0.75 g/24-h	
Intervention(s)	Optimised RASi therapy plus TRF-budesonide 16 mg/day		No intervention (optimised RASi was continued)		Optimised RASi therapy plus TRF-budesonide 16 mg/day (all patients)		Optimised RASi therapy plus TRF-budesonide 16 mg/day or TRF-budesonide 8 mg/day or placebo (1:1:1 randomisation stratified by baseline UPCR)	
Comparator(s)	Optimised RASi therapy plus placebo							
Status	Completed		Completed February 2023		Completed February 2024		Completed	
Indicate if study supports application for marketing authorisation	Yes	X	Yes	X	Yes		Yes	X
	No		No		No	X	No	

Study	NeflgArd Nef-301 (NCT03643965)				Nef-301 OLE (NCT04541043)		Nefigan Nef-202 (NCT01738035)	
	Part A		Part B					
Indicate if study used in the economic model	Yes		Yes	X	Yes	X	Yes	
	No	X	No		No		No	X
Rationale if study not used in model	Superseded by longer-term data from Part B		Not applicable		Not applicable		Phase 2 study	
Primary endpoints	• Ratio of UPCR at 9 months compared with baseline		• **AUC-based endpoint of eGFR calculated as a time-weighted average of eGFR recordings observed at each time point over 2 years**		• Change in UPCR and change in eGFR at 9 months following the first dose of TRF-budesonide compared with baseline		• Mean change from baseline in UPCR over the 9-month treatment phase	
Other reported 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		• 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, inclusive • SF-36 at 9 and 24 months • **Safety variables**		• Incidence of TEAEs from enrolment up to 12 months		• 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	

Abbreviations: eGFR, estimated glomerular filtration rate; IgAN, immunoglobulin A nephropathy, OLE, open-label extension; RAS, renin-angiotensin system; SF-36, short form 36; TRF, targeted-release formulation; UACR, urine albumin to creatinine ratio; UPCR, urine protein to creatinine ratio.
Note: Outcomes marked in bold have been incorporated into the economic model.
Source: NeflgArd Nef-301 Part A CSR (94); NeflgArd Nef-301 Part B CSR (95); Clinical study report Nef-301-OLE (96); Lafayette et al. 2024 (93); clinicaltrials.gov, 2025 (97); Fellström et al. 2017 (2).

Nefigan Nef-202 (NCT01738035) was a Phase 2b, double-blind randomised controlled trial (RCT) comparing optimised RAS inhibitor therapy plus TRF-budesonide 16 mg/day, TRF-budesonide 8 mg/day, and placebo (1:1:1 randomisation stratified by baseline UPCR) in 149 patients with IgAN with 9 months of treatment and 3 months of additional follow-up (2). The results of Nefigan Nef-202 were in line with those of the Phase 3 NefIgArd Nef-301 study.

As such, the more robust, up to date and longer-term data from NefIgArd Nef-301 Part B were used to inform the company submission and economic model. A summary of Nefigan Nef-202 is provided in Appendix K.

2.3 Summary of methodology of the relevant clinical effectiveness evidence

2.3.1 Summary of trial methodology – NefIgArd Nef-301

NefIgArd Nef-301 was a Phase 3, multinational, randomised, double-blind, placebo-controlled, multicentre clinical trial (NCT03643965) to assess the efficacy and safety of TRF-budesonide compared with placebo in patients with primary IgAN at risk of progressing to ESRD despite maximum tolerated treatment with RAS inhibitors.

The methodology for and data from NefIgArd Nef-301 reported in this submission are drawn from multiple sources: NefIgArd Nef-301 Part A clinical study report (CSR) (94), Barrat et al. 2023 (91), NefIgArd Nef-301 Part B CSR (95), Lafayette et al. 2023 (90).

2.3.1.1 Study objectives

NefIgArd Nef-301 had a two-part design (see Section 2.3.1.3).

Part A: The primary objective of Part A was to assess the effect of TRF-budesonide compared with placebo on UPCR over 9 months. Secondary objectives were to assess the effect of TRF-budesonide compared with placebo at 9 and 12 months, and to evaluate other aspects of renal function, as well as safety and tolerability over 9 months.

Part B: The primary objective of Part B was to assess the effect of TRF-budesonide compared with placebo on eGFR over 2 years. Secondary objectives were to assess the effect of TRF-budesonide compared with placebo on aspects of renal function as well as safety and tolerability over 2 years.

2.3.1.2 Study locations

NefIgArd Nef-301 was conducted across 131 nephrology clinics in 20 countries: Argentina, Australia, Belarus, Belgium, Canada, China, Czech Republic, Finland, France, Germany, Greece, Italy, Poland, South Korea, Sweden, Taiwan, Turkey, Spain, US, UK.

2.3.1.3 Trial design

NefIgArd Nef-301 was a Phase 3, multinational, randomised, double-blind, placebo-controlled, multicentre clinical trial (NCT03643965) with a two-part design (Figure 8).

- Part A evaluated the efficacy and safety of TRF-budesonide over 9 months of treatment with TRF-budesonide or placebo and 3 months of untreated follow-up (including a 2-week tapering period)
- Part B was a 12-month observational follow-up period where no study drug was administered, during which the study blinding remained in place.

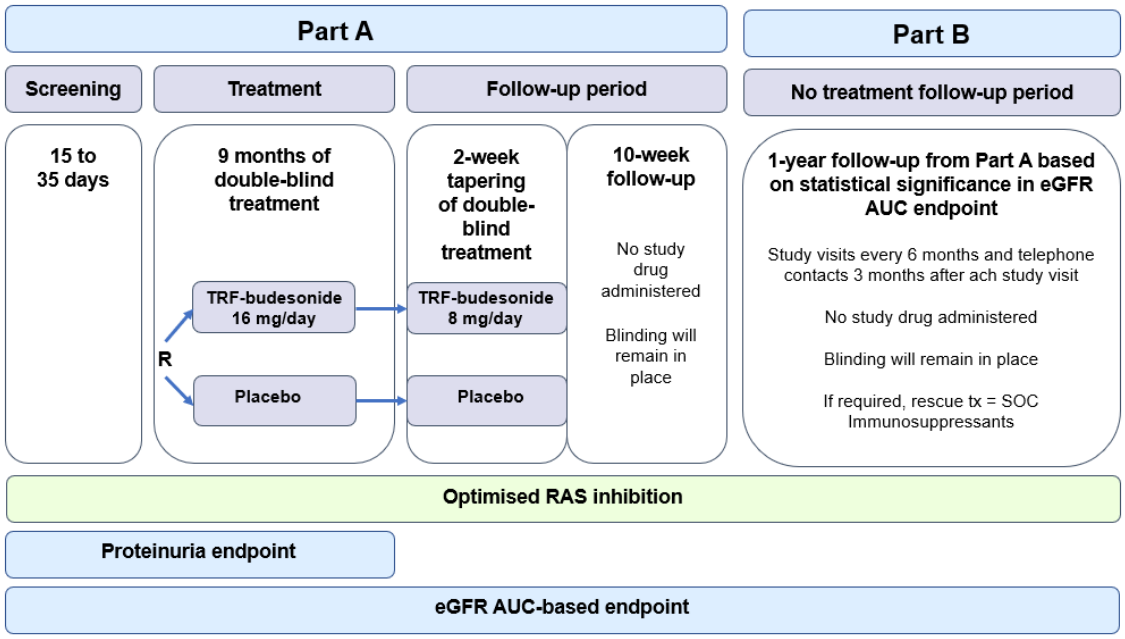
Part A of the trial included a screening period (up to 35 days) followed by a 9-month blinded treatment period, and a 3-month follow-up period (including a 2-week tapering period). The data cut-off date for Part A was 05 October 2020; the Part A data cut-off (DCO) was scheduled to occur once the first 201 randomised patients had had the opportunity to complete their 9-month visit.

Part B consisted of a 12-month (+14 to 35 days) observational follow-up period after Part A had ended. Each patient randomised was followed for 25 months after the first dose (or, if the patient randomised did not receive any study drug, 25 months after the patient was randomised). No study drug was administered during Part B; however rescue medication (steroids and/or immunosuppressive treatment) may have been used by the investigator for patients with a proteinuria level at least above 1 g per 24 hours. The total duration of the study was up to 26.5 months (including the screening period and a final visit for replicate eGFR sampling at 2 years). The

primary analysis in Part B was conducted 25 months after the 360th/last patient was dosed (or, if the 360th/last patient randomised did not receive any study drug, 25 months after the 360th/last patient was randomised). The final follow-up visit (last-patient last-visit) was conducted on 06 February 2023.

NefIgArd Nef-301 therefore provides information on the efficacy and safety of TRF-budesonide over a 2-year period including 9-months of treatment with TRF-budesonide or placebo and 15 months of untreated follow-up.

Figure 8: NefIgArd Nef-301 trial design



Abbreviations: AUC, area under the curve; CSR, clinical study report; eGFR, estimated glomerular filtration rate; R, randomisation; RAS, renin-angiotensin system; SoC, standard of care; TRF, targeted-release formulation; tx, treatment.
Source: NefIgArd Nef-301 Part B CSR (95).

2.3.1.4 Method of randomisation and blinding

Patients were randomised in a 1:1 ratio using an Interactive Response Technology system, to receive:

- TRF-budesonide 16 mg (four 4 mg capsules administered orally once daily)
- Placebo (four matching capsules administered orally once daily).

Randomisation was stratified according to baseline proteinuria (<2 g/24 hours or ≥2 g/24 hours); baseline eGFR (<60 mL/min/1.73 m^2 or ≥60 mL/min/1.73 m^2); and geographic region (Europe, North America, South America, or Asia Pacific).

NefIgArd Nef-301 was a double-blinded study. Patients, investigators, and site staff conducting study procedures, evaluating patients, entering study data, and/or evaluating study data were all blinded to treatment assignment. Blinding remained in place throughout Part A and Part B.

2.3.1.5 Eligibility criteria

Details of the eligibility criteria for NefIgArd Nef-301 are presented in Table 5.

Table 5: Eligibility criteria – NefIgArd Nef-301

Inclusion criteria	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) • 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	• 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 • Treated with any systemic CS within the 3 months before randomisation or treated with any systemic CSs 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

Inclusion criteria	Exclusion criteria
	• 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

Abbreviations: ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CKD-EPI, chronic kidney disease epidemiology collaboration equation; CS, corticosteroid; CSR, clinical study report; DBP, diastolic blood pressure; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; GI, gastrointestinal; 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.
† 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 maximum tolerated dose according to the 2012 KDIGO guideline were permitted into the study if an attempt to reach the maximum allowed dose or maximum tolerated dose had been performed or if such attempt was deemed unsafe for the patient by the investigator.
Source: NefIgArd Nef-301 Part B CSR (95).

2.3.1.6 Trial drugs

Patients were assigned to receive TRF-budesonide 16 mg/day (four 4 mg capsules once daily), or matching placebo (four matching capsules once daily) administered orally for 9 months during the treatment period (Part A).

The daily dose of double-blinded study drug may have been reduced from four capsules once daily (TRF-budesonide 16 mg/day or placebo) to two capsules once daily (TRF-budesonide 8 mg/day or placebo) if clinically relevant adverse events (AEs) developed that the investigator considered related to the study drug and that mandated dose reduction. If a dose reduction was made, then the dose was not to be increased back to four capsules once daily in either treatment group.

After completing 9 months of study treatment, the daily dose of study drug was reduced from four capsules once daily (TRF-budesonide 16 mg or placebo) to two capsules once daily (TRF-budesonide 8 mg or placebo) for 2 weeks to prevent adrenal insufficiency (tapering period in Part A). Patients who had their daily dose of study drug reduced to two capsules once daily during the Part A treatment period remained on this dose of study drug for an additional 2 weeks after completing 9 months of study treatment (during the tapering period in Part A).

Patients who prematurely discontinued treatment while taking four capsules once daily (TRF-budesonide 16 mg or placebo) were to have the daily dose of study

reduced to two capsules once daily (TRF-budesonide 8 mg or placebo) if feasible to prevent adrenal gland insufficiency.

No study drug was administered during Part B.

2.3.1.6.1 Background medication

Optimised supportive care required that patients receive the maximum tolerated or maximum allowed (country-specific) dose of an angiotensin converting enzyme inhibitor and/or an angiotensin II type I receptor blocker for at least 3 months before randomisation. This dose remained stable throughout the duration of the trial.

2.3.1.7 Permitted and disallowed concomitant medications

Permitted concomitant medications:

- Over the entirety of the study (Parts A and B), patients were allowed up to 3 courses of treatment with corticosteroids (CS) in any 2-year period for non-IgAN indications, provided no treatment course was greater than 2 weeks and the CS dose did not exceed the equivalent of 0.5 mg/kg/day prednisolone
- Topical or inhalation products containing CS or immunosuppressants
- Rescue medication (steroids and/or immunosuppressive treatment) was permitted in Part B if the investigator considered it was needed; patients were to have a proteinuria level at least above 1 g per 24 hours as per KDIGO guideline recommendations (5) for rescue medication to be relevant.

Excluded medications:

- Systemic immunosuppressive drugs (including CS), except when used as rescue medications
- Herbs for medicinal use, including Chinese herbs and Chinese traditional medicines, with a known effect on the immune system (e.g. Tripterygium wilfordii) or with a known effect on decreasing proteinuria and creatinine
- Potent inhibitors of cytochrome P450 3A4 (e.g., ketoconazole) were not permitted in Part A. During this time, patients were also instructed to avoid grapefruit and grapefruit juice

- Patients were to avoid starting new medications and making changes to existing medications, however if needed, introduction of new medicines or changes to existing medications were permitted at the discretion of the investigator.

2.3.1.8 Primary outcome

Part A: The primary outcome assessed in NefIgArd Nef-301 Part A was the ratio of UPCR (based on 24-hour urine collections) at 9 months following the first dose of study drug compared with baseline. Analyses were also performed after 3, 6, 9, 12, 18 and 24 months to describe the time course of effect.

Part B: The primary efficacy endpoint in NefIgArd Nef-301 Part B was the time-weighted average of eGFR over 2 years, with eGFR calculated by a central laboratory at each timepoint: 3, 6, 9, 12, 18 and 24 months (two separate measures were taken at both baseline and 24 months). A primary supportive analysis of 2-year eGFR slope was also performed.

2.3.1.8.1 Supportive analysis of primary outcome

A primary supportive analysis of the 2-year eGFR slope was planned using the same random coefficients approach applied to the Part A analyses of eGFR. However, this method does not provide an accurate estimate of the difference in the eGFR decline over 2 years as it underestimates the magnitude of the treatment effect between TRF-budesonide and placebo. Therefore, 2-year eGFR 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 (89).

2.3.1.9 Other outcomes used in the economic model or specified in the scope

Part A: The secondary efficacy outcomes assessed in NefIgArd Nef-301 Part A included:

- Ratio of eGFR at 9, and 12 months compared with baseline calculated using the CKD-EPI formula.

Part B: The secondary outcomes assessed in NefIgArd Nef-301 Part B included:

- Time to 30% reduction from baseline in eGFR (CKD-EPI) confirmed by a second value, with ≥4 weeks of separation between the 2 sampling time points
- Time from the first dose of study drug until receiving rescue medication
- Ratio of UPCR, and eGFR (Chronic Kidney Disease Epidemiology Collaboration [CKD-EPI]) compared with baseline averaged over time points between 12 and 24 months, inclusive, following the first dose of study drug
- Short Form 36 (SF-36) quality of life assessment at 9 and 24 months.

Safety variables in NefIgArd Nef-301 included:

- Treatment-emergent adverse events (TEAEs) – defined as AEs that occurred for the first time after study drug dosing, or that existed before but worsened in severity or relationship to study drug after dosing
- Adverse events of special interest (AESI) (severe infection requiring hospitalisation, new onset of diabetes mellitus, confirmed fracture, new osteonecrosis, GI bleeding requiring hospitalisation, reported occurrence of cataract formation, reported onset of glaucoma).

2.3.2 Baseline characteristics and demographics - NefIgArd Nef-301

Patient demographics and baseline characteristics were balanced across the treatment groups and were representative of the intended primary IgA nephropathy population (Table 6).

Patients 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]) and mild to moderate kidney dysfunction according to the chronic kidney disease nomenclature used by KDIGO (5) (median eGFR 55.49 mL/min per 1·73 m² [45.93–69.84]) at baseline; the majority also had microhaematuria.

The median time from IgA nephropathy biopsy diagnosis to study entry was 2.5 years (IQR 0.6–6.8). Blood pressure was well controlled at study entry. The TRF-

budesonide 16 mg/day group had more patients with diabetes (16 [9%] vs 8 [4%]) and pre-diabetes (71 [39%] vs 50 [27%]) than the placebo group.

Table 6: Patient demographics and disease characteristics at baseline in NefIgArd Nef-301 Part B (FAS)

Characteristic	TRF-budesonide 16 mg (N=182)	Placebo (N=182)
Median age (range), years	43 (21–69)	42 (20–73)
<45 years, n (%)	98 (53.8)	104 (57.1)
≥45 and <65 years	76 (41.8)	75 (41.2)
≥65 years	8 (4.4)	3 (1.6)
Sex, n (%)		
Male	117 (64.3)	123 (67.6)
Female	65 (35.7)	59 (32.4)
Race, n (%)		
White	138 (75.8)	137 (75.3)
Asian	43 (23.6)	40 (22.0)
Black or African American	0	0
Other	1 (0.5)	5 (2.7)
Baseline blood pressure, mm/Hg		
Systolic, median (IQR)	126 (121–132)	124 (117–130)
Diastolic, median (IQR)	79 (76–84)	79 (74–84)
Mean (SD) baseline UPCR, g/g	1.48 (0.85)	1.48 (1.15)
Mean (SD) baseline proteinuria, g/24h	2.71 (1.73)	2.71 (2.20)
<2 g/24h, n (%)	78 (43)	79 (43)
≥2 g/24h, n (%)	104 (57)	103 (57)
Mean (SD) baseline UACR, g/g	1.16 (0.68)	1.16 (0.84)
Mean (SD) baseline total urine albumin, g/24h	2.12 (1.34)	2.11 (1.58)
Median (IQR) eGFR†, mL/min/1.73m^2	56.14 (45.50–70.97)	55.11 (45.96–67.74)
<60 mL/min/1.73m^2, n (%)	109 (59.9)	109 (59.9)
≥60 mL/min/1.73m^2, n (%)	73 (40.1)	73 (40.1)
Median (IQR) time since IgAN biopsy diagnosis at informed consent, years	n=154 2.4 (0.6–6.9)	n=152 2.6 (0.6–6.5)
Treated with systemic glucocorticoids or immunosuppressants for IgAN and/or non-IgAN indications, n (%)	15 (8.2)	19 (10.4)

Characteristic	TRF-budesonide 16 mg (N=182)	Placebo (N=182)
Diabetic at baseline, n (%)	16 (8.8)	8 (4.4)
Pre-diabetic‡ at baseline, n (%)	71 (39.0)	50 (27.5)

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin II type 1 receptor blocker; CSR, clinical study report; eGFR, estimated glomerular filtration rate; FAS, full analysis set; IQR, interquartile range; RAS, renin-angiotensin system; SD, standard deviation; UACR, urine albumin to creatinine ratio. UPCR, urine protein to creatinine ratio.
† Calculated by the central laboratory with the Chronic Kidney Disease Epidemiology Collaboration formula.
‡ Defined as baseline glycated haemoglobin ≥5·7% or fasting blood glucose ≥100 mg/dL.
Source: NefIgArd Nef-301 Part B CSR (95); Lafayette et al. 2023 (90).

Nearly all patients in the study were receiving background RAS inhibitor therapy at baseline and use was similar across the treatment groups (Table 7). Most patients received either an ACEi or an ARB, with <5% of patients in both arms receiving both an ACEi and an ARB. The minor imbalances between the percentage of patients receiving an ACEi or and ARB between the treatment groups was not considered to be clinically important. Approximately 80% of patients were receiving at least 50% of the maximum allowable dose of RAS inhibitor therapy.

Table 7: RAS inhibitor therapy at baseline in NefIgArd Nef-301 Part B (FAS)

	TRF-budesonide 16 mg (N=182)	Placebo (N=182)
Use of any RAS inhibitor therapy (ACEIs and/or ARBs) prior to randomisation, n (%)		
Patients on either ACEI or ARB	[redacted]	[redacted]
Patients on ACEI alone	81 (44.5)	69 (37.9)
Patients on ARB alone	90 (49.5)	102 (56.0)
Patients on both ACEI and ARB	8 (4.4)	8 (4.4)
Level of RAS blockade†, n (%)	n=180	n=179
<50% of maximum allowed dose	39 (21.7)	34 (19.0)
≥50% and <80% of maximum allowed dose	37 (20.6)	52 (29.1)
≥80% of maximum allowed dose	[redacted]	[redacted]

Abbreviations: ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; FAS, full analysis set; RAS, renin angiotensin system.
†For patients taking both ACEIs and ARBs, the sum of the % of the maximum allowed dose for each were summarised.
Patients who were not recorded as having received RAS blockade are included in the <50% category. The dose received was not recorded for some patients; these patients are not included in the summary. The denominator is the number of patients who had available RAS blockade maximum allowed dose.
Source: NefIgArd Nef-301 Part B CSR (95).

2.3.2.1.1 Concomitant medications

Table 8 summarises concomitant medications (defined as medications that were taken on or after the first dose day of study treatment) that were taken by >6% of patients in the Part B full analysis set (FAS). There were no clinically relevant differences in concomitant medications across the treatment groups. Patients were required to be on a stable dose of RAS inhibitor therapy (ACEI and/or ARBs) at the maximum allowed or tolerated dose for 3 months prior to randomisation. Aside from RAS inhibitors, the most common concomitant medications were other viral vaccines (all COVID-19 vaccines; [redacted] of patients in the TRF-budesonide group and [redacted] of patients in the placebo group) and HMG CoA reductase inhibitors ([redacted] of the TRF-budesonide group and [redacted] of the placebo group).

Table 8: Concomitant medications (>6% of patients) by ATC class in NeflgArd Nef-301 (SAS and Part B FAS)

	FAS	
ATC class	**TRF-budesonide 16 mg (N=182)**	**Placebo (N=182)**
Patients who took any concomitant medications	[redacted]	[redacted]
ARBs, plain	[redacted]	[redacted]
Other viral vaccines†	[redacted]	[redacted]
HMG CoA reductase inhibitors	[redacted]	[redacted]
ACEIs, plain	[redacted]	[redacted]
Dihydropyridine derivatives	[redacted]	[redacted]
Preparations inhibiting uric acid production	[redacted]	[redacted]
Anilides	[redacted]	[redacted]
Vitamin D and analogues	[redacted]	[redacted]
Sulfonamides, plain	[redacted]	[redacted]
Other lipid modifying agents	[redacted]	[redacted]
Glucocorticoids	[redacted]	[redacted]
Unspecified herbal and traditional medicine	[redacted]	[redacted]
Proton pump inhibitors	[redacted]	[redacted]
Beta blocking agents, selective	[redacted]	[redacted]
Alpha-adrenoreceptor antagonists	[redacted]	[redacted]
Propionic acid derivatives	[redacted]	[redacted]
Other antihistamines for systemic use	[redacted]	[redacted]
Thyroid hormones	[redacted]	[redacted]
Platelet aggregation inhibitors excl. heparin	[redacted]	[redacted]

	FAS	
ATC class	**TRF-budesonide 16 mg (N=182)**	**Placebo (N=182)**
Antacids with sodium bicarbonate	[redacted]	[redacted]
Influenza vaccines	[redacted]	[redacted]
Iron bivalent, oral preparations	[redacted]	[redacted]
Preparations with no effect on uric acid metabolism	[redacted]	[redacted]
Benzodiazepine derivatives	[redacted]	[redacted]
Combinations of penicillins, incl. beta-lactamase inhibitors	[redacted]	[redacted]
Corticosteroids	[redacted]	[redacted]
Opioids in combination with non-opioid analgesics	[redacted]	[redacted]
Aldosterone antagonists	[redacted]	[redacted]
ARBs and diuretics	[redacted]	[redacted]
Fluroquinolones	[redacted]	[redacted]
Heparin group	[redacted]	[redacted]
Thiazides, plain	[redacted]	[redacted]
Piperazine derivatives	[redacted]	[redacted]
SGLT-2 inhibitors	[redacted]	[redacted]

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II type I receptor blocker; ATC, Anatomical Therapeutic Chemical; COVID-19, Coronavirus Disease 2019; CST, clinical study report; FAS, full analysis set; HMG CoA = 3-hydroxy-3-methyl-glutaryl-coenzyme A; SAS, safety analysis set.
Medication reported terms were coded using the WHO Drug Dictionary (Version March 2019G B3).
Source: NefIgArd Nef-301 Part B CSR (95).

2.3.3 Expert elicitation/opinion

UK clinical and health economic expert opinion was sought to support the previous submission for TRF-budesonide for the treatment of patients with IgAN, with expert opinion collected at an advisory board meeting in February 2023 (85).

An advisory board was conducted with five nephrologists and one health economist in February 2025 in order to gain insight into the following:

- Current treatments for patients with IgAN
- Unmet needs for IgAN patients
- Validation of model assumptions including:
  - Appropriate comparators for the cost-effectiveness model
  - TRF-budesonide treatment effect and retreatment assumptions

- Transition probabilities
- Mortality assumptions in the economic model
- Relevant costs.

A transcript of the advisory board discussion is included in the reference pack (86).

2.3.4 Summary of methodology of non-randomised studies

2.3.4.1 Nef-301 OLE

Nef 301-OLE was a Phase 3b, multicentre, non-randomised, open-label extension (OLE) study designed to evaluate the efficacy and safety of TRF-budesonide in patients with IgAN who had completed the NefIgArd Nef-301 study and who had persistent proteinuria ≥1g/day or UPCR ≥0.8 g/g and eGFR ≥30 mL/min/1.73m^2 despite optimised RAS inhibition. The study included patients who had been treated with TRF-budesonide or placebo in NefIgArd Nef-301.

2.3.4.1.1 Study objectives

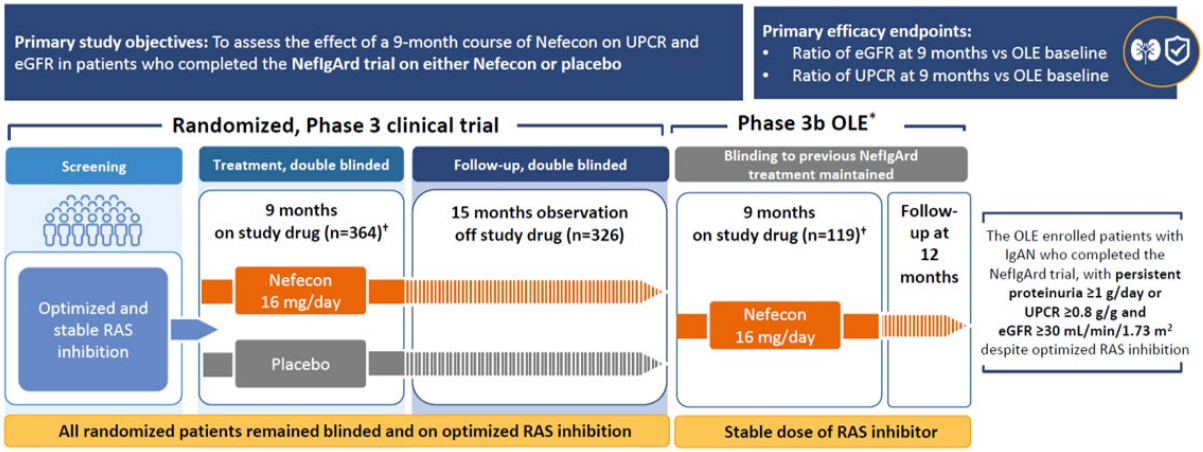
The primary objectives of Nef 301 OLE were:

- To assess the effect of 9 months of retreatment with TRF-budesonide on UPCR and eGFR in patients who completed the NefIgArd Nef-301 study with TRF-budesonide treatment
- To assess the effect of 9 months of treatment with TRF-budesonide on UPCR and eGFR in patients who completed the NefIgArd Nef-301 study with placebo treatment.

2.3.4.1.2 Trial design

An overview of the study design of Nef-301 OLE compared with NefIgArd Nef-301 is presented in Figure 9. During Nef 301 OLE, patients and investigators remained blinded to the treatment received in NefIgArd Nef-301. All patients were required to be receiving a stable dose of RAS inhibitor therapy (ACEi or ARBs) at the maximum allowed or tolerated dose according to the KDIGO 2012 guideline. Patients who received TRF-budesonide in NefIgArd Nef-301 received retreatment, whereas patients who had received placebo in NefIgArd Nef-301 were receiving their first course of TRF-budesonide.

Figure 9: Study design of NefIgArd Nef-301 and Nef-301 OLE



*Patients who completed a full 9-month course of TRF-budesonide 16 mg/day without dose reductions were included; †Followed by a 2-week taper at 8 mg/day.
Abbreviations: eGFR, estimated glomerular filtration rate; IgAN, immunoglobulin A nephropathy; OLE, open-label extension; RAS, renin-angiotensin system; UPCR, urine protein to creatinine ratio.
Source: Lafayette et al. 2024 (93).

2.3.4.1.3 Method of randomisation and blinding

The study was not randomised and all patients were to receive TRF-budesonide 16 mg/day. The study was open-label, however participants and investigators remained blinded to the prior treatment received in NefIgArd Nef-301.

2.3.4.1.4 Eligibility criteria – Nef-301-OLE

Details of the inclusion and exclusion criteria for Nef-301-OLE are presented in Table 9.

Table 9: Eligibility criteria for Nef-301 OLE

Inclusion criteria	Exclusion criteria
• Completed Study NefIgArd Nef-301, defined as Part A (9-month study drug treatment [TRF-budesonide 16 mg/day or placebo] and 3-month follow-up) and Part B (12-month follow-up) • On a stable dose of RAS inhibitor therapy (ACEIs and/or ARBs) at the maximum allowed dose or maximum tolerated dose according to the 2012 KDIGO guideline • Proteinuria based on 2 consecutive measurements (24-hour urine sampling)	• Had a dose reduction to TRF-budesonide 8 mg/day in Study Nef-301 • Systemic diseases that may cause mesangial IgA deposition, including (but not limited to) Henoch Schőnlein purpura, systemic lupus erythematosus, dermatitis herpetiformis, ankylosing spondylitis • Patients who had undergone a kidney transplant • Presence of other glomerulopathies (e.g. C3 glomerulopathy and or diabetes nephropathy • Patients with nephrotic syndrome (i.e. proteinuria >3.5g/day and with serum albumin <3.0g/dL with or without oedema • Acute, chronic or latent infectious disease including hepatitis, tuberculosis, HIV and chronic UTI • Liver cirrhosis

Inclusion criteria	Exclusion criteria
separated by at least 2 weeks and calculated by the central laboratory. Both samples of the same parameter must have shown either of the following: – Proteinuria ≥1 g/day in 2 consecutive measurements – UPCR ≥0.8g/gram in 2 consecutive measurements • eGFR ≥30mL/min per 1.73m2 using the CKD-EPI formula confirmed by the central laboratory at Study Visit 1 or 3	• Poorly controlled type I or II diabetes mellitus (HbA1c >0.8% [64 mmol/mol]) • Unstable angina, class III or IV congestive heart failure and/or clinically significant arrhythmia • Patients with unacceptable blood pressure control above national guidelines for proteinuric renal disease as assessed by the Investigator • Patients with malignancy diagnosed within 5 years, except for treated basal cell carcinoma of the skin, curatively resected squamous cell carcinoma of the skin, colon polyps or cervical carcinoma in situ • Patients with medium or high-risk osteoporosis according to 2010 ACR recommendations • GI disorders that may have interfered with the effects or release of the drug • Known glaucoma, cataracts or history of cataract surgery unless performed on both eyes • Patients with previous severe adverse reactions to steroids including psychotic symptoms, mood disorders, or suicidal ideation • Patients who had received rescue therapy with systemic immunosuppressants in NefIgArd Nef-301 • Patients treated with systemic GCS ≤3 months before screening • Patients who had been treated with any systemic GCSs ≤12 months before screening except for a maximum of 3 periods of 2 weeks with the equivalent of 0.5 mg/kg/day prednisolone or less for non-IgAN indications • Life expectancy ≤5 years

Abbreviations: ACEi, angiotensin converting enzyme inhibitor; ACR, American College of Rheumatology; ARB, angiotensin receptor blocker; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; GCS, glucocorticosteroids; GI, gastrointestinal, HOV, human immunodeficiency virus; KDIGO, Kidney Disease Improving Global Outcomes; RAS, renin-angiotensin system; TRF, targeted-release budesonide; UPCR, urine protein to creatinine ratio; UTI, urinary tract infection.

2.3.4.1.5 Trial drugs

TRF-budesonide 16 mg (four 4 mg capsules once daily [QD]) was administered during the 9-month treatment period.

The dose may have been reduced to 8 mg/day if clinically relevant AEs developed during the 9-month treatment period that the investigator considered related to study drug and that mandated dose reduction.

After completing the 9 months of study treatment, patients entered a 2-week tapering period where the daily dose of study drug was reduced from four capsules QD to two capsules QD to prevent adrenal insufficiency. Any patients who had their daily dose

reduced to two capsules QD due to safety or tolerability reasons during the 9-month treatment period remained on this dose during the 2-week tapering period. Patients who prematurely discontinued study drug whilst taking four capsules QD should have had the daily dose reduced to two capsules QD for 2 weeks, if feasible to prevent adrenal insufficiency.

Background medication

Patients were required to be on a stable dose of RAS inhibitor therapy (ACEis and/or ARBs) at the maximum allowed or maximum tolerated dose according to the 2012 KDIGO guideline during the study. A stable dose was defined as a dose within 25% of the dose at the end of NefIgArd Nef-301.

2.3.4.1.6 Permitted and disallowed concomitant medications

Other investigational medications were prohibited during the study.

Systemic immunosuppressive drugs (including glucocorticosteroids) were prohibited during the study. Herbs for medicinal use, including Eastern herbs and Eastern traditional medicines, with a known effect on proteinuria or creatinine, were not allowed during the study. Patients were encouraged to not use herbs for medicinal use, including Eastern herbs and Eastern traditional medicines, during the study; however, if used, they should have been recorded as concomitant medications.

Potent inhibitors of CYP3A4 (e.g., ketoconazole) were prohibited during treatment with study drug. During this time, patients were also instructed to avoid grapefruit and grapefruit juice.

If a patient received rescue treatment (systemic steroids, immunosuppressive treatment, and/or dialysis), the patient was to be withdrawn from TRF-budesonide treatment and continue with study visits for a total of 12 months follow-up after first dose.

Patients were to avoid starting new medications and making changes to existing medications. However, if needed, the introduction of new medications or changes to existing medications were permitted at the discretion of the Investigator.

2.3.4.1.7 Primary outcome

The primary outcomes of Nef 301 OLE were:

- Ratio of eGFR at 9 months compared with baseline, calculated using the CKD-EPI formula
- Ratio of UPCR at 9 months compared with baseline.

2.3.4.1.8 Other outcomes used in the economic model or specified in the scope

Secondary efficacy endpoints included

- Proportion of patients on dialysis, undergoing kidney transplantation, or with eGFR <15 mL/min per 1.73 m^2
- SF-36 quality of life assessment at 12 months compared with baseline.

Safety endpoints included

- TEAEs defined as AEs that occurred for the first time after dosing in Study Nef-301 OLE, or existed before dosing in Study Nef-301 OLE but worsened in severity after dosing in Study Nef-301 OLE
- AEs leading to study drug discontinuation
- AESIs (including severe infections requiring hospitalisation, new onset of diabetes, confirmed fracture, new osteonecrosis, gastrointestinal bleeding that required hospitalisation, reported occurrence of cataract formation, and reported onset of glaucoma).

2.3.4.2 Baseline characteristics – Nef-301 OLE

Table 10 presents patient demographic and disease characteristics at baseline in Nef-301 OLE. The mean age of patients was 47 years (range 25 to 79 years). The ratio of males (79.0%) to females (21.0%) was consistent with that expected for a predominantly Caucasian (84.0%) IgAN patient population. The median UPCR was 1.33 g/gram and median proteinuria was 2.5 g/24 hours, indicating a population with significant proteinuria. Median eGFR (CKD-EPI) was 49.5 mL/min/1.73 m^2 (IQR 39.9 to 63.5 mL/min/1.73 m^2), reflecting a population of patients with mild to moderate loss of kidney function. Median eGFR at OLE baseline was lower than the median eGFR at NefIgArd Nef-301 baseline (49.5 mL/min/1.73 m^2 compared with 58.0

mL/min/1.73 m^2), indicating a more advanced disease state population in the Nef-301 OLE.

Table 10: Patient demographics and disease characteristics at baseline in Nef-301 OLE SAS and FAS

Characteristic	Patients treated with TRF-budesonide 16 mg in Nef-301 OLE	
	TRF-budesonide 16 mg (N=45)	Placebo (N=74)
Age (years) at OLE baseline		
Median (range)	46 (29 to 70)	47 (25 to 76)
Age distribution, n (%)		
<45 years	17 (37.8)	31 (41.9)
≥45 and <65 years	26 (57.8)	42 (56.8)
≥65 years	2 (4.4)	1 (1.4)
Sex, n(%)		
Male	39 (86.7)	55 (74.3)
Female	6 (13.3)	19 (25.7)
Race, n (%)		
White	36 (80.0)	64 (86.5)
Asian	9 (20.0)	7 (9.5)
Other	0 (0.0)	3 (4.1)
Baseline UPCR (g/gram)		
OLE, median (interquartile range)	1.28 (0.86 to 1.80)	1.37 (1.00 to 1.88)
Nef-301, median (interquartile range)	1.29 (0.92 to 1.58)	1.19 (0.82 to 1.59)
Baseline proteinuria (g/24 hours)		
OLE, median (interquartile range)	2.18 (1.53 to 3.59)	2.64 (1.73 to 3.63)
Nef-301 median (interquartile range)	2.48 (1.68 to 3.14)	2.24 (1.80 to 3.15)
Baseline eGFR (CKD-EPI) (mL/min/1.73 m^2)		
OLE, median (interquartile range)	50.4 (42.0 to 62.0)	49.2 (39.9 to 64.9)
Nef-301 median (interquartile range)	55.5 (45.2 to 67.0)	60.2 (48.5 to 70.8)
Duration since diagnosis of IgAN at Study Nef-301 informed consent (years),		
Median (interquartile range)	3.4 (0.8 to 9.4)	1.6 (0.5 to 5.8)

Abbreviations: CKD-EPI, eGFR, estimated glomerular filtration rate; FAS, full analysis set; IgAN, immunoglobulin A nephropathy; OLE, open-label extension; SAS, safety analysis set; TRF, targeted-release formulation; UPCR, urine protein to creatinine ratio.
Source: Nef-301 OLE CSR (96).

Table 11 details RAS inhibitor therapy at baseline in the Nef-301 OLE safety analysis set (SAS) and FAS. Most patients were treated with either an ACEI or an ARB; a small number of patients [redacted]%) were on combined ACEI and ARB therapy. [redacted] patients were receiving at least 50% of the maximum allowed dose of RAS inhibitor therapy.

Table 11: RAS inhibitor therapy at baseline in the Nef-301 OLE SAS and FAS

	Patients treated with TRF-budesonide 16 mg in Nef-301 OLE	
	TRF-budesonide 16 mg (N=45)	**Placebo (N=74)**
Use of any RAS inhibitor therapy (ACEIs and/or ARBs) prior to Study Nef-301 randomisation, n (%)		
Patients on either ACEI or ARB	[redacted]	[redacted]
Patients on ACEI alone	[redacted]	[redacted]
Patients on ARB alone	[redacted]	[redacted]
Patients on both ACEI and ARB	[redacted]	[redacted]
Level of RAS blockade (% of MAD)†, n (%)	[redacted]	[redacted]
<50%	[redacted]	[redacted]
≥50% and <80%	[redacted]	[redacted]
≥80%	[redacted]	[redacted]

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; FAS, full analysis set; MAD, maximum allowable dose; OLE ,open-label extension; RAS, renin-angiotensin system; SAS, safety analysis set.
Note: % = 100 × n/N.
†For patients taking both ACEIs and ARBs, the sum of the % of the MAD for each were summarised. Note that the level of RAS blockade could be missing if the MAD was not available. The denominator is the number of patients who had available RAS blockade MAD.
Source: Nef-301 OLE CSR (96).

Table 12 summarises concomitant medications taken by >5% of total patients in the FAS/SAS. Other than RAS inhibitors, the most common classes of concomitant medications were:

- Dihydropyridine derivatives ([redacted]% of patients in the NefIgArd Nef-301 TRF-budesonide 16 mg group and [redacted]% of patients in the NefIgArd Nef-301 placebo group)
- HMG CoA reductase inhibitors ([redacted]% of patients in the NefIgArd Nef-301 TRF-budesonide 16 mg group and [redacted]% of patients in the NefIgArd Nef-301 placebo group)

- Preparations inhibiting uric acid production ([redacted]% of patients in the NefIgArd Nef-301 TRF-budesonide 16 mg group and [redacted]% of patients in the NefIgArd Nef-301 placebo group).

Table 12: Concomitant medications (>5% of total patients) by ATC class (SAS and FAS)

	Patients treated with TRF-budesonide 16 mg in Nef-301 OLE	
	TRF-budesonide 16 mg (N=45) n (%)	Placebo (N=74) n (%)
Patients who took any concomitant medications	[redacted]	[redacted]
Dihydropyridine derivatives	[redacted]	[redacted]
ACEIs, plain	[redacted]	[redacted]
ARBs, plain	[redacted]	[redacted]
HMG CoA reductase inhibitors	[redacted]	[redacted]
Preparations inhibiting uric acid production	[redacted]	[redacted]
Anilides	[redacted]	[redacted]
Other viral vaccines†	[redacted]	[redacted]
Vitamin D and analogues	[redacted]	[redacted]
Sulfonamides, plain	[redacted]	[redacted]
Beta blocking agents, selective	[redacted]	[redacted]
Other lipid modifying agents	[redacted]	[redacted]
Influenza vaccines	[redacted]	[redacted]
Proton pump inhibitors	[redacted]	[redacted]
SGLT2 inhibitors	[redacted]	[redacted]
Alpha-adrenoreceptor antagonists	[redacted]	[redacted]
Glucocorticoids	[redacted]	[redacted]
Aldosterone antagonists	[redacted]	[redacted]
Imidazoline receptor agonists	[redacted]	[redacted]
Platelet aggregation inhibitors excl. heparin	[redacted]	[redacted]
Thiazides, plain	[redacted]	[redacted]
Antacids with sodium bicarbonate	[redacted]	[redacted]
Magnesium	[redacted]	[redacted]
Opioids in combination with non-opioid analgesics	[redacted]	[redacted]
Propionic acid derivatives	[redacted]	[redacted]
Thyroid hormones	[redacted]	[redacted]

	Patients treated with TRF-budesonide 16 mg in Nef-301 OLE	
	TRF-budesonide 16 mg (N=45) n (%)	Placebo (N=74) n (%)
Benzodiazepine derivatives	[redacted]	[redacted]
Biguanides	[redacted]	[redacted]
Other antihistamines for systemic use	[redacted]	[redacted]
Piperazine derivatives	[redacted]	[redacted]
Combinations of penicillins, incl. beta-lactamase inhibitors	[redacted]	[redacted]
Folic acid and derivatives	[redacted]	[redacted]
Unspecified herbal and traditional medicine	[redacted]	[redacted]

Abbreviation: ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; ATC, Anatomical Therapeutic Chemical; FAS, full analysis set; HMG CoA, 3-hydroxy-3-methyl-glutaryl-coenzyme A; SAS, safety analysis set; SGLT2, sodium-glucose co-transporter-2; TRF- targeted-release formulation; WHO, World Health Organization.
†All COVID-19 vaccinations.
Note: % = 100 × n/N.
Concomitant medications were defined as any medications that were taken on or after the first dose day of study treatment. Medication reported terms were coded using the WHO Drug Dictionary (Version March 2019G B3).
Source: Nef-301 OLE CSR (96).

2.4 Statistical analysis and definition of study groups in the relevant clinical effectiveness evidence

2.4.1 NefIgArd Nef-301

2.4.1.1 Populations analysed

Details of populations analysed in NefIgArd Nef-301 are provided in Table 13.

Table 13: Populations analysed in NefIgArd Nef-301

Population	Description	N
Part A FAS	All patients regardless of whether they received study drug	N=199 (2 patients randomised in error were excluded)
Part B FAS	All patients randomised at the completion of recruitment to the global part of the study	N=364
SAS	All patients who received at least 1 dose of study drug	N=389

Abbreviations: CSR, clinical study report; FAS, full analysis set.; safety analysis set
Source: NefIgArd Nef-301 Part B CSR (95).

2.4.1.2 Statistical analysis

Part A: The primary outcome assessed in NefIgArd Nef-301 Part A was the ratio of UPCR (based on 24-hour urine collections) at 9 months following the first dose of study drug compared with baseline. Based on the NEFIGAN NEF-202 study (phase 2b, double-blind, randomised controlled trial [RCT]) (2), 200 patients in Part A were required to provide >90% power to demonstrate statistical significance using a 1-sided alpha level of 0.025, assuming a 25% relative reduction in UPCR with TRF-budesonide treatment compared with placebo and a standard deviation of 0.59 for the change in log (UPCR). Type 1 error was controlled across Part A of the study using a pre-defined testing hierarchy in which the Part A primary endpoint was tested at a 1-sided significance level of 0.02. All p-values were 1-sided; the rationale for this was that this was a superiority study and testing was only done in the direction favouring TRF-budesonide. As such, the level of significance was 2.5%.

Part B: In NefIgArd Nef-301 Part B, the primary outcome was the time-weighted average of eGFR over 2 years, with eGFR calculated by a central laboratory at each timepoint. Each time point was given a weight in proportion to the time elapsing from the previous recording. Therefore, recordings made at 18 and 24 months received twice as much weight as those made at 3, 6, 9, and 12 months. The weights summed to 1 so that the treatment effect could be interpreted as the average effect of TRF-budesonide over 2 years. Time-weighted average of eGFR measurements over 2 years were analysed using robust regression, having multiply imputed any missing data first in three phases: an imputation, analysis, and pooling phase. Robust regression was selected because previous eGFR data contained a small sub-population of patients having extreme outlying data resulting from very rapid progression of disease. Robust regression avoids results being unduly influenced by a small subset of patients with outlying data. Data at each individual time point were log-transformed prior to analysis.

The first step of the imputation phase was to create data with a monotone data structure across time points having imputed 20 datasets separately within each treatment arm. The number of burn-in iterations was set to 200, and observations were sampled every 200 iterations within the same chain for each imputed dataset. In the second step of the imputation phase, data at each timepoint were multiply

imputed using a regression method sequentially imputing data across successive timepoints separately by treatment arm from each dataset imputed in the first step. Having imputed any missing data, the time weighted average over 2 years was calculated for each patient within each imputed dataset.

In the analysis phase, time-weighted average was calculated for each patient within each imputed dataset. Each time point was given a weight (0.125 for 3, 6, 9, and 12 months and 0.25 for 18 and 24 months). The time weighted average eGFR data were analysed using robust regression with independent variables of treatment and log-transformed baseline eGFR. M-estimation was used with Huber weights and a cut-off value of 2, with the median method used to estimate the scale parameter. This approach means that standardised residuals with an absolute value of ≤2, corresponding to the central 95% of the data if normally distributed, have equal weight, and outlying data are weighted according to a pre-specified function. Given that dependent variables are categorical and inclusion criteria for the only continuous covariate, log-transformed baseline eGFR, prevents this variable from having outlying values, M-estimation was deemed appropriate.

In the pooling phase, estimated treatment effects and associated standard errors from each imputation were combined using Rubin's rules to provide an overall treatment effect, associated CI, and one-sided p-value.

Results are presented as the ratio of geometric LS mean values, the associated 95% CI, and 1-sided p-value. This was achieved by exponentiating the treatment effect and 95% CI for the mean difference from baseline in log-transformed values obtained from the robust regression model. To aid interpretation, the treatment effects are expressed as the mean change from baseline in eGFR averaged over 2 years in each treatment group. Mean changes from baseline 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 by multiplying the baseline geometric mean eGFR, pooled across treatment arms, with the ratio of geometric LS means within each arm minus 1. The difference in mean changes from baseline represents the treatment effect expressed as an absolute change.

A sensitivity analysis was performed using a mixed model for repeated measures (MMRM) including data from all time points over 2 years. The time-weighted average treatment effect was calculated by weighting the treatment effects estimated at each individual time point by 0.125 for 3, 6, 9, and 12 months and 0.25 for 18 and 24 months. An additional sensitivity analysis was performed using different assumptions regarding missing data. In this sensitivity analysis, patients who discontinued early and did not provide further data had data imputed based on the outcomes of other patients who discontinued at the same time but did provide further follow-up data. A supplementary analysis was also performed to include all observed eGFR data, regardless of the use of rescue medication. This analysis applied a treatment policy estimand and estimated the effect of TRF-budesonide regardless of any other intervention that might have impacted efficacy.

2.4.1.3 Sample size and power calculation

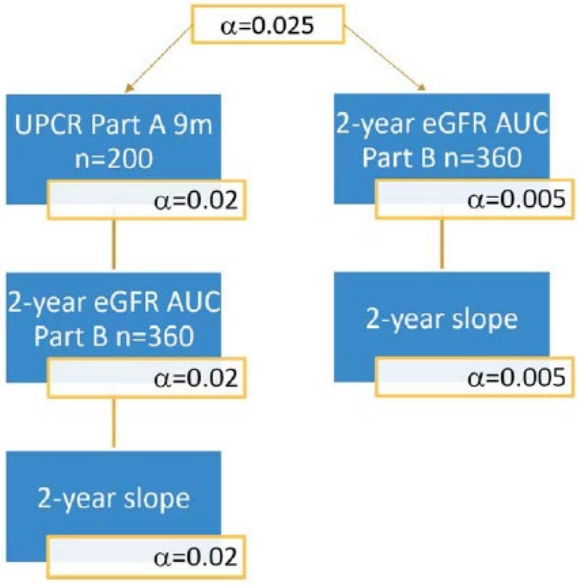
Part A: The NefIgArd NEF-202 study gave an estimated standard deviation of 0.59 for the change in the log of UPCR from baseline after 9 months of treatment (98). Based on this assumption, 200 patients in NefIgArd Nef-301 Part A would provide >90% power to demonstrate statistical significance at a 1-sided alpha level of 0.025 given a true 25% relative reduction in UPCR with TRF-budesonide treatment compared with placebo.

Part B: With 360 patients, the study had 90% power to detect a statistically significant difference in eGFR at 2 years, with use of a one-sided alpha of 2.5%, assuming a difference in mean eGFR of 2.24 mL/min per 1·73 m² at 2 years.

In order to provide strong control of the type I error rate of 2.5% one-sided across the study, the endpoints of UPCR at 9 months in the first 199 randomised patients, time weighted average of eGFR over 2 years in the overall study population, and 2-year eGFR slope in the overall study population were tested in an endpoint hierarchy (Figure 10). This approach required the primary analysis of UPCR at 9 months to be tested at a one-sided significance level of 0.02, in order to preserve 0.005 for the final analysis of 2-year eGFR in the overall study population in case statistical significance was not achieved for UPCR. Because statistical significance at the required threshold was achieved for the analysis of UPCR at 9 months, the primary

time-weighted average of eGFR over 2 years was tested at a one-sided significance level of 0.025. The primary supportive analysis of 2-year eGFR total slope was also included in the endpoint hierarchy. As statistical significance was achieved for the time-weighted average of eGFR over 2 years at the one-sided significance level of 0.025, 2-year eGFR total slope was also tested at a one-sided significance level of 0.025.

Figure 10: Summary of the hypothesis testing strategy



Abbreviations: AUC, area under the curve; eGFR, estimated glomerular filtration rate; UPCR, urine protein to creatinine ratio.
Source: NefIgArd Nef-301 Part B CSR (95).

2.4.1.4 Data management and patient withdrawals

A distinction was made between patients who prematurely discontinued study treatment and those who withdrew consent to any follow-up in the study. If a patient was withdrawn from study treatment, they were still to continue their participation in the study. The reason for premature discontinuation of study treatment or patient withdrawal for any follow-up in the study must have been documented in the electronic case report form. Patients who prematurely discontinued study drug during the treatment period of Part A were to complete the 2-week tapering period, if feasible, to prevent insufficiency of the adrenal glands. All patients who prematurely discontinued study drug were to have eGFR, proteinuria, and creatinine measured at each scheduled visit; it was of particular importance for the 9- and 12-month study

visits. All patients who prematurely discontinued study drug were also to subsequently enter Part B of the study and continue to have eGFR, proteinuria, and creatinine measured unless they had withdrawn their consent to any kind of follow-up.

Participation of a patient may have been permanently discontinued if the patient requested discontinuation and withdrew consent from the study for any follow-up.

For the primary endpoint of Part B, missing data were imputed using a multiple imputation method before calculating the time-weighted average. Missing data could result from the exclusion of data due to rescue medication, the patient having discontinued from the study or, in rare cases, because the patient had died, as well as the lack of recording of data. In all such cases, missing data were imputed conditional on previous outcomes observed within the same patient. Rescue medication was defined as any immunosuppressive medication that would be expected to materially impact efficacy, regardless of whether the medication was used for IgAN.

For the Part B supportive analysis of the 2-year eGFR slope, no missing data were imputed. For continuous endpoints to be analysed using the MMRM, no explicit imputation of missing data was needed as the MMRM analysis was performed on observed cases.

2.4.1.5 Participant flow in the relevant randomised controlled trials

See Appendix B for details of participant flow.

2.4.2 Nef-301 OLE

2.4.2.1 Populations analysed

Table 14 summarises the Nef-301 OLE analysis sets. As all patients who received a dose of study drug provided ≥1 post-OLE baseline efficacy measurement, the number of patients in the FAS and the SAS was the same.

Table 14: Analysis sets – Nef-301 OLE

Population	Description	N
FAS	All patients who received ≥1 dose of TRF-budesonide with ≥1 efficacy measurement (UPCR or eGFR) collected after dosing	119
SAS	All patients who had received ≥1 dose of study drug at the time of the analysis	119

Abbreviations: eGFR, estimated glomerular filtration rate; FAS, full analysis set; OLE, open-label extension; SAS, safety analysis set; TRF, targeted-release formulation; UPCR, urine protein to creatinine ratio.

2.4.2.2 Statistical analysis

Continuous variables were summarised using descriptive statistics including number of observations (n), mean, standard deviation, median, minimum, maximum, first quartile, and third quartile. Categorical variables were tabulated using frequency (n) and percent (%). Summaries were presented by treatment received in NefIgArd Nef-301.

Two reference baseline time points were defined for efficacy endpoints (eGFR, UPCR): baseline for the OLE study and baseline for the original NefIgArd Nef-301 study. Baseline eGFR and UPCR for the OLE study was the geometric mean of the most recent two available measurements prior to dosing. No formal statistical hypothesis testing was performed. The 9-month eGFR and UPCR values were defined as the geometric mean of the values recorded at Study Visits 8 and 9 (OLE visits at Month 9). If outlying data were present for an endpoint, a supplementary description of the data was performed using a robust regression approach.

For the 9-month UPCR, the primary analysis calculated the mean of the change from OLE baseline in log (UPCR), with results back-transformed to provide a geometric mean ratio and 95% confidence interval (CI). These were estimated from a mixed model repeated measures (MMRM) incorporating data from 3 months, 6 months, 9 months, and 12 months. Baseline UPCR was included as a covariate. The model also included terms for treatment group from Study Nef-301, visit, log(baseline) by visit, and visit by Study Nef-301 treatment group interaction. Patient was included as a random effect. An unstructured covariance matrix was used to model the within-patient correlation of data. The Kenward-Roger's degrees-of-freedom adjustment was used. Restricted maximum likelihood was used to obtain parameter estimates.

For the 9-month eGFR, due to the possible presence of outlying data, the primary analysis used the same approach but deriving the mean change in log(eGFR) from OLE baseline and its CI using a robust regression model. In order to handle missing data, the analysis was performed over 3 phases: an imputation, analysis, and pooling phase as described previously in Section 2.4.1.2. Missing data could have resulted from the exclusion of data due to rescue medication, the patient having discontinued from the study or, in rare cases, because the patient had died, as well as the lack of recording of data. In all such cases, missing data were imputed conditional on previous outcomes observed within the same patient.

2.4.2.3 Sample size

All patients who had completed NefIgArd Nef-301 and met all eligibility criteria for Nef-301 OLE were able to participate in the study. Assuming that 75% of the patients who had completed NefIgArd Nef-301 would enter Nef-301 OLE, the total number of patients to be included was estimated in the protocol to be approximately 250 patients, but up to 360 patients may have been enrolled. A total of 119 patients were actually enrolled.

2.4.2.4 Data management and patient withdrawals

Patients who prematurely discontinued TRF-budesonide treatment should have completed the remaining study visits (especially at 9 and 12 months) despite discontinuation of study drug. Patients who prematurely discontinued TRF-budesonide 16 mg/day should have had the dose reduced to 8 mg/day for 2 weeks, if feasible, to prevent adrenal insufficiency.

The following did not fulfil the criteria for withdrawal from the study, but did require discontinuation of study drug:

- Use of rescue treatment (systemic steroids, immunosuppressive treatment, and/or dialysis)
- Occurrence of any medical condition or circumstance that exposed the patient to substantial risk and/or did not allow the patient to adhere to the requirements of the protocol

- Any serious adverse event (SAE), clinically significant AE, severe laboratory abnormality, intercurrent illness, or other medical condition which indicated to the Investigator that continued participation was not in the best interest of the patient
- Pregnancy
- Requirement of prohibited concomitant medication
- Patient failure to comply with protocol requirements or study-related procedures

Descriptive summaries of efficacy and safety measures were based on observed data. No imputation of missing data was implemented.

2.4.2.5 Participant flow

Of the patients who were randomised in NefIgArd Nef-301, 234 total patients were eligible for the OLE study, based on completion of NefIgArd Nef-301 and fulfilment of the UPCR and eGFR criteria at the end of NefIgArd Nef-301. Of these 234 patients, 180 patients were screened for the OLE study while the remaining 54 patients were not screened.

Of the 180 patients screened, 119 patients were enrolled into Study Nef-301 OLE and started OLE study treatment (45 patients from the NefIgArd Nef-301 TRF-budesonide 16 mg group and 74 patients from the NefIgArd Nef-301 placebo group).

A total of 114 (95.8%) patients completed the OLE treatment period (i.e. had at least one valid UPCR or eGFR value available in the 9-month OLE visit window), including 45 (100%) patients from the NefIgArd Nef-301 TRF-budesonide 16 mg group and 69 (93.2%) patients from the NefIgArd Nef-301 placebo group. Of these, 43 (95.6%) patients from the NefIgArd Nef-301 TRF-budesonide 16 mg group and 62 (83.8%) patients from the NefIgArd Nef-301 placebo group completed OLE treatment.

Table 15: Patient disposition – all Nef-301 OLE eligible patients

	TRF-budesonide 16 mg (N=108) n (%)	**Placebo (N=126) n (%)**
NefIgArd Nef-301 patients who would have been eligible for the OLE study‡	108 (100.0)	126 (100.0)
Screened	81 (75.0)	99 (78.6)

	TRF-budesonide 16 mg (N=108) n (%)	Placebo (N=126) n (%)
Enrolled	45 (41.7)	74 (58.7)
	N†=45	**N†=74**
Started OLE study treatment	45 (100.0)	74 (100.0)
Completed OLE treatment period§	45 (100.0)	69 (93.2)
Completed OLE treatment as recorded by the Investigator	43 (95.6)	62 (83.8)
Received 9 months of OLE treatment¶	41 (91.1)	63 (85.1)
Entered OLE tapering period	43 (95.6)	61 (82.4)
Early discontinuation of study treatment as recorded by the Investigator	2 (4.4)	12 (16.2)
Adverse event	0 (0.0)	5 (6.8)
Withdrawal by patient	0 (0.0)	5 (6.8)
Protocol violation	0 (0.0)	1 (1.4)
Other	2 (4.4)	1 (1.4)
Entered the follow-up period††	45 (100.0)	69 (93.2)
Completed the follow-up period‡‡	43 (95.6)	66 (89.2)
Completed the study as recorded by the Investigator	45 (100.0)	68 (91.9)
Early discontinuation of the study as recorded by the Investigator	0 (0.0)	6 (8.1)
Withdrawal by patient	0 (0.0)	3 (4.1)
Sponsor decision	0 (0.0)	1 (1.4)
Other	0 (0.0)	2 (2.7)

Abbreviations: AE, adverse event; eGFR, estimated glomerular filtration rate; OLE, open-label extension; TRF, targeted-release formulation; UPCR, urine protein to creatinine ratio.
†number of patients enrolled in the OLE study. %=100 x n/N for OLE-eligible screened and enrolled patients.%=100 xn/N; ‡Patients who would have been eligible for the OLE study included patients who screened for the OLE study or did not screen but completed the full 2 years of NeflgArd Nef-301, had proteinuria ≥1 g/day or UPCR ≥0.8 g/g for 2 consecutive measurements at the end of NeflgArd Nef-301, and had eGFR ≥30 mL/min/1.73 m^2 at Month 24 in NeflgArd Nef-301; §Completion of OLE Treatment Period was defined as the patient having had at least 1 valid UPCR or eGFR value available in the 9-month OLE visit window.=; ¶ The patient was considered to have received 9 months of OLE treatment if the date of last OLE dose (excluding doses received in the Tapering Period) – date of first OLE dose + 1 ≥255; †† The patient was defined as having entered the OLE Follow-up Period if the patient attended at least 1 study visit or had any AE recorded that was more than 14 days after the last dose of OLE study treatment (including tapering).; ‡‡Completion of the Follow-up Period was defined as the patient having had at least 1 valid UPCR or eGFR value within the 12-month OLE visit window.
Source: Nef-301 OLE CSR (96).

2.5 Critical appraisal of the relevant clinical effectiveness evidence

A summary of quality assessment results for NefIgArd Nef-301 is provided in Table 16. A complete quality assessment for each trial is provided in Appendix B.

Table 16: Quality assessment results for parallel group RCTs

Trial number (acronym)	NefIgArd Nef-301 (90, 91)
Was randomisation carried out appropriately?	Yes
Was the concealment of treatment allocation adequate?	Yes
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes
Were the care providers, participants and outcome assessors blind to treatment allocation?	Yes
Were there any unexpected imbalances in dropouts between groups?	No
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	No

Adapted from Systematic reviews: CRD's guidance for undertaking reviews in health care (University of York Centre for Reviews and Dissemination).

2.6 Clinical effectiveness results of the relevant studies

2.6.1 NefIgArd Nef-301

The following sections detail the key results from NefIgArd Nef-301 Part B. Additional results for clinical trial endpoints that were not specified in the NICE scope (change in UACR and proportion of patients receiving rescue medication) are reported in Appendix J (Section J.1). The results from NefIgArd Nef-301 Part A are also presented in Appendix J (Section J.2).

2.6.1.1 Primary efficacy outcome (Part B): Time-weighted average of eGFR over 2 years

The time-weighted average of eGFR over 2 years showed a statistically significant 10% treatment benefit with TRF-budesonide 16 mg/day vs placebo (ratio of

geometric LS means: 1.10; 95% CI 1.06 to 1.15). Over 2 years, eGFR was on average 5.05 mL/min/1.73 m² [95% CI: 3.24, 7.38] higher with TRF-budesonide compared with placebo (p<0.·0001), with a time-weighted average change of –2.47 mL/min/1.73 m² (95% CI: –3.88, –1.02) reported for TRF-budesonide 16 mg/day and –7.52 (95% CI: –8.83, –6.18) mL/min/1.73 m² for placebo (Table 17).

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 (Appendix J Section J.1.1) (90).

Table 17: Time-weighted average of eGFR over 2 years (mL/min/1.73 m^2) using robust regression in NefIgArd Nef-301 Part B FAS

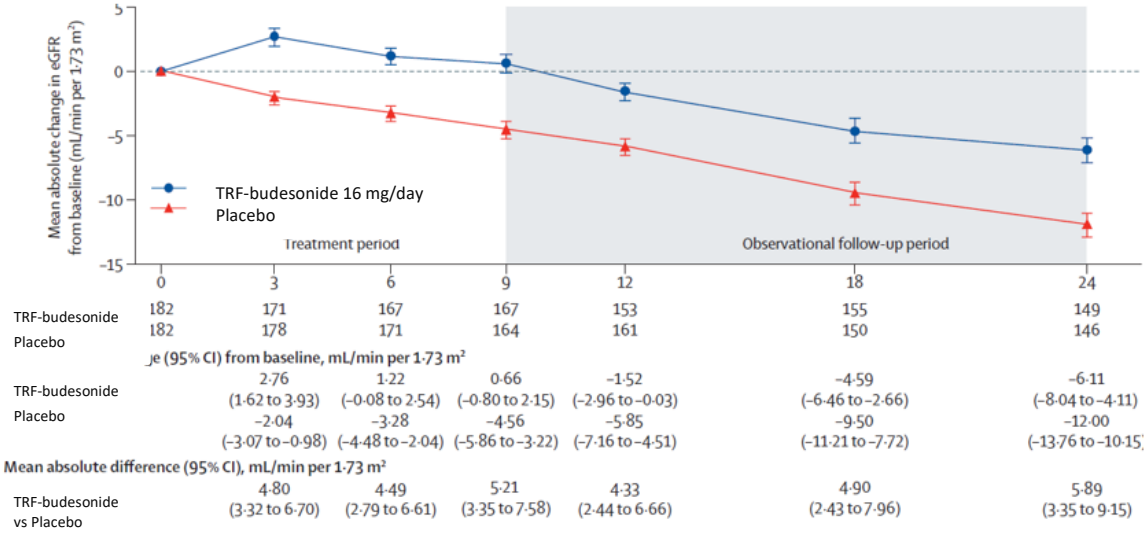
	TRF-budesonide 16 mg/day N=182	Placebo N=182
Ratio of geometric LS mean time-weighted average of eGFR over 2 years (95% CI)	0.96 (0.93 to 0.98)	0.87 (0.84 to 0.89)
Mean change from baseline in eGFR averaged over 2 years (mL/min/1.73 m^2) (95% CI)	-2.47 (-3.88 to -1.02)	-7.52 (-8.83 to -6.18)
TRF-budesonide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

Abbreviations: CI, confidence interval; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; CSR, clinical study report; eGFR, estimated glomerular filtration rate; FAS, full analysis set; LS, least squares; TRF, targeted-release formulation.
Note: The primary endpoint was calculated as a time-weighted average of log-eGFR baseline ratio of measurements at each post-baseline visit compared to baseline for Month 3, 6, 9, 12, 18, and 24, respectively, where recordings made at 18 and 24 months received twice as much weight as those made at 3, 6, 9, and 12 months.
Data included at baseline and 24 months are the log of the geometric mean of the 2 replicate values recorded at each time point, respectively. All patients in the Part B FAS are included in the robust regression analysis, with data multiply imputed, either implicitly or explicitly, prior to analysis.
Mean changes in eGFR averaged over the 2-year period of treatment and observation were derived directly from the robust regression analysis performed on the log scale. Mean change from baseline = baseline geometric mean for the total across both treatment arms × (geometric LS mean of ratio of time-weighted average over 2 years compared to baseline for each treatment arm – 1).
eGFR was calculated by the central laboratory using the CKD-EPI formula.
Source: NefIgArd Nef-301 Part B CSR (95); Lafayette et al. 2023 (90).

Figure 11 presents the mean absolute change in eGFR from baseline for the Part B FAS. The 9-month treatment course with TRF-budesonide 16 mg/day reduced the

rate of eGFR decline over 2 years. The eGFR benefit that had accrued by the end of 9 months of treatment was maintained during 15 months of observational follow-up.

Figure 11: Mean absolute change in eGFR (mL/min/1.73 m^2) from baseline in NeflgArd Nef-301 Part B FAS



Abbreviations: CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; CSR, clinical study report; eGFR, estimated glomerular filtration rate; FAS, full analysis set; LS, least squares; TRF, targeted-release formulation.
Estimated mean percentage change ± standard error was estimated from robust regression analysis of log-transformed post-baseline to baseline ratios at 3, 6, 9, 12, 18, and 24 months, and transformed back into the original scale. eGFR was calculated by the central laboratory using the CKD-EPI formula.
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.
Source: NeflgArd Nef-301 Part B CSR (95); Lafayette et al. 2023 (90).

2.6.1.1.1 Primary supportive analysis of 2-year eGFR total slope

TRF-budesonide 16 mg/day was associated with a statistically significant and clinically meaningful 1.82 mL/min/1.73m^2 per year improvement in 2-year total slope compared with placebo (p=0.0035). This corresponded to a 2-year eGFR slope of -3.55 mL/min/1.73 m^2 per year in the TRF-budesonide 16 mg/day group, and -5.37 mL/min/1.73 m^2 per year in the placebo group (Table 18). Results of pre-planned sensitivity analyses were consisted with the primary supportive analysis (see Appendix J, Section J.1). The primary supportive analysis of eGFR slope and supportive analyses were well in excess of the published threshold (0.72 mL/min/1.73 m^2 per year (89)) and revised threshold (1.23 mL/min/1.73 m^2 per year (90)) considered highly likely to predict long-term clinically meaningful benefits.

Table 18: Primary supportive analysis of 2-year eGFR total slope (mL/min/1.73 m2 per year) using random coefficient regression – NefIgArd Nef-301 Part B FAS

	Difference between TRF-budesonide 16 mg and placebo in 2-year eGFR total slope (95% CI) (mL/min/1.73 m2 per year); 1-sided p-value	eGFR 2-year total slope (95% CI) (mL/min/1.73 m^2 per year)	
		TRF-budesonide 16 mg/day (N=182)	Placebo (N=182)
Primary supportive random coefficients analysis excluding data observed after receiving rescue medication	1.82 (0.50 to 3.13); p=0.0035	-3.55 (-4.48 to -2.62)	-5.37 (-6.30 to -4.43)

Abbreviations: CI, confidence interval; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; eGFR, estimated glomerular filtration rate; FAS, full analysis set; TRF, targeted-release formulation.
Note: In all analyses, missing data were multiply imputed, either implicitly or explicitly, prior to analysis. "N" represents the total number of patients included who either had data observed or imputed.
eGFR was calculated by the central laboratory using the CKD-EPI formula.
Source: NefIgArd Nef-301 Part B CSR (95).

2.6.1.2 Secondary efficacy outcome: ratio of eGFR compared with baseline averaged over time points between 12 and 24 months

Table 19 presents the analysis of the ratio of eGFR averaged over 12 to 24 months compared with baseline using robust regression. The average treatment benefit on eGFR (averaged over 12 to 24 months) was 5.01 mL/min/1.73 m^2 in favour of TRF-budesonide treatment (p<0.0001).

Table 19: Analysis of ratio of eGFR (mL/min/1.73 m^2) averaged over 12 to 24 months compared with baseline using robust regression – NefIgArd Nef-301 Part B FAS

	TRF-budesonide 16 mg/day (N=182)	Placebo (N=182)
Ratio of geometric LS mean eGFR averaged over 12 to 24 months compared to baseline (95% CI)	0.93 (0.90 to 0.96)	0.84 (0.81 to 0.86)
Mean change from baseline in eGFR averaged over 12 to 24 months (95% CI) (mL/min/1.73 m^2)	-4.09 (-5.72 to -2.42)	-9.11 (-10.58 to -7.58)
Comparison of TRF-budesonide 16 mg vs placebo		
Ratio of geometric LS means (95% CI)	1.11 (1.06 to 1.16)	
1-sided p-value	<0.0001	
Average difference in eGFR during observational follow-up (mL/min/1.73 m^2) (95% CI)	5.01 (2.93 to 7.65)	

Abbreviations: CI, confidence interval; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; CSR, clinical study report; eGFR, estimated glomerular filtration rate; FAS, full analysis set; LS, least squares; TRF, targeted-release formulation.
Note: All patients in the Part B FAS were included in the analysis, which implicitly imputed missing data for those patients without a valid eGFR result at the respective time point. The mean change in eGFR was also derived directly from the robust regression model.
eGFR was calculated by the central laboratory using the CKD-EPI formula.
Source: NefIgArd Nef-301 Part B CSR (95).

Table 20: Ratio (TRF-budesonide 16 mg: placebo) of eGFR (mL/min/1.73 m^2) at 3, 6, 9, 12, 18, and 24 months compared with baseline using robust regression – NefIgArd Nef-301 Part B FAS

	Treatment benefit TRF-budesonide 16 mg versus placebo		Mean change from baseline (mL/min/1.73 m^2)	
Time point (n, n)	**Ratio of geometric LS means (95% CI); 1-sided p-value**	**Absolute difference (mL/min/1.73 m^2) (95% CI)**	**TRF-budesonide 16 mg/day**	**Placebo**
3 months (n = 171, 178)	1.09 (1.06 to 1.12); p<0.0001	[redacted]	[redacted]	[redacted]
6 months (n = 167, 171)	1.09 (1.05 to 1.12); p<0.0001	[redacted]	[redacted]	[redacted]
9 months (n = 167, 164)	1.10 (1.06 to 1.14); p<0.0001	[redacted]	[redacted]	[redacted]
12 months (n = 153, 161)	1.09 (1.05 to 1.13); p<0.0001	[redacted]	[redacted]	[redacted]
18 months (n = 155, 150)	1.11 (1.05 to 1.16); p<0.0001	[redacted]	[redacted]	[redacted]
24 months (n = 149, 146)	1.13 (1.07 to 1.20); p<0.0001	5.89 (3.35 to 9.15)	-6.11	-12.0

Abbreviations: CI, confidence interval; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; CSR, clinical study report; eGFR, estimated glomerular filtration rate; FAS, full analysis set; LS, least squares; TRF, targeted-release formulation.
Note: 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 and 95% CIs in eGFR were derived directly from the robust regression model performed on the log scale. Mean change from baseline = baseline geometric mean for total pooled across treatment arms × (geometric LS mean of postbaseline value / baseline value for each treatment arm – 1).
eGFR was calculated by the central laboratory using the CKD-EPI formula.
Source: NefIgArd Nef-301 Part B CSR (95).

2.6.1.3 Secondary efficacy outcome: time to 30% reduction from baseline in eGFR or kidney failure

The time to a confirmed 30% reduction in eGFR was significantly delayed with a risk reduction of 55% in patients who received TRF-budesonide treatment compared with those who received placebo (HR 0.45; 95% CI 0.26 to 0.75; 1-sided p=0.0014; 11.5% versus 21.4% with a confirmed 30% eGFR reduction in the TRF-budesonide and placebo groups, respectively) (Table 21).

A pre-defined supplementary analysis of the time to a confirmed 30% eGFR reduction or use of rescue medication (i.e., use of rescue medication included as an event) provided similar results (HR 0.51; 95% CI 0.33 to 0.79; 1-sided p=0.0013).

In a post hoc analysis, the TRF-budesonide versus placebo treatment benefit for the time to confirmed 30% eGFR reduction or kidney failure was similar for patients with a baseline UPCR <1·5 g/g (HR 0·51 [0·21–1·12]) and baseline UPCR of ≥1·5 g/g (HR 0·42 [0·21–0·83].

Table 21: Time to confirmed 30% reduction in eGFR (mL/min/1.73 m^2) using the IPCW method – NefIgArd Nef-301 Part B FAS

	TRF-budesonide 16 mg/day (N=182)	Placebo (N=182)
Patients with a confirmed 30% reduction in eGFR in the absence of rescue medication, n (%)	21 (11.5)	39 (21.4)
Censored, n (%)	[redacted]	[redacted]
Received rescue medication prior to a 30% reduction, n (%)	[redacted]	[redacted]
24-month eGFR values recorded without a 30% reduction, n (%)	[redacted]	[redacted]
Did not have 24-month eGFR values and no 30% reduction, n (%)	[redacted]	[redacted]
Comparison of TRF-budesonide vs placebo		
HR† (95% CI)	0.45 (0.26 to 0.75)	
1-sided p-value	0.0014	

Abbreviations: CI, confidence interval; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; eGFR, estimated glomerular filtration rate; FAS, full analysis set; HR, hazard ratio; IPCW, inverse probability of censoring weights; TRF, targeted-release budesonide.
eGFR was calculated by the central laboratory using the CKD-EPI formula.
Time to 30% reduction in eGFR (CKD-EPI) (in days) was measured from the time of the first dose of study drug or the time of randomisation (if the patient randomised did not receive any study drug) and included all data not impacted by the use of rescue medication.
†The HR was estimated using an IPCW method. The aim of the analysis was to estimate the HR in the absence of rescue and using IPCW, as censoring due to rescue was considered informative.
Source: NefIgArd Nef-301 Part B CSR (95); Lafayette et al. 2023 (90).

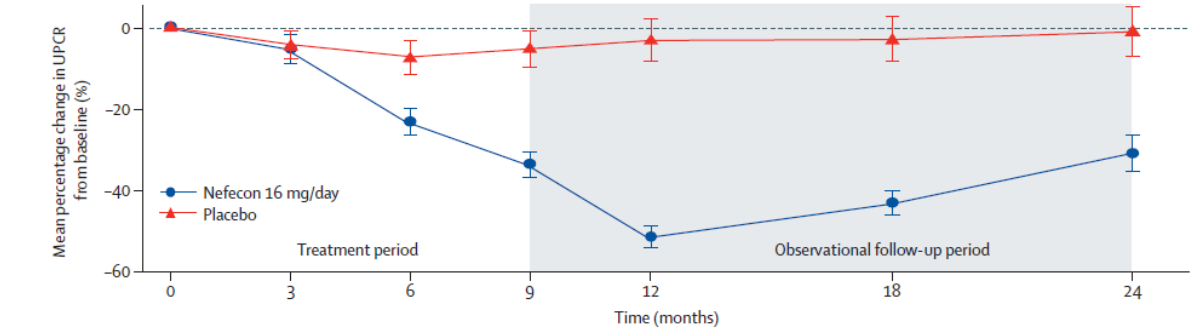
2.6.1.4 Secondary efficacy endpoint: change from baseline in UPCR

A durable reduction in proteinuria was recorded in the TRF-budesonide 16 mg/day group, with a 40.9% (95% CI: 31.9, 48.7) reduction in time-averaged UPCR between 12 and 24 months compared with the placebo group (p<0.0001) (Table 22). Time-averaged UPCR was reduced from baseline by 40.3% in the TRF-budesonide 16 mg/day group, compared with a 1.0% increase in the placebo group (Table 22).

The percentage reduction in UPCR in the TRF-budesonide 16 mg/day group versus the placebo group at 24 months was very similar to that observed at the end of the 9-month treatment period (30% reductions at both timepoints) (Figure 12). A maximal

effect of TRF-budesonide 16 mg/day versus placebo was observed at 12 months, with a reduction in UPCR of 49.7% (95% CI: 41.6, 56.6).

Figure 12: Mean percentage change in UPCR (g/g) from baseline to 24 months – NeflgArd Nef-301 Part B FAS



Nefecon, n	182	173	169	166	157	155	145
Placebo, n	182	176	169	164	160	151	142
Mean percentage change (95% CI) from baseline, %							
Nefecon 16 mg/day		−5·2 (−11·8 to 1·9)	−23·1 (−29·5 to −16·1)	−33·6 (−39·6 to −27·0)	−51·3 (−56·2 to −45·9)	−43·1 (−49·0 to −36·6)	−30·7 (−38·9 to −21·5)
Placebo		−4·3 (−10·9 to 2·9)	−7·3 (−15·0 to 1·2)	−5·2 (−13·8 to 4·3)	−3·2 (−12·8 to 7·5)	−2·9 (−13·0 to 8·3)	−1·0 (−12·8 to 12·4)
Percentage reduction (95% CI), %							
Nefecon 16 mg/day *vs* placebo		1·0 (−9·6 to 10·5)	17·1 (6·1 to 26·7)	30·0 (19·9 to 38·8)	49·7 (41·6 to 56·6)	41·4 (31·7 to 49·8)	30·1 (16·4 to 41·5)

Abbreviations: CI, confidence interval; CSR, clinical study report; FAS, full analysis set; UPCR, urine protein to creatinine ratio.
Estimated geometric mean percentage change (and standard error) 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 reduction and confidence interval was derived from (1 – ratio of geometric least squares means) × 100.
Source: NeflgArd Nef-301 Part B CSR (95); Lafayette et al. 2023 (90).

Table 22: Ratio (TRF-budesonide 16 mg/day: placebo) of UPCR (g/g) at 3, 6, 9, 12, 18, and 24 months compared with baseline using MMRM – NeflgArd Nef-301 Part B FAS

	Comparison of TRF-budesonide 16 mg/day vs placebo		Percentage change from baseline	
Time point (n, n)	**Ratio of geometric LS means (95% CI); 1-sided p-value**	**Corresponding Percentage Reduction (95% CI)**	**TRF-budesonide 16 mg/day**	**Placebo**
3 months (n = 173, 176)	0.99 (0.89 to 1.10); p=0.4248	1% (-10% to 11%)	-5.2%	-4.3%
6 months (n = 169, 169)	0.83 (0.73 to 0.94); p=0.0016	17% (6% to 27%)	-23.1%	-7.3%
9 months (n = 166, 164)	0.70 (0.61 to 0.80); p<0.0001	30% (20% to 39%)	-33.6%	-5.2%
12 months (n = 157, 160)	0.50 (0.43 to 0.58); p<0.0001	50% (42% to 57%)	-51.3%	-3.2%
18 months	0.59 (0.50 to 0.68);	41% (32% to 50%)	-43.1%	2.9%

	Comparison of TRF-budesonide 16 mg/day vs placebo		Percentage change from baseline	
Time point (n, n)	**Ratio of geometric LS means (95% CI); 1-sided p-value**	**Corresponding Percentage Reduction (95% CI)**	**TRF-budesonide 16 mg/day**	**Placebo**
(n = 155, 151)	p<0.0001			
24 months (n = 145, 142)	0.70 (0.59 to 0.84); p<0.0001	30% (16% to 41%)	-30.7%	-1.0%

Abbreviations: CI, confidence interval; FAS, full analysis set; LS, least squares; MMRM, mixed-effects model for repeated measures; UPCR, urine protein to creatinine ratio.
Note: All patients in the Part B FAS were included in the analysis, which implicitly imputed missing data for those patients without a valid UPCR result at the respective time point. Corresponding percentage reduction and CI were derived from (1 – ratio of geometric LS means) × 100.
Source: NeflgArd Nef-301 Part B CSR (95)

2.6.1.5 HRQoL outcomes

There were no differences observed between the treatment groups on any quality of life domains measured by SF-36v2 at Month 9 or Month 24 (Table 23).

Table 23: Summary of SF-36v2 scores at baseline, Month 9 and Month 24 in NeflgArd Nef-301 Part B FAS

Score	Median (IQR) SF-36 scores at baseline†		Median (IQR) SF-36 scores at 9 months		Median (IQR) SF-36 scores at 24 months	
	TRF-budesonide (n=177)	**Placebo (n=176)**	**TRF-budesonide (n=170)**	**Placebo (n=170)**	**TRF-budesonide (n=159)**	**Placebo (n=164)**
Bodily pain	55.6 (50.7, 62.0)	62.0 (51.1, 62.0)	55.6 (50.7, 62.0)	62.0 (50.7, 62.0)	55.6 (46.7, 62.0)	55.6 (46.7, 62.0)
General health	46.1 (40.4, 53.2)	48.4 (41.3, 55.6)	46.1 (41.3, 53.2)	48.4 (40.4, 55.6)	48.4 (38.9, 54.6)	48.4 (38.9, 53.2)
Mental component summary	53.4 (47.6, 57.3)	53.1 (48.1, 57.8)	51.1 (45.2, 56.6)	50.8 (44.9, 56.2)	52.7 (47.0, 57.6)	52.5 (44.4, 56.9)
Mental health	53.5 (45.6, 56.1)	50.9 (45.6, 56.7)	50.9 (43.0, 56.1)	50.9 (45.6, 56.1)	53.5 (45.6, 58.7)	53.5 (45.7, 58.7)
Physical component summary	53.8 (48.3, 57.2)	55.1 (49.9, 58.3)	54.3 (48.9, 57.5)	55.6 (50.6, 58.3)	53.7 (47.4, 57.0)	53.5 (47.5, 57.6)
Physical functioning	55.6 (51.8, 57.5)	55.6 (53.7, 57.5)	55.6 (51.8, 57.5)	55.6 (53.7, 57.5)	55.6 (51.8, 57.5)	55.6 (50.8, 57.5)
Role emotional	56.2 (49.2, 56.2)	56.2 (49.2, 56.2)	52.7 (45.7, 56.2)	56.2 (45.7, 56.2)	56.2 (45.7, 56.2)	56.2 (45.7, 56.2)
Role physical	57.2 (48.2, 57.2)	57.2 (50.4, 57.2)	54.9 (45.9, 57.2)	57.2 (50.4, 57.2)	54.9 (48.2, 57.2)	56.0 (45.9, 57.2)

Score	Median (IQR) SF-36 scores at baseline†		Median (IQR) SF-36 scores at 9 months		Median (IQR) SF-36 scores at 24 months	
	TRF-budesonide (n=177)	Placebo (n=176)	TRF-budesonide (n=170)	Placebo (n=170)	TRF-budesonide (n=159)	Placebo (n=164)
Social function	57.3 (52.3, 57.3)	57.3 (47.3, 57.3)	57.3 (47.3, 57.3)	57.3 (47.3, 57.3)	57.3 (47.3, 57.3)	57.3 (47.3, 57.3)
Vitality	52.6 (49.6, 58.5)	55.6 (49.6, 61.5)	52.6 (46.7, 58.5)	55.6 (46.7, 58.5)	55.6 (46.7, 61.5)	52.6 (46.7, 58.5)

Abbreviations: FAS, full analysis set; IQR, interquartile range; SD, standard deviation; SF-36, Short Form-36; TRF- targeted-release formulation.

†Baseline was defined as the last measurement prior to the first dose of study drug.
Source: Barratt et al. 2024 (92).

2.6.2 Nef 301-OLE

2.6.2.1 Primary efficacy outcome: ratio of eGFR at 9 months compared with baseline

Table 24 presents the primary analysis of the ratio of eGFR at 9 months compared with baseline using robust regression for the FAS. At 9 months, the absolute change from baseline in eGFR was -1.28 mL/min/1.73 m^2 in the NefIgArd Nef-301 TRF-budesonide 16 mg group and -1.53 mL/min/1.73 m^2 in the NefIgArd Nef-301 placebo group.

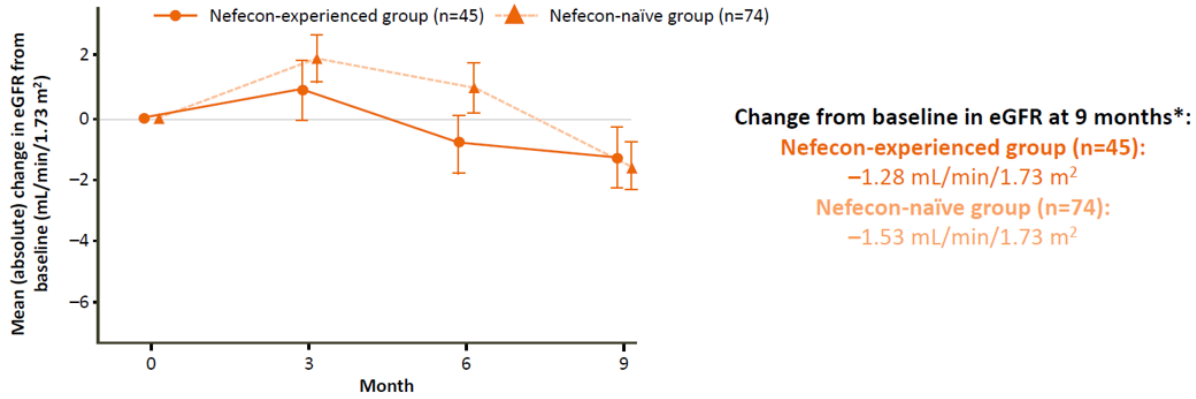
Table 24: Primary analysis of the ratio of eGFR (CKD-EPI) (mL/min/1.73 m^2) at 9 months compared with baseline using robust regression in Nef-301 OLE FAS

	Patients treated with TRF-budesonide 16 mg in Nef-301 OLE	
	NeflgArd Nef-301 TRF-budesonide 16 mg (N=45)	**NeflgArd Nef-301 placebo (N=74)**
OLE baseline†		
n	45	74
Geometric mean	50.96	49.95
Month 9 value / OLE baseline value		
N	44	69
Ratio of geometric LS mean eGFR at 9 months compared with OLE baseline (95% CI)‡	0.97 (0.94 to 1.01)	0.97 (0.94 to 1.00)
Absolute change from OLE baseline in eGFR at 9 months (mL/min/1.73 m^2) (95% CI)§	-1.28 (-3.20 to 0.72)	-1.53 (-3.07 to 0.05)

Note: eGFR was calculated by the central laboratory using the CKD-EPI formula.
†OLE baseline was defined as the geometric mean of the two most recent measurements prior to the first dose of OLE study drug; ‡for the Month 9 visit, the geometric mean of all available measurements within the corresponding analysis window was used; § Absolute change from baseline = baseline geometric mean for total × (geometric LS mean of Month 9 value / baseline value for each Nef-301 treatment arm – 1).
Abbreviations: CI, confidence interval; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; eGFR, estimated glomerular filtration rate; FAS, full analysis set; LS, least squares; OLE, open-label extension.
Source: Nef-301 OLE CSR (96).

Figure 13 presents the mean absolute change in eGFR from baseline for the FAS. Both treatment groups showed an initial increase in eGFR at 3 months and stabilisation by 9 months.

Figure 13: Mean absolute change in eGFR from baseline in Nef-301 OLE FAS



Abbreviations: eGFR, estimated glomerular filtration rate; FAS, full analysis set.
Source: Lafayette et al. 2024 (93).

2.6.2.2 Primary efficacy outcome: ratio of UPCR at 9 months compared with baseline

Table 25 presents the primary analysis of the ratio of UPCR at 9 months compared with baseline using MMRM for the FAS. After 9 months of treatment with TRF-budesonide 16 mg/day, UPCR was reduced from baseline by 33.3% in the NefIgArd Nef-301 TRF-budesonide 16 mg group and by 31.0% in the NefIgArd Nef-301 placebo group.

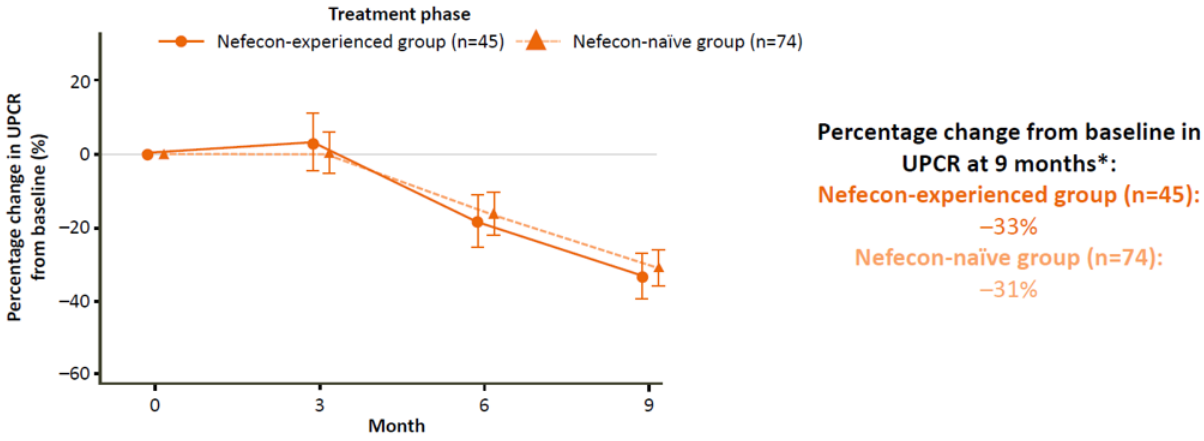
Table 25: Primary analysis of the ratio of UPCR (g/gram) at 9 months compared with baseline using MMRM in Nef-301 OLE FAS

	Patients treated with TRF-budesonide 16 mg in Nef-301 OLE	
	NefIgArd Nef-301 TRF-budesonide 16 mg (N=45)	**NefIgArd Nef-301 placebo (N=74)**
OLE baseline†		
n	45	74
Geometric mean	1.25	1.34
Month 9 value / OLE baseline value		
n	44	69
Ratio of geometric LS mean UPCR at 9 months compared with OLE baseline (95% CI)‡	0.67 (0.56 to 0.80)	0.69 (0.60 to 0.80)
Percent change from OLE baseline in UPCR at 9 months (%) (95% CI)	-33.3 (-44.4 to -19.9)	-31.0 (-40.2 to -20.2)

†OLE baseline was defined as the geometric mean of the two most recent measurements prior to the first dose of OLE study drug; ‡ For the Month 9 visit, the geometric mean of all available measurements within the corresponding analysis window was used.
Abbreviations: CI, confidence interval; FAS, full analysis set; LS, least squares; MMRM, mixed model for repeated measures; OLE, open-label extension; TRF, targeted-release formulation; UPCR, urine protein to creatinine ratio.
Source: Nef-301 OLE CSR (96).

Figure 14 presents the mean percentage change in UPCR from baseline, with both treatment groups showing a similar reduction over the 9-month treatment period.

Figure 14: Mean percentage change in UPCR (g/gram) from baseline in Nef-301 OLE FAS



Abbreviations: FAS, full analysis set; OLE, open-label extension; UPCR, urine protein to creatinine ratio.
Source: Lafayette et al. 2024 (93).

2.6.2.3 Secondary efficacy outcome: Proportion of patients on dialysis, undergoing kidney transplant or with eGFR <15 mL/min/1.73m²

Table 26 details the proportion of patients with ESRD, sustained eGFR <15 mL/min/1.73 m², doubling of serum creatinine, and categorised eGFR reductions in Nef-301 OLE. Two patients in the NefIgArd Nef-301 TRF-budesonide group and no patients in the NefIgArd Nef-301 placebo group had ESRD.

Table 26: Proportion of patients with ESRD, sustained eGFR <15 mL/min/1.73 m², doubling of serum creatinine, and categorised eGFR reductions from Nef-301 OLE FAS

	Patients treated with TRF-budesonide 16 mg in Nef-301 OLE	
	NefIgArd Nef-301 TRF-budesonide 16 mg (N=45)	NefIgArd Nef-301 placebo (N=74)
Patients with ESRD	2 (4.4)	0 (0.0)
Patients receiving dialysis	[redacted]	[redacted]
Patients receiving renal transplant	[redacted]	[redacted]
Patients with renal-related death	[redacted]	[redacted]
Patients with sustained eGFR <15 mL/min/1.73 m²	[redacted]	[redacted]
Patients with ESRD or a sustained doubling of serum creatinine†	[redacted]	[redacted]
Patients with ESRD or a confirmed 30% reduction in eGFR‡	[redacted]	[redacted]

	Patients treated with TRF-budesonide 16 mg in Nef-301 OLE	
	NeflgArd Nef-301 TRF-budesonide 16 mg (N=45)	NeflgArd Nef-301 placebo (N=74)
Patients with ESRD or a confirmed 40% reduction in eGFR‡	[redacted]	[redacted]

Abbreviations: eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; FAS, full analysis set; OLE, open-label extension.
Note: % = 100 × n/N.
†Doubling of serum creatinine was approximately equal to a 57% decline in eGFR; ‡A patient was defined as having a confirmed reduction in eGFR if any of the following criteria were met: a. An initial reduction confirmed at a later time point by another reduction; b. An initial reduction occurred at Visit 10 with no additional data available; c. An initial reduction confirmed by the occurrence of an ESRD event; or d. The occurrence of an ESRD event before any sufficient reductions were recorded.
Source: Nef-301 OLE CSR (96).

2.6.2.4 Secondary efficacy endpoint – SF-36 scores at 12 months vs baseline

Table 27 details SF-36 subscale scores at baseline and 12 months in Nef-301 OLE. There were no meaningful changes from baseline to Month 12 in quality of life domains.

Table 27: Summary of SF-36v2 scores at 12 months compared with baseline from Nef-301 OLE FAS

		Patients treated with TRF-budesonide 16 mg in Nef-301 OLE	
Subscale		**NeflgArd Nef-301 TRF-budesonide 16 mg (N=45)**	**NeflgArd Nef-301 placebo (N=74)**
Bodily pain	OLE baseline, n	[redacted]	[redacted]
	OLE baseline mean (SD)	[redacted]	[redacted]
	OLE month 10/12, n	[redacted]	[redacted]
	OLE month 10/12 mean (SD)	[redacted]	[redacted]
	Change from OLE baseline to month 10/12, n	[redacted]	[redacted]
	Change from OLE baseline to month 10/12 mean (SD)	[redacted]	[redacted]
General health	OLE baseline, n	[redacted]	[redacted]
	OLE baseline mean (SD)	[redacted]	[redacted]
	OLE month 10/12, n	[redacted]	[redacted]
	OLE month 10/12 mean (SD)	[redacted]	[redacted]

		Patients treated with TRF-budesonide 16 mg in Nef-301 OLE	
Subscale		**NeflgArd Nef-301 TRF-budesonide 16 mg (N=45)**	**NeflgArd Nef-301 placebo (N=74)**
	Change from OLE baseline to month 10/12, n	[redacted]	[redacted]
	Change from OLE baseline to month 10/12 mean (SD)	[redacted]	[redacted]
Mental component summary	OLE baseline, n	[redacted]	[redacted]
	OLE baseline mean (SD)	[redacted]	[redacted]
	OLE month 10/12, n	[redacted]	[redacted]
	OLE month 10/12 mean (SD)	[redacted]	[redacted]
	Change from OLE baseline to month 10/12, n	[redacted]	[redacted]
	Change from OLE baseline to month 10/12 mean (SD)	[redacted]	[redacted]
Mental health	OLE baseline, n	[redacted]	[redacted]
	OLE baseline mean (SD)	[redacted]	[redacted]
	OLE month 10/12, n	[redacted]	[redacted]
	OLE month 10/12 mean (SD)	[redacted]	[redacted]
	Change from OLE baseline to month 10/12, n	[redacted]	[redacted]
	Change from OLE baseline to month 10/12 mean (SD)	[redacted]	[redacted]
Physical component summary	OLE baseline, n	[redacted]	[redacted]
	OLE baseline mean (SD)	[redacted]	[redacted]
	OLE month 10/12, n	[redacted]	[redacted]
	OLE month 10/12 mean (SD)	[redacted]	[redacted]
	Change from OLE baseline to month 10/12, n	[redacted]	[redacted]
	Change from OLE baseline to month 10/12 mean (SD)	[redacted]	[redacted]
Physical functioning	OLE baseline, n	[redacted]	[redacted]
	OLE baseline mean (SD)	[redacted]	[redacted]
	OLE month 10/12, n	[redacted]	[redacted]
	OLE month 10/12 mean (SD)	[redacted]	[redacted]
	Change from OLE baseline to month 10/12, n	[redacted]	[redacted]
	Change from OLE baseline to month 10/12 mean (SD)	[redacted]	[redacted]
	OLE baseline, n	[redacted]	[redacted]

		Patients treated with TRF-budesonide 16 mg in Nef-301 OLE	
Subscale		**NeflgArd Nef-301 TRF-budesonide 16 mg (N=45)**	**NeflgArd Nef-301 placebo (N=74)**
Role emotional	OLE baseline mean (SD)	[redacted]	[redacted]
	OLE month 10/12, n	[redacted]	[redacted]
	OLE month 10/12 mean (SD)	[redacted]	[redacted]
	Change from OLE baseline to month 10/12, n	[redacted]	[redacted]
	Change from OLE baseline to month 10/12 mean (SD)	[redacted]	[redacted]
Role physical	OLE baseline, n	[redacted]	[redacted]
	OLE baseline mean (SD)	[redacted]	[redacted]
	OLE month 10/12, n	[redacted]	[redacted]
	OLE month 10/12 mean (SD)	[redacted]	[redacted]
	Change from OLE baseline to month 10/12, n	[redacted]	[redacted]
	Change from OLE baseline to month 10/12 mean (SD)	[redacted]	[redacted]
Social function	OLE baseline, n	[redacted]	[redacted]
	OLE baseline mean (SD)	[redacted]	[redacted]
	OLE month 10/12, n	[redacted]	[redacted]
	OLE month 10/12 mean (SD)	[redacted]	[redacted]
	Change from OLE baseline to month 10/12, n	[redacted]	[redacted]
	Change from OLE baseline to month 10/12 mean (SD)	[redacted]	[redacted]
Vitality	OLE baseline, n	[redacted]	[redacted]
	OLE baseline mean (SD)	[redacted]	[redacted]
	OLE month 10/12, n	[redacted]	[redacted]
	OLE month 10/12 mean (SD)	[redacted]	[redacted]
	Change from OLE baseline to month 10/12, n	[redacted]	[redacted]
	Change from OLE baseline to month 10/12 mean (SD)	[redacted]	[redacted]

Abbreviations: FAS, full analysis set; OLE, open-label extension; SD, standard deviation; SF-36, Short Form-36; TRF, targeted-release formulation.
Note: Higher scores indicate better health. OLE baseline was defined as the last measurement prior to the first dose of OLE study drug.
Source: Nef-301 OLE CSR (96).

2.7 Subsequent treatments used in the relevant studies

In NefIgArd Nef-301, a total of 15 (8.2%) TRF-budesonide 16 mg-treated patients and 20 (11%) placebo-treated patients received rescue medication during the 2-year study period.

In Nef-301 OLE, one patient in the NefIgArd Nef-301 TRF-budesonide group and no patients in the NefIgArd Nef-301 placebo group received rescue medication that led to exclusion of all data from the primary analysis. Four other patients received rescue medication that led to exclusion of data only at the Month 12 visit and the dose and duration of treatment were considered unlikely to have impacted subsequent efficacy data.

2.8 Subgroup analysis

The primary endpoints for Part A and Part B as well as eGFR at 9 months were summarised for the following subgroups: age (<45 years, ≥45 and <65 years, or ≥65 years), sex (male or female), race (white, black, or others), ethnicity (Hispanic/Latino vs not Hispanic/Latino), region (Europe, North America, South America or Asia Pacific), baseline eGFR (<60 mL/min/1.73 m^2 or ≥60 mL/min/1.73 m^2), baseline proteinuria (<2 g/24 hours or ≥2 g/24 hours), dose of RAS inhibitor therapy (ACEis and/or ARBs) with patients split into three groups: <50%, ≥50% to <80% and ≥80% of the maximum allowed dose), baseline UPCR (1.5 g/gram or ≥1.5 g/gram).

If a subgroup level had fewer than 20 patients exposed to TRF-budesonide, data in that subgroup level were not assessed. The heterogeneity in treatment effects across levels of each subgroup factor was assessed by the statistical significance of a treatment-by-subgroup interaction term in an MMRM model for UPCR and in a robust regression for eGFR, in both cases having added a main effect for subgroup. For subgroup levels that were categorisations of underlying continuous variables, the interaction term was constructed using the continuous version of the variable, log-transforming for baseline proteinuria, baseline eGFR, and baseline UPCR. Results were displayed in forest plots using stratification levels described above.

The time-weighted average of eGFR over 2 years was highly consistent across subgroups (see Appendix C, Section C.1)

2.9 Meta-analysis

NefIgArd Nef-301 is the only Phase 3 RCT which has assessed the efficacy and safety of TRF-budesonide treatment over 2 years (9 months of treatment with 15 months additional follow-up). Therefore, a meta-analysis was not required for this submission.

2.10 Indirect and mixed treatment comparisons

As outlined in Section 1.3.4, TRF-budesonide is the only treatment which targets the underlying pathophysiology of IgAN (18). In 2024 draft KDIGO guidelines, corticosteroids are only recommended for use in settings where TRF-budesonide is not available (18). Therefore, the relevant comparator for this submission is SoC without TRF-budesonide. The NefIgArd Nef-301 study compared the efficacy, safety, and tolerability of oral TRF-budesonide with placebo in patients with primary IgAN treated with optimised RAS inhibition therapy (i.e. SoC) (90, 95). It provides sufficient comparative evidence vs SoC; as such, an indirect treatment comparison (ITC) was not deemed necessary.

2.11 Adverse reactions

2.11.1 Studies identified in Section 2.2

The following section summarises the safety results from the pivotal phase 3 randomised controlled trial NefIgArd Nef-301 and the subsequent follow-up study Nef-301 OLE. Safety data from the phase 2 Nefigan Nef-202 study which was also identified in the SLR (see Section 2.2, Table 4) is summarised in Appendix K.

2.11.1.1 NefIgArd Nef-301

2.11.1.1.1 Study drug exposure

Table 28 presents details of study drug exposure and average daily dose of treatment received for the SAS and the Part B FAS. Overall treatment exposure was similar between the treatment groups. The median average daily dose received during the 9-month treatment period prior to discontinuation of study treatment was 15.9 mg in both treatment groups. For the placebo group, this corresponds to the average blinded dose for comparison with active treatment.

Table 28: Study drug exposure in NefIgArd Nef-301 (SAS and Part B FAS)

	SAS		Part B FAS	
	TRF-budesonide **16 mg**/day **N=195**	**Placebo N=194**	TRF-budesonide **16 mg N=180**	**Placebo N=179**
Overall exposure (days)†				
n	195	194	180	179
Median (IQR)	287 (281 to 293)	287 (283 to 291)	287 (281 to 292)	287 (283 to 290)
Range	11 to 330	4 to 324	11 to 330	4 to 324
Exposure to a 16 mg dose prior to the tapering period (days)‡				
n	195	194	180	179
Median (IQR)	273 (267 to 278)	273 (269 to 276)	272 (267 to 278)	273 (269 to 276)
Range	11 to 316	4 to 309	11 to 316	4 to 309
Exposure to a reduced 8 mg dose prior to the tapering period (days) ‡				
n	11	3	10	3
Median (IQR)	35 (28 to 162)	14 (10 to 251)	35 (28 to 162)	14 (10 to 251)
Range	14 to 238	10 to 251	14 to 238	10 to 251
Exposure during the tapering period (days)§				
n	178	184	164	169
Median (range)	14 (11 to 20)	14 (12 to 15)	14 (11 to 20)	14 (12 to 15)
Average daily dose received prior to discontinuation (mg)¶				
n	195	194	180	179
Median (IQR)	15.9 (15.5 to 16.0)	15.9 (15.5 to 16.0)	15.9 (15.5 to 16.0)	15.9 (15.4 to 16.0)
Range	0 to 18.9	0 to 26.2	0 to 18.9	0 to 26.2
% of maximum intended dose received during the treatment period††				
n	195	194	180	179
Median (IQR)	98 (94 to 100)	99 (96 to 100)	98 (93 to 100)	99 (95 to 100)
Range	0 to 110	0 to 118	0 to 110	0 to 118

Abbreviations: CSR, clinical study report; FAS, full analysis set; IQR, interquartile range; SAS, safety analysis set; TRF, targeted-release formulation.
†Overall exposure = date of last dose (including the tapering period) – date of first dose + 1. Note the exposure calculation was intended to describe the length of time a patient was exposed to study treatment and therefore did not take study treatment interruptions into account; ‡ Exposure to 16 mg or 8 mg prior to the tapering period (days) = date of last dose of 16 mg or 8 mg prior to the tapering period – date of first dose of 16 mg or 8 mg prior to the tapering period + 1; § Exposure during the tapering period (days) = date of last dose – date of first dose in the tapering period + 1; ¶ Average daily dose received prior to discontinuation (mg) = 4 × [total number of capsules taken by the patient during the 9-month treatment period / (date of last dose – date of first dose + 1)]. The tapering period was not included in the calculation; †† % of maximum intended dose received during the treatment period = 100 × [total dose (mg) the patient received within 9 months of their first dose / (16 mg × 273 days)]. The tapering period was not included in the calculation.
Source: NefIgArd Nef-301 Part B CSR (95).

2.11.1.1.2 Adverse events during treatment

During treatment, TRF-budesonide 16 mg/day was well tolerated, with an AE profile consistent with that expected for a locally acting oral budesonide product (90). In the SAS, TEAEs were reported by [redacted] of patients in the TRF-budesonide group and [redacted]% of patients in the placebo group. The majority of TEAEs were mild or moderate severity (Table 29). In total, [redacted]% of patients in the TRF-budesonide 16 mg/day group experienced severe TEAEs compared with [redacted]% of the placebo group. The frequency of TEAEs considered to be possibly related to study treatment was higher in the TRF-budesonide 16 mg/day group ([redacted]%) than the placebo group ([redacted]%). [redacted] was reported in the TRF-budesonide 16 mg/day group; a fatal coronavirus infection considered unrelated to study treatment.

Table 29: Overview of TEAEs during treatment in NeflgArd Nef-301 (SAS and Part B FAS)

	SAS		FAS	
	TRF-budesonide 16 mg[§] (n=195)	**Placebo[§] (n=194)**	**TRF-budesonide 16 mg[§] (n=182)**	**Placebo[§] (n=182)**
Any TEAEs	[redacted]	[redacted]	159 (87.4)	125 (68.7)
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 treatment-related TEAE†	[redacted]	[redacted]	[redacted]	[redacted]
Mild	[redacted]	[redacted]	[redacted]	[redacted]
Moderate	[redacted]	[redacted]	[redacted]	[redacted]
Severe	[redacted]	[redacted]	[redacted]	[redacted]
Any TEAESI	[redacted]	[redacted]	[redacted]	[redacted]
Any treatment-related TEAESI	[redacted]	[redacted]	[redacted]	[redacted]
Any SAE	[redacted]	[redacted]	[redacted]	[redacted]
Any TESAE	[redacted]	[redacted]	18 (9.9)	9 (4.9)
Any treatment-related TESAE	[redacted]	[redacted]	4 (2.2)	4 (2.2)

	SAS		FAS	
	TRF-budesonide 16 mg§ (n=195)	Placebo§ (n=194)	TRF-budesonide 16 mg§ (n=182)	Placebo§ (n=182)
Any TEAE leading to death	[redacted]	[redacted]	1 (0.5)	0
Any TEAE leading to study discontinuation	[redacted]	[redacted]	17 (9.3)	3 (1.6)

Abbreviations: AE, adverse event; CSR, clinical study report; FAS, full analysis set; SAS, safety analysis set; SAE, serious adverse event; TEAE, treatment-emergent adverse event; TEAESI, treatment-emergent adverse event of special interest; TESAE, treatment-emergent serious adverse event; TRF, targeted-release formulation.
Note: % = 100 × n/N. e = number of events. 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.
Source: NefIgArd Nef-301 Part B CSR (95); Lafayette et al. 2023 (90).

2.11.1.1.3 Adverse events during follow-up

Table 30 provides an overview of TEAEs reported during the 15 months of observational follow-up for the SAS and FAS. The overall incidence of TEAEs was similar between the TRF-budesonide 16 mg/day group ([redacted]) and the placebo group ([redacted]).

Table 30: Overview of TEAEs during follow-up in NefIgArd Nef-301 (SAS and Part B FAS)

	SAS		FAS	
	TRF-budesonide 16 mg (n=195)	Placebo (n=194)	TRF-budesonide 16 mg (n=175)	Placebo (n= 174)
All TEAEs	[redacted]	[redacted]	127 (72.6)	124 (71.3)
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)
Any treatment-related TEAE†	[redacted]	[redacted]	[redacted]	[redacted]
Mild	[redacted]	[redacted]	[redacted]	[redacted]
Moderate	[redacted]	[redacted]	[redacted]	[redacted]
Severe	[redacted]	[redacted]	[redacted]	[redacted]
Any TEAESI	[redacted]	[redacted]	[redacted]	[redacted]
Any TESAE	[redacted]	[redacted]	14 (8.0)	14 (8.0)

	SAS		FAS	
	TRF-budesonide 16 mg (n=195)	Placebo (n=194)	TRF-budesonide 16 mg (n=175)	Placebo (n= 174)
Any treatment-related TESAE	[redacted]	[redacted]	0	1 (0.6)
Any TEAE leading to death	[redacted]	[redacted]	1 (0.6)	0

Abbreviations: AE, adverse event; CSR, clinical study report; FAS, full analysis set; SAS, safety analysis set; TEAE, treatment-emergent adverse event; TESAE, treatment-emergent serious adverse event; TEAESI, treatment-emergent adverse event of special interest; TRF, targeted-release formulation.
Note: % = 100 × n/N'. e = number of events.
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.
† 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.
Source: NeflgArd Nef-301 Part B CSR (95) and Lafayette et al. 2023 (90).

Table 31 summarises TEAEs by preferred term that occurred in >5% of patients in either treatment group. In the SAS, the most commonly reported TEAEs that were reported with a >5% greater incidence in the TRF-budesonide group compared with the placebo group were peripheral oedema, hypertension, muscle spasms, acne, face oedema, and white blood cell count increased. TEAEs of weight increased, dyspepsia, and arthralgia were also reported slightly more often among TRF-budesonide-treated patients than placebo treated patients.

Table 31: Summary of TEAEs (>5% of patients in either treatment group) during treatment by preferred term in NeflgArd Nef-301 (SAS and Part B FAS)

Preferred term	SAS		FAS	
	TRF-budesonide 16 mg (N=195)	Placebo (N=194)	TRF-budesonide 16 mg (N=182)	Placebo (N=182)
Patients with any TEAE	[redacted]	[redacted]	159 (87.4)	125 (68.7)
Oedema peripheral†	[redacted]	[redacted]	31 (17.0)	7 (3.8)
Hypertension	[redacted]	[redacted]	22 (12.1)	6 (3.3)
Muscle spasms	[redacted]	[redacted]	22 (12.1)	7 (3.8)
Acne	[redacted]	[redacted]	20 (11.0)	2 (1.1)
Nasopharyngitis	[redacted]	[redacted]	17 (9.3)	19 (10.4)
Headache	[redacted]	[redacted]	19 (10.4)	14 (7.7)
Upper respiratory tract infection	[redacted]	[redacted]	10 (5.5)	10 (5.5)
Face oedema	[redacted]	[redacted]	14 (7.7)	1 (0.5)
Dyspepsia	[redacted]	[redacted]	13 (7.1)	4 (2.2)
Weight increased	[redacted]	[redacted]	10 (5.5)	5 (2.7)

Preferred term	SAS		FAS	
	TRF-budesonide 16 mg (N=195)	Placebo (N=194)	TRF-budesonide 16 mg (N=182)	Placebo (N=182)
Arthralgia	[redacted]	[redacted]	12 (6.6)	4 (2.2)
White blood cell count increased	[redacted]	[redacted]	8 (4.4)	0 (0.0)
Insomnia	[redacted]	[redacted]	10 (5.5)	7 (3.8)
Fatigue	[redacted]	[redacted]	10 (5.5)	7 (3.8)
Diarrhoea	[redacted]	[redacted]	[redacted]	[redacted]
Rash	[redacted]	[redacted]	10 (5.5)	7 (3.8)
Nausea	[redacted]	[redacted]	[redacted]	[redacted]
Back pain	[redacted]	[redacted]	[redacted]	[redacted]
Pyrexia	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: AE, adverse event; CSR, clinical study report; FAS, full analysis set; SAS, safety analysis set; TEAE, treatment-emergent adverse event; TRF, targeted-release formulation.
Note: % = 100 × n/N. e = number of events.
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.
AE reported terms were coded using the Medical Dictionary for Regulatory Activities Version 22.0.
† PTs were grouped for oedema peripheral (oedema peripheral and peripheral swelling) and face oedema (face oedema and swelling face).
Source: NefIgArd Nef-301 Part B CSR (95) and Lafayette et al. 2023 (90).

Table 32 summarises TEAEs occurring in >3% of the TRF-budesonide group that were reported during the follow-up period. The most common TEAE in both treatment groups was coronavirus infection. The frequencies of the other most commonly reported TEAEs were similar between the treatment groups.

Table 32: Summary of TEAEs (>3% of patients in the TRF-budesonide group) during follow-up by preferred term in NefIgArd Nef-301 (SAS and Part B FAS)

	SAS		FAS	
Preferred Term	TRF-budesonide 16 mg (N=195)	Placebo (N=194)	TRF-budesonide 16 mg (N=175)	Placebo (N=174)
Patients who had a study visit during the follow-up period, n	[redacted]	[redacted]	175	174
Patients with any TEAE that started >14 days after the last dose	[redacted]	[redacted]	127 (72.6)	124 (71.3)
Coronavirus infection	[redacted]	[redacted]	26 (14.9)	30 (17.2)
Oedema peripheral†	[redacted]	[redacted]	14 (8.0)	10 (5.7)

	SAS		FAS	
Preferred Term	**TRF-budesonide 16 mg (N=195)**	**Placebo (N=194)**	**TRF-budesonide 16 mg (N=175)**	**Placebo (N=174)**
Gout	[redacted]	[redacted]	11 (6.3)	8 (4.6)
Hypertension	[redacted]	[redacted]	10 (5.7)	12 (6.9)
Pyrexia	[redacted]	[redacted]	[redacted]	[redacted]
Arthralgia	[redacted]	[redacted]	[redacted]	[redacted]
Diarrhoea	[redacted]	[redacted]	[redacted]	[redacted]
Back pain	[redacted]	[redacted]	[redacted]	[redacted]
Nasopharyngitis	[redacted]	[redacted]	[redacted]	[redacted]
Abdominal pain†	[redacted]	[redacted]	[redacted]	[redacted]
Anaemia†	[redacted]	[redacted]	[redacted]	[redacted]
Constipation	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: AE, adverse event; CSR, clinical study report; FAS, full analysis set; SAS, safety analysis set; TEAE, treatment-emergent adverse event; TRF, targeted-release formulation.
Note: % = 100 × n/N. e = number of events.
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.
AE reported terms were coded using the Medical Dictionary for Regulatory Activities Version 22.0.
†PTs were grouped for oedema peripheral (oedema peripheral and peripheral swelling), abdominal pain (abdominal pain, abdominal pain upper, and abdominal pain lower), and anaemia (anaemia and iron deficiency anaemia).
Source: NefIgArd Nef-301 Part B CSR (95) and Lafayette et al. 2023 (90).

2.11.1.2 Nef-301 OLE

An overview of exposure to TRF-budesonide in Nef-301 is presented in Table 33. The overall median exposure of 287 days (9.4 months) and median duration of treatment prior to tapering of 273 days (9 months) reflects the intended 9-month treatment course.

Table 33: Study drug exposure in Nef-301 OLE SAS

	Patients treated with TRF-budesonide 16 mg in Nef-301 OLE	
	NefIgArd Nef-301 TRF-budesonide 16 mg (N=45)	**NefIgArd Nef-301 placebo (N=74)**
Overall exposure (days)†		
n	[redacted]	[redacted]
Median (IQR)	[redacted]	[redacted]
Range	[redacted]	[redacted]

	Patients treated with TRF-budesonide 16 mg in Nef-301 OLE	
	NefIgArd Nef-301 TRF-budesonide 16 mg (N=45)	**NefIgArd Nef-301 placebo (N=74)**
Exposure to 16 mg dose prior to the tapering period (days) ‡		
n		
Median (IQR)		
Range		
Exposure to 8 mg for patients who had dose reduction prior to the tapering period (days)‡		
n		
Median (IQR)		
Range		
Exposure during the tapering period§		
n		
Median (IQR)		
Average daily dose received prior to discontinuation (mg)¶		
n		
Median (IQR)		
Range		

Abbreviations: OLE, open-label extension; SAS, safety analysis set; TRF, targeted-release formulation.
†Overall exposure = date of last OLE dose (including the tapering period) – date of first OLE dose + 1. Note the exposure calculation was intended to describe the length of time a patient was exposed to study treatment and therefore did not take study treatment interruptions into account; ‡ Exposure to 16 mg or 8 mg prior to the tapering period (days) = date of last OLE dose of 16 mg or 8 mg prior to the tapering period – date of first dose of 16 mg or 8 mg prior to the tapering period + 1; § Exposure during the tapering period (days) = date of last OLE dose – date of first OLE dose in the tapering period + 1; ¶ Average daily dose received prior to discontinuation (mg) = 4 × [total number of capsules taken by the patient during the 9-month OLE treatment period / (date of last OLE dose – date of first OLE dose + 1)]. The tapering period was not included in the calculation.
Source: Nef-301 OLE CSR (96).

Table 34 presents a summary of TEAEs reported in the Nef-301 OLE SAS. TEAEs were reported by 93.3% of patients in the NefIgArd Nef-301 TRF-budesonide 16 mg group and 83.8% of patients in the NefIgArd Nef-301 placebo group. TEAEs that were considered to be study treatment-related occurred in 37.8% of patients in the NefIgArd Nef-301 TRF-budesonide 16 mg group and 41.9% of patients in the NefIgArd Nef-301 placebo group. No deaths occurred during the study.

Table 34: Overview of treatment emergent adverse events in the Nef-301 OLE SAS

	Patients treated with TRF-budesonide 16 mg in Nef-301 OLE	
	NefIgArd Nef-301 TRF-budesonide 16 mg (N=45)	NefIgArd Nef-301 placebo (N=74)
Any TEAEs	42 (93.3)	62 (83.8)
Any study treatment-related TEAEs†	17 (37.8)	31 (41.9)
Any TEAESIs	0 (0.0)	5 (6.8)
Any study treatment-related TEAESIs	0 (0.0)	2 (2.7)
Any TESAEs	5 (11.1)	5 (6.8)
Any study treatment related TESAE	0 (0.0)	0 (0.0)
Any TEAEs leading to study treatment discontinuation	1 (2.2)	6 (8.1)
Any AEs leading to death	0 (0.0)	0 (0.0)

Abbreviations: AE, adverse event; OLE, open-label extension; SAS, safety analysis set; TEAE, treatment-emergent adverse event; TEAESI, treatment-emergent adverse event of special interest; TESAE, treatment-emergent serious adverse event; TRF, targeted-release formulation.
Note: % = 100 × n/N. Only TEAEs that started during the OLE were summarised.
TEAEs were defined as AEs that occurred for the first time after dosing with OLE study treatment, or existed before but worsened in severity or relationship to study treatment after OLE dosing. The number of events by maximum severity counted all of the events that occurred under each severity. AEs that were established potentially clinically significant consequences of steroid treatment were considered AESIs, including severe infections requiring hospitalisation, new onset of diabetes, confirmed fracture, new osteonecrosis, gastrointestinal bleeding that required hospitalisation, reported occurrence of cataract formation, and reported onset of glaucoma.
†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..
Source: Nef-301 OLE CSR (96).

Table 35 summarises TEAS that occurred in >5% of patients in either treatment arm by preferred term for the SAS. The most commonly reported TEAEs (>10%) in the NefIgArd Nef-301 TRF-budesonide 16 mg group were coronavirus infection (26.7% of patients), hypertension (17.8% of patients) and muscle spasms (13.3% of patients). The most commonly reported TEAEs (>10%) in the NefIgArd Nef-301 placebo group were coronavirus infection (17.6% of patients), hypertension (16.2% of patients), peripheral oedema (13.5% of patients), and weight increased (10.8% of patients).

Table 35: Summary of TEAEs occurring in >5% of patients in either NefIgArd Nef-301 treatment group in the Nef-301 OLE SAS

Preferred term	Patients treated with TRF-budesonide 16 mg in Nef-301 OLE	
	NefIgArd Nef-301 TRF-budesonide 16 mg (N=45)	NefIgArd Nef-301 placebo (N=74)
Patients with any TEAE	40 (88.9)	60 (81.1)
Coronavirus infection	12 (26.7)	13 (17.6)
Hypertension	8 (17.8)	12 (16.2)
Muscle spasms	6 (13.3)	5 (6.8)
Oedema peripheral	1 (2.2)	10 (13.5)
Weight increased	3 (6.7)	8 (10.8)
Acne	3 (6.7)	6 (8.1)
Insomnia	3 (6.7)	6 (8.1)
Proteinuria	4 (8.9)	5 (6.8)
Cushingoid	2 (4.4)	6 (8.1)
Headache	4 (8.9)	4 (5.4)
Arthralgia	4 (8.9)	3 (4.1)
Back pain	3 (6.7)	3 (4.1)
Fatigue	4 (8.9)	2 (2.7)
Nasopharyngitis	1 (2.2)	4 (5.4)
Nausea	3 (6.7)	2 (2.7)
Upper respiratory tract infection	3 (6.7)	2 (2.7)
Folliculitis	0 (0.0)	4 (5.4)
Pyrexia	0 (0.0)	4 (5.4)

Abbreviations: OLE, open-label extension; SAS, safety analysis set; TEAE, treatment-emergent adverse event; TRF, targeted-release budesonide. Note: % = 100 × n/N. e = number of events.
TEAEs were defined as AEs that occurred for the first time after dosing with OLE study treatment, or existed before but worsened in severity or relationship to study treatment after OLE dosing.
AEs that started >14 days after the last dose of OLE treatment were excluded from the summary. The last dose was defined as the last OLE dose the patient received, including the Tapering Period, regardless of the duration of treatment.
AE reported terms were coded using the Medical Dictionary for Regulatory Activities Version 22.0.
Source: Nef-301 OLE CSR (96).

2.11.2 Safety overview

In NefIgArd Nef-301, TRF-budesonide was well-tolerated with a safety profile consistent with that expected for a locally acting oral budesonide product. The majority of TEAEs with TRF-budesonide were mild to moderate in severity, with peripheral oedema, hypertension, muscle spasms and acne reported by >10% of patients during the 9-month treatment phase. During the 15-month observational

follow-up phase, the incidence of TEAEs was similar between the TRF-budesonide and placebo groups. In the Nef-301 OLE study, TRF-budesonide was generally well tolerated with no new safety signals observed.

2.12 Ongoing studies

Not applicable.

2.13 Interpretation of clinical effectiveness and safety evidence

2.13.1 Principal (interim) findings from the clinical evidence highlighting the clinical benefits and harms of the technology

NefIgArd Nef-301 is the pivotal phase 3 randomised controlled trial confirming the efficacy of TRF-budesonide, a targeted immunomodulatory medication, in significantly reducing proteinuria and slowing the decline in eGFR in patients with primary IgAN already receiving optimised and stable RAS inhibition.

The primary endpoint was the time-weighted average of eGFR observed at each time point over 2 years, with the treatment effect interpreted as the average effect of TRF-budesonide compared with placebo over 2 years. eGFR is a validated surrogate endpoint which can be used to demonstrate the long-term impact on CKD progression (see Section 2.13.2) (5, 99-101). TRF-budesonide met its primary endpoint, demonstrating that 9 months of treatment provided a statistically significant and clinically relevant reduction in eGFR decline, which was maintained during the 15-month of observational follow-up. Averaged over 2 years, eGFR was on average 5.05 mL/min/1.73 m^2 higher with TRF-budesonide than placebo ($p<0.0001$). Furthermore, the primary supportive analysis of eGFR slope for TRF-budesonide versus placebo (1.82 mL/min/1.73 m^2 per year; $p=0.0035$) was well in excess of thresholds considered highly likely to predict long-term clinically meaningful benefits (89, 90). Results of sensitivity and supportive analyses were consistent with the primary efficacy analysis and the beneficial eGFR treatment effect was achieved irrespective of UPCR at baseline and was consistent across all investigated subgroups.

The preservation of kidney function during the study period was reflected in a significant 55% risk reduction in the time from randomisation to a confirmed 30%

reduction in eGFR or kidney failure with TRF-budesonide compared with placebo (HR 0.45; 95% CI 0.26 to 0.75; p=0.0014). Furthermore, statistically significant and clinically relevant improvements in UPCR levels seen with TRF-budesonide after 9 months of treatment were maintained for the entire additional 15 month follow up period, with a maximum effect observed of 49.7% at 12 months (three months after the final dose).

TRF-budesonide was well-tolerated, with a safety profile consistent with that expected for a locally acting oral budesonide product. Few patients receiving TRF-budesonide required dose reductions (the median % of maximum intended dose received was 98% across the 9-month treatment period) and the majority of AEs reported were mild to moderate in intensity. During the 15 months of observational follow-up, the overall incidence of TEAEs was similar across both treatment groups.

In an open-label extension (OLE) of NefIgArd Nef-301 (Nef-301 OLE) which included patients with persistent proteinuria ≥1 g/day or UPCR ≥0.8 g/gram and eGFR ≥30 mL/min per 1.73 m^2, a similar treatment benefit in both eGFR and UPCR was observed after 9 months of treatment with TRF-budesonide regardless of whether patients received TRF-budesonide or placebo in the Phase 3 NefIgArd-Nef 301 study. TRF-budesonide was generally well tolerated, with no new safety signals observed (96).

2.13.2 Strengths and limitations of the clinical evidence base for the technology

Internal validity

NefIgArd Nef-301 was a double-blind, randomised, placebo-controlled study consisting of two parts, Part A and Part B. Part A included a screening period, a 9-month treatment period and a 3-month follow-up period. Part B consisted of an additional 12-month follow up period after Part A had ended, during which no study drug was administered. Study blinding remained in place throughout Part B follow-up. As there were no other treatments approved for patients with IgAN at risk of progressing to ESRD, a placebo comparator was deemed appropriate. In line with KDIGO standard of care guideline recommendations, all patients were required to be on a background of optimised RAS inhibitor therapy with ACEIs and/or ARBs (5).

The NefIgArd Nef-301 study was of high quality, with oversight by the Data and Safety Monitoring Board. Early discontinuation rates were low and similar between the TRF-budesonide and placebo groups (12.6% vs 8.2%). Treatment compliance was high, with >94% of patients taking ≥80% of the expected number of capsules Furthermore, a high proportion of patients completed the Part B long-term follow up period (88.5% of the TRF-budesonide group and 90/7% of the placebo group). Data continued to be collected for any patients who discontinued study treatment early, thus minimising the amount of missing data.

The Nef-301 OLE was also of high quality. Overall compliance with study treatment was good, based on the average daily dose of TRF-budesonide received prior to discontinuation (15.8 mg in both Nef-301 groups) and the proportion of patients who discontinued study treatment early (11.8%). Data continued to be collected for any patients who discontinued study treatment early, thus minimising the amount of missing data.

Surrogate endpoints, which are reliable predictors of long-term kidney outcomes, were used in the Nef-301 studies (see external validity section, below).

External validity

The design of the NefIgArd Nef-301 trial represented a novel approach to study new treatments for IgAN that originated from a collaboration between the US Food and Drug Administration and the American Society of Nephrology's Kidney Health Initiative (91). The primary endpoints of change in eGFR (Part B) and change in UPCR (Part A) are accepted surrogate endpoints for long-term clinical outcomes in IgAN (5, 85, 100, 102).

Glomerular filtration rate is generally considered the most useful overall measure of kidney function, with CKD stages defined by eGFR levels (85, 100). Decreases in eGFR levels over time (measured by eGFR slope) are associated with an elevated risk of progression to ESRD and an increased mortality risk in patients with IgAN (16, 30, 103, 104). As a severe reduction in eGFR is defined as kidney failure, by definition, a decline in eGFR is representative of progression to kidney failure (100). A reduction in eGFR from baseline over a 2- to 3-year period is considered by

regulatory authorities to be an acceptable surrogate outcome measure for kidney failure in clinical trials (5, 100, 101). In addition, in a meta-analysis of 13 IgAN clinical trials conducted by Inker et al. 2019, a treatment effect on 1-year eGFR slope was demonstrated to be a major, independent predictor of treatment effect on long-term clinical outcomes in IgAN, supporting its use as a surrogate endpoint (99). The study reported that a sustained effect on eGFR slope provided a clear indication of a disease-modifying treatment effect (99).

In a study which used the linear regression model published by Inker et al. 2019 (89) to extrapolate the long-term impact of TRF-budesonide on kidney outcomes based on eGFR slope data, TRF-budesonide was associated with a 62% reduction in the risk of the composite outcome of kidney failure, eGFR <15 ml/min/1.73 m^2 , or sustained doubling of serum creatinine compared with supportive care only (105). This was predicted to result in a delay in progression to the composite clinical outcome of kidney failure, eGFR <15 ml/min/1.73 m^2 , or sustained doubling of serum creatinine median of 12.8 years in a real-world UK IgAN patient cohort (105).

Reducing proteinuria (assessed by measuring proteinuria over 24 hours, UPCR, and/or urine albumin to creatinine ratio [UACR]) slows the progression of CKD and is accepted as a surrogate endpoint for improved outcomes in IgAN by KDIGO, the European Medicines Agency, and clinical experts in England (18, 85, 100, 102). Associations between reduced proteinuria and a lower risk of decline in kidney function, progression to ESRD, and mortality in patients with IgAN and CKD have been consistently demonstrated (100, 102, 106-108). For example, an analysis of patient level data from two UK registries including patients with IgAN (Leicester General Hospital) and patients with nephrotic syndrome (UK National Registry of Rare Kidney Disease) showed that a 30% reduction in proteinuria in patients with IgAN conferred a 50% lower risk of ESRD, extending the median time to ESRD by 10.7 years (from 12.4 to 23.1 years) and increased the 5-year ESRD-free survival rate from 78% to 88% (107). Similarly, an individual-patient level meta-analysis demonstrated that a 50% decline in proteinuria at nine months was associated with a 60% lower risk of doubling of serum creatinine, ESRD or death (106). A study by Inker et al. 2021 (109) further supports the use of early reduction in proteinuria as a surrogate endpoint for studies of CKD progression in IgAN. The individual patient

meta-analysis included data from 1,037 patients across 12 trials and demonstrated that effects on proteinuria at 6 months were predictive of positive treatment effects on eGFR slope at various later time points (including 2 years) in patients with IgAN. Early benefits in UPCR levels are likely to translate into a slower decline in eGFR over time. This assumption is supported by published evidence in IgAN demonstrating a strong association between treatment effects on UPCR and subsequent changes in the rate of eGFR decline and the risk of development of kidney failure (102, 106, 109-111).

The majority of patients (>75%) in NefIgArd Nef-301 were Caucasian, which is in line with the expected characteristics of people with IgAN in the UK (85). However, the positive results observed in NefIgArd Nef-301 require confirmation in diverse patient populations. Another limitation of this study was that kidney biopsies were not performed at study entry, preventing association of histologic features with indications for and/or response to treatment. In addition, the postulated location of, and mechanism of action of TRF-budesonide, which distinguishes it from other formulations of budesonide, albeit appealing, is still speculative at this time (112). However, exploratory biomarker analyses indicate that TRF-budesonide has a positive effect on the levels of immune complexes involved in the pathogenesis of IgAN (113, 114), interstitial fibrosis (115), and B cell homeostasis (116).

In order to be eligible for the NefIgArd Nef-301 trial, patients had to be receiving a stable dose of RAS inhibitor therapy (ACEIs and/or ARBs) at the maximum allowed or maximum tolerated dose (95), which represented SoC at that time the trial was conducted (5). More recently, the SGLT-2 inhibitor dapagliflozin has been recommended for use in patients with CKD by NICE (117) and is being increasingly used by nephrologists as part of SoC for patients with IgAN. There are currently no clinical data reporting on the use of TRF-budesonide on a background of SoC which includes SGLT-2 inhibitors, however clinical experts have stated that the two treatments have a different mechanism of action and would be used together in clinical practice to provide an additive effect (19, 85, 86).

3 Cost effectiveness

Overview

- A cohort-level model was developed to determine the cost-effectiveness of TRF-budesonide versus standard of care (SoC) in the treatment of primary immunoglobulin A nephropathy (IgAN)
- The population considered in the economic model is consistent with the anticipated licensed indication for TRF-budesonide and the patient population included in the NefIgArd Nef-301 clinical trial; adults with primary IgAN with a urine protein excretion ≥1.0 g/day (or urine protein-to-creatinine ratio ≥0.8 g/g)
- The economic analysis used data from the NefIgArd Nef-301 clinical trial (transition probabilities for CKD 1–4 and adverse events), which is the most relevant and representative dataset for this submission
- Real-world evidence and data sourced from the published literature was utilised where the trial data could not inform the model
- This analysis was conducted from the perspective of the NHS and personal social services (PSS) in line with current NICE guidance. Costs and benefits were discounted at a rate of 3.5%, a lifetime horizon was adopted, and monthly cycles used
- In the deterministic base case economic analysis, treatment with TRF-budesonide compared with SoC was associated with an increase in life years ([redacted] years per patient), increased quality-adjusted life-years (QALYs; [redacted] per patient), and a decrease in total costs of [redacted] per patient. This demonstrated that TRF-budesonide is dominant compared to SoC at a willingness-to-pay threshold of £30,000
- The probabilistic analyses were consistent with the deterministic analyses, demonstrating that TRF-budesonide is associated with an 80% probability of being cost effective versus SoC at a willingness to pay threshold of £30,000

- The cost-effectiveness analysis indicates that TRF-budesonide is a cost-effective treatment when assessed against the NICE willingness to pay threshold of £20,000 to £30,000 per QALY

3.1 Published cost-effectiveness studies

An SLR was conducted in November 2022 and updated in January 2025 to identify economic evaluations for patients with primary IgAN (see Appendix E). The SLR identified one UK cost-effectiveness analysis for IgAN, as described in NICE Technology Appraisal TA937 (19).

In TA937, a *de novo* economic model was developed to assess the cost-effectiveness of TRF-budesonide compared to relevant alternative treatments for patients with IgAN at risk of rapid disease progression and a baseline UPCR of ≥1.5 g/g. The model structure, functionality, assumptions and data sources were informed by previous NICE technology appraisals for the treatment of CKD.

The methods used in the de novo model in TA937 were validated against a US based cost-effectiveness model in IgAN that was subsequently published after the initial development of the *de novo* economic model (19). During the development of the previous submission to NICE, clinical and health economics experts also validated the model methods at a UK Advisory Board (19, 85). Subsequently, the model was reviewed by an external assessment group (EAG) as part of its submission to NICE whereby its structure, comparators, and calculations were reviewed and scrutinised by clinical and health economic experts. The model structure was deemed appropriate for decision making and the submission resulted in NICE recommending TRF-budesonide as an option for treating primary IgAN when there is a risk of rapid disease progression in adults with a UPCR ≥1.5 g/g (19). Therefore, the same model structure was adopted to assess the cost-effectiveness of TRF-budesonide in patients with primary IgAN with a urine protein excretion ≥1.0 g/day or UPCR ≥0.8 g/g.

3.2 Economic analysis

The objective of the economic evaluation was to assess the cost-effectiveness of TRF-budesonide in patients with primary IgAN with a urine protein excretion ≥1.0 g/day (or UPCR ≥0.8 g/g).

3.2.1 Patient population

The population considered in the economic model is consistent with the anticipated licensed indication for TRF-budesonide and the patient population included in the NefIgArd Nef-301 clinical trial (described in Section 2.3.2), namely adults with primary immunoglobulin A nephropathy (IgAN) with a urine protein excretion ≥1.0 g/day (or UPCR ≥0.8 g/g).

Baseline characteristics were derived from the FAS of the NefIgArd Nef-301 study (Table 36). Age and sex determined background mortality rates. An average patient weight was used to determine the weight-based dosing regimen for the immunosuppressive therapy given to patients following a transplant.

Table 36: Baseline patient characteristics used in the economic model

Parameter	Mean	Standard deviation†	Source
Age	42.7 years	10.76	NefIgArd Part B data (Section 2.3.2)
Proportion female	34.1%	-	
Average weight	84.5 kg	18.99	
Model baseline distribution across CKD states			
CKD stage 1	2.2%	-	NefIgArd Part B data
CKD stage 2	38.5%	-	
CKD stage 3a	37.1%	-	
CKD stage 3b	22.3%	-	
CKD 4	0.0%	-	

Abbreviations: CKD, chronic kidney disease.

3.2.2 Model structure

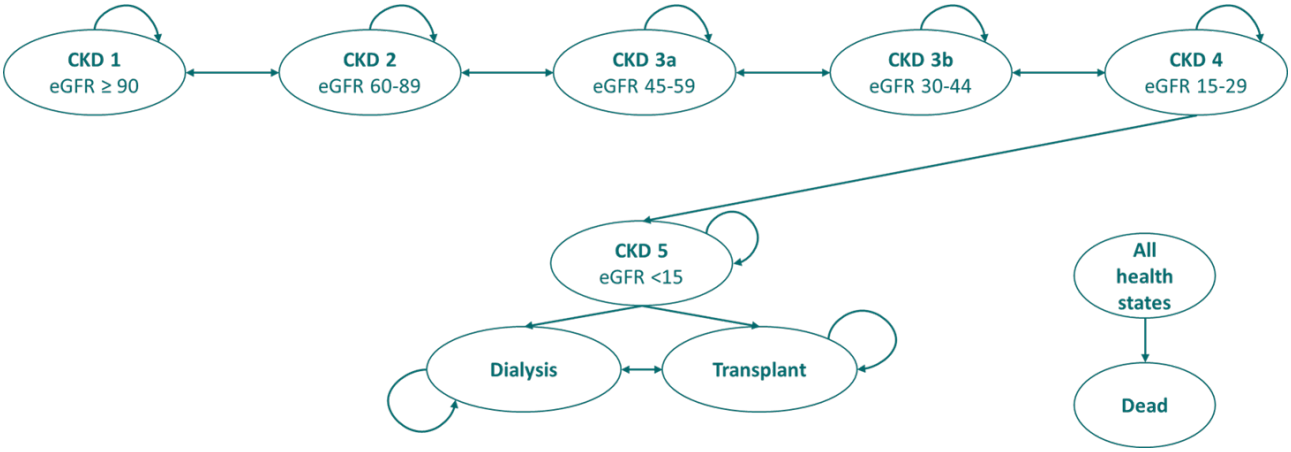
The cost-effectiveness model (CEM) was developed in Microsoft® Excel (Microsoft, Washington, USA, 2022), using Visual Basic for Applications functionality to determine the cost-effectiveness of TRF-budesonide versus relevant comparators. In line with the previous NICE appraisal of TRF-budesonide (TA937) (19), a cohort-level approach was utilised for the following reasons:

- Given the limited trial data (24 months) and the rarity of IgAN, a cohort-level approach was considered optimal as it requires fewer data inputs than a patient-level simulation. While this approach may offer less flexibility than a patient-level simulation, the requirement for fewer inputs allows the model to effectively utilise the available trial data, reducing the need to fill data gaps with external sources or assumptions.
- A cohort-level approach was used in the only previous NICE submission for IgAN, as identified in the economic SLR. Additionally, this approach was the most commonly used structure in previous CKD HTA submissions identified in the economic SLR conducted for TA937 (19), which was considered by clinicians to be a good proxy for patients with IgAN.

The CEM structure is the same model structure which was used and approved by the NICE committee in the TA937 NICE submission (19) and is presented in Figure 15. The model's health states are mostly defined by CKD state; that is, by eGFR levels. The primary objective of the NefIgArd Nef-301 Part B study was to assess the effect of the TRF-budesonide 16 mg treatment given in Part A on kidney function decline over 2 years as measured by eGFR.

There is a well-established and published cost-effectiveness precedent in CKD that links CKD health states to patient utility, health resource use, and transition probability data. Furthermore, there is no precedent for UPCR-defined states in CKD, and no identified published CEM precedent specific to IgAN. Therefore, defining health states by eGFR was deemed most appropriate for the economic evaluation.

Figure 15: TRF-budesonide 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/1.73m^2).
Abbreviations: CEM, cost-effectiveness model; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; TRF, targeted-release formulation.

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 B study (95). The arrows in Figure 15 represent the permitted transitions between health states.

Reflecting the observed patient movements in the NefIgArd Nef-301 study, clinician feedback provided in TA937 and given the relatively short monthly CEM time cycle for a chronic disease, movements between CKD states were assumed to be restricted to immediate neighbouring 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 in TA937 by clinical experts at a UK advisory board (19, 85). Furthermore, an assumption that patients could transition to improved health states was deemed acceptable for decision making purposes in the economic model used in the NICE TA775 submission (dapagliflozin for treating chronic kidney disease) (117).

As indicated in Figure 15, 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 model structure (117).

As indicated in Figure 15, 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. Furthermore, the NefIgArd-OLE study did not report mortality as an efficacy outcome. 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 3.3.2.2).

The risk of CKD 5 was also informed by real-world evidence from UK RaDaR (118) 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 TRF-budesonide 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.

3.2.2.1 Perspective, time horizon, and discounting

The base-case analysis takes the perspective of the NHS and PSS in the UK. The model base case assumed a lifetime horizon of 57 years and adopts a monthly cycle length. Costs and benefits occurring in future years were discounted at a rate of 3.5% per annum, as per the NICE reference case (119).

3.2.2.2 Feature of the economic analysis

A summary of the features of the economic analysis is presented in Table 37**.**

Table 37: Features of the economic analysis

Factor	Chosen values	Reference in submission	Justification
Time horizon	Lifetime horizon (57 years)	Section 3.2.2.1	In concordance with the NICE scope which recommends a lifetime horizon (119)

Factor	Chosen values	Reference in submission	Justification
Cycle length	Monthly (30.4375 days)	Section 3.2.2.1	IgAN is a chronic disease and therefore a monthly cycle length is appropriate. Cycle length was validated by KOLs in TA937 (19)
Model structure	Cohort state-transition model	Section 3.2.2	A cohort state-transition model requires fewer data assumptions than a patient-level approach. Cohort state-transition model have also been used in previous CKD submissions.
Source of efficacy	NefIgArd Nef-301 (95)	Section 3.3.2	In accordance with NICE guidance (119)
Source of AE rates	NefIgArd Nef-301 (95)	Section 3.3.2.4	The NefIgArd Nef-301 trial is the most robust source of evidence for AEs associated with TRF-budesonide
Source of utilities	Cooper et al. 2020 (120)	Section 3.4.3	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
Source of TRF-budesonide treatment costs	NHS National schedule of costs 2023/24 (121) and sources from the literature	Section 3.5.1.1	In accordance with NICE guidance (119)
Source of standard care treatment cost	eMIT (122) and BNF (123)	Section 3.5.1.2	SoC was applied to both arms in the NefIgArd Nef-301 trial and SoC will be given along with TRF-budesonide
Source of health state resource use/unit costs	Kent et al. 2015 (71), NHS National schedule of costs 2023/24 (121)	Section 3.5.2	To align with previous NICE HTA submissions for IgAN

3.2.3 Intervention technology and comparators

As there are no active comparators for TRF-budesonide that are currently used in UK clinical practice or recommended by NICE, and in line with the NICE scope, the comparator for the purpose of this submission is SoC (see Section 3.2.3.2).

3.2.3.1 TRF budesonide

In line with the NefIgArd Nef-301 study and the anticipated MHRA licensed indication, the model assumes TRF-budesonide is self-administered as four 4 mg tablets (16 mg) once daily for 9 months. Before discontinuation, the dose is reduced to 8 mg once daily for 2 weeks (during the last month of the 9-month treatment period). TRF-budesonide is assumed to be provided to patients as a 120-tablet (30-day) pack, and to be used alongside current SoC. A tapering pack is also expected to become available in Q3/Q4 of 2025 which contains 28 tablets (see Section 3.5.1.1.1).

The licensed indication states that the TRF-budesonide dose may be reduced further to 4 mg once daily for an additional 2 weeks, at the discretion of the treating physician. This is referred to as the “treatment tapering” period.

3.2.3.1.1 TRF-budesonide re-treatment

The EMA SmPC and the draft MHRA SmPC states that re-treatment may be considered at the discretion of the treating physician (124, 125). Therefore, the CEM includes the functionality to explore cost-effectiveness projections for various TRF-budesonide retreatment scenarios. At the point of retreatment, retreatment-eligible patients are assumed to follow the same cost and patient utility pathways as used for the starting treatment with TRF-budesonide (see Section 3.5.1.1.5).

3.2.3.2 SoC

The placebo arm of NefIgArd Nef-301 was assumed to provide a good proxy for SoC in reflecting optimised supportive care, as described in Chapter 2 of the public review draft KDIGO 2024 Clinical Practice Guideline for the Management of immunoglobulin A nephropathy (IgAN) and immunoglobulin A vasculitis (IgAV) (18). Patients in both treatment arms of NefIgArd Nef-301 received optimised and stable RAS blockade, which is assumed to represent optimised supportive care. The draft KDIGO 2024 guidelines recommend the following to manage the consequences of IgAN-induced nephron loss: blood pressure management; maximally tolerated dose of ACEi/ARB; lifestyle modification; and addressing cardiovascular risk. The guidelines also suggest that SGLT2 inhibitors may be considered as part of the treatment regimen

for patients with IgAN, particularly those with proteinuria and preserved kidney function.

SGLT2 inhibitors were expected by clinical experts to be included as a component of SoC in clinical practice. To align with the KDIGO guidelines and clinical opinion, in the model base case, the cost of dapagliflozin treatment was included within SoC costs.

SGLT-2 inhibitors were not recommended for use in the treatment of IgAN at the time that the NefIgArd Nef-301 trial was conducted, so the model assumes they have no impact on clinical efficacy. Although evidence is limited, SGLT-2 inhibitors like dapagliflozin have a different mechanism of action compared to TRF-budesonide. Dapagliflozin primarily reduces glucose reabsorption in the kidneys, lowering blood sugar levels and providing additional benefits for kidney function. In contrast, TRF-budesonide is a targeted-release formulation that suppresses mucosal B-cells in the ileum, reducing IgA antibody production and kidney inflammation in IgA nephropathy. Due to their differing mechanisms, clinical experts and draft KDIGO guidelines state that SGLT-2 inhibitors and TRF-budesonide should be used together to create an additive effect (18, 19, 85, 86). Clinical experts and draft KDIGO guidelines have suggested that using SGLT2 inhibitors in IgAN patients may delay disease progression and therefore the need for TRF-budesonide (18, 86). Therefore, the inclusion of SGLT2 inhibitors impacts only costs in the economic analysis and does not affect efficacy.

3.3 Clinical parameters and variables

3.3.1 Clinical expert opinion

An advisory board was conducted with five nephrologists and one health economist in order to gain insight into the following:

- Current treatments for patients with IgAN
- Unmet needs for IgAN patients
- Validation of model assumptions including
  - Appropriate comparators for the cost-effectiveness model
  - TRF-budesonide treatment effect and retreatment assumptions

- Transition probabilities
- Mortality assumptions in the economic model
- Relevant costs.

A transcript of the advisory board discussion is included in the reference pack (86).

3.3.2 Clinical data

3.3.2.1 CKD 1–4 health state transition matrices for TRF-budesonide and SoC

3.3.2.1.1 Transitions between 0–24 months

Data from NefIgArd Nef-301 was used to inform transition probabilities from baseline to 24 months (96). 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 TRF-budesonide 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). 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 38.

Table 38: NefIgArd Nef-301 logistic regression output

Treatment	CKD stage	Log odds
Progressed disease		
Placebo	3b (reference group)	[redacted]
Placebo	1	[redacted]
Placebo	2	[redacted]
Placebo	3a	[redacted]
TRF-budesonide	-	[redacted]
Improved disease		
Placebo	3b (reference group)	[redacted]
Placebo	2	[redacted]

Treatment	CKD stage	Log odds
Placebo	3a	[redacted]
TRF-budesonide	-	[redacted]

Abbreviations: CKD, chronic kidney disease; TRF, targeted-release formulation.

The log odds in Table 38 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 39.

Table 39: NefIgArd Nef-301-informed cycle transition probabilities (0–24 months)

Treatment	CKD 1	CKD 2	CKD 3a	CKD 3b	CKD 4	Total
TRF-budesonide 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%
SoC transition probabilities						
CKD 1	[redacted]	[redacted]	-	-	-	100.0%
CKD 2	[redacted]	[redacted]	[redacted]	-	-	100.0%

Treatment	CKD 1	CKD 2	CKD 3a	CKD 3b	CKD 4	Total
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.

Patients that discontinue treatment still incur the TRF-budesonide transition probabilities presented in Table 39. 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 TRF-budesonide treatment.

3.3.2.1.2 Transitions beyond 24 months

There is no data from NefIgArd Nef-301 beyond 24 months from baseline. As such, the transition probabilities beyond 24 months in the SoC arm are assumed equivalent to observed transition probabilities in the NefIgArd arm (95), as presented in Section 3.3.2.1.1.

Applying the CKD 1-4 transition probabilities in the TRF-budesonide arm for only 24 months was considered a conservative assumption by clinicians (86).

By applying SoC transition probabilities to patients in the TRF-budesonide arm after 24 months, it is assumed they experience disease progression at the same rate as patients receiving SoC beyond this timepoint unless they receive retreatment with TRF-budesonide. In other words, only the incremental treatment effect is being removed after 24 months.

TRF-budesonide is formulated to release its active component in the distal ileum, where it is expected to act on Peyer's patches – key sites of Gd-IgA1 production. By modulating mucosal B-cell activity, it reduces the formation of Gd-IgA1 and subsequent immune complex formation in the blood. This targeted effect is anticipated to lower glomerular immune complex deposition, thereby reducing kidney inflammation and slowing disease progression (87, 126). Treatment with TRF-budesonide therefore alters the patient's eGFR slope of decline and the trajectory of their disease progression. A previous study has estimated that difference in 2-year

eGFR total slope following a single course of treatment with TRF-budesonide is predictive of a 12.8-year delay in progression to kidney failure, eGFR < 15 ml/min/1.73 m^2, or sustained doubling of serum creatinine compared with SoC (105).

There is no clinical evidence to suggest that there would be a greater rate of decline after 2 years in patients that had received TRF budesonide compared with patients receiving SoC, and to incorporate this into the model would require several assumptions on the rate and deterioration of duration and at what points treatments would converge. Given the lack of clinical data to support such assumptions, and the previous publication quoted on the impact of TRF budesonide on long term outcomes, a similar rate of decline in both arms was the most clinically plausible assumption.

3.3.2.2 Risk of CKD 5 (eGFR <15 mL/min/1.73m^2)

3.3.2.2.1 SoC arm

As per the model structure in Section 3.2.2, 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 collected in the UK RaDaR database, which is a national registry that collects data on patients with rare kidney diseases, including IgAN. The risk of CKD 5 data was obtained from patients with IgAN and UPCR ≥0.8 g/g that also has an eGFR corresponding to that of CKD 4 (eGFR between 15 and 29 mL/min/1.73 m²) (118). Figure 16 presents the Kaplan-Meier (KM) curve which estimates the probability of progressing from CKD 4 to ESRD over time. The model assumes ESRD is equivalent to CKD 5.

Figure 16: UK RaDaR KM curve estimating time to diagnosis of ESRD

Abbreviations: ESRD, end stage renal disease; KM, Kaplan-Meier; UK RaDaR, United Kingdom National Registry of Rare Kidney Diseases.
Source: Calliditas Therapeutics. Data on file. UK RaDaR data analyses 2024 (118).
t represents time from CKD 4 diagnosis

The KM curve presented in Figure 16 was digitised using Engauge Digitizer 12.1 software (127). Pseudo patient level data (PLD) was generated from the digitised data using the R packages “MASS” and “splines” (128). Although the KM dataset is complete, the option to use the raw KM data is not included in the model because the number of patients informing the data substantially diminishes at year 4 such that only two patients informed the data at year 6. Therefore, the complete dataset may not reflect clinical practice as it suggests that all patients transition to CKD 5 after 7 years, which is potentially unrealistic. Therefore, parametric survival modelling was done to extrapolate beyond the currently available data, using the R packages “survival” and “flexsurv” (128). Figure 17 presents the digitised KM data with seven parametric extrapolations fitted.

Figure 17: Digitised UK RaDaR KM data and fitted parametric extrapolations to estimate time to CKD 5

Abbreviations: CKD, chronic kidney disease; KM, Kaplan-Meier; SoC, standard of care; UK RaDaR, United Kingdom National Registry of Rare Kidney Diseases.

As presented in Table 40, the AIC identified the log-normal model as the best fit for the observed data, followed by the Weibull model. In contrast, the BIC ranked the exponential model as the best fit, with the log-normal model as the second best.

Since the base Markov model is memoryless, the calculated probability of progressing from CKD 4 to ESRD in each cycle is unable to account for the duration of time each patient has spent in CKD 4. However, it is assumed that the patients who informed the KM curve shown in Figure 16 had varying durations in CKD 4, thus implicitly capturing variations in the duration each patient spends in CKD 4 in the KM curve. Furthermore, the transition probabilities used to inform the movements between CKD stages 1–4 do not account for the duration of time spent in each CKD stage, as this memoryless characteristic is a key feature of Markov models in general.

The model applied an exponential distribution to extrapolate the KM curve in Figure 17. The exponential model was chosen because its distribution is time-invariant, thus

putting it in line with the memory-less Markov model. This property implies that the probability of an event occurring in the future is independent of how much time has already elapsed, which aligns with the structure of the model. Additionally, the exponential distribution was identified as the best fitting model according to the BIC. Alternative model extrapolations are explored in scenario analyses (see Section 3.11.3).

Table 40: AIC and BIC statistics for time to CKD 5 models

Model	AIC	AIC rank	BIC	BIC rank
Exponential	232.54	5	234.85	1
Generalised gamma	232.65	7	239.57	7
Gompertz	232.41	3	237.02	4
Log-logistic	232.64	6	237.25	6
Log-normal	231.03	1	235.64	2
Weibull	231.99	2	236.60	3
Gamma	232.46	4	237.07	5

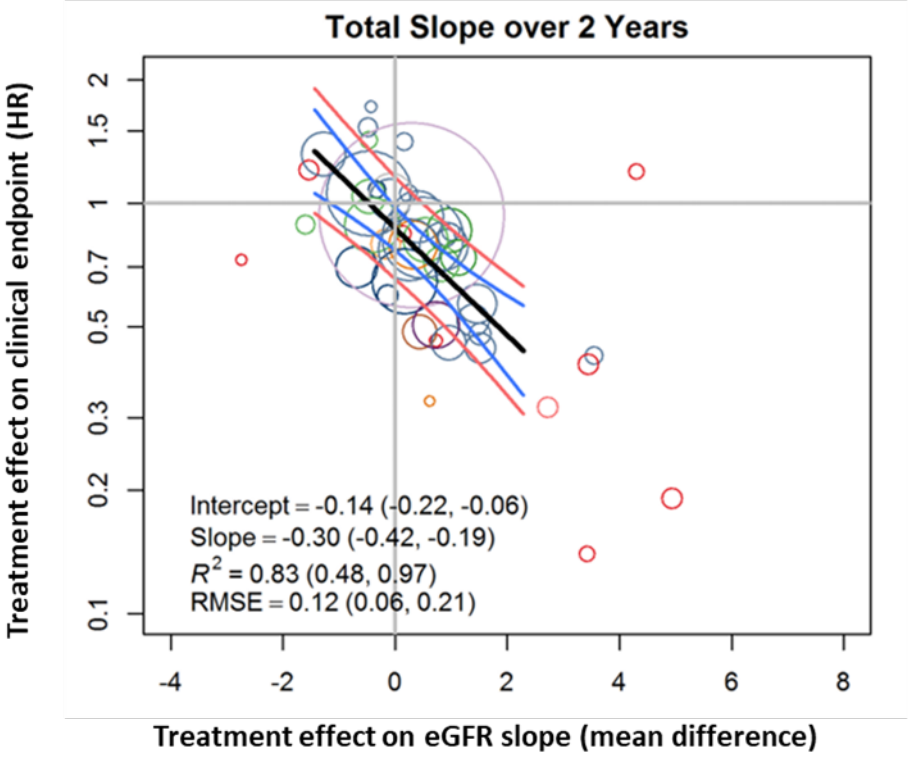
Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion; CKD, chronic kidney disease.

3.3.2.2.2 TRF-budesonide arm

The risk of CKD 5 in the TRF-budesonide arm is informed by applying a HR to the risk of CKD 5 in the SoC arm (presented in Figure 17).

In the model base case, movements from the CKD 4 health state to the CKD 5 health state in the TRF-budesonide arm are calculated by applying a HR of 0.38 to the extrapolated KM data presented in Figure 17. A published meta-analysis was used to estimate the reduction in risk of the clinical outcome (HR), and associated 95% CI, allowing for the uncertainty in the TRF-budesonide 16 mg treatment effects on 2-year eGFR slope and the relationship between endpoints (89). The observed treatment effect on 2-year eGFR total slope in the UPCR ≥0.8 g/g subpopulation of patients with IgAN of 2.78 mL/min/1.73 m^2 per year (95% CI: 1.39, 4.17) in NefIgArd Nef-301 arm of the indirect treatment comparison (ITC) predicts a HR of 0.38 for the clinical outcome.

Figure 18: Relationship between treatment effect on 2-year eGFR slope and clinical outcome, with predicted HR for TRF-budesonide 16 mg



Abbreviations: eGFR, estimated glomerular filtration rate; HR, hazard ratio; TRF, targeted release.
Source: Adapted from Figure 5 of Inker et al. 2019 (89). 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 TRF-budesonide 16 mg versus placebo in Nef-301.

The equation used to calculate the HR using the coefficients presented in Figure 18 and the observed treatment effect on 2-year eGFR total slope of 2.78 mL/min/1.73 m^2 per year is presented below:

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

$$HR = e^{(-0.14 + [-0.30 \times 2.78])} = 0.38$$

Figure 19 presents the risk of transitioning to the CKD 5 health state while receiving TRF-budesonide by applying the HR of 0.38 to the digitised KM data and fitted survival models in Figure 17.

Figure 19: Digitised UK RaDaR KM data with fitted gamma extrapolation and HR of 0.38 applied

Abbreviations: CKD, chronic kidney disease; HR, hazard ratio; KM, Kaplan-Meier; SoC, standard of care; UK RaDaR, United Kingdom National Registry of Rare Kidney Diseases.

The HR of 0.38 is only applied to the SoC curve for as long as TRF-budesonide is assumed to have a treatment effect within the model. The base case treatment effect duration is 2 years (further detail in Section 3.3.2.1). After this time point, patients in the TRF-budesonide 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 TRF-budesonide treatment.

3.3.2.3 Transitions 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. Therefore, the transitions between CKD 5, dialysis, and transplant health states are sourced from NICE TA775; specifically, the dapagliflozin arm transition probability matrix from month 5 onwards. The transitions from CKD 5 reported in TA775 were sourced directly from the DAPA-CKD trial whereas the transitions from dialysis and transplant were obtained from an SLR by Sugrue et al. 2019 (129). The same transition probabilities from CKD 5, dialysis and transplant were applied over time for both TRF-budesonide

and SoC. In this, it was assumed that there is no difference (i.e., no lasting treatment effect) for TRF-budesonide patients compared with SoC once patients reach the CKD 5 health state. Table 41 presents the monthly transition probabilities from CKD 5, dialysis, and transplant used in the model.

Table 41: Transition probabilities from CKD 5, dialysis, and transplant

Health state	CKD 5	Dialysis	Transplant	Total
CKD 5	95.30%	4.50%	0.20%	100%
Dialysis		99.50%	0.50%	100%
Transplant		0.70%	99.30%	100%

Abbreviations: CKD, chronic kidney disease

A scenario analysis, assuming a 6% monthly transition probability from CKD 5 to dialysis, is included in Section 3.11.3, to align with the scenario requested by the EAG in TA937. This scenario analysis demonstrates the impact of a monthly transition rate that results in the majority of CKD 5 patients receiving dialysis within one year on the ICER, as the annual probability corresponding to a monthly transition probability of 6% is approximately 52.41%.

3.3.2.4 Adverse events

The adverse events rates for both the TRF-budesonide and SoC arm were sourced from Part B NefIgArd Nef-301 CSR (Safety Analysis Set [SAS]). All treatment-related AEs occurring in ≥4% of patients in either treatment arm of the 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-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 42.

Table 42: Adverse event rates by treatment

Treatment-emergent AE	TRF-budesonide 16 mg (N=195) n (%)	Placebo (N=194) n (%)
Treatment-related treatment-emergent AE (≥4% of patients in either treatment group)		
Acne	[redacted]	[redacted]
Cushingoid	[redacted]	[redacted]
Dyspepsia	[redacted]	[redacted]
Face oedema	[redacted]	[redacted]
Hypertension	[redacted]	[redacted]
Oedema peripheral	[redacted]	[redacted]
Weight increase	[redacted]	[redacted]
White blood cell count increased	[redacted]	[redacted]
Neutrophil count increased	[redacted]	[redacted]
Treatment-emergent severe/serious AE (occurring in >1 patient)		
Pulmonary embolism	[redacted]	[redacted]
Renal impairment	[redacted]	[redacted]
Coronavirus infection	[redacted]	[redacted]
Pneumonia	[redacted]	[redacted]
Acute kidney injury	[redacted]	[redacted]
Hypertension – severe	[redacted]	[redacted]

Abbreviations: AE, adverse event; NR, not reported; SAEs, serious adverse events; TRF, targeted-release formulation.
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. AE reported terms were coded using the Medical Dictionary for Regulatory Activities Version 22.0.
The cut-off of ≥4% of patients aligns with how treatment-related TEAEs were reported in the CSR.
Source: NefIgArd Nef-301 Part B CSR (95).

3.3.2.5 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 latest available data from the Office of National Statistics (ONS) England and Wales life tables (130).

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

3.3.2.5.1 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 from IgAN patients 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 43.

Table 43: Standard mortality ratios

Health state	SMR – All patients	SMR –UPCR ≥ 0.8g/g
CKD 1	[redacted]	[redacted]
CKD 2	[redacted]	[redacted]
CKD 3a	[redacted]	[redacted]
CKD 3b	[redacted]	[redacted]
CKD 4	[redacted]	[redacted]
CKD 5	[redacted]	[redacted]
Renal replacement therapy (dialysis and transplant)	[redacted]	[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.

A scenario analysis was conducted using SMRs calculated from UK RaDaR 10-year survival rates for IgAN patients with a baseline UPCR ≥ 0.8g/g. However, due to the low number of patients with UPCR ≥ 0.8g/g informing these SMRs, the results did not align with clinical expectations, as discussed by nephrologists at the advisory board (86). Consequently, the clinical experts agreed that the values presented in Table 43 should be used to inform the base case. The values in Table 43 also align with those used in TA937 (19). Scenario analyses that assume the same risk of mortality for CKD 1–3b, as suggested by the clinicians, are also considered in Section 3.11.3.

3.4 Measurement and valuation of health effects

3.4.1 Health-related quality-of-life data from clinical trials

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 (85) and accepted by NICE in the HTA submission for TRF-budesonide (TA937) (19).

3.4.2 Mapping

Not applicable.

3.4.3 Health-related quality-of-life studies

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.

An SLR was conducted in November 2022 and updated in January 2025 to identify studies reporting health-state utility values (HSUVs) for patients with primary IgAN (see Appendix F). The SLR identified a single UK study conducted by Zhou et al. 2025 that estimated health state utility values for patients with IgAN (131). The study used a vignette-based approach and conducted time trade-off interviews based on developed vignettes describing the symptoms and quality of life associated with IgAN. Due to recruitment challenges in finding patients with IgAN, the interviews were conducted with members of the general public. Participants were repeatedly

asked to compare living 10 years in an IgAN health state versus living fewer years in full health until they were indifferent between the two options.

Although this was a UK study, it was not deemed appropriate for use in the base case. This is because no patients with IgAN participated in the study. Furthermore, although the vignettes were based on published literature and refined using feedback from nephrologists experienced in treating IgAN and one patient advocacy representative, no other patients diagnosed with IgAN were consulted. Therefore, aspects of the disease may have been over-emphasised or omitted, leading to bias. Finally, the study included only a limited number of health states, which could not account for every potential symptom or level of severity, thus failing to reflect the heterogeneous nature of IgAN.

Instead, the same utility values used in TA937 were applied, which were identified by reviewing the references listed in recent CKD submissions to NICE (19). Cooper et al. 2020 was included in the TA775 NICE HTA submission reference list which reports a SLR of HRQoL utility weights for CKD stages used in economic evaluations (117, 120). The study 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 (119). 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 (132), as referenced by Cooper et al. 2020 (120).

Although the utility values from Cooper et al. 2020 are derived from CKD patients, these utility scores are considered applicable to IgAN patients due to several key similarities. Both CKD and IgAN lead to progressive kidney damage, resulting in overlapping symptoms such as fatigue, swelling, and changes in urination (133, 134). The treatment burdens, including medications, dietary restrictions, and in severe cases, dialysis or kidney transplantation, are comparable for both conditions. During the UK advisory board held for TA937 (19), clinicians stated that utility values are expected to be similar between IgAN and CKD patients, particularly in the later

stages of CKD, where dialysis significantly impacts quality of life. This clinical consensus underscores the relevance of CKD-derived utility scores for IgAN patients, reinforcing the argument that the health-related quality of life impacts are analogous between these two patient groups.

It should be noted that the Cooper et al. 2020 study incorrectly labelled this value from Jesky et al. 2016 as a USA specific value in Table 4. However, Jesky et al. 2016 is a UK study exploring the relationship between pre-dialysis CKD and HRQoL outcomes using the Euroqol EQ-5D-3 L (132).

The utility values from Cooper et al. 2020 are presented in Table 44.

Table 44: Summary of utility values from Cooper et al. 2020

Health state	Utility value	Standard error	Reference
CKD 1	0.85	0.08	Cooper et al. 2020 (120)
CKD 2	0.85	0.08	
CKD 3a	0.80	0.08	
CKD 3b	0.80	0.08	
CKD 4	0.74	0.06	
CKD 5	0.73	0.10	

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

For the dialysis and transplant health states, utility values were also sourced from Cooper et al. 2020 (120). Patients in the dialysis health state are assumed to receive either haemodialysis (87.5%) or peritoneal dialysis (12.5%) based on the English and Welsh distributions reported in the United Kingdom Renal Registry (UKRR) 26th Annual report (135). 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 UKRR 26th Annual report (135).

Table 45: Summary of utility values for the dialysis and transplant health states from Cooper et al. 2020

Health state	Utility value	Standard error	Reference
Haemodialysis	0.44	0.03	Cooper et al. 2020 (120)
Peritoneal dialysis	0.53	0.07	
Post transplant	0.71	0.02	

Standard error calculated as (1-mean)/(1.96*2)

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 (120). 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 given in TA937 (19). Section 3.11.3 includes scenario analyses that inform the health state utility values for CKD stages 1 to 5, using values published in Zhou et al. 2025 (131) and Gorodetskaya et al. 2005 (136). The study by Gorodetskaya et al. 2005 derived utility weights from 205 patients with CKD in the US using a Time Trade-Off approach.

3.4.4 Adverse reactions

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 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, the AE durations were based on a simplifying assumption of either a one-week or one-month duration.

The disutility and duration assumptions applied for each AE are presented in Table 46 and Table 47.

Table 46: Adverse event rates duration

Treatment-emergent AE	Duration (days)	Source
Acne	7.000	Assumption
Acute kidney injury	30.438	Assumption
Coronavirus infection	30.438	Assumption
Cushingoid	7.000	Assumption
Dyspepsia	7.000	Assumption

Treatment-emergent AE	Duration (days)	Source
Face oedema	7.000	Assumption
Hypertension	7.000	Assumption
Hypertension – severe	30.438	Assumption
Neutrophil count increased	7.000	Assumption
Oedema peripheral	7.000	Assumption
Pneumonia	30.438	Assumption
Pulmonary embolism	30.438	Assumption
Renal impairment	30.438	Assumption
Weight increase	7.000	Assumption
White blood cell count increased	7.000	Assumption

Abbreviations: AE, adverse event.
30.438 days represents 1 month in the model

Table 47: Adverse event rates disutility

Treatment-emergent AE	Disutility	Standard error	Source
Acne	0.000	0.000	Assumption
Acute kidney injury	0.110	0.021	Sullivan et al. 2011 (137)
Coronavirus infection	0.000	0.000	Assumption
Cushingoid	0.156	0.040	Sullivan et al. 2011 (137)
Dyspepsia	0.044	0.007	Sullivan et al. 2011 (137)
Face oedema	0.156	0.030	Assumed same as cushingoid
Hypertension	0.046	0.004	Sullivan et al. 2011 (137)
Hypertension - severe	0.046	0.004	Sullivan et al. 2011 (137)
Neutrophil count increased	0.000	0.000	Assumption
Oedema peripheral	0.156	0.030	Assumed same as cushingoid
Pneumonia	0.000	0.000	Assumption
Pulmonary embolism	0.018	0.002	NICE. Venous thromboembolic diseases: Diagnosis, management, and thrombophilia testing: Guidance. 2020 (138).
Renal impairment	0.060	0.006	Sullivan et al. 2006 (139)
Weight increase	0.000	0.000	Assumption
White blood cell count increased	0.001	0.020	Sullivan et al. 2011 (137)

Abbreviations: AE, adverse event; SAE, serious adverse event.

Data in Table 46 and Table 47 were used to estimate the QALY loss attributed to each AE. This estimate was then multiplied by the respective AE occurrence rate data in Table 42, to estimate the total AE-attributable quality adjusted life-years (QALYs) lost per treatment arm. These QALY loss estimates, presented in Table 48, were then applied as one-off QALY decrements in the first model cycle of their respective treatment arm.

Table 48: QALY loss per AE and per treatment arm

Treatment-emergent AE	QALY loss per event	Total QALYs lost per treatment arm	
		TRF-budesonide	SoC
Acne	0.00000	[redacted]	[redacted]
Acute kidney injury	-0.27994	[redacted]	[redacted]
Coronavirus infection	0.00000	[redacted]	[redacted]
Cushingoid	-0.09076	[redacted]	[redacted]
Dyspepsia	-0.02551	[redacted]	[redacted]
Face oedema	-0.09076	[redacted]	[redacted]
Hypertension	-0.02686	[redacted]	[redacted]
Hypertension – severe	-0.11677	[redacted]	[redacted]
Neutrophil count increased	0.00000	[redacted]	[redacted]
Oedema peripheral	-0.09076	[redacted]	[redacted]
Pneumonia	0.00000	[redacted]	[redacted]
Pulmonary embolism	-0.04566	[redacted]	[redacted]
Renal impairment	-0.15295	[redacted]	[redacted]
Weight increase	0.00000	[redacted]	[redacted]
White blood cell count increased	-0.00064	[redacted]	[redacted]

Abbreviations: AE, adverse event; QALY, quality-adjusted life year; SAE, serious adverse event.

When retreatment with TRF-budesonide 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 TRF-budesonide patients who are eligible to receive retreatment (i.e., residing in CKD stages 1 to 3b).

3.4.5 Age-adjusted general-population utility

To estimate heath state utilities for the modelled patient populations, age- and sex-adjusted general population utility were first estimated using the algorithm published by Ara and Brazier (140). This was performed to ensure that a decrease in utility

over time was incorporated so that utility values were adjusted based on the expected utility decrements associated with gender and aging. The linear regression model used to estimate the general population utility was:

$$EQ5D = 0.9508566 + 0.0212126 * male - 0.0002587 * age - 0.0000332 * age^2$$

3.4.6 Health-related quality-of-life data used in the cost-effectiveness analysis

In the base case cost-effectiveness analysis, each of the CKD stage health states and each of the dialysis or transplant health states were associated with a utility weighting. The proportion of patients residing within each heath state in each cycle informed the accrual of QALYs over time.

The impact of AEs was captured as one-off utility decrements to the proportion of patients who experienced the AE, in a multiplicative manner in line with NICE technical support document (TSD) 12 (141).

The health state utility values and the clinical event disutilities applied in the base case cost effectiveness analysis are summarised in Table 49.

Table 49: Summary of utility values applied to the cost-effectiveness model

	Mean utility value	Standard error	Reference
Health state utilities			
CKD 1	0.85	0.08	Cooper et al. 2020 (120)
CKD 2	0.85	0.08	
CKD 3a	0.80	0.08	
CKD 3b	0.80	0.08	
CKD 4	0.74	0.06	
CKD 5	0.73	0.10	
Haemodialysis	0.44	0.032	Cooper et al. 2020 (120)
Peritoneal dialysis	0.53	0.066	
Post transplant	0.71	0.019	
AEs			
Acne	0.000	0.000	Assumption
Acute kidney injury	0.110	0.021	Sullivan et al. 2011 (137)
Coronavirus infection	0.000	0.000	Assumption
Cushingoid	0.156	0.040	Sullivan et al. 2011 (137)

	Mean utility value	Standard error	Reference
Dyspepsia	0.044	0.007	Sullivan et al. 2011 (137)
Face oedema	0.156	0.030	Assumed same as cushingoid
Hypertension	0.046	0.004	Sullivan et al. 2011 (137)
Hypertension - severe	0.046	0.004	Sullivan et al. 2011 (137)
Neutrophil count increased	0.000	0.000	Assumption
Oedema peripheral	0.156	0.030	Assumed same as cushingoid
Pneumonia	0.000	0.000	Assumption
Pulmonary embolism	0.018	0.002	NICE. Venous thromboembolic diseases: Diagnosis, management, and thrombophilia testing: Guidance. 2020 (138)
Renal impairment	0.060	0.006	Sullivan et al. 2006 (139)
Weight increase	0.000	0.000	Assumption
White blood cell count increased	0.001	0.020	Sullivan et al. 2011 (137)

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

3.5 Cost and healthcare resource use identification, measurement and valuation

An SLR was conducted in November 2022 and updated in January 2025 to identify evidence for costs and resource utilisation associated with patients with primary IgAN. The methodology and results of the SLR are described in Appendix G. Of the 23 studies included in the SLR, one was conducted in the UK (Baxter et al. 2024 (142)) and was considered relevant for inclusion in the economic model (see Section 3.5.2 for further details).

3.5.1 Intervention and comparators' costs and resource use

3.5.1.1 TRF-budesonide treatment costs

As described in Section 3.2.3.1 and in line with the NefIgArd Nef-301 study and MHRA and EMA license wording (124, 125), TRF-budesonide is self-administered as four 4 mg tablets once daily for nine months within the CEM. The list price per pack of TRF-budesonide used in the model was £4,681.24. The net price of TRF-budesonide was assumed to be [redacted] per pack following a [redacted] discount

applied to the list price. The discount applied to the list price should be reviewed for its appropriateness in the local setting.

As TRF-budesonide is self-administered orally, the cost of TRF-budesonide administration is assumed to be zero in the CEM.

3.5.1.1.1 Dose reduction and treatment tapering period

The EMA license and draft MHRA license wording outlines that when treatment is to be discontinued, the dose should be reduced to 8 mg once daily for 2 weeks of therapy (124, 125). The model functionality applies a dose reduction for 2 weeks during the last month of treatment. A reduced dose is included in the model base case and the cost of a reduced dose of TRF-budesonide which was applied in month 9 of the model.

Table 50 presents the monthly treatment costs for TRF-budesonide for a reduced dose model cycle. This cost accounts for the time the patient receives the full dose before switching to a reduced dose of 8 mg daily during the final two weeks.

Table 50: TRF-budesonide cost per cycle, reduced dose

Treatment	Reduced dose	Reduced dose frequency	Reduced dose frequency per cycle (days)†	Total dose per cycle‡	Packs per cycle§	Treatment cost with reduced dose per cycle
TRF-budesonide	8 mg	2 weeks	14	375.00	0.78	[redacted]

Abbreviations: TRF, targeted-release formulation.
† Equal to the model cycle length divided by the reduced dose frequency (7 days / 2 weeks)
‡ The dose per cycle is calculated as follows: the full-dose frequency (equal to the model cycle length minus the reduced dose frequency per cycle, i.e., 30.4375 – 14) multiplied by 16 mg, plus the reduced dose required per cycle (14 x 8 mg).
§ Packs per cycle calculated as total dose per cycle divided by table size (4 mg) divided by the pack size.
Figures presented in the table are rounded to two significant figures.

The license wording also describes an optional treatment tapering period of 4 mg once daily for an additional 2 weeks following the end of the 9-month course and 2 weeks of reduced therapy. However, in line with TA937, only the dose reduction period of the final 2 weeks of the 9-month treatment period was included in the base case model results.

The treatment tapering period of 4 mg once daily for an additional 2 weeks was explored as a scenario analysis in Section 3.11.3. As it is expected that a tapering

pack which contains 28 4 mg tablets will be launched in Q3/Q4 of 2025, Section 3.11.3 explores the impact this pack has when tapering is included in the model.

3.5.1.1.2 Wastage

The model base case calculates the cost of TRF-budesonide using a cost-per-mg approach. This approach implicitly assumes the exact dose of TRF-budesonide over 9 months is dispensed and therefore there are no unused tablets left after the treatment cycle. Therefore, it is assumed there will be no wastage associated with the treatment of TRF-budesonide. The cost of TRF-budesonide using the cost per mg approach is presented in Table 51.

Table 51: TRF-budesonide cost per mg

Treatment	Tablet size	Pack size	Cost per pack	Discounted cost per pack	Cost per mg†
TRF-budesonide	4 mg	120	£4,681.24	[redacted]	[redacted]

†Cost per mg calculated as the cost per pack divided by the pack size, divided by tablet size ((£4,681.24/120)/4)

3.5.1.1.3 Relative dose intensity

Relative dose intensity (RDI) was not captured by the CEM. While RDI was recorded in the NefIgArd Nef-301 study, it is anticipated in practice that any dose reductions or treatment breaks will have no consequence for treatment acquisition costs. This is because the cost for the full treatment course of TRF-budesonide will be used in clinical practice. Section 3.11.3 explores the impact RDI has on the ICER.

3.5.1.1.4 Time to treatment discontinuation

As per the MHRA and EMA license (87, 124), which recommends a daily dose of 16 mg for 9 months, the model assumes all treatment will stop after 9 months. 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 20.

Figure 20: Digitised KM curve of time to discontinuation of study treatment – TRF-budesonide

Abbreviations: KM, Kaplan-Meier; TRF, targeted-release formulation.

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 20 show the proportion of patients on treatment decreases slowly until just before month 9 when there is a substantial decrease. Therefore, it is assumed that all patients on treatment at the start of the month 9 received the reduced dose for 2 weeks.

3.5.1.1.5 Retreatment

The EMA license states that re-treatment may be considered at the discretion of the treating physician (124), and during the advisory board, clinicians agreed they would retreat patients if the patient was considered suitable to receive another round of TRF-budesonide (i.e. they responded to initial treatment and did not experience significant side effects) (86). Therefore, the base case model includes one retreatment round (two rounds of treatment in total). A single retreatment cycle is considered conservative, as patients are not anticipated to develop resistance to TRF-budesonide or to experience a waning of treatment effect if receiving multiple

rounds of therapy. Therefore, in clinical practice, patients will likely continue receiving rounds of treatment to delay the onset of ESRD.

At the point of retreatment, retreatment-eligible patients are assumed to follow the same cost and patient utility pathways as used for the starting treatment with TRF-budesonide.

The public review draft KDIGO guidelines suggest a single 9-month treatment course of TRF-budesonide is unlikely to produce a sustained clinical response in terms of proteinuria reduction or stabilisation of eGFR and it is likely that many patients will need either repeated 9-month treatment cycles or a reduced-dose maintenance regimen.

In the TA937 submission, clinical experts highlighted during the advisory board that they do not expect TRF-budesonide's treatment effect to diminish with retreatment cycles, however, the model conservatively assumed TRF-budesonide will experience a treatment waning effect of 10% in subsequent treatment rounds. The same assumption has been applied to this economic evaluation. This assumption is considered conservative because the NefIgArd-OLE study demonstrated that the TRF-budesonide's efficacy in retreatment cycles is similar to the initial round of treatment.

In the absence of available data to inform the duration between retreatment cycles, 14.75 months was assumed based on the time between completion of 9 months of treatment in the NefIgArd Nef-301 trial and the start of the NefIgArd-OLE study. In the OLE study, eligible patients from both arms enrolled in the NefIgArd Nef-301 trial received TRF-budesonide over a 9-month period, starting at the visit scheduled at approximately 24 months from the NefIgArd Nef-301 trial baseline. Patients were included in the NefIgArd-OLE study if they had completed the NefIgArd Nef-301 trial and continued treatment with the maximum tolerable dose of RAS inhibitor therapy. Patients were required to have had proteinuria based on 2 consecutive measurements separated by at least 2 weeks and calculated by the central laboratory showing either ≥1 g/day (≥1000 mg/day) or UPCR ≥0.8 g/gram (≥90 mg/mmol). Patients also needed eGFR ≥30 mL/min per 1.73 m^2 to partake in the NefIgArd-OLE study.

Of the 180 patients in the NefIgArd Nef-301 trial, [redacted] patients were screened and met the OLE inclusion criteria. [redacted] patients were screened and met proteinuria level but were excluded from OLE for other reasons and [redacted] patients were not screened but met the OLE inclusion criteria. As such, a total of [redacted] patients would be eligible for retreatment. The model therefore assumes [redacted]% ([redacted]/180) of patients are eligible for retreatment 24 months after initiating their first round of treatment (143).

Retreatment scenarios in the CEM are confined to the following assumptions and limitations:

- **Eligibility**: 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). Of these patients, the model assumes [redacted]% of patients are eligible for retreatment based on the NefIgArd-OLE study.
- **Transition probabilities**: Patients are assumed to follow the 0–24-month TRF-budesonide transition probabilities in the initial 24 months of any retreatment round. After this time (until the start of the next retreatment round or indefinitely if the final treatment round has been completed), the SoC CKD stage transition probabilities are applied, dependent on the selected duration of the TRF-budesonide treatment effect (further details in Section 3.3.2.1).
- **Risk of CKD 5**: Retreatment is assumed to have the same relative effect upon the risk of CKD 5 as shown after initial treatment with TRF-budesonide. In effect, the hazard ratio applied to the SoC risk of CKD 5 is applied to all TRF-budesonide patients undergoing retreatment for the duration of the assumed treatment effect.
- **Time to treatment discontinuation**: The proportion of patients on treatment, as defined by the time to treatment discontinuation (TTD) curve observed in the NefIgArd Nef-301 Part B trial, is applied to all eligible patients from the start of each retreatment round (further details in Section 3.5.1.1.4).
- **Dose reduction and tapering**: When included, the costs associated with a reduced dosing period and treatment tapering are also included in retreatment cycles (further details in Section 3.5.1.1.5).

3.5.1.2 Standard of care

To account for patients living longer whilst receiving TRF-budesonide, and therefore receiving SoC for longer, the costs of SoC are applied to all patients in the TRF-budesonide and SoC arms.

SoC costs comprised concomitant medications received by ≥ 10% of patients in either treatment arm of NefIgArd Nef-301 Part B FAS (please see the document named “Data on file. SoC costs from NICE” for further details). Although not included in NefIgArd Nef-301, dapagliflozin was also included in the cost of SoC based on feedback received from clinical experts (86) and the draft KDIGO 2024 guidelines (18).

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 day). The average monthly cost of each SoC treatment class was weighted by the proportion of receiving each medication. This yielded a total SoC monthly cost of £80.18, as shown in Table 52.

Table 52: Weighted average monthly cost of SoC

Treatment	Weighting	Weight source	Monthly cost (122)	Weighted average cost
SGLT2i	100.0%	Assumption	£59.66 (123)	£59.66
ARBs, plain	[redacted]	NefIgArd Nef-301 Part B study – FAS (95)	£3.17	£1.62
Other viral vaccines†	[redacted]		£0.00	£0.00
HMG CoA reductase inhibitors	[redacted]		£0.82	£0.37
ACEIs, plain	[redacted]		£2.32	£0.99
Dihydropyridine derivatives	[redacted]		£17.57	£6.76
Preparations inhibiting uric acid production	[redacted]		£2.14	£0.67
Anilides	[redacted]		£6.71	£2.08
Vitamin D and analogues	[redacted]		£5.10	£1.42
Sulfonamides, plain	[redacted]		£3.64	£0.72
Other lipid modifying agents	[redacted]		£1.70	£0.34
Glucocorticoids	[redacted]		£23.96	£4.48
Unspecified herbal and traditional medicine	[redacted]		£0.00	£0.00
Proton pump inhibitors	[redacted]		£1.64	£0.28
Beta blocking agents, selective	[redacted]		£3.51	£0.58
Alpha-adrenoreceptor antagonists	[redacted]		£1.78	£0.20
Weighted average cost of SoC				**£80.18**

Abbreviations: ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; FAS, full analysis set; HMG-CoA, 3-hydroxy-3-methylglutaryl coenzyme-A; SGLT2i, sodium-glucose cotransporter 2 inhibitor; SoC, standard of care.
† Not considered relevant

3.5.2 Health-state unit costs and resource use

A cycle cost for medical resource use (MRU) was assumed for each health state in the CEM. For CKD stages 1–5, the MRU costs were sourced from Kent et al. 2015 (71) a study exploring the impact of CKD stage and cardiovascular disease on the annual cost of hospital care in moderate to severe kidney disease. The study reported the cost of secondary care, including inpatient admissions, day cases and outpatient attendances. The costs from Kent et al. 2015 costs were adjusted to 2024 values using Personal Social Services Research Unit (PSSRU) inflation indices (144).

Two alternative papers, Pollock et al. 2022 and Baxter et al. 2024, which report healthcare costs by CKD stage, were identified and considered in scenario analyses (see Section 3.11.3) (142, 145).

Pollock et al. 2022 examined the impact of CKD stage on healthcare resource utilisation and costs in UK patients from the DISCOVER CKD cohort. The study provided annual costs for hospitalisations, outpatient visits, ambulance usage, GP visits, and critical care for CKD stages 2–5. In the scenario analysis, these costs were adjusted to 2024 values using PSSRU inflation indices (144). GP visit costs were excluded from MRU costs as primary care costs were already accounted for, and critical care costs were excluded due to insufficient data across all CKD stages. Costs for CKD stage 1 were assumed to be equivalent to those for CKD stage 2. However, the patient population in Pollock et al. 2022 included a higher proportion of individuals with comorbid conditions such as type 2 diabetes and hypertension. These conditions often require more frequent monitoring, treatment of complications, and hospitalisations, contributing to higher healthcare costs. Consequently, the cost data from Pollock et al. may overestimate costs for a general CKD population without these comorbidities. In contrast, the patient population in Kent et al. 2015 had fewer comorbid conditions, making the cost data more representative of the general CKD population, which better aligns with the IgAN population.

Baxter et al. 2024, identified in the SLR, reported the mean cost of healthcare visits in IgAN, stratified by CKD stage (see Appendix F). However, there are several reasons why this paper is not appropriate for use in the base case. Firstly, the study is only available as an abstract, which means that detailed information regarding the methodology used is omitted. This lack of methodological transparency makes it difficult to assess the reliability and validity of the findings. Secondly, the abstract has not undergone peer review, which is critical for ensuring the quality and credibility of scientific research. Without peer review, the findings may be subject to bias or errors that have not been identified and corrected. Therefore, due to the absence of detailed methodology and the lack of peer review, the paper by Baxter et al. 2024 is not deemed suitable to inform the MRU costs for the base case.

Finally, the costs from Kent et al. 2015 were used in TA937 (19) and accepted by the EAG. Additionally, in a recent NICE committee meeting for ID6308, the company argued for using Kent et al. 2015 to inform costs in their base case, and the EAG later agreed with this decision (88).

The primary care costs in the CEM comprise general practitioner (GP) appointments and blood tests. The cost of a GP appointment was sourced from the PSSRU, with the cost of blood tests obtained from the NHS National Cost Collection 2023/24 (121). The model assumes GP appointments and blood tests occur twice a year for CKD stages 1–3b and quarterly for CKD 4 and CKD 5.

MRU unit costs for dialysis were sourced from the NHS National Cost Collection 2023/24 (121). Patients in the dialysis health state are assumed to receive either haemodialysis (87.5%) or peritoneal dialysis (12.5%) based on the English and Welsh proportions reported in the UKRR 26th Annual report (135). Patients receiving haemodialysis were then further distributed by the modalities: hospital haemodialysis (36.6%), satellite haemodialysis (57.8%) and home haemodialysis (5.7%), also sourced from the UKRR 26th Annual Registry report (135). The unit costs for haemodialysis were calculated as weighted averages of the healthcare resource groups (HRG) codes outlined in Table 53.

Patients receiving hospital and satellite haemodialysis were also assigned a transportation cost sourced from Liu et al. (2015) (70), comprising of hospital-provided car, hospital-arranged taxi or hospital transport vehicle, with the transport type frequency sourced from the National Kidney Care Audit, Patient Transport survey 2010 (146).

The CEM applies the costs of nephrologist outpatient appointments, blood tests and hospitalisations to patients receiving dialysis. To align with TA937, nephrology appointments were assumed to occur quarterly in the model base case. Based on clinical opinions, blood tests were assumed to be conducted monthly (86). It was also assumed that 50% of all dialysis patients would require one hospitalisation per year.

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 are applied upon transition to the transplant health state. For patients remaining in the transplant health state, a per cycle maintenance cost is 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 (147). 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 CEM 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 CEM. In the model base case, nephrology appointments and blood tests were assumed to occur twice annually, in addition to two GP appointments and two blood tests as per patients in CKD 3b. Hospitalisations can also be considered for transplant patients. The unit cost for hospitalisation was calculated as the weighted average of HRG codes obtained from the NHS National Cost Collection 2023/24 (121) as presented in Table 53. Hospitalisations were assumed to occur once annually for 50% of patients in the transplant health state, as per the clinical expert opinion given in TA937 (19).

The MRU unit costs assumed in the model and their respective sources are summarised in Table 53. The sources for the frequency of each MRU type per health state are summarised in Table 54.

Table 53: MRU unit costs

Resource use	Unit cost	Source
GP appointment	£33.00	PSSRU: Unit Costs of Health and Social Care 2024 (144). General Practitioner. Cost per surgery consultation lasting 10 minutes, excluding direct medical costs, without qualification costs
Blood tests	£3.10	NHS National schedule of costs 2023/24 (121). PATH05-Haematology

Resource use	Unit cost	Source
Nephrologist visits	£196.88	NHS National schedule of costs 2023/24 (121). Total Outpatient Attendance - Service code 361, Nephrology
Hospital haemodialysis	£218.45	NHS National schedule of costs 2023/24 (121). Total HRGs - weighted average LD01A, LD02A, LD03A, LD04A
Satellite haemodialysis	£203.13	NHS National schedule of costs 2023/24 (121). Total HRGs - weighted average LD05A, LD06A, LD07A, LD08A
Home haemodialysis	£281.14	NHS National schedule of costs 2023/24 (121). Total HRGs - weighted average LD09A, LD10A
Haemodialysis transport	£14.556	Liu et al. 2015 (70) (inflated using PSSRU inflation indices) (144)
Peritoneal dialysis	£105.99	NHS National schedule of costs 2023/24 (121). Total HRGs - weighted average LD11A, LD12A, LD13A
Transplantation pre-assessment	£528.51	NHS National schedule of costs 2023/24 (121). Total HRGs - weighted average LA11Z, LA12A
Transplantation procedure cost	£19,307.41	NHS National schedule of costs 2023/24 (121). Total HRGs - weighted average LA01A, LA02A, LA03A
Transplantation post-transplant assessment	£320.50	NHS National schedule of costs 2023/24 (121). Total HRGs - weighted average LA13A, LA14Z
Tacrolimus	£42.92	BNF (148): Adaport 0.5mg capsule, pack size 50
Hospitalisation	£3,037.05	NHS National schedule of costs 2023/24 (121). Non elective short stay - weighted average LA08G, LA08H, LA08J, LA08K, LA08L, LA08M, LA08N, LA08P

Abbreviations: BNF, British National Formulary; GP, general practitioner; HRG, healthcare resource groups; NHS, Nation Health Service.

Table 54: Frequency of MRU annually, by health state

Annual frequency of MRU	CKD stages 1 to 3b	CKD 4 & CKD 5	HD	PD	Transplant	Source
GP appointment	2	4	0	0	2	Assumption
Nephrologist visits	0	0	4	4	2	
Blood tests	2	4	12	12	2	Based on clinical input (86)
Hospital haemodialysis	-	-	156†	-	-	NHS, Dialysis overview (149)
Satellite haemodialysis	-	-	156†	-	-	
Home haemodialysis	-	-	156†	-	-	
Haemodialysis transport	-	-	156‡	-	-	NHS Digital, National Kidney Care Audit, Patient Transport Survey (146)

Annual frequency of MRU	CKD stages 1 to 3b	CKD 4 & CKD 5	HD	PD	Transplant	Source
Peritoneal dialysis	-	-	-	365.25	-	NHS, Dialysis overview (149)
Hospitalisation	-	-	1¶	1¶	1§	Assumption

Abbreviations: CKD, chronic kidney disease; ESRD, end-stage renal disease; GP, general practitioner; HD, haemodialysis; MRU, medical resource use; PD, peritoneal dialysis.
† Patients assigned haemodialysis are distributed according to the probability of each type of dialysis; ‡ Haemodialysis transport costs are applied to hospital and satellite haemodialysis only; § Hospitalisation is assumed for 50% of transplant patients; ¶ A single hospitalisation is assumed for 50% of all dialysis patients.

Table 55 presents the total costs applied per cycle for each health state, in addition to the one-off costs of transplantation.

Table 55: MRU costs per cycle by health state

Health state	Total cost per health state
CKD 1	£124.86
CKD 2	£124.86
CKD 3a	£124.86
CKD 3b	£124.86
CKD 4	£428.14
CKD 5	£1,471.00
Dialysis	£3,175.43
Transplant (Transplantation maintenance)	£1,388.36
One-off transplantation cost	
Transplantation procedural costs	£20,156.42†

Abbreviations: CKD, chronic kidney disease; ESRD, end-stage renal disease; MRU, medical resource use.
† Transplantation procedural costs are applied only upon the transition to the transplant health state.

3.5.3 End of life costs

End of life care costs were sourced from Kerr et al. (2017), a large-scale study that used Hospital Episode Statistics data and ONS mortality data to explore end-of-life care for people with CKD. Kerr et al. (2017) evaluated the cause and place of death and cost of hospital care in the final 3 years before death, reporting the cost of hospital care by periods to death of 30 days, 3 months, and 12 months (74). The 30-day value is chosen to inform the CEM base case in order to avoid potential double-counting with MRU costs. The cost for hospital care from 30 days to death calculated by Kerr et al. (2017) was inflated using the latest inflation indices from the PSSRU

inflation indices (144). The inflated end of life cost implemented in the CEM is £3,622.74, which is applied upon transition to the death state prices using PSSRU inflation indices (144).

3.5.4 Adverse reaction unit costs and resource use

Costs associated with the resolution of AEs are sourced from the NHS National Cost Collection 2023/24 (121). The cost per AE was calculated as the weighted average of HRG codes presented in Table 56.

Table 56: List of adverse reactions and summary of costs in the economic model

Treatment-emergent AE	Cost	Source
Acne	£0.00	Assumption
Cushingoid	£204.88	NHS National schedule of costs 2023/24 (121): Total Outpatient Attendance - Service code 302, Endocrinology
Dyspepsia	£161.19	NHS National schedule of costs 2023/24 (121): Total Outpatient Attendance - Service code 301, Gastroenterology
Face oedema	£0.00	Assumption
Hypertension	£201.80	NHS National schedule of costs 2023/24 (121): Total Outpatient Attendance - Service code 361, Nephrology
Oedema peripheral	£0.00	Assumption
Weight increase	£0.00	Assumption
White blood cell count increased	£1,534.73	NHS National schedule of costs 2023/24 (121): Total HRGs - weighted average SA08G, SA08H, SA08J
Neutrophil count increased	£1,534.73	NHS National schedule of costs 2023/24 (121): Total HRGs - weighted average SA08G, SA08H, SA08J
Pulmonary embolism	£2,048.26	NHS National schedule of costs 2023/24 (121): Total HRGs - weighted average DZ09J, DZ09K, DZ09L, DZ09M, DZ09N, DZ09P, DZ09Q
Renal impairment	£1,828.65	NHS National schedule of costs 2023/24 (121): Total HRGs - weighted average LA09J, LA09K, LA09L, LA09M, LA09N, LA09P, LA09Q
Coronavirus infection	£1,937.90	NHS National schedule of costs 2023/24 (121): Total HRGs - weighted average WJ03A, WJ03B, WJ03C, WJ03D, WJ03E, WJ03F, WJ03G
Pneumonia	£2,593.94	NHS National schedule of costs 2023/24 (121): Total HRGs - weighted average DZ11K, DZ11L, DZ11M, DZ11N, DZ11O, DZ11P, DZ11Q, DZ11R, DZ11S, DZ1T, DZ11U, DZ11V

Treatment-emergent AE	Cost	Source
Acute kidney injury	£2,601.08	NHS National schedule of costs 2023/24 (121): Total HRGs - weighted average LA07H, LA07J, LA07K, LA07L, LA07M, LA07N, LA07P
Hypertension - severe	£758.83	NHS National schedule of costs 2023/24 (121): Total HRGs - weighted average EB04Z

Abbreviations: AE, adverse event NHS, National Health Service; SAE, serious adverse event.

The cost of AE resolution for patients undergoing retreatment are applied in the first cycle of each retreatment round for those at risk of incurring an AE. 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.

3.5.5 Miscellaneous unit costs and resource use

There are no additional costs that have not been covered elsewhere in the submission.

3.6 Severity

Not applicable.

3.7 Uncertainty

Whilst all practical measures have been taken to minimise uncertainty in the analysis, there are still several key areas of uncertainty. These are described in the following section along with explanations of how they have been addressed.

Furthermore, uncertainty in the model is explored in Section 3.11. Uncertainty relating to the model parameters is assessed through probabilistic sensitivity analysis (PSA) in Section 3.11.1 and deterministic sensitivity analysis (DSA) in Section 3.11.2. Scenario analyses are also used to analyse the impact of uncertainty on model inputs and assumptions and are discussed in Section 3.11.3.

3.7.1 Uncertainty in clinical inputs

The rare nature of IgAN places substantial limitations on the ability to collect efficacy data. There is no evidence currently available to demonstrate TRF-budesonide's

effect extends beyond 24 months (as described in Section 3.11.3). Therefore, the model makes the conservative assumption that treatment effect stops after 2 years in all patients. The model structure is flexible to capture the impact of varying the duration of treatment effect has on the economic output.

The rarity of IgAN and the lack of published cost-effectiveness studies in IgAN made it difficult to identify suitable additional inputs for the economic model. The decision to define the model's health state based on eGFR levels allowed data from the published cost-effectiveness analyses in CKD to inform CKD health states to patient utility, health resource use, and transition probability data. However, there is still uncertainty regarding whether CKD data inputs are representative of patients with IgAN. Due to the lack of published IgAN specific literature and no identified published CEM precedent in IgAN, this was considered the best available approach for the economic evaluation. The model includes scenario analyses which varies the studies used to inform the model in Section 3.11.3.

3.7.2 Uncertainty in clinical practice

The model base case assumes patients receive 1 additional round of treatment with TRF-budesonide after the first 9-month treatment cycle. However, the draft MHRA license wording indicates that retreatment may be considered at the discretion of the treating physician. Although the model has the functionality to include retreatment with TRF-budesonide, the safety and efficacy of treatment with subsequent courses of TRF-budesonide have not been established. Assumptions regarding the efficacy of one additional round of treatment have been made. Including further rounds of retreatment would increase the model's uncertainty; therefore, the base case only considers two rounds of treatment (one initial round and one retreatment). The retreatment assumptions were varied in the scenario analyses (see Section 3.11.3).

There is also uncertainty regarding the extent to which patients will receive a tapered daily dose of 4 mg for 2 weeks after they have completed a full 9-month course of 16 mg once daily dose and a reduced dose of 8 mg for 2 weeks. The MHRA license wording indicates that dose tapering may be considered at the discretion of the treating physician. Although tapering was excluded from the model base case based

on clinician feedback (86), the impact tapering would have on the ICER is explored in the scenario analysis.

3.8 Managed access proposal

Not applicable.

3.9 Summary of base-case analysis inputs and assumptions

3.9.1 Summary of base-case analysis inputs

The base-case inputs for the economic model are summarised in Table 57.

Table 57: Summary of variables applied in the economic model

Variable	Value	Measurement of uncertainty (distribution)	Reference to section in submission
Model setup parameters			
Time horizon	57 years	Fixed	Section 3.2.2
Cycle length	1 month	Fixed	
Discount rate – Costs	3.5%	Fixed	
Discount rate - QALYs	3.5%	Fixed	
Discount rate – Lys	3.5%	Fixed	
Patient characteristics			
Age at baseline	43 years	Normal	Section 3.2.1
Proportion female	34.1%	Beta	
Average weight	84.5 kg	Normal	
Distribution across CKD stages at baseline			
CKD 1	2.2%	Dirichlet	Section 3.2.2
CKD 2	38.5%	Dirichlet	
CKD 3a	37.1%	Dirichlet	
CKD 3b	22.3%	Dirichlet	
CKD 4	0.0%	Dirichlet	
TRF-budesonide treatment effect			
HR applied to SoC risk of CKD 5	0.38	Log-normal	Section 3.3.2.2
Time point from where no treatment effect is assumed	2 years	Normal	
Health utility values			
CKD 1	0.85	Beta	Section 3.4.3

Variable	Value	Measurement of uncertainty (distribution)	Reference to section in submission
CKD 2	0.85	Beta	
CKD 3a	0.80	Beta	
CKD 3b	0.80	Beta	
CKD 4	0.74	Beta	
CKD 5	0.73	Beta	
Haemodialysis	0.44	Beta	
Peritoneal dialysis	0.53	Beta	
Post transplant	0.71	Beta	
Adverse event disutilities			
Acne	0.000	Beta	Section 3.4.4
Acute kidney injury	0.110	Beta	
Coronavirus infection	0.000	Beta	
Cushingoid	0.156	Beta	
Dyspepsia	0.044	Beta	
Face oedema	0.156	Beta	
Hypertension	0.046	Beta	
Hypertension – severe	0.046	Beta	
Neutrophil count increased	0.000	Beta	
Oedema peripheral	0.156	Beta	
Pneumonia	0.000	Beta	
Pulmonary embolism	0.018	Beta	
Renal impairment	0.060	Beta	
Weight increase	0.000	Beta	
White blood cell count increased	0.001	Beta	
Adverse event rate duration (days)			
Acne	7.000	Normal	Section 3.4.4
Acute kidney injury	30.438	Normal	
Coronavirus infection	30.438	Normal	
Cushingoid	7.000	Normal	
Dyspepsia	7.000	Normal	
Face oedema	7.000	Normal	
Hypertension	7.000	Normal	
Hypertension – severe	30.438	Normal	
Neutrophil count increased	7.000	Normal	

Variable	Value	Measurement of uncertainty (distribution)	Reference to section in submission
Oedema peripheral	7.000	Normal	
Pneumonia	30.438	Normal	
Pulmonary embolism	30.438	Normal	
Renal impairment	30.438	Normal	
Weight increase	7.000	Normal	
White blood cell count increased	7.000	Normal	
Adverse event rates – TRF-budesonide			
Acne	[redacted]	Normal	Section 3.3.2.4
Cushingoid	[redacted]	Normal	
Dyspepsia	[redacted]	Normal	
Face oedema	[redacted]	Normal	
Hypertension	[redacted]	Normal	
Oedema peripheral	[redacted]	Normal	
Weight increase	[redacted]	Normal	
White blood cell count increased	[redacted]	Normal	
Neutrophil count increased	[redacted]	Normal	
Pulmonary embolism	[redacted]	Normal	
Renal impairment	[redacted]	Normal	
Coronavirus infection	[redacted]	Normal	
Pneumonia	[redacted]	Normal	
Acute kidney injury	[redacted]	Normal	
Hypertension – severe	[redacted]	Normal	
Adverse event rates – SoC			
Acne	[redacted]	Normal	Section 3.3.2.4
Cushingoid	[redacted]	Normal	
Dyspepsia	[redacted]	Normal	
Face oedema	[redacted]	Normal	
Hypertension	[redacted]	Normal	
Oedema peripheral	[redacted]	Normal	
Weight increase	[redacted]	Normal	
White blood cell count increased	[redacted]	Normal	
Neutrophil count increased	[redacted]	Normal	
Pulmonary embolism	[redacted]	Normal	

Variable	Value	Measurement of uncertainty (distribution)	Reference to section in submission
Renal impairment	[redacted]	Normal	
Coronavirus infection	[redacted]	Normal	
Pneumonia	[redacted]	Normal	
Acute kidney injury	[redacted]	Normal	
Hypertension – severe	[redacted]	Normal	
TRF-budesonide treatment costs			
Full dose monthly cost	[redacted]	Normal†	Section 3.5.1.1
Reduce dose 2-weekly cost	[redacted]	Normal†	
Administration cost per dose	£0.00	Normal†	
SoC treatment cost			
Monthly treatment cost	£80.18	Normal†	Section 3.5.1.2
Monthly administration cost	£0.00	Normal†	
Resource use costs			
GP appointment	£33.00	Normal†	Section 3.5.2
Blood tests	£3.10	Normal†	
Nephrologist visits	£196.88	Normal†	
Hospital haemodialysis	£218.45	Normal†	
Satellite haemodialysis	£203.13	Normal†	
Home haemodialysis	£281.14	Normal†	
Haemodialysis transport	£14.55	Normal†	
Peritoneal dialysis	£105.99	Normal†	
Transplantation pre-assessment	£528.51	Normal†	
Transplantation procedure cost	£19,307.41	Normal†	
Transplantation post-transplant assessment	£320.50	Normal†	
Tacrolimus	£42.92	Normal†	
Hospitalisation	£3,037.05	Normal†	
End of life costs			
Hospital care – 30 days to death	£3,622.74	Normal†	Section 3.5.3

Abbreviations: CKD, chronic kidney disease; GP, general practitioner; LY, life year; QALY, quality-adjusted life year

† The individual components that are used to calculate the value in the table are normally distributed in the PSA

3.9.2 Assumptions

The main assumptions of the economic model alongside supporting justifications are presented in Table 58.

Table 58: Key assumptions of the analysis

Model input and cross reference	Source / assumption	Justification
Time horizon (3.2.2.1)	Lifetime (up to 70 years from baseline) assuming a mean starting age of 43.	Duration is sufficient to capture all benefits and costs of treatments for a chronic disease such as IgAN, as per NICE reference case (119).
Perspective (3.2.2.1)	The perspective is that of the NHS in England and Wales, and PSS.	Preference specified in NICE reference case (119).
Patient population (3.2.1)	The experience of NefIgArd patients is assumed to be representative of the TRF-budesonide-eligible patient experience in routine practice, across jurisdictions.	A similar assumption is routinely accepted in HTA, unless there is strong reason to believe the pivotal trial patients, care or setting is meaningfully different to the that in the jurisdiction at hand, with implication for clinical effectiveness conclusions and cost-effectiveness estimates.
Standard of care (3.2.3.2)	The placebo arm of NefIgArd is assumed to be a good proxy for SoC in reflecting optimised supportive care.	Patients in both NefIgArd Nef-301 trial arms were maintained on optimised and stable RAS blockade (95), which is assumed to represent optimised supportive care. Draft KDIGO 2024 guidelines recommend the following to manage the consequences of IgAN-induced nephron loss: blood pressure management; maximally tolerated dose of ACEi/ARB; lifestyle modification; and addressing cardiovascular risk. The guidelines also suggest that SGLT2 inhibitors may be considered as part of the treatment regimen for patients with IgAN (18).
Comparators (3.2.3.2)	The decision problem is assumed to be addressed by a comparison to optimised supportive care only.	As per NICE scope.
Inclusion of SGLT2 inhibitors within SoC (3.2.3.2)	SGLT2 inhibitors are included as part of the SoC for all patients within the model, but do not have any impact on efficacy versus that seen in the placebo arm of the NefIgArd Nef-301 trial.	Assumption based on the draft KDIGO 2024 guidelines which state SGLT2 inhibitors may be considered as part of the treatment regimen for patients with IgAN (18). This also aligns with expert clinical feedback who anticipated that SGLT2is would form part of standard treatment for all patients defined as part of this decision problem.

Model input and cross reference	Source / assumption	Justification
		As stated in the draft KDIGO guidelines, reported data from the 2 SGLT2i trials provide high certainty of evidence for reduction in kidney disease progression (defined as halving of eGFR, sustained low eGFR, kidney failure, or death from kidney failure) based on an existing systematic review (RR: 0.49; 95% CI: 0.32–0.74),80. Furthermore, the mechanism of action of SGLT2is is expected to be compatible with TRF-budesonide and is not expected preclude TRF-budesonide's treatment effect.
Data from outside of the NefIgArd Nef-301 study (3.3.2.2 & 3.4)	Data from outside of NefIgArd, or NefIgArd data projected beyond the limits of observed data, are assumed to be representative of likely patient and health service experiences, for Patient risks of CKD 5, dialysis and kidney transplant Patient risk of death Patient HRQoL Health service resource use and cost	Assumptions of generalisability are required when relying on data from patients and in settings not directly applicable to the decision problem. The most appropriate data available has been sought, and use of external data is all but inevitable in cost-effectiveness modelling for HTA, though assumptions in the delivered CEM have been made in absence of validation by relevant clinical experts. UK RaDaR data was used to inform: • Patient risk of CKD 5 • Patient risk of death
Retreatment eligibility (3.5.1.1.5)	Only patients in CKD stages 1-3b at the time of retreatment are eligible to receive retreatment with TRF-budesonide. Among these patients, those who met the criteria of the NefIgArd-OLE study were assumed to receive an additional round of treatment with TRF-budesonide. This resulted in [redacted]% of patients with CKD 1 – 3b receiving retreatment.	Data from the NefIgArd-OLE study was used to inform the proportion of patients potentially eligible for retreatment with TRF-budesonide. This proportion is only applied to patients in CKD stages 1 to 3b at the time of retreatment.
Retreatment efficacy (3.5.1.1.5)	It is conservatively assumed that TRF-budesonide's treatment effect wanes by 10% in retreatment cycles compared to the initial round of treatment	The EMA and draft MHRA licence wording states retreatment may be considered at the discretion of the treating physician. The NefIgArd-OLE study demonstrated that a similar treatment benefit in both eGFR and UPCR was observed after 9 months of treatment with TRF-budesonide regardless of whether patients received TRF-budesonide or placebo in the Phase 3 NefIgArd-Nef 301 study.

Model input and cross reference	Source / assumption	Justification
		However, it was conservatively assumed that the safety and efficacy data for retreatment with TRF-budesonide waned by 10% compared to the safety and efficacy data for the initial treatment of TRF-budesonide. This is the same assumption applied in TA937 (19).
Adverse events (3.3.2.4)	All treatment-related AEs occurring in ≥4% of patients in either treatment arm of the FAS were included in the model as well as TESAEs occurring in more than one patient	To align with the CSR, all TEAEs were included as they would likely incur costs from the model's perspective. 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.
Transitions between CKD health states (3.3.2.1)	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, except for movements to CKD 5. This approach aligns with TA937 (19).
Transitions to CKD 5 (3.3.2.2)	Risk of progression to CKD 5 is only possible from CKD 4 health state.	Assumption validated by clinical experts in TA937 (19).

Abbreviations: CEM, cost-effectiveness model; CKD, chronic kidney disease; EMA, European Medicines Agency; HTA, health technology assessment; KDIGO, Kidney Disease Improving Global Outcomes; MHRA, Medicines and Healthcare products Regulatory Agency; OLE, open label extension; TESAE, treatment-emergent serious adverse event

3.10 Base-case results

The base case results are presented in Table 59 and Table 60. Disaggregated results of the base-case incremental cost-effectiveness analysis are presented in Appendix J.

All results presented in Section 3.10 and 3.11 use the price based on the commercial arrangement for TRF-budesonide. List prices are used for all other treatments.

3.10.1 Base-case incremental cost-effectiveness analysis results

Table 59: Base-case results

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
TRF-budesonide	[redacted]	[redacted]	[redacted]	-	-	-	-	-
SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	Dominant

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years; SoC, standard of care; TRF, targeted-release formulation.

Table 60: Net health benefit

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	NHB at £20,000	NHB at £30,000
TRF-budesonide	[redacted]	[redacted]	-	-	-	-
SoC	[redacted]	[redacted]	[redacted]	[redacted]	0.309	0.308

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; NHB, net health benefit; QALYs, quality-adjusted life years; SoC, standard of care; TRF, targeted-release formulation.

The base case results show that TRF-budesonide is associated with an increase of [redacted] life years, and [redacted] QALYs compared to SoC. TRF-budesonide is associated with a decrease in costs of [redacted] versus SoC, based on the commercial arrangement price for TRF-budesonide. This demonstrated that TRF-budesonide is dominant compared to SoC at a willingness-to-pay threshold (WTP) of £30,000. The base case net health benefit at £20,000 and £30,000 WTP are shown in Table 60. The base case net health benefit shows a net health benefit (NHB) of 0.309 at the £20,000 WTP threshold, and a NHB of 0.308 at the £30,000 WTP threshold.

3.11 Exploring uncertainty

3.11.1 Probabilistic sensitivity analysis

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 sample from Dirichlet distribution

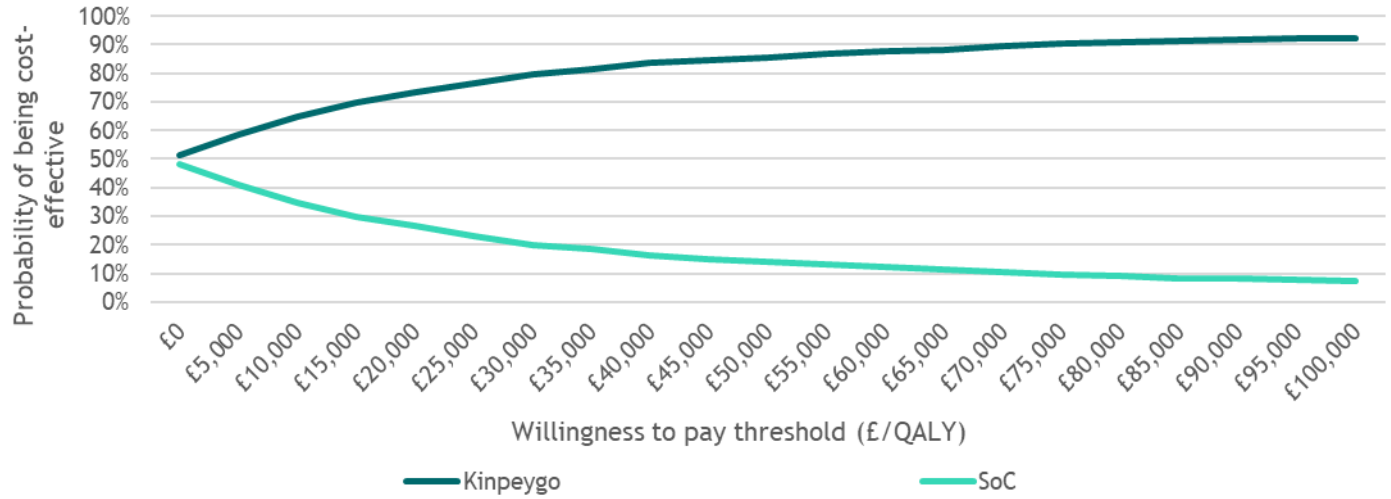
The PSA results are presented in Table 61. Cost-effectiveness acceptability curves are presented in Figure 21.

Table 61: Base-case probabilistic incremental cost-effectiveness results

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
TRF-budesonide	[redacted]	[redacted]	[redacted]	-	-	-	-	-
SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£1,211	£1,211

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years; SoC, standard of care; TRF, targeted-release formulation.

Figure 21: Cost-effectiveness acceptability curve



Abbreviations: SoC, standard of care

3.11.2 Deterministic sensitivity analysis

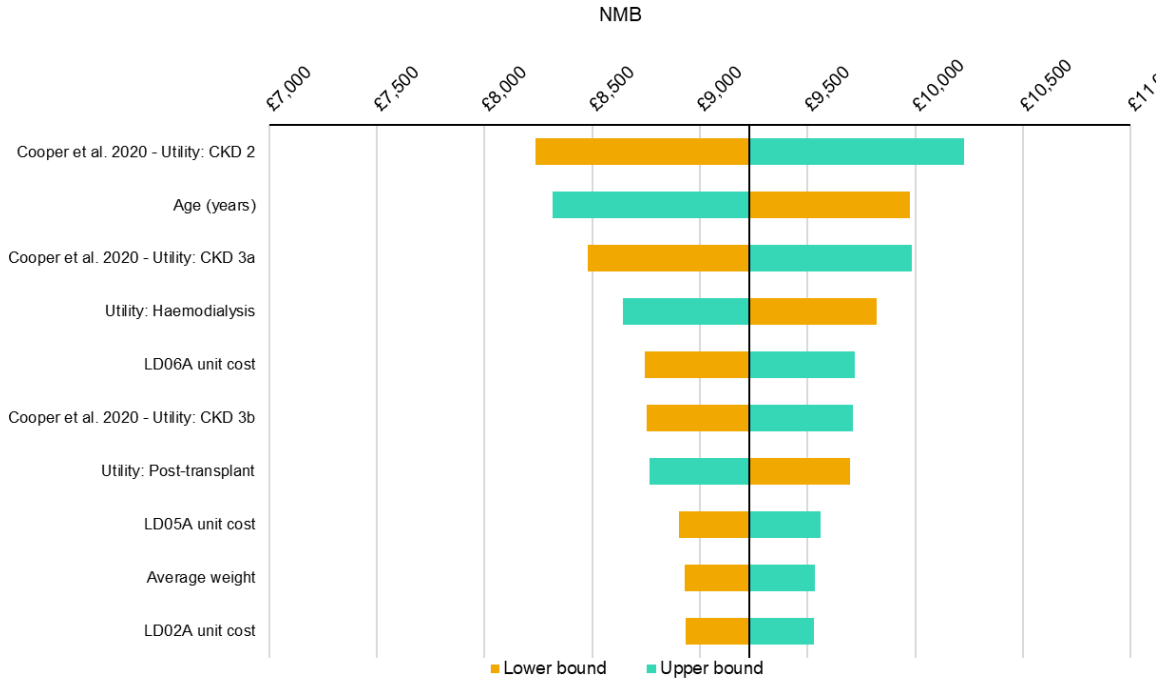
Deterministic sensitivity analysis (DSA) is designed to handle uncertainty of parameters included in the model. The DSA was programmed to identify the main parameters and assumptions which have the greatest impact on results. Upper and lower values of model inputs (e.g. resource use, unit costs, utilities) were estimated by varying the base value by 10% and were tested in the model one by one while comparing the obtained results. The base case net monetary benefit (NMB) was £9,231.

Table 62: DSA results for TRF-budesonide versus SoC

Variable	Low NMB estimate	High NMB estimate	Change in NMB
Cooper et al. 2020 - Utility: CKD 2	£8,235	£10,227	£1,992
Age (years)	£9,973	£8,315	£1,658
Cooper et al. 2020 - Utility: CKD 3a	£8,479	£9,983	£1,505
Utility: Haemodialysis	£9,818	£8,644	£1,175
LD06A unit cost	£8,743	£9,720	£977
Cooper et al. 2020 - Utility: CKD 3b	£8,754	£9,709	£955
Utility: Post-transplant	£9,696	£8,766	£930
LD05A unit cost	£8,902	£9,560	£658
Average weight	£8,930	£9,533	£603
LD02A unit cost	£8,932	£9,530	£598

Abbreviations: CKD, chronic kidney disease; NMB, net monetary benefit

Figure 22: Tornado diagram for TRF-budesonide versus SoC



Abbreviations: CKD, chronic kidney disease; NMB, net monetary benefit

The results of the DSA demonstrate that the most influential parameter was the utility value associated with CKD stage 2. Age was the second most influential parameter in the model. This is because changes in patient age affect the age- and sex-adjusted utility multiplier, which is applied to the utility values in the model. The unit costs associated with LD06A and LD05A, which inform the cost of satellite haemodialysis, were also influential parameters. LD02A unit costs which informs the costs of hospital haemodialysis was another influential parameter. Additionally, the utility values for CKD stages 3a and 3b, as well as for patients receiving haemodialysis and post-transplant care, were among the top 10 most influential parameters. Finally, the average weight of patients was also an influential factor, as it informs the dose required for immunosuppressive therapy (tacrolimus).

3.11.3 Scenario analysis

A summary of the scenario analyses explored in the model and justification for their use is presented in Table 63.

Table 63: Scenario analyses

Variable	Base case	Scenario analysis	Justification
Time horizon	58 years	20 years	

Variable	Base case	Scenario analysis	Justification
		30 years	To explore the impact of alternative time horizons on the model results
		40 years	
		50 years	
Distribution of patients across CKD states at baseline	Part B NefIgArd Nef-301	Part A NefIgArd Nef-301	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	
		UK RaDaR data - apportioned to exclude CKD 4	
Risk of ESRD	UK RaDaR data - Patients UPCR ≥0.8 g/g	UK RaDaR data – Patients UPCR ≥0.8 g/g and on ACEi/ARB patients	To explore uncertainty in the method for estimation of risk of CKD 5 in the SoC arm
		Leicester General Hospital data with HR applied	
Parametric extrapolations to estimate time to CKD 5	Exponential	Log-normal	To explore the uncertainty associated with parametric survival model fitted to extrapolate the risk of CKD 5 data
		Generalised gamma	
		Gompertz	
		Log-logistic	
		Gamma	
		Weibull	
SoC acquisition costs	£119.73	£0	To assess the impact of SoC costs associated with improved life expectancy
Time point from where no treatment effect is assumed	2 years	2.5 years	To explore uncertainty in the timepoint at which TRF-budesonide no longer has a treatment effect
		5 years	
		Treatment effect assumed to continue over the entire time horizon	
Mortality assumption	Different risk of mortality associated with CKD 1–3b	Assume the same mortality across CKD 1–3b	To explore the suggestion made by clinicians at the advisory board, we assumed the same risk of mortality for patients in CKD 1–3b
Mortality source	UK RaDaR data – Patients with UPCR ≥0.8 g/g	UK RaDaR data: ≥0.8g/g UPCR	To assess the impact of using various sources of mortality rates
		Greene et al. 2019 (150)	
		Hastings et al. 2018 (17)	
CKD stage utility source	Cooper et al. 2020	Gorodetskaya et al. 2005 (136)	

Variable	Base case	Scenario analysis	Justification
		Zhou et al. 2025 (131)	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	Excluded	Included	To explore the impact the inclusion of a reduce dose of 4 mg for the two weeks after treatment discontinuation has on the model results
		Included with tapering pack	
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
Societal costs	Excluded	Included	To determine the impact societal costs have 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	90%	70%	To determine the impact a lower efficacy in retreatment cycles has on the model results
		80%	
		100%	
Setting equivalent utility values	Utility values based on Cooper et al. 2020 (120)	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)	
Dispensing charge	Excluded	Including a dispensing charge of £10.00	To determine the impact a dispensing cost has on the

Variable	Base case	Scenario analysis	Justification
			model results. The dispensing fee was assumed to be £10
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	47.8%	25%	To explore the impact reducing the proportion of patients eligible for retreatment has on the model results
		33%	
		50%	
Time between retreatment cycles	14.75 months	20.75 months	To explore the impact increasing the time between retreatment cycles has on the model results
		26.75 months	
		32.75 months	
Monthly transition probability from CKD 5 to dialysis	4.5%	6%	The transitions from CKD 5 to dialysis and transplantation were sourced directly from the DAPA-CKD data as reported in TA775 (117). The estimated monthly probability of patients in CKD 5 to dialysis is 4.5% results in a probability of still being in CKD 5 without dialysis after 1 year of >50%. A scenario analysis was run to explore the impact increasing the transition probability such that the majority of patients with CKD 5 will receive dialysis after 1 year has on the ICER
Exclusion of dapagliflozin as a cost component of SoC	The cost of dapagliflozin is included as part SoC's cost	The cost of dapagliflozin is excluded as part SoC's cost	To explore the impact removing dapagliflozin from SoC has on the model outcomes.
Hospital care cost source	Kent et al. 2015 (71)	Pollock et al. 2022 (145)	To assess the impact of using various sources of hospital care costs has on the ICER
		Baxter et al. 2024 (142)	

Abbreviations: CKD, chronic kidney disease; CSR, clinical study report; FAS, full analysis set; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year; SoC, standard of care- TRF- targeted-release formulation; TTD, time to treatment discontinuation.

The results of the scenario analyses are presented in Table 63.

Table 64: Scenario analyses

Variable	Scenario analysis	ICER
Time horizon	20 years	Dominant
	30 years	Dominant
	40 years	Dominant

Variable	Scenario analysis	ICER
	50 years	Dominant
Distribution of patients across CKD states at baseline	Part A NefIgArd Nef-301	Dominant
	UK RaDaR data	Dominant
	UK RaDaR data - apportioned to exclude CKD 4	£1,498
Risk of ESRD	UK RaDaR data – Patients UPCR ≥0.8 g/g and on ACEi/ARB patients	£836
	Leicester General Hospital data with HR applied	£4,969
Parametric extrapolations to estimate time to CKD 5	Log-normal	Dominant
	Generalised gamma	Dominant
	Gompertz	Dominant
	Log-logistic	Dominant
	Gamma	Dominant
	Weibull	Dominant
SoC acquisition costs	£0	Dominant
Time point from where no treatment effect is assumed	2.5 years	Dominant
	5 years	Dominant
	Treatment effect assumed to continue over the entire time horizon	Dominant
Mortality assumption	Assume the same mortality across CKD 1-3b	£343
Mortality source	UK RaDaR data: ≥0.8g/g UPCR	Dominant
	Greene et al. 2019	£10,120
	Hastings et al. 2018	£539
CKD stage utility source	Gorodetskaya et al. 2005	Dominant
	Zhou et al. 2024	Dominant
Age-adjusted utilities	Excluded	Dominant
TRF-budesonide dose reduction	Excluded	£226
TRF-budesonide treatment tapering period	Included	£6
	Included with tapering pack	£225
Treatment stopping approach	Use the TTD curve from the CSRs	Dominant
Societal costs	Included	Dominant
TRF-budesonide retreatment	3 rounds of treatment	Dominant
	4 rounds of treatment	Dominant
	5 rounds of treatment	Dominant
	6 rounds of treatment	Dominant

Variable	Scenario analysis	ICER
	No subsequent rounds of treatment	£1,469
Treatment effect in subsequent treatments	70%	£11,532
	80%	£4,661
	100%	Dominant
Setting equivalent utility values	Same utility values for CKD 1–3b health states (health states are assumed equivalent to the CKD 1 value)	Dominant
	Same utility values for CKD 1–4 health states (health states are assumed equivalent to the CKD 1 value)	Dominant
Dispensing charge	Including a dispensing charge of £10.00	£533
Relative dose intensity	Included	Dominant
Proportion of CKD 1–3b patients eligible for retreatment	25%	£234
	33%	£15
	50%	Dominant
Time between retreatment cycles	20.75 months	Dominant
	26.75 months	Dominant
	32.75 months	Dominant
Monthly transition probability from CKD 5 to dialysis	6%	Dominant
Exclusion of dapagliflozin as a cost component of SoC	The cost of dapagliflozin is excluded as part SoC's cost	Dominant
Hospital care cost source	Kent et al. 2015	£5,284
	Baxter et al. 2024	£8,198

Abbreviations: CKD, chronic kidney disease; CSR, clinical study report; FAS, full analysis set; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year; SoC, standard of care- TRF- targeted-release formulation; TTD, time to treatment discontinuation.

3.12 Subgroup analysis

Not applicable – no subgroup analysis was performed.

3.13 Benefits not captured in the QALY calculation

Not applicable.

3.14 Validation

3.14.1 Validation of cost-effectiveness analysis

The technical accuracy of calculations in the model was assessed by a senior health economist who was not involved in the development of the model. Validation consisted of the following:

- Systematically checking individual formulae on a sheet-by-sheet basis
- Testing the model using extreme input values to ensure results remain valid and directionally correct
- Cross checking input values against source references
- Ensuring transformation and derivation of model input values is as described and has been conducted correctly
- Testing functionality (including navigation and any other macros) for errors
- A check of the PSA and DSA including distributions used and rationales used for distribution choices.

Furthermore, the model structure adopted was the same as that used in TA937 (19), which was validated through consultation with health economic experts and deemed appropriate by the EAG. Additionally, any assumptions and parameter inputs that differed from those used in TA937 were validated with clinical experts.

3.15 Interpretation and conclusions of economic evidence

The economic analysis estimates the cost-effectiveness of TRF-budesonide versus SoC for the treatment of adults with primary IgAN with a urine protein excretion ≥1.0 g/day (or UPCR ≥0.8 g/g).

The economic model adopted a cohort-level structure, mirroring the economic model which was used and approved by the NICE committee in the TA937 NICE submission. A lifetime horizon of 57 years was used to estimate the costs and outcomes from the perspective of the NHS and PSS in the UK. The efficacy and safety of TRF-budesonide and SoC in the analysis were based on the NefIgArd Nef-301 clinical trial (transition probabilities for CKD 1–4 and adverse events), which is the most relevant and representative dataset for this submission. Real-world

evidence and data sourced from published literature were utilised where the trial data could not inform the model. Health-state utility values and cost estimates were derived from relevant, publicly available data sources.

The results of the evaluation show that TRF-budesonide is associated with an increase in life years ([redacted] years per patient), increased quality-adjusted life-years (QALYs; [redacted] per patient), as well as a decrease in total costs of [redacted] per patient. This demonstrated that TRF-budesonide was dominant compared to SoC. The higher total QALYs associated with TRF-budesonide is reflective of the clinically meaningful and statistically significant improvements in CKD progression compared with SoC as demonstrated in the NefIgArd Nef-301 clinical trial, and the higher utility associated with remaining in less severe stages of CKD. Although TRF-budesonide arm is associated with higher treatment costs, its better efficacy compared to SoC slows the progression to later stages of CKD and the delayed progression results in lower resource use costs, including dialysis and transplant costs. Since later stages of CKD are associated with a higher risk of mortality, the delay in progression reduces mortality and, therefore, end-of-life costs. The decrease in resource use costs is substantial enough to offset the increase in treatment costs associated with the TRF-budesonide compared to SoC and results in an overall decrease in total costs.

Sensitivity and scenario analyses were conducted to identify key drivers within the model, and to assess the extent to which uncertainty in model parameters might impact the cost-effectiveness results. The DSA showed that parameters related to the patient's age, the utility values associated with CKD stages and the cost of haemodialysis had a large impact on the model results.

The PSA showed that the probabilistic results are consistent with the deterministic results and that TRF-budesonide is cost-effective compared with SoC. TRF-budesonide is associated with 80% probability of being cost effective at a willingness to pay threshold of £30,000.

The scenario analysis demonstrated that varying factors such as the time horizon, the mortality source and the hospital care cost source influenced the ICER. All the scenario analyses remained below the willingness-to-pay (WTP) threshold of

£30,000 per QALY. Furthermore, 68% of the scenario analyses produced a dominant ICER.

The main strengths of the evaluation are:

- The economic analysis uses a Markov model cohort structure that was validated by experts in the TA937 submission and deemed representative of patients with IgAN.
- The analysis also incorporates clinical efficacy and safety data from a range of sources including clinical trials and real-world evidence to help fill gaps in data due to the rarity of IgAN and the inherent lack of data for this patient population.
- Extensive sensitivity analyses have been conducted including PSA, DSA and scenario analyses, which showed that the results are robust to changes in parameter and structural assumptions.

A limitation of the model is the uncertainty surrounding the retreatment of patients with TRF-budesonide. The NefIgArd Nef-301 trial did not include retreatment, and although the NefIgArd-OLE study involved patients previously treated with TRF-budesonide in the NefIgArd Nef-301 trial, it did not provide data to inform transition probabilities within the model. As a result, the model relies on assumptions regarding the safety and efficacy of retreatment, which introduces additional uncertainty into the analysis.

Additionally, the rarity of IgAN made it challenging to identify suitable inputs for the economic model. The model's health states are defined by eGFR levels to allow for data from the published cost-effectiveness precedent in CKD to inform the CKD health states utility, health resource use and transition probability inputs. However, there is still uncertainty regarding whether CKD data inputs are representative of patients with IgAN. However, due to the lack of published IgAN-specific literature and no identified published CEM precedent in IgAN, this was considered the best available approach to the economic evaluation.

3.15.1 Conclusion

The results of this cost-effectiveness analysis indicate that TRF-budesonide is a cost-effective treatment when assessed against the NICE willingness to pay threshold of £20,000–£30,000 per QALY. It can be considered a cost-effective option versus SoC for the treatment of adults with primary IgAN with a urine protein excretion ≥1.0 g/day (or UPCR ≥0.8 g/g) from the perspective of the UK NHS and PSS. This conclusion was consistent across the PSA and the scenario analyses.

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5 Appendices

Appendix A: Summary of product characteristics (SmPC) and UK public assessment report

Appendix B: Identification, selection and synthesis of clinical evidence

Appendix C: Subgroup analysis

Appendix D: Adverse reactions

Appendix E: Published cost-effectiveness studies

Appendix F: Health-related quality-of-life studies

Appendix G: Cost and healthcare resource identification, measurement and valuation

Appendix H: Clinical outcomes and disaggregated results from the model

Appendix I: Price details of treatments included in the submission

Appendix J: Additional clinical data from NeflgArd Nef-301

Appendix K: Overview of results from Nefigan Nef-202

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Targeted-release budesonide for treating primary IgA nephropathy (review of TA937) [ID6485]

Summary of Information for Patients (SIP)

May 2025

File name	Version	Contains confidential information	Date
ID6485 budesonide SIP 22May25	1.0	No	22nd May 2025

Summary of Information for Patients (SIP):

The pharmaceutical company perspective

What is the SIP?

The Summary of Information for Patients (SIP) is written by the company who is seeking approval from NICE for their treatment to be sold to the NHS for use in England. It is a plain English summary of their submission written for patients participating in the evaluation. It is not independently checked, although members of the public involvement team at NICE will have read it to double-check for marketing and promotional content before it is sent to you.

The **Summary of Information for Patients** template has been adapted for use at NICE from the Health Technology Assessment International – Patient & Citizens Involvement Group (HTAi PCIG). Information about the development is available in an open-access IJTAHC journal article

SECTION 1: Submission summary

Note to those filling out the template: Please complete the template using plain language, taking time to explain all scientific terminology. Do not delete the grey text included in each section of this template as you move through drafting because it might be a useful reference for patient reviewers. Additional prompts for the company have been in red text to further advise on the type of information which may be most relevant and the level of detail needed. You may delete the red text.

1a) Name of the medicine (generic and brand name):

Response: TRF-budesonide (Kinpeygo®)

1b) Population this treatment will be used by. Please outline the main patient population that is being appraised by NICE:

Response: Adults with primary immunoglobulin A nephropathy (IgAN) with a urine protein excretion ≥1.0 g/day (or urine protein-to-creatinine ratio ≥0.8 g/g).

1c) Authorisation: Please provide marketing authorisation information, date of approval and link to the regulatory agency approval. If the marketing authorisation is pending, please state this, and reference the section of the company submission with the anticipated dates for approval.

Response: Marketing authorisation approval is pending, please see Section 1.2 of the Company Submission for anticipated timelines.

1d) Disclosures. Please be transparent about any existing collaborations (or broader conflicts of interest) between the pharmaceutical company and patient groups relevant to the medicine. Please outline the reason and purpose for the engagement/activity and any financial support provided:

Response:
Not applicable.

SECTION 2: Current landscape

2a) The condition – clinical presentation and impact

Please provide a few sentences to describe the condition that is being assessed by NICE and the number of people who are currently living with this condition in England.

Please outline in general terms how the condition affects the quality of life of patients and their families/caregivers. Please highlight any mortality/morbidity data relating to the condition if available. If the company is making a case for the impact of the treatment on carers this should be clearly stated and explained.

Response:

Immunoglobulin A nephropathy (IgAN) is a rare disease that occurs when immunoglobulin A (IgA) antibodies, which normally help the body fight infection, become trapped in the kidney (1-3). The build-up of IgA antibodies in the kidneys causes inflammation and scarring, which can lead to a loss of kidney function, development of chronic kidney disease (CKD) and eventually kidney failure (also called end-stage renal disease [ESRD]) (1-3). Treatment options for people who have progressed to kidney failure are limited to either a kidney transplant or chronic dialysis, which substantially increase disease burden (1, 4-7).

The average age at which people are diagnosed with IgAN in the UK is 41 years and currently, most people with IgAN progress to kidney failure within 10–15 years of diagnosis with current treatment (8).

People with IgAN may experience a range of symptoms, which may include blood and/or protein in the urine, loin pain, high blood pressure (9-11), as well as tiredness and fatigue which can cause physical limitations and restrict daily activities (7, 11-14). People with IgAN face an average 10-year reduction in life expectancy (15, 16) and have a high risk of developing other conditions, such as cardiovascular disease (17).

The symptoms and emotional burden of IgAN and its treatment can have a life-changing impact on patients' lives, causing physical limitations and restricting daily activities at all disease stages (7, 12, 13). Debilitating fatigue can prevent patients from achieving simple daily tasks and leading a normal life, while dietary restrictions, recommended in patients with IgAN, can also negatively affect quality of life and lifestyle (1, 5, 12, 18). Patients with IgAN may experience anxiety, depression, and fear of progression to kidney failure (ESRD) (12, 13).

The impact of kidney disease on patients can also place a substantial burden on their family and caregivers, due to pressures relating to performing tasks, managing lifestyle restrictions, and the debilitating burden of dealing with the patients' emotional load(12, 19, 20). Carers of patients with kidney disease can be impacted by depressive symptoms or anxiety, with some caregivers reporting battling an unrelenting and debilitating burden(19).

2b) Diagnosis of the condition (in relation to the medicine being evaluated)

Please briefly explain how the condition is currently diagnosed and how this impacts patients. Are there any additional diagnostic tests required with the new treatment?

Response:
The first step towards a diagnosis of IgAN typically includes a urine test to measure protein levels and a blood test to measure kidney function (21, 22). A confirmed diagnosis of IgAN requires a kidney biopsy to look for the presence of IgA (1, 5, 10). As IgAN may not produce any specific symptoms in the early stages, many people affected experience a delay in securing a diagnosis (median time from first clinical sign to diagnosis: 5.0 months; interquartile range [IQR]: 0.9–29.3) (23) and many patients have substantial kidney damage by the time they are diagnosed (24). There are no additional diagnostic tests required in order to receive treatment with TRF-budesonide.

2c) Current treatment options:

The purpose of this section is to set the scene on how the condition is currently managed:

- What is the treatment pathway for this condition and where in this pathway the medicine is likely to be used? Please use diagrams to accompany text where possible. Please give emphasis to the specific setting and condition being considered by NICE in this review. For example, by referencing current treatment guidelines. It may be relevant to show the treatments people may have before and after the treatment under consideration in this SIP.
- Please also consider:
    - if there are multiple treatment options, and data suggest that some are more commonly used than others in the setting and condition being considered in this SIP, please report these data.
    - are there any drug–drug interactions and/or contraindications that commonly cause challenges for patient populations? If so, please explain what these are.

Response:

In clinical practice in England, treatment of IgAN for most people is focused on optimised supportive care (also called standard of care), which includes lifestyle modification, blood pressure management, treatment with renin-angiotensin system (RAS) inhibitors, and treatment with sodium-glucose cotransporter-2 (SGLT-2) inhibitors (25, 26). Supportive care is focused on treating chronic kidney disease (CKD). CKD is the result of IgAN, occurring because of the build-up of disease-causing types of IgA antibodies called galactose deficient (gd)-IgA in the kidneys which affect their ability to function normally. For most people with IgAN, there are currently no available treatments that can target the underlying cause of IgAN and reduce the build up of IgA antibodies in order to slow down progression of CKD.

TRF-budesonide is a medicine designed specifically for people with IgAN. It is a type of corticosteroid which works by specifically targeting cells in the part of the intestine where most disease-causing IgA antibodies are produced, leading to a reduction in the level of IgA antibodies circulating in the blood and preventing the harmful effects of their build up in the kidneys and slowing down CKD progression. More information on how TRF-budesonide works is presented in Section 3a. TRF-budesonide is different from systemic corticosteroids (also called glucocorticoids) in terms of how it works (as described in Section 3a) and because most of the medicine is neutralised in the liver before it reaches the rest of the body. It therefore has the potential for fewer side effects than systemic corticosteroids which are rarely used in the UK to treat IgAN, because they affect the whole body and can cause unpleasant side effects.

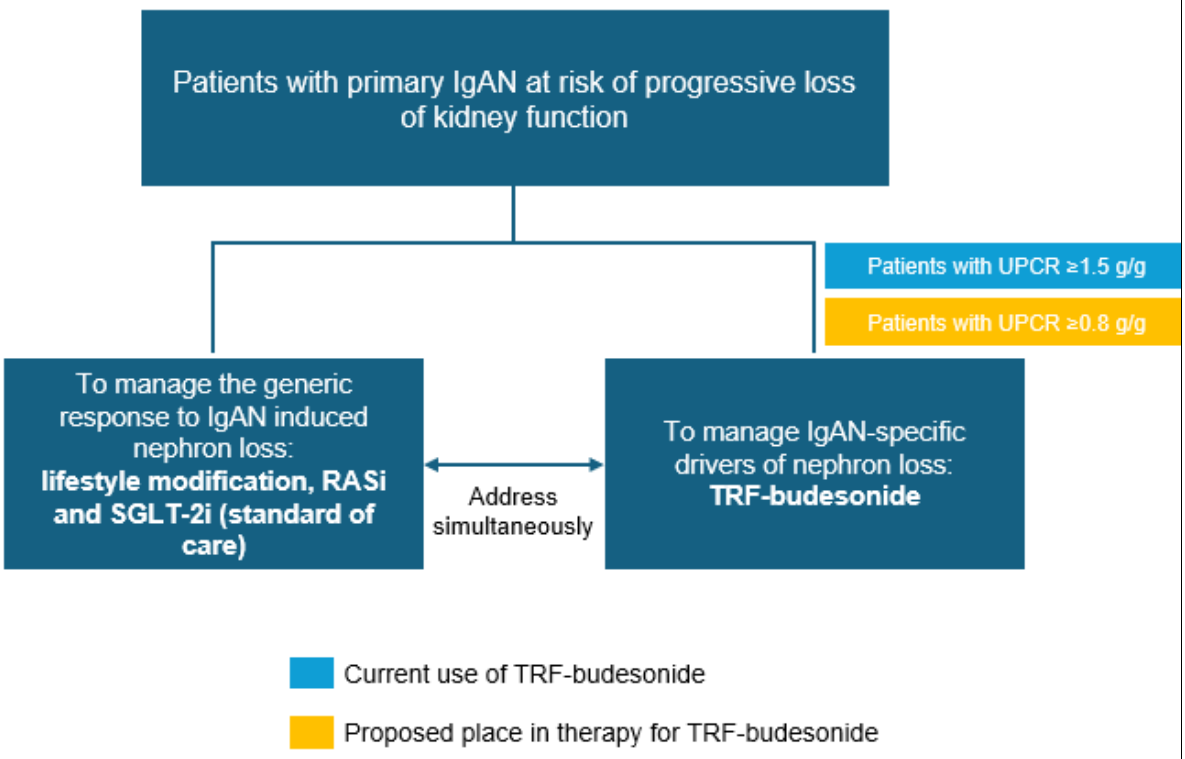
In 2023, NICE recommended TRF-budesonide as an add-on to optimised standard of care as an option for treating primary IgAN when there is a risk of rapid disease progression in adults with a urine protein-to-creatinine ratio of 1.5 g/g or more (TA937) (27), however TRF-budesonide is not currently recommended by NICE for the treatment of primary IgAN in adults with a urine protein to creatinine ratio (UPCR) of <1.5 g/g.

Draft treatment guidelines developed by Kidney Disease Improving Global Outcomes (KDIGO) in 2024 state that in order to reduce the progressive loss of kidney function in people with IgAN, the underlying cause of the disease (IgAN specific drivers of nephron loss) and CKD which results from this (generic response to IgAN induced nephron loss) should be treated at the same time (outlined in Figure 1).

This appraisal seeks a recommendation to expand the use of TRF-budesonide for people with IgAN and UPCR ≥0.8g/g or urine protein excretion ≥1.0 g/day (see Figure 1).

For people with IgAN who progress to ESRD, treatment options are limited to dialysis or kidney transplantation, which substantially increase disease burden and associated treatment costs (1, 4-7, 28).

Figure 1: Treatment pathway for IgAN in the UK



Abbreviations: IgAN, immunoglobulin A nephropathy; RASi, renin-angiotensin system inhibitor; SGLT-2i, sodium-glucose cotransporter-2 inhibitor; TRF, targeted-release formulation; UPCR, urine protein to creatinine ratio.

2d) Patient-based evidence (PBE) about living with the condition

Context:

- **Patient-based evidence (PBE)** is when patients input into scientific research, specifically to provide experiences of their symptoms, needs, perceptions, quality of life issues or experiences of the medicine they are currently taking. PBE might also include carer burden and outputs from patient preference studies, when conducted in order to show what matters most to patients and carers and where their greatest needs are. Such research can inform the selection of patient-relevant endpoints in clinical trials.

In this section, please provide a summary of any PBE that has been collected or published to demonstrate what is understood about **patient needs and disease experiences**. Please include the methods used for collecting this evidence. Any such evidence included in the SIP should be formally referenced wherever possible and references included.

Response:

A retrospective social media listening study by Tyagi et al. 2019 (12) gathered data from 1,336 relevant posts of patients with IgAN and caregivers in the UK and US. Patients reported symptoms of IgAN to include pain in the kidney area, pelvic pain, back pain, body aches(12). Episodes of tiredness and loss of energy resulted in limiting physical activity, exhaustion, and low stamina. Patients with IgAN also reported feelings of anxiety, fear of disease progression, and sadness (12).

A systematic review of the health-related quality of life (HRQoL) impact of IgAN which included 8 studies reported that the considerable physical and mental health burden of IgAN increases with disease progression, particularly when dialysis becomes necessary (13). In one study of the priorities for outcomes in chronic kidney disease (CKD) including adult patients with CKD (all stages) and caregivers in the US, Australia, and UK, a diagnosis of CKD was reported to often cause trauma and distress, with uncertainty about the future prompting patients to re-evaluate their lives (19). Furthermore, people who care for patients with CKD can also be impacted by depressive symptoms or anxiety, with some caregivers mentioning battling unrelenting and debilitating burden (19). In studies of the HRQoL of people with CKD, late-stage kidney disease has been reported to be associated with worse HRQoL scores and perceived health scores compared with early-stage disease and healthy controls (29-33).

During previous NICE appraisals concerning IgAN, patient representatives have highlighted the importance of delaying disease progression to the point where dialysis or a kidney transplant is needed, as this can have a significant impact on young adults leading to substantial limitations in ability to work, travel, fulfil day to day responsibilities and maintain relationships (27, 34).

Dialysis itself has a substantial impact on patients; a UK, retrospective, interview-based study by Bristowe et al. 2015 (35) of 20 patients receiving haemodialysis showed that patients were struggling to come to terms with the need for dialysis, with associated feelings of denial, numbness, disbelief, fear, grief, intense sadness and anger at the loss of their health at first exposure to the haemodialysis unit. Regular dialysis requirements can result in patients leaving their jobs and/or missing work frequently. In the Greek study by Stavrianou et al. 2007 (36) in patients with ESRD receiving haemodialysis (n=146), 77% of patients said that they were either on sick leave or received a disability pension, with only 23% of patients maintaining employment. Reasons given for being unable to work included disease-specific symptoms, diminished physical working capacity, inability to continue fulltime employment and difficulties in coping with family responsibilities and social lives alongside working (36).

SECTION 3: The treatment

3a) How does the new treatment work?

What are the important features of this treatment?

Please outline as clearly as possible important details that you consider relevant to patients relating to the mechanism of action and how the medicine interacts with the body

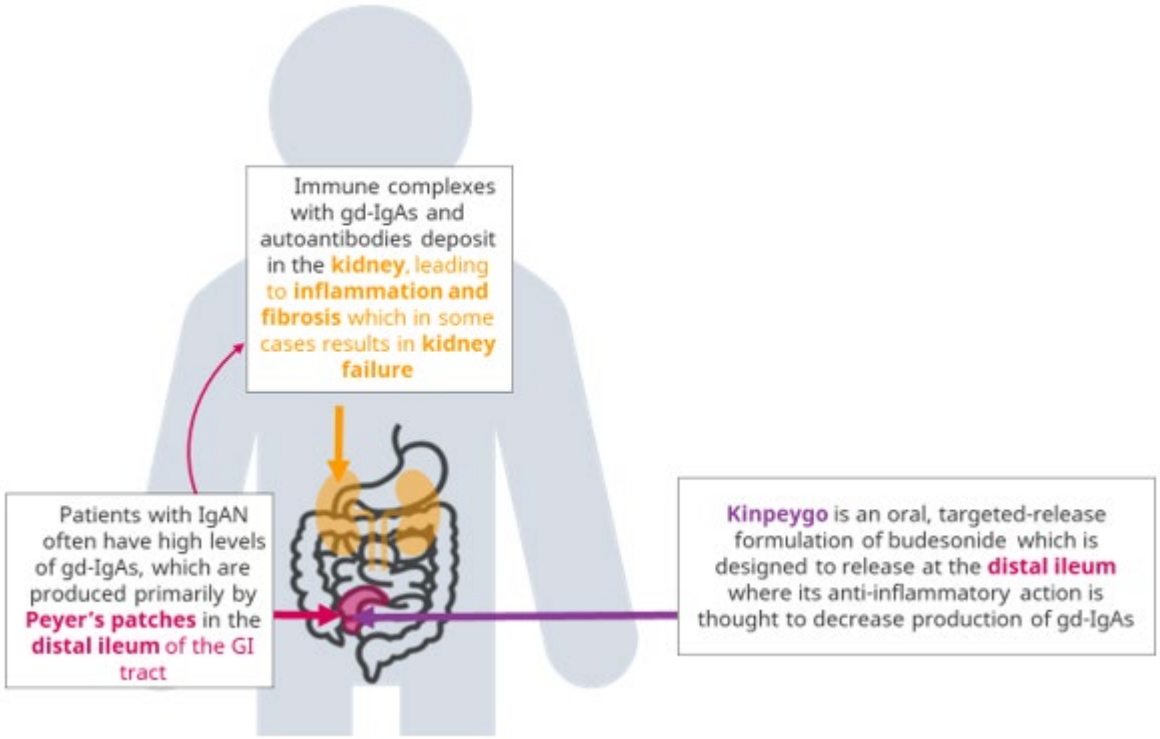
Where possible, please describe how you feel the medicine is innovative or novel, and how this might be important to patients and their communities.

If there are relevant documents which have been produced to support your regulatory submission such as a summary of product characteristics or patient information leaflet, please provide a link to these.

Response:

TRF-budesonide is the first and only approved treatment which can address the underlying cause of IgAN. It has been formulated to release the active component, budesonide (a type of corticosteroid), in a segment of the small intestine called the distal ileum (37). Here, TRF-budesonide is expected to have an anti-inflammatory effect at a primary site of galactose deficient (gd)-IgA antibody production called the Peyer's patches (37) (Figure 2). By reducing the levels of gd-IgA antibodies circulating in the blood, TRF-budesonide may prevent the effects of their build-up in the kidneys, such as kidney inflammation, damage, and loss of function (37, 38), slowing disease progression.

Figure 2: The targeted action of TRF-budesonide in IgAN



Abbreviations: GI, gastrointestinal; gd-IgA, galactose-deficient immunoglobulin A IgAN, immunoglobulin A nephropathy.
Sources: Pattrapornpisut et al. 2021(1); Del Vecchio et al. 2021(37); Fellström et al. 2017(39).

3b) Combinations with other medicines

Is the medicine intended to be used in combination with any other medicines?

- Yes / No

If yes, please explain why and how the medicines work together. Please outline the mechanism of action of those other medicines so it is clear to patients why they are used together.

If yes, please also provide information on the availability of the other medicine(s) as well as the main side effects.

If this submission is for a combination treatment, please ensure the sections on efficacy (3e), quality of life (3f) and safety/side effects (3g) focus on data that relate to the combination, rather than the individual treatments.

Response:
TRF-budesonide is intended to be used in combination with other medicines that form part of standard of care for people with IgAN. Current standard of care includes lifestyle modification, blood pressure management, and maximum-tolerated RAS inhibitors (5, 25). In clinical practice in England, patients with IgAN are also treated with SLGT-2 inhibitors

as part of standard of care to provide cardiovascular protection (25). SGLT-2 inhibitors were not used as part of standard of care in the TRF-budesonide clinical trial (NefIgArd Nef 301) (40), however clinical experts have indicated that the safety and efficacy of TRF-budesonide should not be affected if it was used in combination with SGLT-2 inhibitors as the two treatments work in different ways (25).

3c) Administration and dosing

How and where is the treatment given or taken? Please include the dose, how often the treatment should be given/taken, and how long the treatment should be given/taken for.

How will this administration method or dosing potentially affect patients and caregivers? How does this differ to existing treatments?

Response:

The recommended dose of TRF-budesonide is 16 mg (four 4 mg capsules) self-administered orally once daily in the morning, at least one hour before a meal, for 9 months (38).

When treatment is to be discontinued, the dose should be reduced to 8 mg once daily for 2 weeks; the dose may be reduced to 4 mg once daily for an additional 2 weeks, at the discretion of the treating doctor (38).

3d) Current clinical trials

Please provide a list of completed or ongoing clinical trials for the treatment. Please provide a brief top-level summary for each trial, such as title/name, location, population, patient group size, comparators, key inclusion and exclusion criteria and completion dates etc. Please provide references to further information about the trials or publications from the trials.

Response:

The key study investigating the efficacy and safety of TRF-budesonide is NefIgArd Nef-301, a multinational, randomised, double-blind, placebo-controlled, multicentre clinical trial (NCT03643965) (41). In NefIgArd Nef-301 adults with primary IgAN were randomised 1:1 to receive either oral TRF-budesonide 16 mg/day (N=182) or placebo (N=182) for 9 months in addition to standard of care including optimised RAS inhibition therapy. The 9-month treatment period was followed by a 15-month observational follow-up period of the patients during which no study medication was taken by participants.

Following completion of the NefIgArd Nef-301 study, participants with persistent proteinuria ≥1 g/day or UPCR ≥0.8 g/gram and eGFR ≥30 mL/min per 1.73 m^2 despite optimised RAS inhibition were eligible to enter Nef-301 OLE (NCT04541043), an open-label extension study where all participants, regardless of whether they received TRF-budesonide or placebo in NefIgArd Nef-301 received a 9-month course of TRF-budesonide (42).

3e) Efficacy

Efficacy is the measure of how well a treatment works in treating a specific condition.

In this section, please summarise all data that demonstrate how effective the treatment is compared with current treatments at treating the condition outlined in section 2a. Are any of the outcomes more important to patients than others and why? Are there any limitations to the data which may affect how to interpret the results? Please do not include academic or commercial in confidence information but where necessary reference the section of the company submission where this can be found.

Response:

The impact of TRF-budesonide treatment was assessed using the following outcomes:

Estimated glomerular filtration rate (eGFR) – a measure of the amount of creatinine (a waste product which is removed by the kidneys) in the blood to measure how well the kidneys are working. An eGFR score of 90 or higher is considered normal, an eGFR score of 60-90 may mean reduced kidney function and a score of ≤15 may mean kidney failure. eGFR is measured using a blood test.
Urine protein to creatinine ratio – a measure of the amount of protein and creatinine in the urine which can indicate how well the kidneys are working. A normal UPCR level is ≤150 mg/g. A higher result than this may mean reduced kidney function. This test is performed using a urine sample.

Treatment with TRF-budesonide slowed the decline in eGFR and significantly reduced levels of protein in the urine (proteinuria) in people with primary IgAN who were already receiving optimised and stable standard care (including RAS inhibitors) (41). As changes in eGFR and proteinuria (UPCR) provide an indication of the level of kidney function and disease progression in patients with kidney disease (5, 15, 43-50), the improvements observed in people treated in NefIgArd Nef-301 indicates TRF-budesonide can delay worsening of kidney function in people with IgAN and delay progression to kidney failure.

After 9 months of treatment in NefIgArd Nef-301, TRF-budesonide 16 mg/day maintained kidney function (eGFR 0.66 mL/min/1.73 m^2 increase), whereas participants receiving placebo experienced a –4.56 mL/min/1.73 m^2 deterioration in eGFR versus baseline. After a further 15 months of follow-up where participants received supportive therapy only, the change in eGFR from baseline was –6.11 mL/min per 1·73 m² (–8·04 to –4·11) in the TRF-budesonide group, compared with –12.00 mL/min per 1.73 m² (–13.76 to –10.15) in the placebo (supportive therapy only) group which is equivalent to approximately 50% less kidney function decline. In addition, a 30.0% reduction in UPCR was observed after 9 months of treatment with TRF-budesonide 16 mg/day compared with placebo (95% CI: 19.9, 38.8). This treatment benefit was maintained during 15 months of untreated follow-up with a maximum UPCR reduction of 51.3% at 12 months and a 30.1% reduction in UPCR observed at 24 months compared with placebo (40).

In Nef-301 OLE, a second course of TRF-budesonide for patients who had previously received TRF-budesonide in NefIgArd Nef-301 resulted in a treatment benefit on eGFR and UPCR over 9 months which was similar to the treatment benefit observed in patients who were receiving a first course of TRF-budesonide treatment (51).

3f) Quality of life impact of the medicine and patient preference information

What is the clinical evidence for a potential impact of this medicine on the quality of life of patients and their families/caregivers? What quality of life instrument was used? If the EuroQol-5D (EQ-5D) was used does it sufficiently capture quality of life for this condition? Are there other disease specific quality of life measures that should also be considered as supplementary information?

Please outline in plain language any quality of life related data such as **patient reported outcomes (PROs).**

Please include any **patient preference information (PPI)** relating to the drug profile, for instance research to understand willingness to accept the risk of side effects given the added benefit of treatment. Please include all references as required.

Response:

There were no differences in quality of life observed between the TRF-budesonide and placebo groups, assessed using the short-form 36 (SF-36) questionnaire in either the TRF-budesonide or placebo groups in NefIgArd NEF-301 when compared with baseline.

Similarly in Nef-301 OLE, there were no meaningful changes from baseline in quality of life over the treatment course.

However, it is anticipated that the clinical benefits of TRF-budesonide in significantly reducing proteinuria and slowing the decline in eGFR would in turn reduce the risk of

quality of life decline associated with kidney failure and dialysis in patients with primary IgAN.

3g) Safety of the medicine and side effects

When NICE appraises a treatment, it will pay close attention to the balance of the benefits of the treatment in relation to its potential risks and any side effects. Therefore, please outline the main side effects (as opposed to a complete list) of this treatment and include details of a benefit/risk assessment where possible. This will support patient reviewers to consider the potential overall benefits and side effects that the medicine can offer.

Based on available data, please outline the most common side effects, how frequently they happen compared with standard treatment, how they could potentially be managed and how many people had treatment adjustments or stopped treatment. Where it will add value or context for patient readers, please include references to the Summary of Product Characteristics from regulatory agencies etc.

Response:

Like all medicines, people receiving TRF-budesonide may experience side effects, however for most people they will be mild to moderate in severity and manageable. In the NefIgArd Nef-301 study, 87% of participants in the TRF-budesonide group and 69% of participants in the placebo group reported treatment-emergent adverse events (TEAEs) during the 9-month treatment phase. The majority of TEAEs were of mild or moderate severity and reversible. The most commonly reported TEAEs reported by >5% of participants receiving TRF-budesonide were peripheral oedema (swelling cause by fluid retention in the lower legs or hands), hypertension (high blood pressure), muscle spasms, acne, and headache (40).

In Nef-301 OLE, treatment with TRF-budesonide for 9 months was well-tolerated by participants who had completed NefIgArd Nef-301, with no new safety signals identified in participants who had previously received treatment with TRF-budesonide, or those who were receiving their first course of TRF-budesonide after having received placebo in NefIgArd Nef-301 (51).

3h) Summary of key benefits of treatment for patients

Issues to consider in your response:

- Please outline what you feel are the key benefits of the treatment for patients, caregivers and their communities when compared with current treatments.
- Please include benefits related to the mode of action, effectiveness, safety and mode of administration
-

Response:

Mechanism of action

TRF-budesonide has been specifically designed to reduce inflammation within the small intestine which is a key site of IgA production, leading to the development of IgAN (1, 37, 52). By reducing the levels of IgA antibodies circulating in the blood, it is anticipated that TRF-budesonide will prevent the downstream effects of their deposition in the kidneys, such as kidney inflammation, damage, and loss of function (37, 38), slowing disease progression.

Efficacy and safety

The clinical benefits of TRF-budesonide versus placebo have been demonstrated in the NefIgArd Nef-301 trial. When added to standard of care, TRF-budesonide resulted in stabilisation of eGFR and an improvement in UPCR (i.e. a delay in disease progression)

compared with placebo added to standard of care (40). Whilst participants received treatment with TRF-budesonide for 9 months, the benefits of treatment continued over two years (40).

In Nef-301 OLE, a second course of TRF-budesonide for participants who had previously received TRF-budesonide in NefIgArd Nef-301 resulted in a clear treatment benefit on eGFR and UPCR over 9 months which was similar to the treatment benefit observed in participants who were receiving a first course of TRF-budesonide treatment, having previously received placebo in NefIgArd Nef-301 (42).

Treatment with TRF-budesonide was also well tolerated, with an acceptable safety profile in line with that expected for an oral budesonide product (40). In Nef-301 OLE, treatment with a second course of TRF-budesonide for 9 months was also well tolerated with no new safety signals identified (51).

These results support the potential clinical benefit in delaying the progression of CKD associated with the use of TRF-budesonide for people with primary IgAN. A published study which has looked at what the long-term impact of stabilising eGFR to the level seen in the NefIgARd Nef-301 clinical trial could be has estimated that a single treatment course of TRF-budesonide could delay progression to kidney failure, eGFR <15 ml/min/1.73 m^2 , or sustained doubling of serum creatinine by approximately 12.8 years (53).

3i) Summary of key disadvantages of treatment for patients

Issues to consider in your response:

- Please outline what you feel are the key disadvantages of the treatment for patients, caregivers and their communities when compared with current treatments. Which disadvantages are most important to patients and carers?
- Please include disadvantages related to the mode of action, effectiveness, side effects and mode of administration
- What is the impact of any disadvantages highlighted compared with current treatments

Response:

TRF-budesonide was generally well tolerated. Adverse events were generally considered to be manageable and in line with the known safety profile of an oral budesonide product.

3i) Value and economic considerations

Introduction for patients:

Health services want to get the most value from their budget and therefore need to decide whether a new treatment provides good value compared with other treatments. To do this they consider the costs of treating patients and how patients' health will improve, from feeling better and/or living longer, compared with the treatments already in use. The drug manufacturer provides this information, often presented using a health economic model.

In completing your input to the NICE appraisal process for the medicine, you may wish to reflect on:

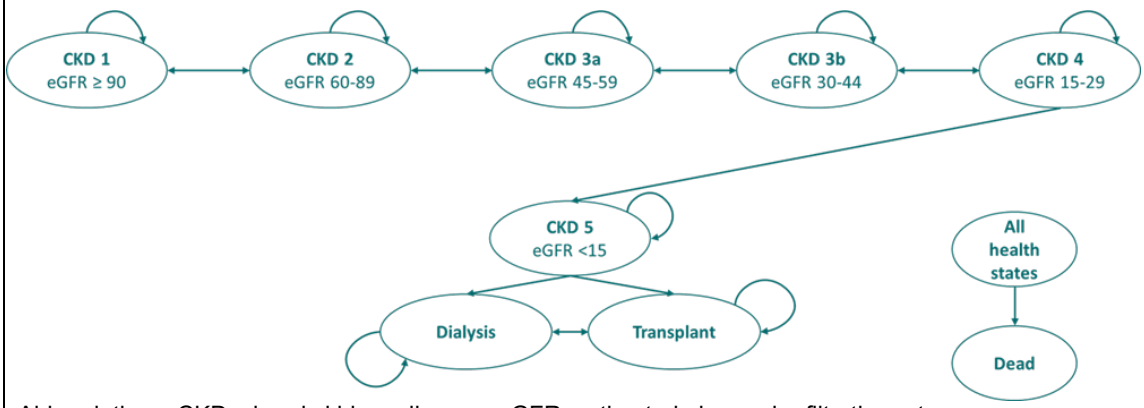
- The extent to which you agree/disagree with the value arguments presented below (e.g., whether you feel these are the relevant health outcomes, addressing the unmet needs and issues faced by patients; were any improvements that would be important to you missed out, not tested or not proven?)
- If you feel the benefits or side effects of the medicine, including how and when it is given or taken, would have positive or negative financial implications for patients or their families (e.g., travel costs, time-off work)?

- How the condition, taking the new treatment compared with current treatments affects your quality of life.

How the model reflects the condition

- An economic model was used to determine the cost-effectiveness of TRF-budesonide added to standard of care compared with standard of care alone for the treatment of people with IgAN. The model uses the same structure that was used in the previous NICE appraisal of TRF-budesonide (TA937) (27).
- In the model, hypothetical IgAN patients move between different disease stages or 'health states', over time in order to reflect disease progression experienced by people with IgAN.
- Figure 3 presents the health states used in the model. The health states used reflect the different stages of CKD (from stage 1 to stage 5) that people with IgAN experience as their disease progresses and these are defined by kidney function measured by eGFR. People who reach CKD stage 5 may subsequently go on to receive either dialysis or a kidney transplant. All health states have a risk of death.
- The model uses data from the NefIgArd Nef-301 clinical trial in order to determine the distribution of CKD stages at which hypothetical IgAN patients enter the model, and at what rate they progress through the model health states depending on their response to treatment in the trial. Patients experience different quality of life depending on which health state they are in.

Figure 3: Modelled health states



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

Modelling how much a treatment extends life

- Treatment with TRF-budesonide added to standard of care extends life by delaying progression through the different CKD stages compared with standard of care alone. In particular, TRF-budesonide can delay the expected time taken to reach the CKD 5 health state, where those affected may need to receive a kidney transplant or dialysis.
- The model uses eGFR outcomes reported in the NefIgArd Nef-301 trial for the TRF-budesonide arm and the placebo arm in order to determine how quickly patients move through the health states. Outcomes data sourced from other published studies were also used in the model where the data was not available from the clinical trial.

Modelling how much a treatment improves quality of life

- The model considers quality of life to be mainly driven by the health state patients occupy, rather than the treatment they are receiving. TRF-budesonide is assumed to improve the quality of life of patients as they spend, on average, more time in less severe CKD health states.

- The model also considers that patients may experience adverse events (for example, face oedema), which may negatively impact quality of life; the likelihood of experiencing these events can vary across treatments.
- The benefit of treatment with TRF-budesonide is estimated based both on patient's quality of life and the number of years they live for, expressed as a total number of quality-adjusted life years (QALYs).

Modelling how the costs of treatment differ with the new treatment

- TRF-budesonide is administered orally alongside standard of care.
- Standard of care costs are applied monthly to all patients in the CKD 1 to 5 health states in the model.
- The cost of TRF-budesonide is calculated as a monthly cost and applied over the 9-month course of treatment.
  - After a 9-month treatment course is completed, retreatment may be considered at the discretion of the treating physician (38). Patients eligible for retreatment are assumed to follow the same cost, relative clinical effectiveness versus SoC, and patient quality of life pathways as used for the starting treatment with TRF-budesonide. The time between on-treatment periods is assumed to be 14.75 months based on the time between completion of 9 months of treatment in the NefIgArd Nef-301 trial and the start of the NefIgArd-OLE study.

Uncertainty

- Uncertainty exists in the modelling of the cost-effectiveness of TRF-budesonide, as the rare nature of IgAN means that the only clinical data comes from the NefIgArd Nef-301 trial and the Nef-301 OLE open-label extension in a limited number of patients. The small sample size is a major source of uncertainty, particularly given differences within the patient population, including different treatment histories.
- Because of the rarity of IgAN, there are a lack of other published cost-effectiveness studies that can be used to inform the model inputs. As a result of this, the model uses some data for people with CKD (for example quality of life utility values in different health states, healthcare resource use costs) however it is not clear whether these data are completely representative of people with IgAN.
- Retreatment with TRF-budesonide may be considered at the discretion of the treating physician (38). Whilst data for one round of re-treatment are available from the Nef-301 OLE, it is unclear how many rounds of retreatment could be used, or how effective multiple rounds of retreatment may be. Different assumptions on retreatment have been explored in scenario analyses.

3j) Innovation

NICE considers how innovative a new treatment is when making its recommendations.
If the company considers the new treatment to be innovative please explain how it represents a 'step change' in treatment and/ or effectiveness compared with current treatments. Are there any QALY benefits that have not been captured in the economic model that also need to be considered (see section 3f)

Response:

TRF-budesonide is the first and only approved treatment which can address the underlying cause of IgAN. As described in Section 2c) and 3a), TRF-budesonide can reduce the inflammation associated with IgA nephropathy and prevent the deposition of harmful IgA deposits in the kidney. When used in combination with current standard of

care treatments which are used to treat the CKD that results from IgAN, TRF-budesonide can maintain kidney function, slowing CKD progression and delay the time to ESRD and the need for a kidney transplant or dialysis. It has been estimated that a single treatment course of TRF-budesonide could delay progression to kidney failure, eGFR <15 ml/min/1.73 m^2 , or sustained doubling of serum creatinine by approximately 12.8 years (53). This delay may represent vital time for people in the prime of their lives who want to be able to work, travel, fulfil day to day responsibilities and maintain relationships (27, 34).

3k) Equalities

Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged.
Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics

More information on how NICE deals with equalities issues can be found in the NICE equality scheme
Find more general information about the Equality Act and equalities issues here

Response:
No equality issues associated with the use of TRF-budesonide in this indication have been identified or are foreseen.

SECTION 4: Further information, glossary and references

4a) Further information

Feedback suggests that patients would appreciate links to other information sources and tools that can help them easily locate relevant background information and facilitate their effective contribution to the NICE assessment process. Therefore, please provide links to any relevant online information that would be useful, for example, published clinical trial data, factual web content, educational materials etc.
Where possible, please provide open access materials or provide copies that patients can access.

Response:

Further information on IgAN:

- https://ukkidney.org/rare-renal/clinician/iga-nephropathy
- https://www.kidneyresearchuk.org/conditions-symptoms/iga-nephropathy/

Further information on TRF-budesonide:

- https://kinpeygopatient.co.uk

Further information on NICE and the role of patients**:**

- Public Involvement at NICE Public involvement | NICE and the public | NICE Communities | About | NICE
- NICE's guides and templates for patient involvement in HTAs Guides to developing our guidance | Help us develop guidance | Support for voluntary and community sector (VCS) organisations | Public involvement | NICE and the public | NICE Communities | About | NICE
- EUPATI guidance on patient involvement in NICE: https://www.eupati.eu/guidance-patient-involvement/

- EFPIA – Working together with patient groups: https://www.efpia.eu/media/288492/working-together-with-patient-groups-23102017.pdf
- National Health Council Value Initiative. https://nationalhealthcouncil.org/issue/value/
- INAHTA: http://www.inahta.org/
- European Observatory on Health Systems and Policies. Health technology assessment - an introduction to objectives, role of evidence, and structure in Europe: http://www.inahta.org/wp-content/themes/inahta/img/AboutHTA_Policy_brief_on_HTA_Introduction_to_Objectives_Role_of_Evidence_Structure_in_Europe.pdf

4b) Glossary of terms

Response:

Kidney biopsy: a medical procedure that involves taking a small sample of tissue from the kidney so it can be examined under a microscope.

Urine protein to creatinine ratio (UPCR): a measurement of the ratio of urine protein and creatinine which can be used to assess kidney function.

Estimated glomerular filtration rate (eGFR): a measure of the amount of creatinine (a waste product which is removed by the kidneys) in the blood to measure how well the kidneys are working.

Immunoglobulin A (IgA): an antibody that forms a part of the immune system.

Chronic kidney disease (CKD): a long-term condition where the kidneys don't work as well as they should.

End-stage renal disease (ESRD): the last stage of CKD where the kidneys can no longer support the needs of the body.

Renin-angiotensin system (RAS) inhibitor: treatment with angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARBs); agents that work by blocking different stages of the renin-angiotensin system.

SGLT2 inhibitor: treatments that reduce blood glucose (sugar) levels.

Treatment-emergent adverse events (TEAEs): undesirable events not present prior to medical treatment, or an already present event that worsens either in intensity or frequency following the treatment.

People at risk of progressive loss of kidney function: Draft KDIGO guidelines consider people at progressive loss of kidney function are those with proteinuria ≥0.5 g/d (or equivalent), while on or off treatment for IgAN.

4c) References

Please provide a list of all references in the Vancouver style, numbered and ordered strictly in accordance with their numbering in the text:

Response:

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

Targeted-release budesonide for treating primary IgA nephropathy (review of TA937) [ID6485]

Clarification questions

July 2025

File name	Version	Contains confidential information	Date
ID6485 budesonide EAG Clarification letter_company response [REDACTED] 030725	1.0	Yes	3rd July 2025

Notes for company

Highlighting in the template

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Section A: Clarification on effectiveness data

Decision problem

A1. Priority question: CS Table 1 states that no evidence is presented in the CS for the subgroup of people at high risk of rapidly progressive IgA nephropathy (urine protein-to-creatinine ratio of 1.5g/gram or more) because the evidence for clinical and cost-effectiveness of TRF-budesonide in this group has previously been submitted to and accepted by NICE in TA937. Has any new or updated evidence become available for this subgroup since TA937? If so, please provide this.

The company would like to reiterate our position outlined in the submission that, with the updated licensed indication which has now been granted for adults with primary IgAN with a urine protein excretion ≥1.0 g/day (or urine protein-to-creatinine ratio ≥0.8 g/g) (1), the subgroup of patients with UPCR ≥1.5 g/g is no longer a relevant subgroup.

The NefIgArd Nef-301 study was completed during the previous appraisal (TA937). Whilst the original company submission only included data for Part A of the study, data for Part B became available during the post-submission stages; these data

were shared with the EAG and NICE committee and were used in the decision making process (2). No further data have since been collected from NefIgArd Nef-301.

In the Nef-301 OLE, the number of patients with a baseline UPCR ≥1.5g/g was [redacted] ([redacted] patients [redacted] who previously received TRF-budesonide in NefIgArd Nef-301 and [redacted] patients [redacted] who previously received placebo in NefIgArd Nef-301) (data on file). Due to the low patient numbers, we do not believe that a subgroup analysis of this population would allow us to draw any meaningful conclusions.

Preliminary results have been published on the use of TRF-budesonide for patients with IgAN from a real-world, multicentre study conducted in Greece. The study included patients with IgAN and UPCR >1.5 g/g despite conventional treatment (consisting of the maximum tolerated dose of RAS inhibition and/or SGLT-2 inhibitors) for at least 6 months (3).

Results were presented for the first 6 months of the 9-month TRF-budesonide treatment course for 37 patients. All patients (100%) were receiving RAS inhibition and 23 (62%) patients were receiving SGLT-2 inhibitors. eGFR remained stable over time with values of 57.29 ±23.52 mL/min/1.73 m^2 at Month 0, 52.71 ±19.91 mL/min/1.73 m^2 at Month 3 and 58.90 ±26.3 mL/min/1.73 m^2 at Month 6 (p=0.78), while proteinuria was gradually reduced, from 2.83 ±1.6 g/24h at Month 0 to 2.56 ±1.85 g/24h at Month 3 and 1.98 ±1.47 g/24h at Month 6 (p=0.009). After 6 months, 29/37 patients (78.3%) had experienced a ≥30% reduction in proteinuria.

Systematic review methods

A2. Was each of the quality assessments reported in CS Table 4 conducted by a single reviewer or two independent reviewers?

Quality assessment was conducted by one reviewer and then checked in full by a second reviewer. Any discrepancies were resolved through discussion or the intervention of a third reviewer.

A3. Priority question: Please provide a risk of bias assessment for the Nef-301 open-label extension (e.g. using the Robins-I tool which is NICE's preferred risk of bias tool for non-randomised studies).

A risk of bias assessment for the Nef-301 OLE is provided as an Excel file in the reference pack, document name 'ID6485 ROBINS-I ROB_OLE_v1'.

NeflgArd Nef-301 trial

A4. In the NeflgArd trial, did 'optimised supportive care' include any interventions other than "the maximum tolerated or maximum allowed (country-specific) dose of an angiotensin converting enzyme inhibitor and/or an angiotensin II type I receptor blocker" (CS section 2.3.1.6.1) (e.g. lifestyle modification)?

The following lifestyle choices were recommended to patients in both arms of the study at the screening visit of NeflgArd Nef-301 and patients were encouraged to maintain stable lifestyle choices while participating in the study (4):

- Weight normalisation
- Smoking cessation
- Physical activity
- Diet (low salt and low protein).

Optimised supportive care in the NeflgArd Nef-301 trial was defined as optimised RAS inhibitor therapy with ACEIs and/or ARBs only, according to the KDIGO 2012 guideline for the management of glomerular diseases (4). Whilst no other interventions were considered as part of optimised supportive care during the study, a list of concomitant medications which were taken by >6% of patients in either treatment arm is presented in Table 8 of the CS.

A5. CS section 2.3.1.6 states that, if feasible, patients who prematurely discontinued TRF-budesonide 16mg or placebo had the daily dose reduced from 4 capsules to two capsules once daily. Was this reduction maintained for 2 weeks as it was for the tapering period in Part A for those who completed study treatment?

Patients who prematurely discontinued study treatment while taking 4 capsules QD (TRF-budesonide 16 mg or placebo) were to have the daily dose of study drug

reduced to 2 capsules QD (TRF-budesonide 8 mg or placebo) for 2 weeks, if feasible, to prevent insufficiency of the adrenal glands (4).

A6. Priority question: CS Section 2.3.1.8.1 states that there was a pre-specified 2-year eGFR total slope analysis using a linear spline mixed-effects analysis. Is this reported in CS Appendix J.1.2 Table 24 as the 'Sensitivity analysis using robust regression'? If not, please supply the results from the linear spline mixed-effects analysis.

An analysis using the linear spline mixed-effects model is presented in Table 1. This analysis estimated the improvement in 2-year eGFR total slope, in the absence of rescue medication, to be [redacted] mL/min/1.73 m^2 per year with TRF-budesonide compared with placebo ([redacted]), corresponding to a 2-year eGFR total slope of -[redacted]mL/min/1.73 m^2 per year in the TRF-budesonide group and [redacted] mL/min/1.73 m^2 in the placebo group. As expected, given the acute increase in eGFR observed between baseline and 3 months in TRF-budesonide treated patients compared with the deterioration in eGFR observed in placebo-treated patients as presented in CS Figure 11, the difference in acute slope between TRF-budesonide and placebo was nominally significant ([redacted]). The chronic slope was not significant but indicated a slower rate of decline for TRF-budesonide treated patients compared with placebo ([redacted]) further supporting the lack of convergence seen in the eGFR trajectories from 3 months through to the end of observational follow-up. Once the TRF-budesonide acute effect had stabilised, the eGFR treatment benefit relative to placebo was maintained through to 2 years (see CS Figure 11), reflected in a statistically significant and clinically relevant difference in the 2-year eGFR total slope ([redacted]) (Table 1 and Figure 1). An analysis using the linear spline mixed-effects model and including data observed after the use of rescue medication provided similar results. A sensitivity analysis using generalised estimating equations to assess any sensitivity to the use of robust standard errors in this modelling approach also provided consistent results (Table 1).

Table 1: Analyses of eGFR 2-year slope using linear spline mixed-effects model (mL/min/1.73 m^2 per year) in NeflgArd Nef 301 Part B FAS

Linear spline mixed-effects model	Difference between TRF-budesonide 16 mg and placebo (mL/min/1.73 m^2 per year) (95% CI); 1-sided p-value			eGFR 2-year total slope (95% CI) (mL/min/1.73 m^2 per year)	
	Acute slope	Chronic slope	Total 2-year slope	TRF-budesonide 16 mg (N=182)	Placebo (N=182)
Excluding data observed after rescue medication	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Including data observed after rescue medication	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Generalised estimating equations approach to assess any sensitivity to the use of robust standard errors, excluding data observed after rescue medication	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CI, confidence interval; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; eGFR, estimated glomerular filtration rate; FAS, full analysis set; TRF, targeted-release formulation.
Note: In all analyses, missing data were multiply imputed, either implicitly or explicitly, prior to analysis. "N" represents the total number of patients included who either had data observed or imputed.
eGFR was calculated by the central laboratory using the CKD-EPI formula.
Source: NeflgArd Nef-301 Part B CSR (4).

Figure 1: Illustration of 2-year eGFR total slope estimated by the linear spline mixed-effects model in NeflgArd Nef 01 Part B FAS

Abbreviations: eGFR, estimated glomerular filtration rate; FAS, full analysis set.
Mean of imputed, non-transformed eGFR values per time point are displayed, reflecting that data were not log-

transformed in the linear spline mixed-effects analysis.
Source: NefIgArd Nef-301 Part B CSR (4).

To assess the impact of any potential uncertainty in the 2-year eGFR total slope, the confidence interval values (1.39 and 4.17) are used to inform the hazard ratio, which subsequently informs the estimated risk of progressing to CKD stage 5 in the TRF-budesonide arm. The results of these analyses are presented in Table 2.

Table 2: Results based on 2-year eGFR total slope confidence intervals

2-year eGFR total slope used to inform the HR in risk of CKD 5 in the TRF-budesonide arm	Incremental costs	Incremental QALYs	ICER
Lower confidence interval ([redacted])	[redacted]	[redacted]	£2,901
Upper confidence interval ([redacted])	[redacted]	[redacted]	Dominant

Abbreviations: CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; HR, hazard ratio; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year; TRF, targeted-release formulation.

A7. CS 2.4.1.4 states that missing data could result because of exclusion due to rescue meditation, patient discontinuation from study, the patient had died or because data had not been recorded. Please indicate how much missing data was due to each of these reasons.

A summary of reasons for missing data in the NefIgArd Nef-301 study is presented in Table 3. A summary of eGFR data recorded is presented in Table 4.

Table 3: Reasons for missing data from NefIgArd Nef-301 Part B (FAS)

	TRF-budesonide 16 mg (N=182)	Placebo (N=182)
Early discontinuation from study	[redacted]	[redacted]
Death	[redacted]	[redacted]
Patients receiving rescue medication or prohibited immunosuppressive medicine for non-IgAN indications	[redacted]	[redacted]

Abbreviations: FAS, full analysis set; IgAN, immunoglobulin A nephropathy; TRF, targeted-release formulation.
Source: NefIgArd Nef-301 Part B CSR (4).

Table 4: Summary of eGFR data recorded in NefIgArd Nef 01 Part B FAS

	TRF-budesonide 16 mg (N=182)	Placebo (N=182)
Month 3, n (%)		
Data recorded and all values included in analysis	[redacted]	[redacted]

	TRF-budesonide 16 mg (N=182)	Placebo (N=182)
Data recorded and at least one value excluded due to rescue therapy	[redacted]	[redacted]
Data not recorded	[redacted]	[redacted]
Month 6, n (%)		
Data recorded and all values included in analysis	[redacted]	[redacted]
Data recorded and at least one value excluded due to rescue therapy	[redacted]	[redacted]
Data not recorded	[redacted]	[redacted]
Month 9, n (%)		
Data recorded and all values included in analysis	[redacted]	[redacted]
Data recorded and at least one value excluded due to rescue therapy	[redacted]	[redacted]
Data not recorded	[redacted]	[redacted]
Month 12, n (%)		
Data recorded and all values included in analysis	[redacted]	[redacted]
Data recorded and at least one value excluded due to rescue therapy	[redacted]	[redacted]
Data not recorded	[redacted]	[redacted]
Month 18, n (%)		
Data recorded and all values included in analysis	[redacted]	[redacted]
Data recorded and at least one value excluded due to rescue therapy	[redacted]	[redacted]
Data not recorded	[redacted]	[redacted]
Month 24, n (%)		
Data recorded and all values included in analysis	[redacted]	[redacted]
Data recorded and at least one value excluded due to rescue therapy	[redacted]	[redacted]
Data not recorded	[redacted]	[redacted]

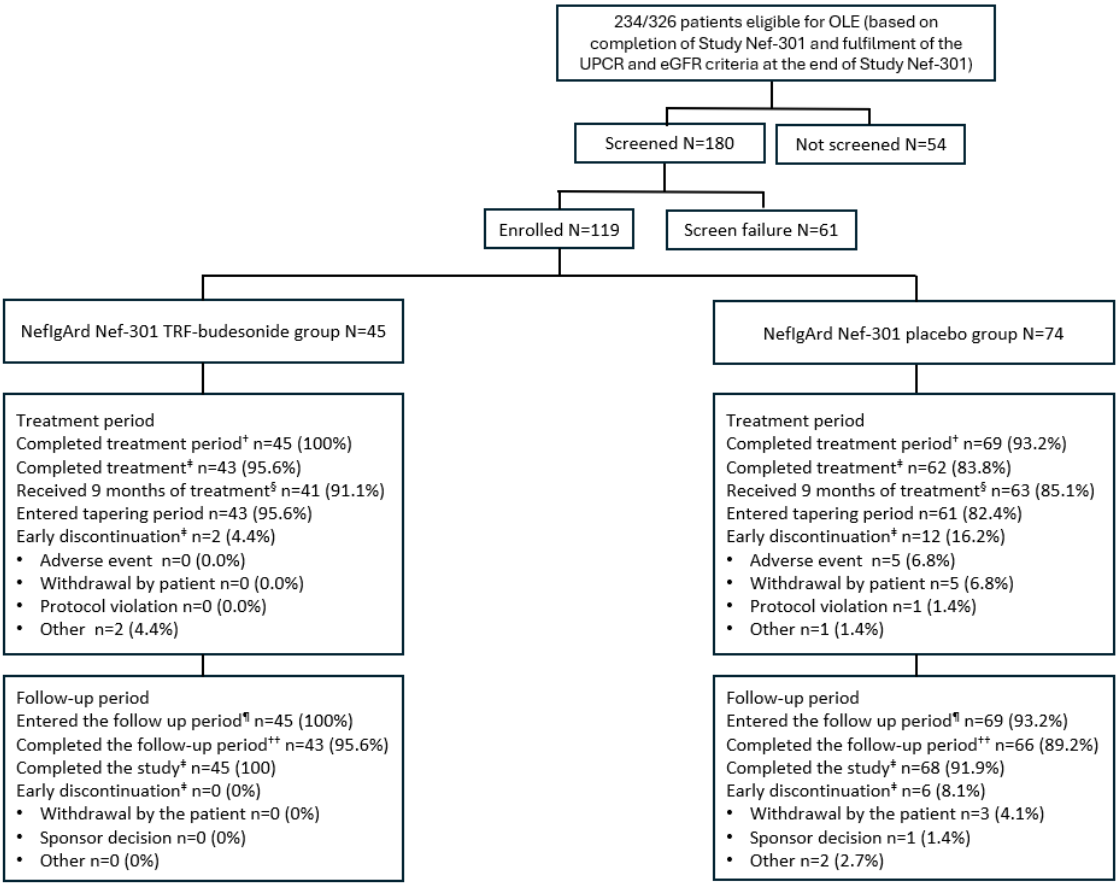
Abbreviations: FAS, full analysis set; TRF, targeted-release formulation.
Source: NeflgArd Nef-301 Part B CSR (4).

NeflgArd Nef-301 Open-label extension

A8. Priority question: Please provide a patient flow diagram for the NeflgArd Nef-301 open-label extension (OLE).

A diagram of participant flow in Nef-301 OLE is presented in Figure 2.

Figure 2: Patient disposition – Nef-301 OLE



†Completion of OLE Treatment Period was defined as the patient having had at least 1 valid UPCR or eGFR value available in the 9-month OLE visit window; ‡as reported by the Investigator; §The patient was considered to have received 9 months of OLE treatment if the date of last OLE dose (excluding doses received in the Tapering Period) – date of first OLE dose + 1 ≥255; ¶The patient was defined as having entered the OLE Follow-up Period if the patient attended at least 1 study visit or had any AE recorded that was more than 14 days after the last dose of OLE study treatment (including tapering), ††Completion of the Follow-up Period was defined as the patient having had at least 1 valid UPCR or eGFR value within the 12-month OLE visit window (Day 320 to Day 395).
Source: Nef-301 OLE CSR (5).

A9. Priority question: CS Reference "STADA Data on File Retreatment Eligibility from the NeflgArd OLE_UK-KINPE-159" (which we believe is CS reference 143) states that [redacted] patients were screen failures because [redacted] and [redacted] patients were not screened for the same reason. Is it expected that these patients could

[redacted] **become eligible for retreatment?**

There is currently no evidence from clinical studies to indicate when patients may become eligible for retreatment beyond the OLE data that was presented in the company submission.

To address this query we sought input from Professor Jonathan Barratt, Professor of Renal Medicine at Leicester University. The following information summarises his response to this question, supplemented with references from the published literature, where available. TRF-budesonide targets the underlying cause of IgAN, however it is not a curative treatment (6). All patients would therefore be expected to meet the criteria for retreatment at some point and would require repeated courses of treatment to achieve sustained life time disease control. The average time to meeting the eligibility criteria for re-treatment is likely be between 24 and 36 months, however this could be shorter for some patients and longer for others.

Some patients (approximately 10%) will not go on to receive re-treatment for various reasons which may include progression to CKD5/ESRD ([redacted] patients [redacted] of the TRF-budesonide treatment group progressed to CKD5/ESRD in NefIgArd Nef 301 (4)), adverse events that led to discontinuation of the initial treatment course (in NefIgArd Nef-301, 9.3% of patients discontinued due to adverse events (4) – patients and physicians are unlikely to want to retreat), and potential availability of alternative disease modifying treatments in the future.

A10. Priority question: CS section 2.13.2 reports that clinical experts have stated that TRF-budesonide and SGLT-2 inhibitors would be used together and are expected to provide an additive effect.

a) **What impact do you expect this to have on the proportion of patients eligible for retreatment with TRF-budesonide, as per the NefIgArd Nef-301 and OLE eligibility criteria (remaining in CKD stages 1-3b with eGFR ≥35 mL/min/1.73m2 with proteinuria based on 2 consecutive measurements separated by at least 2 weeks and calculated by the**

central laboratory showing either ≥1 g/day (≥1000 mg/day) or UPCR ≥0.8 g/gram (≥90 mg/mmol))?

b) **Would you expect the use of TRF-budesonide and SGLT-2 inhibitors together to affect the length of time to retreatment with TRF-budesonide? If so, would you expect the retreatment interval to be longer or shorter?**

As there is no clinical evidence on the impact of the addition of SGLT-2 inhibitors to standard of care and used in combination with TRF-budesonide, we also sought clinical opinion from Professor Jonathan Barratt for this response.

a) Data from a recent global clinical trial suggests that 37–43% of IgAN patients on a stable dose of RAS inhibitors are also receiving SGLT-2 inhibitors (7) and this is expected to be similar in the UK. Use of SGLT-2 inhibitors is not expected to impact the proportion of patients that would need retreatment with TRF-budesonide, however they may reduce the number of people who are initially eligible for treatment with TRF-budesonide. SGLT-2 inhibitors provide a reduction in proteinuria of around 15-20% (8, 9) shifting the treatment curve rightward (delaying retreatment) but not flattening it (they don't reduce the need for retreatment, or stop continued decline in kidney failure) as they are not treating the underlying cause of IgAN.

b) As above, it is likely that use of SGLT-2 inhibitors added to standard of care may have an impact on the proportion of people eligible for TRF-budesonide treatment, however as they are simply resetting the baseline, there is unlikely

to be an impact on response to TRF-budesonide or frequency of redosing because of the different mode of action.

Section B: Clarification on cost-effectiveness data

B1. Priority question: Please provide more information about the analysis used to estimate transition probabilities between CKD 1 to 4 for 0-24 months (CS section 3.3.2.1.1) and the internal validity of the results:

a) **How many observed transitions were there between CKD stages 1 to 4 in the NeflgArd Nef-301 dataset over the period from baseline to month 24? Please report the results in the same format as CS Table 39 (with a 5 by 5 matrix for each treatment arm).**

The observed transitions between CKD stages 1 to 4 from baseline to 24 months in the NeflgArd Nef-301 trial are presented in Table 5. At 24 months, there were [redacted] patients in the TRF-budesonide arm and [redacted] patients in the SoC arm with missing eGFR observations. Missing 24-month eGFR observations were imputed with a single-step last observation carried forward (LOCF) approach to inform the logistic regression. Please note, ESRD observations presented in Table 5 reflect patients with an eGFR < 15mL/min/1.73m^2 at the 24-month observation only. In the clinical study report (CSR), patients are reported as having ESRD if they have an ESRD event (renal-related death, dialysis and/or transplant) or a sustained eGFR <15mL/min/1.73m^2 at any point during the 2 year follow up (4).

Table 5: NeflgArd Nef-301: Observed transitions at 24 months

Treatment	CKD 1	CKD 2	CKD 3a	CKD 3b	CKD 4	ESRD	Missing	Total
TRF-budesonide								
CKD 1	[redacted]							5
CKD 2	[redacted]							69
CKD 3a	[redacted]							67
CKD 3b	[redacted]							41
CKD 4	[redacted]							0
Total	[redacted]							182
SoC								
CKD 1	[redacted]							3
CKD 2	[redacted]							71
CKD 3a	[redacted]							68
CKD 3b	[redacted]							40
CKD 4	[redacted]							0
Total	[redacted]							182

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

b) How well does a Markov model using the monthly transition probabilities in Table 39 predict the observed transitions over the 24-month follow up period?

Table 6 presents the predicted movements between baseline and 24-months using the monthly Markov transition probabilities implemented in the economic model (presented in CS Table 39).

To calculate the predicted movements, the baseline distribution of patients across CKD stages 1 to 3b were multiplied by the probability at 24 months of residing in each CKD stage. Please see the excel file '2025-07-02_ID6485 Clarification Q B1 calculations.xlsc' in the reference pack for full calculations.

Table 6: Markov model predicted transitions at 24-months

Treatment	CKD 1	CKD 2	CKD 3a	CKD 3b	CKD 4	Total
TRF-budesonide						
CKD 1	[redacted]					5
CKD 2	[redacted]					69
CKD 3a	[redacted]					67
CKD 3b	[redacted]					41

Treatment	CKD 1	CKD 2	CKD 3a	CKD 3b	CKD 4	Total
CKD 4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	182
SoC						
CKD 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	3
CKD 2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	71
CKD 3a	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	68
CKD 3b	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	40
CKD 4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	182

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

The monthly transition probabilities in CS Table 39 produce a reasonable representation of the observed 24-month movement between CKD stages 1 to 4 in both the TRF-budesonide and SoC arms.

c) Similarly, how well does a Markov model with the monthly transition probabilities from Table 39 predict observed transitions in the NeflgArd Nef-301 dataset from baseline to the end of 9-month treatment period?

The observed transitions between CKD stages 1 to 4 in the NeflgArd Nef-301 trial data between months 0 to 9 are presented in Table 7. There were 11 missing observations in the TRF-budesonide arm and 15 in the SoC arm.

Table 7: NeflgArd Nef-301: Observed transitions at 9 months

Treatment	CKD 1	CKD 2	CKD 3a	CKD 3b	CKD 4	ESRD	Missing	Total
TRF-budesonide								
CKD 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	5
CKD 2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	69
CKD 3a	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	67
CKD 3b	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	41
CKD 4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	182
SoC								
CKD 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	3
CKD 2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	71

Treatment	CKD 1	CKD 2	CKD 3a	CKD 3b	CKD 4	ESRD	Missing	Total
CKD 3a	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	68
CKD 3b	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	40
CKD 4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	182

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

Table 8 presents the predicted movements between baseline and 9-months using the monthly Markov transition probabilities implemented in the economic model (presented in CS Table 39).

Table 8: Markov model predicted transitions at 9-months

Treatment	CKD 1	CKD 2	CKD 3a	CKD 3b	CKD 4	Total
TRF-budesonide						
CKD 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	5
CKD 2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	69
CKD 3a	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	67
CKD 3b	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	41
CKD 4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	182
SoC						
CKD 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	3
CKD 2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	71
CKD 3a	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	68
CKD 3b	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	40
CKD 4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	182

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

The model reproduces the observed CKD stage transitions at 9-months between CKD stages 1 to 4 reasonably well.

B2. Did you explore any alternative specifications for the logistic regression reported in CS Table 38? For example, including additional co-variates, data from intermediate data collection points (3, 6, 9, 12 or 18 months), or a multinomial approach?

Logistic regression analyses were explored for the following time intervals: 0–24 months, 0–12 months, 12–24 months and 0–9 months. In the 0–24, 0–12 and 0–9 month analyses, the transition probabilities from the CKD 4 health state are assumed equal to CKD 3b owing to no patients in the NefIgArd Nef-301 study having stage 4 CKD at baseline. For the 12–24 month interval analysis, there were some patients residing in CKD 4 at 12 months. As such, transition probabilities from CKD 4 are estimated using the logistic regression in this analysis.

Table 9: Transition probabilities: 0 – 12 months

Treatment	CKD 1	CKD 2	CKD 3a	CKD 3b	CKD 4	Total
TRF-budesonide transition probabilities: 0-12 months						
CKD 1	[redacted]	[redacted]	-	-	-	100.0%
CKD 2	[redacted]	[redacted]	[redacted]	-	-	100.0%
CKD 3a	-	[redacted]	[redacted]	[redacted]	-	100.0%
CKD 3b	-	-	[redacted]	[redacted]	-	100.0%
CKD 4	-	-	-	[redacted]	-	100.0%
SoC transition probabilities: 0-12 months						
CKD 1	[redacted]	[redacted]	-	-	-	100.0%
CKD 2	[redacted]	[redacted]	[redacted]	-	-	100.0%
CKD 3a	-	[redacted]	[redacted]	[redacted]	-	100.0%
CKD 3b	-	-	[redacted]	[redacted]	-	100.0%
CKD 4	-	-	-	[redacted]	-	100.0%

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

Table 10: Transition probabilities: 12 – 24 months

Treatment	CKD 1	CKD 2	CKD 3a	CKD 3b	CKD 4	Total
TRF-budesonide transition probabilities: 12-24 months						
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%
SoC transition probabilities: 12-24 months						
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

Table 11: Transition probabilities: 0 – 9 months

Treatment	CKD 1	CKD 2	CKD 3a	CKD 3b	CKD 4	Total
TRF-budesonide transition probabilities: 12-24 months						
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%
SoC transition probabilities: 12-24 months						
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

The only covariate included in scenario analyses was baseline UPCR, based on the following categories: UPCR <1.5g/g and UPCR ≥1.5g/g. Separate transition probabilities were calculated for the UPCR subgroups. However, as the population relevant to this submission is for people with UPCR >0.8g/g, the subgroup analyses were not implemented in the economic model.

A multinomial approach was not conducted for the following reasons:

1. Binary logistic regression estimates require fewer parameters and are less sensitive to small cell counts as it only estimates one log-odds ratio at a time. Therefore, the estimates from the binary logistic regression were considered to provide more robust results than a multinomial approach

2. As there are small numbers of events to inform some transitions (e.g., “improved”), a multinomial logistic regression model is likely to produce inflated standard errors, or may fail to converge owing to the model needing to estimate several log-odds ratios simultaneously (≥3 outcome categories)

B3. Please confirm if any patients in NefIgArd Nef-301 RCT or OLE have transitioned to CKD stage 5? If so, please state the numbers and compare the risk of

CKD 5 from the trial with the estimate for SoC from the UK RaDaR data (CS Figure 16), and the adjusted risk using the HR from the Inker et al. (2019) meta-analysis.

Table 12 shows the number of patients in ESRD from Part B of the NeflgArd Nef-301 RCT (24 months follow up) (4).

Table 12: Proportion of patients with ESRD or categorised declines in eGFR from Nef-301 Part B

	Patients treated with TRF-budesonide 16 mg in Nef-301 Part B	
	NeflgArd Nef-301 Part B TRF-budesonide 16 mg (N=182)	**NeflgArd Nef-301 Part B placebo (N=182)**
Patients with ESRD	[redacted]	[redacted]
Patients receiving dialysis	[redacted]	[redacted]
Patients receiving renal transplant	[redacted]	[redacted]
Patients with renal-related death	[redacted]	[redacted]
Patients with ESRD or a sustained eGFR <15 mL/min/1.73 m^2	[redacted]	[redacted]
Patients with ESRD or a sustained doubling of serum creatinine†	[redacted]	[redacted]

Abbreviations: eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; FAS, full analysis set; OLE, open-label extension.
Note: % = 100 × n/N.
†Doubling of serum creatinine was approximately equal to a 57% decline in eGFR;
Source: Nef-301 Part B CSR , Table 14.2.2.1.8 (4).

In an advisory board, clinicians recommended that UK RaDaR data ought to be used as the small population sample in the NeflgArd Nef-301 RCT would decrease the validity of the data informing transition probabilities (10).

Patients who completed NeflgArd Nef-301 and were eligible entered the Nef-301 OLE, where all participants received TRF-budesonide, regardless of their original treatment assignment. After 12 months in the OLE, [redacted] out of 119 patients ([redacted]%) developed ESRD (11). These two patients were from the TRD-budesonide arm in NeflgArd Nef-301 ([redacted]%).

As the Nef-301 OLE does not include a placebo arm (results are reported by prior treatment group from the NeflgArd Nef-301 RCT), a direct comparison with SoC CKD stage 5 risk data from UK RaDaR is not possible. Additionally, patients in UK

RaDaR were not treated with TRF-budesonide, whereas the Nef-301 cohort includes both TRF-budesonide-naïve patients and those previously treated with TRF-budesonide.

In the model, [redacted]% of patients in the TRF-budesonide arm are predicted to transition to CKD stage 5 after 1 year (cell AY27 on the 'PFlow – Kinpeygo' sheet). However, direct comparison between this figure and total proportion of total patients that progressed to ESRD in Nef-301 OLE is not appropriate as the Nef-301 OLE population includes a mix of TRF-budesonide-naïve and previously treated patients, while the model assumes a fully TRF-budesonide-naïve population.

A more relevant comparison is between the proportion of patients in the CKD stage 5, dialysis, and transplant health states at year 3 in the model, and the proportion of patients with ESRD in the Nef-301 OLE who were treated with TRF-budesonide in NefIgArd Nef-301 ([redacted]%). This aligns with the 24-month follow-up in NefIgArd Nef-301 and the additional 12 months in Nef-301 OLE. The model predicts that [redacted]% of patients in the TRF-budesonide arm will have ESRD at year 3 (calculated as the sum of cells AY51, BC51, and BG51 on the 'PFlow – Kinpeygo' sheet). The slight differences in values may be attributable to the difference in median eGFR at the baseline. The median eGFR at the OLE baseline was lower than the median eGFR at NefIgArd Nef-301 baseline (49.5 mL/min/1.73 m^2 compared with 58.0 mL/min/1.73 m^2), indicating a more advanced disease state population in the OLE study.

B4. Please comment on the plausibility of the standardised mortality rates (SMRs) estimated from Uk RaDaR data (CS Table 43). Is it realistic that the SMR for CKD 3a and 3b are lower than for CKD 2?

The SMRs from UK RaDaR were presented to clinical experts, who confirmed that the SMRs derived from all patients with IgAN in UK RaDaR were more appropriate than those based solely on IgAN patients with a baseline UPCR ≥ 0.8 g/g (12). No specific concerns were raised regarding the SMRs for CKD stages 3a and 3b being lower than those for CKD stage 2. It was noted that some clinical experts considered it appropriate to apply the same mortality risk across CKD stages 1 to 3b. This assumption was included as a scenario analysis in the CS.

However, other studies—such as those by Greene et al. (2019) (13) and Hastings et al. (2018) (14), both of which were considered as scenario analyses in the CS—show that the risk of mortality tends to increase with worsening kidney function and lower eGFR. The estimated SMRs from UK RaDaR may deviate from this trend because the sample size of patients included in UK RaDaR was smaller than in these studies. Furthermore, UK RaDaR focused specifically on patients with IgAN, whereas the cited studies examined broader CKD populations. To account for this potential uncertainty, Table 13 presents an alternative scenario analysis that assumes the same risk of mortality for CKD stages 2 to 3b. Table 13 also presents a scenario in which the same risk of mortality is assumed for CKD stages 1 and 2, allowing for the risk associated with CKD 1–2 to be lower than that of CKD 3a and 3b.

Table 13: Results based on different mortality assumptions

Scenario	Incremental costs	Incremental QALYs	ICER
The same risk of mortality for CKD stages 2 to 3b	[redacted]	[redacted]	Dominant
The same risk of mortality for CKD stages 1 and 2	[redacted]	[redacted]	£393

Abbreviations: CKD, chronic kidney disease; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life years.

Section C: Textual clarification and additional points

C1. There appears to be an error in this sentence: “The minor imbalances between the percentage of patients receiving an ACEi or and ARB between the treatment groups was not considered to be clinically important.” (CS section 2.3.2.) Please clarify the meaning of the sentence and to which row(s) in Table 7 it relates.

The sentence refers to the rows describing the number of patients receiving an ACEi alone and patients receiving an ARB alone in Table 7. The sentence should read as follows: “The minor imbalances between the percentage of patients receiving an ACEi alone or an ARB alone between the treatment groups were not considered to be clinically important”.

C2. Please provide the protocols and the statistical analysis plans for the NeflgARd Nef-301 trial and Nef-301 OLE.

The protocols and statistical analysis plans have been included in the reference pack with the following file names

- NeflgArd Nef-301 study protocol (15) – file name ‘Callidatas NeflgArd Nef-301 study protocol’
- NeflgArd Nef-301 SAP (16) – file name ‘Callidatas NeflgArd Nef-301 SAP’
- Nef-301 OLE protocol (17) – file name ‘Callidatas Nef-301 OLE protocol’
- Nef-301 OLE SAP (18) – file name ‘Callidatas Nef-301 OLE SAP’

C3. The incremental LYG and incremental QALYs are reported in the wrong columns in CS Table 59.

Thank you for flagging this. The corrected version of Table 59 from the CS is presented in Table 14.

Table 14: Base-case results

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
TRF-budesonide	[redacted]	[redacted]	[redacted]	-	-	-	-	-
SoC	[redacted]	[redacted]	[redacted]	***	***	***	Dominant	Dominant

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years; SoC, standard of care; TRF, targeted-release formulation.

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NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Targeted-release budesonide for treating primary IgA nephropathy (review of TA937) [ID6485]

Patient Organisation Submission

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type. [Please note that declarations of interests relevant to this topic are compulsory].

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

NICE National Institute for Health and Care Excellence

About you

1.Your name	[redacted]
2. Name of organisation	Kidney Research UK
3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	Kidney Research UK is the leading kidney research charity in the UK. We fund and promote research into kidney disease and related topics; bring together patients and researchers in networks and clinical study groups; campaign for the adoption of best practice by the NHS and improved health outcomes for patients. Our latest annual report 2023/24 shows most of our income is from donations, gifts, and legacies. The remainder is from trusts, partnerships, investments, trading, and government funding. We are not a membership organisation but have an extensive supporter base and a significant number of active volunteers, many of whom are kidney patients.
4b. Has the organisation received any funding from the company bringing the treatment to NICE for evaluation or any of the comparator treatment companies in the last 12 months? [Relevant companies are listed in the appraisal stakeholder list.] **If so, please state the name of the company, amount, and purpose of funding.**	Not from the company bringing the treatment to NICE for evaluation. For comparator companies during the year 2024-5: - AstraZeneca: £39,600 - Novartis: £66,600

4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No
5. How did you gather information about the experiences of patients and carers to include in your submission?	Email request for information to patients with lived experience of IgAN.

Living with the condition

6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	The following comments were from a patient with IgAN who responded to my email request for further information. "I am 37 years old. I was diagnosed in 2009 at the age of 22 years. "In early 2022, following the COVID-19 pandemic, my kidney function declined significantly, and I was suddenly confronted with the prospect of requiring dialysis. I have been undergoing dialysis since June 2024, and my life has changed entirely "I wasn't affected until my kidneys declined in 2022. At that time, I was also quite tired and could feel the decline of kidney functions in loss of energy over the next two years. "I was studying for a PhD, which I was able to finish before starting dialysis. Due to dialysis it's quite difficult to work, particularly full time. However, I am targeting a career in research as it provides a bit more flexibility compared to office hours. "For me, it is an invisible and silent condition, though not without consequences. It appears to be something about which little can be done. I was diagnosed in 2009, despite having no obvious symptoms or limitations at the time and have attended annual check-ups since then.

Current treatment of the condition in the NHS

7. What do patients or carers think of current treatments and care available on the NHS?	"Throughout, the care I have received from the NHS at the New Stobhill Clinic in Glasgow has been exemplary. "The staff have consistently demonstrated professionalism and kindness. I have always felt that I was treated with the utmost expertise and in accordance with the most up-to-date medical knowledge available."
8. Is there an unmet need for patients with this condition?	From our previous submission for ID1434: - There is a need for specific disease-modifying therapies that are approved for the treatment of IgA nephropathy. - Transplantation and dialysis are not sustainable treatment options. - Earlier treatment that may slow down the progress of IgA is needed for this group of patients.

Advantages of the technology

9. What do patients or carers think are the advantages of the technology?	From email responses: "I am unable to comment on the specific benefits of budesonide. However, I am generally in favour of trialling the latest medical treatments if there is a possibility of improving the condition or even achieving a cure. "In 2022, I was prescribed a medication called Forxiga, an SGLT2 inhibitor, which was at the time a relatively new treatment. It significantly slowed the progression of my kidney decline and afforded me two additional years before the initiation of dialysis. I am grateful for this, as it gave me more time to live without dialysis but also gave me time to prepare." From our previous submission for ID1434: There are several advantages to delaying progression of kidney disease to the point of requiring dialysis or transplantation: 1. Improved quality of life: Dialysis and transplantation are both intensive treatments that require significant time commitments and can have significant side effects. 2. Cost savings: Dialysis and transplantation are both expensive treatments. Delaying the need for these treatments can result in significant cost savings for the healthcare system. 3. Time to prepare for treatment: Delaying the need for dialysis or transplantation can provide patients with more time to prepare for these treatments. This can include education about the treatments, arranging for financial support, and identifying potential living donors for transplantation.

Disadvantages of the technology

10. What do patients or carers think are the disadvantages of the technology?	It is important that potential side effects are seriously considered, and that educational and well-being support is offered to patients and their familes.

Patient population

11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	Kidney disease disproportionally affects people from deprived communities and ethnic minority groups; people in these cohorts progress faster to end stage renal failure.

Equality

12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	There is a greater level of prevalence of IgAN in East and Southeast Asians. In this patient population, IgAN also tends to be a more aggressive disease carrying a greater risk of kidney failure, as seen in data from the RaDaR study in the UK.

Other issues

13. Are there any other issues that you would like the committee to consider?	No

Key messages

14. In up to 5 bullet points, please summarise the key messages of your submission.	• There is an urgent need for new treatments for patients with IgA nephropathy (IgAN). • When a patient's kidneys fail treatment options, such as dialysis and transplantation, are gruelling and not permanent. Treatments that slow down disease progression would be particularly welcomed by patients and their families. • IgAN is a severe disease that can significantly impact a patient's quality of life, as well as that of their loved ones, particularly given the youth of those being diagnosed. • The uncertainty surrounding disease progression is a significant burden, and the suddenness of disease onset when a patient's kidneys fail can be devastating. • IgAN disproportionately affects people living in deprived communities and from ethnic minority groups, as does kidney disease as a whole.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

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Single Technology Appraisal

Targeted-release budesonide for treating primary IgA nephropathy (review of TA937) [ID6485]

Professional organisation submission

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

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- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 13 pages.

About you

1. Your name	[redacted]
2. Name of organisation	The UK Kidney Association
3. Job title or position	[redacted]
4. Are you (please select Yes or No):	An employee or representative of a healthcare professional organisation that represents clinicians? Yes or No A specialist in the treatment of people with this condition? Yes or No A specialist in the clinical evidence base for this condition or technology? Yes or No Other (please specify):
5a. Brief description of the organisation (including who funds it).	The UKKA was created through merger of the Renal Association, British Renal Society and its affiliates, to support the multi-professional team with delivery of kidney care, education and research – enabling people to live well with kidney disease. UKKA is funded by its members, grants, events, project work and capitation.
5b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.] **If so, please state the name of manufacturer, amount, and purpose of funding.**	AstraZeneca £126,000 EVENT SPONSORSHIP AstraZeneca £5,000 MEMBERSHIP Baxter £31,200 EVENT SPONSORSHIP BI £41,000 EVENT SPONSORSHIP BI £10,000 MEMBERSHIP BI £9,000 KQIP TRAINING BI £100,000 CKD PROJECT Novartis £272,000 RADAR Sanofi £5,000 MEMBERSHIP Takeda £50,000 RADAR Takeda £5,000 MEMBERSHIP Takeda £6,500 TF GRANT Takeda £2,500 EVENT SPONSORSHIP Thornton Ross £15,000 MEMBERSHIP Thornton Ross £56,100 EVENT SPONSORSHIP Vifor £98,000 EVENT SPONSORSHIP Vifor £6,000 GUIDELINES GRANT Vifor £24,000 EDUCATION GRANT

5c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	n/a

The aim of treatment for this condition

6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	To slow or stop the progression of kidney function decline in patients with IgA nephropathy, to ultimately prevent patients requiring renal replacement therapy (dialysis or transplant).
7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	Surrogate endpoints considered indicative of a treatment response and that have been accepted by regulatory authorities, that are associated with a long-term reduction in progression to kidney failure, include: a ≥30% reduction in proteinuria, and an attenuation of the annual eGFR decline (eGFR slope) by at least 0.75 mL/min/1.73 m² per year.
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes, there is a significant unmet need in this condition. UK renal registry (RaDaR) data indicate that most patients with IgA nephropathy will progress to reaching kidney failure within their lifetime if managed with supportive care (i.e. renin-angiotensin system inhibition) alone. If treated with a kidney transplant, recurrent IgA nephropathy in the transplant is common, and leads to reduced graft survival. Kidney failure itself is associated with substantially increased morbidity and mortality and is associated with high healthcare resource utilisation and costs.

What is the expected place of the technology in current practice?

9. How is the condition currently treated in the NHS?	In patients considered at high risk of kidney disease progression, often defined by proteinuria exceeding 0.5 g/day, treatment typically includes maximally tolerated renin–angiotensin system (RAS) inhibition. Targeted-release budesonide is an option under the previously approved NICE guidance for patients with IgAN and proteinuria (UPCR) above 1.5 g/g. SGLT2 inhibitors are used according to guidelines for the treatment of chronic kidney disease (CKD).
9a. Are any clinical guidelines used in the treatment of the condition, and if so, which?	The 2021 KDIGO guidelines have been widely adopted and are recognised by UK nephrologists as a standard reference for the management of this condition
9b. Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	The care pathway is well established, and clinical practice is generally consistent among nephrologists across the UK.
9c. What impact would the technology have on the current pathway of care?	Lowering the proteinuria threshold for NICE reimbursement of targeted-release budesonide would enable a greater number of patients who are at high risk of kidney function decline to access this treatment.
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Yes, this treatment is available and is being used for patients with IgA nephropathy in other countries, where there is a lower threshold for proteinuria for reimbursement. Within the NHS, it is being prescribed for patients with IgAN and proteinuria greater than 1.5 g/g, in line with current NICE guidance.
10a. How does healthcare resource use differ between the technology and current care?	No difference

10b. In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Nephrology clinics in secondary care
10c. What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	No new investment needed
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes
11a. Do you expect the technology to increase length of life more than current care?	Yes, treatment with this technology is expected to prevent or substantially delay progression to kidney failure, which itself carries an increased risk of mortality and serious morbidity
11b. Do you expect the technology to increase health-related quality of life more than current care?	Yes - due to a delay (or prevention) in reaching advanced stages of CKD and kidney failure
12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	No. Subgroup analyses from the Phase 3 NEFIGARD study demonstrated that the technology provides consistently beneficial effects across all evaluated patient groups.

The use of the technology

13. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	No difference to current care
14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	No additional rules
15. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	No
16. Do you consider the technology to be	Yes. Targeted-release budesonide is currently the only approved disease-modifying treatment for IgA nephropathy, which acts directly to reduce Gd-IgA1 production by the gut and pathogenic immune complex

innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	formation. Therefore it is expected (according to clinical trial data and modelling studies) to significantly slow kidney function decline compared to existing non-disease modifying supportive therapies (RASi, SGLT2i). An additive effect is expected when TR-budesonide is used in combination with supportive care.
16a. Is the technology a 'step-change' in the management of the condition?	Yes
16b. Does the use of the technology address any particular unmet need of the patient population?	Yes
17. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Steroid-related side effects were reported in a minority of the trial population; however, the majority were mild to moderate in severity and resolved upon discontinuation of treatment, minimizing long-term impact on patient management and quality of life.

Sources of evidence

18. Do the clinical trials on the technology reflect current UK clinical practice?	Yes. The Phase 3 NEFIGARD study recruited patients from UK hospital sites, and the baseline characteristics of the study population are consistent with those of a typical UK patient population.
18a. If not, how could the results be extrapolated to the UK setting?	No extrapolation needed

18b. What, in your view, are the most important outcomes, and were they measured in the trials?	Reduction in proteinuria, attenuation of eGFR decline, numbers of patients who reached kidney failure, and safety. Yes, all these outcomes were assessed in the clinical trials.
18c. If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	Yes
18d. Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	No, not that I am aware of
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
20. How do data on real-world experience compare with the trial data?	Emerging published real-world experience is compatible with the trial data.

Equality

21a. Are there any potential equality issues that should be taken into account when considering this treatment?	No
21b. Consider whether these issues are different from issues with current care and why.	Not applicable

Key messages

22. In up to 5 bullet points, please summarise the key messages of your submission.	• IgA nephropathy (IgAN) is the most common primary glomerular disease in the UK and a leading cause of progressive chronic kidney disease (CKD) and kidney failure. It is often diagnosed in younger adults. There remains a significant unmet need as current standard therapies, including renin–angiotensin system (RAS) blockade and SGLT2 inhibitors, provide only a slowing of kidney function decline. Targeted-release budesonide has demonstrated a disease-modifying effect by substantially reducing the rate of kidney function decline and can be used in conjunction with existing supportive therapies. Phase 3 data from the NEFIGARD trial showed consistent benefits across patient subgroups including those with baseline proteinuria less than 1.5g/g, although current NICE guidance restricts use to patients with proteinuria above 1.5 g/g. • There remains a significant unmet need in IgA nephropathy (IgAN) from both patient and caregiver perspectives. IgAN is associated with reduced quality of life and increased mortality, with an estimated reduction in life expectancy of 6 to 10 years, primarily due to complications of kidney failure. Many patients progress to kidney failure during working age, limiting their ability to contribute to the workforce. • Compared to most other kidney diseases, IgAN is associated with a faster rate of progression to kidney failure. However, following kidney failure, patients with rare kidney diseases, including IgAN, tend to have longer survival, likely due to fewer comorbidities, which contributes to higher cumulative healthcare costs. Recurrence of IgAN after kidney transplantation is common and is a notable cause of graft loss. • Widening access to this technology (TR-budesonide) to all those who can benefit, in order to delay or stop the decline in kidney function, is therefore a clinical priority in the management of IgAN.

Thank you for your time.

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NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Targeted-release budesonide for treating primary IgA nephropathy (review of TA937) [ID6485]

Professional organisation submission

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this submission

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- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 13 pages.

About you

1. Your name	[redacted]
2. Name of organisation	The Renal Pharmacy Group (part of The UK Kidney Association)
3. Job title or position	[redacted]
4. Are you (please select Yes or No):	An employee or representative of a healthcare professional organisation that represents clinicians? Yes A specialist in the treatment of people with this condition? Yes A specialist in the clinical evidence base for this condition or technology? Yes Other (please specify):
5a. Brief description of the organisation (including who funds it).	The UKKA was created through merger of the Renal Association, British Renal Society and its affiliates, to support the multi-professional team with delivery of kidney care, education and research – enabling people to live well with kidney disease. UKKA is funded by its members, grants, events, project work and capitation.
5b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.] **If so, please state the name of manufacturer, amount, and purpose of funding.**	AstraZeneca £ 11,000 RPG SPONSORSHIP BI £3,000 RPG SPONSORSHIP Takeda £7,000 RPG SPONSORSHIP Vifor £10,840 RPG SPONSORSHIP
5c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	n/a

The aim of treatment for this condition

6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	Reduction of progression of IgA nephropathy to kidney failure requiring dialysis or a kidney transplant.
7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	Reduction in proteinuria with a reduction in baseline urine protein creatinine ratio (UPCR). Longer-term, a reduction in the progression of chronic kidney disease (CKD) with a slowing in the rate of decline of estimated glomerular filtration rate (eGFR) and a delay or avoidance of end-stage kidney failure and the requirement for dialysis and/or a kidney transplant.
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes, there are limited safe and effective treatments for the treatment of rapidly progressive IgA nephropathy (IgAN) despite optimised supportive care. Optimised supportive care includes highest tolerated dose of angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB) and SGLT2 inhibitors unless contra-indicated. In 2023, target-release budesonide was approved for IgA nephropathy by NICE (TA 937). The target urine protein-to-creatinine ratio for this TA is 1.5 g/g or more. This limits patients who may otherwise benefit from receiving this medication and slowing their progression to ESRD. These patients may not meet the criteria for proteinurea due to previously optimised supportive therapy.

What is the expected place of the technology in current practice?

9. How is the condition currently treated in the NHS?	There is currently no specific UK guidance on IgAN. The KDIGO 2021 guidelines are utilised and there is a UKKA commentary on these guidelines. The clinical practice guidelines for IgA nephropathy and immunoglobulin A vasculitis 2024 are currently in draft form.

	The standard of care is the highest tolerated dose of angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB) unless contra-indicated. Second-line therapy can include the use of: • Glucocorticoids • Sodium-glucose cotransporter-2 (SGLT2) inhibitors • Targeted-release budesonide (uPCR 1.5 g/g or more) Immunosuppressive agents including mycophenolate mofetil and cyclophosphamide can also be used to treat people with rapidly progressing IgA nephropathy. However efficacy is unclear and there are associated adverse effects. Sparsentan is currently undergoing NICE appraisal approval and is expected to be published for treatment of IgA nephropathy June 2025.
9a. Are any clinical guidelines used in the treatment of the condition, and if so, which?	Currently the only guidance for IgA nephropathy published by the National Institute for Health and Clinical Excellence is targeted-release budesonide, which has been approved for treating primary IgA nephropathy and a NICE technology appraisal guidance is available (TA 937). The KDIGO 2021 guidelines are utilised for the treatment of IgAN in the UK and there is a UKKA commentary on these guidelines. Sparsentan is currently undergoing NICE appraisal approval and is expected to be published for treatment of IgA nephropathy June 2025. There are published NICE Guidelines for the assessment and management of CKD (NG203) however this does not contain specific information on the treatment of patients with IgAN.
9b. Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	The pathway of care is well defined from a supportive management perspective with first-line supportive management includes highest tolerated dose of angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB). It is less well defined for second-line therapies and there is uncertainty regarding the efficacy and safety of immunosuppressant drugs in progressive disease and therefore it is recommended that patients are offered the opportunity to be part of a clinical trial. Target-release budesonide is an option for add-on therapy as per NICE TA 937 for patients with uPCR of 1.5 g/g or more. The KDIGO update suggests using disease modifying therapies such as targeted-release budesonide at the same time as treating the CKD by reducing proteinurea and blood pressure. Regional or sub-regional MDTs are recommended for the approval of target-release budesonide to ensure the drug is being used cost effectively and to ensure equity of access between ICBs.

9c. What impact would the technology have on the current pathway of care?	The NICE TA 937 is already available as a second-line treatment option for treating IgAN in adults, when there is a risk of rapid disease progression and a uPCR of 1.5 g/g or more and only as an add-on therapy to optimised standard of care, including the highest tolerated dose of angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB). Reducing the target uPCR to 0.8 g/g or more would allow more patients to be eligible for this medication once optimised on standard of care therapy and slow the progression to ESRD requiring haemodialysis or transplantation.
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	The NICE TA 937 is already available as a second-line treatment option for treating IgAN in adults, when there is a risk of rapid disease progression and a uPCR of 1.5 g/g or more and only as an add-on therapy to optimised standard of care, including the highest tolerated dose of angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB). Reducing the target uPCR to 0.8 g/g or more would allow more patients to be eligible for this medication once optimised on standard of care therapy and slow the progression to ESRD requiring haemodialysis or transplantation.
10a. How does healthcare resource use differ between the technology and current care?	The NICE TA 937 is already available as a second-line treatment option for treating IgAN in adults, when there is a risk of rapid disease progression and a uPCR of 1.5 g/g or more and only as an add-on therapy to optimised standard of care, including the highest tolerated dose of angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB). Reducing the target uPCR to 0.8 g/g or more would allow more patients to be eligible for this medication once optimised on standard of care therapy and slow the progression to ESRD requiring haemodialysis or transplantation.
10b. In what clinical setting should the technology be used? (For example,	Secondary care, specialist clinics under a nephrologist.

primary or secondary care, specialist clinics.)	
10c. What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	Investment is required for drug cost, delivery and pharmacist time to organise the homecare prescriptions.
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes, a sustained reduction in proteinuria and resultantly in progression of CKD in individuals with rapidly progressive IgAN with a delay or avoidance of the need for renal replacement therapy. Reducing the target uPCR will allow targeted-release budesonide to be prescribed for a wider range of patients and therefore allow more patients to be prescribed it more proactively in their disease progression.
11a. Do you expect the technology to increase length of life more than current care?	Yes due to reduced progression of CKD and therefore reduced associated symptoms and complications and also a delay or avoidance of the need for renal replacement therapy. Reducing the target uPCR will allow target-release budesonide to be prescribed for a wider range of patients and therefore allow more patients to be prescribed it more proactively in their disease progression.
11b. Do you expect the technology to increase health-related quality of life more than current care?	Yes due to reduced progression of CKD and therefore reduced associated symptoms and complications and also a delay or avoidance of the need for renal replacement therapy. Reducing the target uPCR will allow target-release budesonide to be prescribed for a wider range of patients and therefore allow more patients to be prescribed it more proactively in their disease progression.
12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	There is no evidence that any specific groups of IgAN patients will respond differently to targeted-release budesonide. The NICE TA suggests patients with rapidly progressing disease are more appropriate for therapy; this is assessed by consultants with expertise in the clinical areas at a specialist MDT.

The use of the technology

13. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	There are no expected difficulties for patients or healthcare patients and changing the target uPCR will have no impact other than increasing the number of prescriptions required through secondary care. The medication is easy to use and no known specific monitoring is required over and above what is already undertaken.
14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	To only be initiated for patients with rapid progressive disease and with whom meet the target uPCR range. No additional testing is required.
15. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	I am not an expert in health economics however I anticipate that widening the use of target-release budesonide will improve quality of life for individuals with IgAN by reducing or avoiding progression of CKD and associated symptoms as per trial data which will likely be reflected in the QALY calculation.

16. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	Yes, there are limited options for IgAN and target-release budesonide was the first specific approved treatment. Widening the eligibility criteria will increase the number of patients whereby significant impacts can be made.
16a. Is the technology a 'step-change' in the management of the condition?	It does not introduce a new step in the management, however it widens the criteria for use of this medication.
16b. Does the use of the technology address any particular unmet need of the patient population?	Yes, currently there are limited options for the treatment of IgAN with the only specific approved treatment being targeted-release budesonide. Widening the criteria allows for the patients who do not have the required level of proteinuria to be prescribed this medication.
17. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	The adverse effects of target-release budesonide are the same as other corticosteroids, however the dose for IgAN is equivalent to 5-7.5 mg oral prednisolone, therefore the side effect profile is much reduced compared to higher doses of oral prednisolone that are required to treat IgAN prior to the availability of NICE TA 937.

Sources of evidence

18. Do the clinical trials on the technology reflect current UK clinical practice?	Yes, all patients enrolled onto the trial had already received the highest tolerated standard of care treatment (highest tolerated dose of ACE inhibitor or ARB for at least 3 months) as per KDIGO guidelines and UK practice and still had ongoing proteinuria of >1g/day therefore a second-line treatment was indicated.
18a. If not, how could the results be extrapolated to the UK setting?	NA
18b. What, in your view, are the most important outcomes, and were they measured in the trials?	The most important efficacy outcomes are change from baseline in UPCR, the rate of change of eGFR and proportion of patients reaching the composite kidney failure end point. The most important safety outcomes included the adverse effects, the most common reported of which included peripheral oedema, hypertension, muscle spasms and headache.
18c. If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	eGFR is used as a surrogate outcome measure for future kidney failure. There is, however, consensus that eGFR slope is highly predictive of future kidney failure risk.
18d. Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	No
19. Are you aware of any relevant evidence that might not be found by a	No

systematic review of the trial evidence?	
20. How do data on real-world experience compare with the trial data?	

Equality

21a. Are there any potential equality issues that should be taken into account when considering this treatment?	No
21b. Consider whether these issues are different from issues with current care and why.	

Key messages

22. In up to 5 bullet points, please summarise the key messages of your submission.	• There are currently limited safe and effective treatments available for the treatment of IgA nephropathy • The presence of proteinuria despite maximum tolerated RASi therapy has been consistently shown to be a risk factor for progressive decline in renal function in patients with IgAN • Currently, NICE TA 937 allows patients to be prescribed targeted-release budesonide with a urine protein-to-creatinine ration of 1.5 g/g or more. Reducing this to 0.8 g/g will allow wider use for patients to be prescribed this medication.

Thank you for your time.

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NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Targeted-release budesonide for treating primary IgA nephropathy (review of TA937) [ID6485]

Clinical expert statement

Information on completing this form

In part 1 we are asking for your views on this technology. The text boxes will expand as you type.

In part 2 we are asking you to provide 5 summary sentences on the main points contained in this document.

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Do not include medical information about yourself or another person that could identify you or the other person.

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Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Please underline all confidential information, and separately highlight information that is submitted as 'confidential [CON]' in turquoise, and all information submitted as 'depersonalised data [DPD]' in pink. If confidential information is submitted, please also

send a second version of your comments with that information redacted. See Health technology evaluations: interim methods and process guide for the proportionate approach to technology appraisals (section 3.2) for more information.

The deadline for your response is **5pm** on **Wednesday 22 October 2025.** Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments received, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

NICE National Institute for Health and Care Excellence

Part 1: Treating primary IgA nephropathy and current treatment options

Table 1 About you, aim of treatment, place and use of technology, sources of evidence and equality

1. Your name	Dr Chee Kay Cheung
2. Name of organisation	UK Kidney Association (UKKA); University Hospitals of Leicester NHS Trust
3. Job title or position	Consultant Nephrologist and Honorary Associate Professor
4. Are you (please tick all that apply)	☒ An employee or representative of a healthcare professional organisation that represents clinicians? ☒ A specialist in the treatment of people with primary IgA nephropathy? ☒ A specialist in the clinical evidence base for primary IgA nephropathy or technology? ☐ Other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☒ Yes, I agree with it ☐ No, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ Other (they did not submit one, I do not know if they submitted one etc.)
6. If you wrote the organisation submission and/or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission)	☒ Yes
7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	
Additional information:	KDIGO guidelines have been recently updated: https://pubmed.ncbi.nlm.nih.gov/40975564/

NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Targeted-release budesonide for treating primary IgA nephropathy (review of TA937) [ID6485]

Clinical expert statement

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Part 1: Treating primary IgA nephropathy and current treatment options

Table 1 About you, aim of treatment, place and use of technology, sources of evidence and equality

1. Your name	Jonathan Barratt
2. Name of organisation	University of Leicester & UHL NHS Trust
3. Job title or position	Professor of Renal Medicine
4. Are you (please tick all that apply)	☒ An employee or representative of a healthcare professional organisation that represents clinicians? ☒ A specialist in the treatment of people with primary IgA nephropathy? ☒ A specialist in the clinical evidence base for primary IgA nephropathy or technology? ☐ Other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☒ Yes, I agree with it ☐ No, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ Other (they did not submit one, I do not know if they submitted one etc.)
6. If you wrote the organisation submission and/or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission)	☒ Yes
7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	NIL
8. What is the main aim of treatment for primary IgA nephropathy? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability)	To slow the rate of loss of kidney function to that seen in the healthy population - which is on average a loss of kidney function of 1ml/min/year after the age of 40years. This generally difficult to assess on a clinic by clinic basis and so the

Clinical expert statement

	KDIGO 2025 Guideline recommends aiming for the maximum reduction in proteinuria possible- aiming for less than 0.5g/d and ideally less than 0.3g/d
9. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount)	A clinically significant treatment response is a substantial reduction in proteinuria- typically equal to or greater than 30%
10. In your view, is there an unmet need for patients and healthcare professionals in primary IgA nephropathy?	Yes- please see the RaDaR data which shows that the majority of patients with IgAN in the UK will develop kidney failure in their lifetime.
11. How is primary IgA nephropathy currently treated in the NHS? • Are any clinical guidelines used in the treatment of the condition, and if so, which? • Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.) • What impact would the technology have on the current pathway of care?	Please see the 2025 KDIGO Guideline for IgAN- this is the standard of care we should follow in the UK- simultaneous treatment of the immune aspect of IgAN alongside general treatments for CKD- treatment must be in parallel if we are to prevent kidney failure in the lifetime of our patients. The KDIGO guideline is the internationally accepted guideline for the treatment of IgAN. The recommendation is to use nefecon in all patients who are at risk of progression (proteinuria>0.5g/d) -in the UK based on the label this would be for all IgAN patients with proteinuria>1.0g/d)-currently NICE guidance is to use nefecon in patients with proteinuria>1.5g/d- this change will increase access to nefecon for high risk IgAN patients (but not the entire at risk UK population)
12. Will the technology, targeted-release budesonide, be used (or is it already used) in the same way as current care in NHS clinical practice? Please note: the technology is being evaluated for adults with primary IgA nephropathy with a urine protein-to-creatinine ratio of 0.8 g/gram or more. This is a review of NICE TA937, which recommended targeted-release budesonide in adults with a urine protein-to-creatinine ratio of 1.5 g/gram or more.	Use will be the same as currently but more at risk patients will have access to nefecon. These patients will be seen in the same nephrology clinics as existing patients and prescription would be in second care only-as now. No new investment needed. As per the 2025 KDIGO guideline patients should be on immune directed care and general CKD care (SGLT2i/RASi or sparsentan) -it is likely if there is better

• How does healthcare resource use differ between the technology and current care? • In what clinical setting should the technology be used? (for example, primary or secondary care, specialist clinic) • What investment is needed to introduce the technology? (for example, for facilities, equipment, or training) **12(a). Do you expect the technology to alter the composition or use of current care?** • Please comment on the place of RASi, SGLT2i and sparsentan in current care for IgA nephropathy, including any expected impact on their use should the technology become recommended in adults with primary IgA nephropathy and a urine protein-to-creatinine ratio of 0.8 g/gram or more.	control of the immunological aspect of IgAN there will be less requirement for multiple CKD treatments.
13. Do you expect the technology (for IgA nephropathy in adults with a urine protein-to-creatinine ratio of 0.8 g/gram or more) to provide clinically meaningful benefits compared with current care? • Do you expect the technology to increase length of life more than current care? • Do you expect the technology to increase health-related quality of life more than current care?	Yes- control of the immunological aspect of IgAN will slow the rate of loss of kidney function more than existing treatments in this new indication group of at risk IgAN patients. As mortality in IgAN is closely linked to the development of kidney failure- delaying significantly the onset of kidney failure will directly impact on length of life.
14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	no

15. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use? (For example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed)	Just the same- an oral medications requiring no specific monitoring above standard clinical care
16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	no
17. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation? • Do the instruments that measure quality of life fully capture all the benefits of the technology or have some been missed? For example, the treatment regimen may be more easily administered (such as an oral tablet or home treatment) than current standard of care	no
18. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met? • Is the technology a 'step-change' in the management of the condition? • Does the use of the technology address any particular unmet need of the patient population?	Yes- this is the first approved treatment for IgAN that has been shown to target the fundamental pathophysiology of the disease and reduce proteinuria and slow the rate of loss of kidney function. It is safe and well tolerated compared to systemic corticosteroids.

19. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Nefecon treatment can be associated with some systemic steroid side effects but these are temporary and reverse on stopping the treatment- nefecon is given as 4 x 4mg tablets and it is possible to titrate the dose when needed to reduce unwanted side effects if needed.
20. Do the clinical trials on the technology reflect current UK clinical practice? • If not, how could the results be extrapolated to the UK setting? • What, in your view, are the most important outcomes, and were they measured in the trials? • If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes? • Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	Yes- UPCR and eGFR are the standard outcomes and both change in UPCR and eGFR slope are globally recognised as validated surrogates for kidney failure. I am not aware of any adverse effects that have come to light post marketing that were not identified in the NeflgArd and NEFIGAN trials.
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	no
22. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance TA775 Dapagliflozin for treating chronic kidney disease, which has been updated and replaced by TA1075: Dapagliflozin for treating chronic kidney disease?	CKD treatments are not a relevant comparator to immune directed in treatments in IgAN- these agent must be used together as they target different drivers for nephron loss.
23. How do data on real-world experience compare with the trial data?	From what has been presented at nephrology meetings RWE is very similar to trial outcomes in the P2 and 3 studies.
24. NICE considers whether there are any equalities issues at each stage of an evaluation. Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of	No equality issues identified (very few black patients included in the trials but this is because IgAN is very rare in people of African ancestry)

people with this condition are particularly disadvantaged. Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics. Please state if you think this evaluation could • exclude any people for which this treatment is or will be licensed but who are protected by the equality legislation • lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population • lead to recommendations that have an adverse impact on disabled people. Please consider whether these issues are different from issues with current care and why. More information on how NICE deals with equalities issues can be found in the NICE equality scheme. Find more general information about the Equality Act and equalities issues here.	

Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

IgAN carries a significant lifetime risk of kidney failure-see the UK RaDaR data

Use of CKD treatments (RASi/SGLT2i/sparsentan) modestly slow the rate of loss of eGFR but will not prevent kidney failure in IgAN

The only way to give the patient the best chance of preventing kidney failure in their lifetime is to treat both the immune aspect of the disease and the CKD consequences together

Nefecon targets the fundamental pathophysiology of the disease, reducing circulating IgA immune complexes, resulting in proteinuria reduction and protection against loss of kidney function

The revised MHRA label does not capture the entire at risk UK IgAN population (and differs from the FDA label) - meaning that there will still be a substantial number of at risk UK IgAN patients unable to access nefecon who will go on to develop kidney failure (1 in 4 at 10 years- see UK RaDaR)

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NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Targeted-release budesonide for treating primary IgA nephropathy (review of TA937) [ID6485]

Patient expert statement

Thank you for agreeing to give us your views on this treatment and its possible use in the NHS.

Your comments are really valued. You can provide a unique perspective on conditions and their treatment that is not typically available from other sources

Information on completing this form

In part 1 we are asking you about living with primary IgA nephropathy or caring for a patient with primary IgA nephropathy. The text boxes will expand as you type.

In part 2 we are asking you to provide 5 summary sentences on the main points contained in this document.

Help with completing this form

If you have any questions or need help with completing this form please email the public involvement (PIP) team at pip@nice.org.uk (please include the ID number of your appraisal in any correspondence to the PIP team).

NICE National Institute for Health and Care Excellence

Please use this questionnaire with our hints and tips for patient experts. You can also refer to the Patient Organisation submission guide. **You do not have to answer every question** – they are prompts to guide you. There is also an opportunity to raise issues that are important to patients that you think have been missed and want to bring to the attention of the committee.

Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable. Please type information directly into the form.

We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Your response should not be longer than 15 pages.

The deadline for your response is **5pm** on **Friday 28 November 2025.** Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

Patient expert statement

Part 1: Living with this condition or caring for a patient with primary IgA nephropathy

Table 1 About you, primary IgA nephropathy, current treatments and equality

1. Your name	[redacted]
2. Are you (please tick all that apply)	☒ A patient with primary IgA nephropathy? ☐ A patient with experience of the treatment being evaluated? ☐ A carer of a patient with primary IgA nephropathy? ☐ A patient organisation employee or volunteer? ☐ Other (please specify):
3. Name of your nominating organisation	Kidney Research UK
4. Has your nominating organisation provided a submission? (please tick all options that apply)	☐ No (please review all the questions and provide answers when possible) ☐ Yes, my nominating organisation has provided a submission ☐ I agree with it and **do not wish to** complete a patient expert statement ☐ Yes, I authored / was a contributor to my nominating organisations submission ☐ I agree with it and **do not wish to** complete this statement ☒ I agree with it and **will be** completing
5. How did you gather the information included in your statement? (please tick all that apply)	☒ I am drawing from personal experience ☐ I have other relevant knowledge or experience (for example, I am drawing on others' experiences). Please specify what other experience: ☐ I have completed part 2 of the statement **after attending** the expert engagement teleconference

	☐ I have completed part 2 of the statement **but was not able to attend** the expert engagement teleconference ☐ I have not completed part 2 of the statement
6. What is your experience of living with primary IgA nephropathy? **If you are a carer (for someone with primary IgA nephropathy) please share your experience of caring for them**	I was only [redacted] when my life shifted in a way I never saw coming. In [redacted], what started as a simple sore throat turned into something terrifying — I began seeing blood in my urine. I remember feeling confused, scared, and completely unprepared. Up until that moment, everything felt normal. I was going out with friends every evening, working full-time, and had just earned my [redacted] degree. I was proud, excited, and ready for the next chapter. Then everything changed so quickly. My kidney function dropped fast — my eGFR fell from over 90 in September to just 36 by November. Watching those numbers fall was like watching my life shrink around me. A biopsy confirmed the worst: crescentic IgA nephropathy, the rarest and most aggressive form of the disease. Hearing those words felt like the floor had disappeared beneath me. Treatment began with 60 mg of prednisolone, followed by cyclophosphamide. Hearing the word *chemotherapy* used in relation to my kidneys was overwhelming [redacted] Almost immediately, I was pushed into making urgent decisions about fertility preservation. To preserve my fertility, I was told I'd need to undergo egg preservation, a process involving daily hormone injections to stimulate my ovaries so the eggs could be collected. But the whole process required two to three weeks — time I wasn't sure I even had. I needed to know whether my kidneys could hold on long enough. That same day, I was rushed into appointments with one of the top fertility preservation teams. I met a whole group of doctors and nurses who walked me through everything. I even had all the prescriptions ready — the hormones, the injections, everything. But then I froze. I remember thinking: *What's the point of going through all this if my kidneys fail in the meantime? What's the point of preserving fertility if I might not live to become a mother at all?* It was one of the most gut-wrenching moments of my life. I *had* to make a decision, and neither option felt fair.

	In the end, I made the heartbreaking choice not to proceed with fertility preservation and instead start chemotherapy immediately. As painful as it was, I'm glad I chose the treatment right away. My doctors told me that if my crescentic IgAN continued at the pace it was going and I had delayed those extra three weeks, I likely would have lost my kidneys and ended up on dialysis. Cyclophosphamide treatment was physically demanding. I experienced persistent nausea, headaches, hair thinning and severe fatigue, and I had to take off a year from my job [redacted] due to infection risk while immunocompromised. Despite this, I completed the full six-month CYCLOPS protocol, and my kidneys responded exceptionally well, with my eGFR returning to above 90. Even after recovering from the worst of it, IgA nephropathy still shapes my daily life. [redacted] but ongoing fatigue means I can now only manage part-time work [redacted] It's been a painful adjustment, especially because I look completely fine on the outside. Every day feels like a push — doing tasks that used to be effortless, trying to function at even half the level of a "normal" person. [redacted] Even after aggressive treatment, I still battle fatigue and have to monitor my iron levels constantly. When I first returned to work, I didn't realise how unwell I still was. I was dizzy, light-headed, and holding onto corridor corners and the backs of chairs just to stay upright because my blood pressure kept dropping so low. I've always been a fighter and I've taken every medication my renal team believed would help, but when even a tiny 2 mg dose of candesartan made me barely able to function, I knew I had to stop. Kidney doctors love to put patients on blood pressure medication to protect the heart and kidneys long-term — which makes sense — but after all my

	treatment, my blood pressure fell into the 80s systolic. No wonder I felt awful. I even tried the SGLT2 inhibitor dapagliflozin, but the dizziness continued. I've learned that managing this disease is a constant process of trial and error — figuring out what medication your body can tolerate while still allowing you to live some kind of normal life. Managing my energy now requires constant pacing and careful balance, and it has limited my ability to work to my full potential. Financially, it's also taken a toll. My earning potential has dropped significantly. [redacted] The psychological impact has also been significant. The disease creates an ongoing sense of uncertainty — even when stable, I worry that something as simple as a sore throat could trigger another flare. My renal team referred me to a specialist renal psychologist, and although there was a long wait, that support has been essential in helping me adjust to living with a chronic, unpredictable condition.
	At present, treatment options for IgA nephropathy are extremely limited. Existing medications focus on slowing the progression of the disease rather than treating the underlying cause, meaning that for many patients, dialysis or kidney transplantation remain likely outcomes. There is no curative therapy. My own options are even more restricted. I am unable to tolerate several standard treatments, because I already have low blood pressure. As a result, I have had to remain on azathioprine, which carries long-term risks. Attempts to reduce or stop azathioprine leave me vulnerable to relapse, so I feel trapped between risks of specific drugs and the fear of the disease returning. Prednisolone has also been both beneficial and extremely challenging. While it is highly effective at reducing inflammation, the side effects were severe and long-lasting for me. Even now, I am still recovering from the physical and psychological

	impact of high-dose long term steroid therapy. Overall, current treatments rely heavily on drugs that patients often struggle to tolerate and that come with significant risks. From the moment I was diagnosed, I felt supported by my renal team. Their communication, compassion, and expertise made an enormous difference at a very frightening time. I was also referred [redacted] a leading expert in IgA nephropathy, which gave me even more confidence that I was receiving the best possible care. The quality of support has been excellent; however, the limitations are not in the care itself but in the lack of effective and tolerable treatment options available to clinicians.
8. If there are disadvantages for patients of current NHS treatments for primary IgA nephropathy (for example, how they are given or taken, side effects of treatment, and any others) please describe these	**Poor tolerability and severe side effects**, particularly with steroids and chemotherapy-based regimens. Fatigue, low iron, moon face, weight gain, hair thinning, infection risk, hair growth, mood swings **Limited alternative options**, especially for patients who cannot tolerate first-line medications. **Long-term risks,** skin cancer with azathioprine, fertility issues + bladder issues with cyclophosphamide, **Significant impact on daily life**, including fatigue, immunosuppression and inability to work normally. I became so weak from all of my treatments my iron dropped very low and oral iron medication made me feel even more nauseous. I couldn't lift my head off pillow… eventually I had to have iron infusion.
9a. If there are advantages of targeted-release budesonide over current treatments on the NHS please describe these. For example, the effect on your quality of life, your ability to continue work, education, self-care, and care for others?	I think the side effects of targeted-release budesonide are less systemic when it comes to things like weight gain and moon face. That was one of the hardest parts of dealing with IgAN during treatment — my entire appearance changed, almost overnight. People I thought were my friends drifted away. Prednisolone was a double-edged sword: it saved my kidneys, but it destroyed my confidence and the body I once recognised. [redacted] all I could feel was the world staring at my moon face. It was impossible to hide. I remember avoiding

9b. If you have stated more than one advantage, which one(s) do you consider to be the most important, and why? **9c. Does targeted-release budesonide help to overcome or address any of the listed disadvantages of current treatment that you have described in question 8? If so, please describe these** **9d. Would making targeted-release budesonide available to more people based on expanded access criteria (urine protein excretion of 1.0 g/day or more or a urine protein-to-creatinine ratio of 0.8 g/g or more) be an advantage compared with current practice?**	photos completely, refusing to be in them because I couldn't bear the idea of seeing myself later. When I looked in the mirror, I didn't see *me*. I saw a puffy, swollen [redacted] who was just trying to survive. To everyone else, it probably looked like I'd simply "eaten too many cakes." They had no idea what was actually happening. I felt ashamed of how I looked, and I promised myself that if I'm ever in a situation where I have to go back on high-dose steroids again, I won't do it unless it's absolutely necessary. Even now, two years later, people still say things like, *"You look so much better now that you've lost weight — you looked awful before."* I've even heard rumours people spread about me during that time. I truly hope that targeted-release budesonide can be used more often before resorting to heavy systemic immunosuppression like high-dose steroids or cyclophosphamide. Treatments like budesonide have the potential to protect a patient's quality of life while still treating the disease effectively. If I had been eligible for budesonide before or alongside cyclophosphamide, I genuinely believe I could have reintegrated socially so much more easily after treatment. [redacted] **It's important to recognise what this means for a [redacted] when appearance feels so tied to identity. These side effects don't just fade when the medication stops; they linger, and they shape how you see yourself long after treatment ends.** The targeted release form of budesonide means that the drug is more targeted, less systemic, less toxic, designed specifically for IgAN and often better tolerated.

	Ultimately, patients want to have the best long-term outcomes. Proteinuria is the best measure of predicting kidney outcomes. If patients are able to access drugs which lower their proteinuria effectively without debilitating side effects, it would be a huge win! Knowing that IgAN can come back even after a transplant — and that transplants don't last forever —everything possible should be done to prevent patients from reaching the point of needing dialysis or a transplant in the first place. Using treatments like targeted-release budesonide is one way to help delay that progression and protect people's kidneys for as long as possible.
10. If there are disadvantages of targeted-release budesonide over current treatments on the NHS please describe these. For example, are there any risks with targeted-release budesonide? If you are concerned about any potential side effects you have heard about, please describe them and explain why	Benefits are not long lasting - I have heard that targeted release budesonide lowers proteinuria initially for 4 months and keeps things stable, but then the proteinuria goes back up to what it was. Delayed side effects
11. Are there any groups of patients who might benefit more from targeted-release budesonide or any who may benefit less? If so, please describe them and explain why Consider, for example, if patients also have other health conditions (for example difficulties with mobility, dexterity or cognitive impairments) that affect the suitability of different treatments	Patients who are at higher risk of end-stage kidney disease should be offered targeted-release budesonide earlier. The aim is to give people as much time as possible before needing invasive, life-altering treatments like dialysis or a transplant. My whole experience with IgAN initially was enormous shock. Offering patients in my position the *least-worst* option can genuinely help reduce the horrible side effects of traditional steroids. I looked completely different — the weight gain, the moon face — and the psychosocial impact was huge, especially for someone [redacted] People were spreading rumours that I was having a mental breakdown. I had no choice but to take steroids, but the personal cost was massive. It felt like after my treatment, I didn't really have a place to return to. I actually couldn't face

	returning to one of my workplaces and I had to quit – imagine how hard this was when I was so ill.
12. Are there any potential equality issues that should be taken into account when considering primary IgA nephropathy and targeted-release budesonide ? Please explain if you think any groups of people with this condition are particularly disadvantage Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics More information on how NICE deals with equalities issues can be found in the NICE equality scheme Find more general information about the Equality Act and equalities issues here.	**High variation by country/region**: The proportion of IgAN among *primary glomerulonephritis* (from biopsy registries) is much higher in **China (~40–58%)** and **Japan (~31–45%)**, compared to **UK (around 30–40%)** in different studies. **Detection bias**: Countries like Japan have mass urinary screening programs, which likely increase the detection rate of IgAN. PMC **Biopsy practices**: The decision to biopsy varies by country, which strongly affects "recorded" prevalence. PMC+2Karger Publishers+2 **Genetic contribution**: Some of the higher frequency in East Asia is likely due to genetic risk factors.
13. Are there any other issues that you would like the committee to consider?	[redacted] [redacted] It is so important to look at the patient holistically. One of the most important points I need to make is that I can *only* manage part-time work because of the sheer number of medical appointments I have every single [redacted] the flexibility I need to attend these appointments — but it also limits my career, my progression, and my income. If you looked at my calendar over the past year, you'd see it packed almost every day with medical commitments: hospital reviews, blood tests, scans, [redacted]

	[redacted] A&E visits, GP check-ins, [redacted] psychologist sessions, medication reviews with pharmacists, and ongoing assessments with specialist nurses. It feels never-ending. What makes it even harder is that every hour I take off work for these appointments is *unpaid*. On top of that, the practical costs add up — constant car parking fees at the hospital, petrol for the regular journeys back and forth, and all the small but relentless expenses that come with being in and out of medical care. This is one of the toughest parts of living with a chronic illness: trying to work, trying to live some kind of normal life, yet constantly needing to drop everything for the next appointment. These visits aren't optional — they're essential — and they dictate my routine, my finances, my energy, and my ability to plan for the future. I think if we become good enough at detecting IgAN early enough we can prevent a lot of unnecessary treatments and manage the disease on a lower level of care. This prevents the costly use of dialysis and transplants.

Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

- Current IgAN treatments—particularly high-dose steroids—have severe side effects, including extreme weight gain, moon-face, and unwanted hair growth, which can profoundly affect patients' appearance, identity, and social life.
- The psychosocial impact is significant: patients may experience isolation, strained relationships, and difficulties returning to work or education while coping with treatment and disease effects.
- The physical burden, ongoing fatigue, and energy limitations often force patients to lower career aspirations, limiting progression and reducing financial stability at a young age.
- IgAN can recur even after kidney transplant, and transplants do not last indefinitely; treatments that delay progression, such as targeted-release budesonide, are critical to protect kidney function and reduce the need for dialysis or transplantation.
- The psychological burden of IgAN is substantial, as patients must manage constant fear of flare-ups while coping with treatment side effects, tapering, highlighting the urgent need for more tolerable, effective therapies that support adherence and quality of life.

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External Assessment Group Report commissioned by the NIHR Evidence Synthesis Programme on behalf of NICE

Targeted-release budesonide for treating primary IgA nephropathy (review of TA937)

Produced by	**Southampton Health Technology Assessments Centre (SHTAC)**
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- Professor Alan Salama, Consultant in Nephrology and Director of the UCL Department of Renal Medicine, at the UCL Faculty of Medical Sciences

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- Neelam Kalita, Senior Research Fellow SHTAC for providing a quality assurance review of the cost effectiveness chapters of the draft report.

Declared competing interests of the authors and advisors

The authors state none. Professor Salama states none. Dr Shah is the Principal Investigator for four commercial trials evaluating treatments in IgA nephropathy but none are sponsored by Genus Pharmaceuticals and all are investigating other types of therapy: A Proliferation-inducing Ligand (APRIL) inhibitor; B-cell activating factor (BAFF) inhibitor; Factor B inhibitor.

Rider on responsibility for report

The views expressed in this report are those of the authors and not necessarily those of the NIHR Evidence Synthesis Programme. Any errors are the responsibility of the authors.

This report should be referenced as follows:

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Contributions of authors

Joanna Picot critically appraised the clinical effectiveness systematic review, drafted the report and is the project co-ordinator and guarantor; Joanne Lord critically appraised the health economic systematic review and the economic evaluation, critiqued, validated and revised the economic model, and drafted the report; Karen Pickett contributed to initial project co-ordinator tasks, critically appraised the clinical effectiveness systematic review and drafted the report; Bogdan Grigore critically appraised the health economic systematic review and the economic evaluation, critiqued, validated and revised the economic model, and drafted the report.

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ACE	Angiotensin-converting enzyme
ACEi	Angiotensin-converting enzyme inhibitor
AE	Adverse event
ARB	Angiotensin-receptor blocker
BNF	British National Formulary
CI	Confidence interval
CIC	Commercial in confidence
CKD	Chronic kidney disease
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CS	Company submission
CSR	Clinical study report
EAG	External Assessment Group
eGFR	Estimated glomerular filtration rate
EMA	European Medicines Agency
eMIT	Drugs and pharmaceutical electronic market information tool
EQ-5D-3L	European Quality of Life Working Group Health Status Measure 3 Dimensions, 3 Levels
ESRD	End-stage renal disease
FAS	Full analysis set
Gd-IgA1	Galactose-deficient IgA1
GFR	Glomerular filtration rate
g/g	Grams per gram
HRQoL	Health-related quality of life
HTA	Health technology assessment
ICER	Incremental cost-effectiveness ratio
IgA	Immunoglobulin A
IgAN	Immunoglobulin A nephropathy
Incr	Incremental
INMB	Incremental net monetary benefit
ITC	Indirect treatment comparison
ITT	Intention-to-treat
KDIGO	Kidney disease – Improving global outcomes
KM	Kaplan-Meier curve
MMRM	Mixed model for repeated measures

NHS	National Health Service
NICE	National Institute for Health and Care Excellence
OLE	Open-label extension
PAS	Patient Access Scheme
PP	Per protocol
PSA	Probabilistic sensitivity analysis
PSS	Personal Social Services
QALY	Quality-adjusted life year
RaDaR	National Registry of Rare Kidney Diseases
RASi	Renin-angiotensin system inhibitor
RCT	Randomised controlled trial
RDI	Relative dose intensity
RR	Relative risk
RRT	Renal replacement therapy (dialysis or transplant)
SD	Standard deviation
SGLT2	Sodium/glucose cotransporter 2
SGLT2i	Sodium/glucose cotransporter 2 inhibitor
SmPC	Summary of product characteristics
SMR	Standardised mortality ratio
SoC	Standard of care
TA	Technology appraisal
TEAE	Treatment-emergent adverse event
TRF-budesonide	Targeted-release formulation budesonide
TTD	Time to treatment discontinuation
UK	United Kingdom
US	United States
UACR	Urine albumin to creatinine ratio
UPCR	Urine protein-to-creatinine ratio

1 EXECUTIVE SUMMARY

This summary provides a brief overview of the key issues identified by the external assessment group (EAG) as being potentially important for decision making. It also includes the EAG's preferred assumptions and the resulting incremental cost-effectiveness ratios (ICERs).

Section 1.1 provides an overview of the key issues. Section 1.2 provides an overview of key model outcomes and the modelling assumptions that have the greatest effect on the ICER. Sections 1.3 to 1.6 explain the key issues in more detail. Background information on the condition, health technology, evidence and information on the issues are in the main EAG report.

All issues identified represent the EAG's view, not the opinion of the National Institute for Health and Care Excellence (NICE).

1.1 Overview of the EAG's key issues

Table 1 Summary of key issues

ID	Summary of issue	Report sections
1	Change in standard of care - Sodium/glucose cotransporter 2 (SGLT2) inhibitors and sparsentan – level of use, impact on effectiveness estimates and re-treatment.	2.2.3, 3.2.1.1.2
2	Uncertainty about the generalisability of the results for retreatment, a lack of long-term follow-up data for re-treatment and no evidence for additional rounds of re-treatment.	3.2.1.1.2, 3.2.2.2 and 3.2.6
3	High uncertainty about the transition probabilities between CKD state 1 to 4, due to sparse data on observed transitions.	4.2.6.1
4	Lack of clarity about dosing and wastage assumptions for targeted release formulation (TRF)-budesonide in NHS practice, and implications for costing	4.2.10.1.1

The key differences between the company's preferred assumptions and the EAG's preferred assumptions are changes to the cost of standard care (EAG correction and cost of SGLT2 inhibitors); relative mortality rates by chronic kidney disease (CKD) stage (assumption that rates are the same for CKD stage 2 to 3b).

1.2 Overview of key model outcomes

NICE technology appraisals compare how much a new technology improves length (overall survival) and quality of life in a quality-adjusted life year (QALY). An ICER is the ratio of the extra cost for every QALY gained.

Overall, the technology is modelled to affect QALYs by:

- Reducing the rate of disease progression, which improves patients' quality of life.
- Reducing the rate of disease progression also reduces the mortality rate.

Overall, the technology is modelled to affect costs by:

- Increasing drug acquisition costs by adding TRF-budesonide to standard care
- Reducing healthcare resource use and costs by slowing the rate of progression to more advanced stages of kidney disease.

The modelling assumptions that have the greatest effect on the ICER are:

- Assuming a lower rate of disease progression in standard care (e.g. SGLT2 inhibitors)
- Assumptions regarding the waning of effectiveness of TRF-budesonide on retreatment
- Alternative sources for estimates of relative mortality by stage of disease
- Alternative sources for healthcare costs by stage of disease

1.3 The decision problem: summary of the EAG's key issues

The EAG have not identified any key issues in relation to the company's decision problem but we acknowledge that the subgroup of people at risk of rapidly progressive immunoglobulin A (IgA) nephropathy (urine protein-to-creatinine ratio (UPCR) ≥1.5 g/g) is not included in the company's decision problem (also see section 1.6 below).

1.4 The clinical effectiveness evidence: summary of the EAG's key issues

Issue 1 Change in standard of care

Report section	2.2.3 and 3.2.1.1.2
Description of issue and why the EAG has identified it as important	The standard of care (SoC) has changed since the NeflgArd Nef-301 randomised controlled trial (RCT) and the Nef-301 open-label extension (OLE) were conducted. SoC in both the NeflgArd Nef-301 and the Nef-301 OLE was optimised (maximum tolerated) renin-angiotensin system inhibitor (RASi) therapy alongside encouragement to participants to make and maintain healthy lifestyle choices, including weight management, stopping smoking, being physically active and consuming a low salt and low protein diet. SGLT2 inhibitors did not form part of SoC when the trial was conducted

	although a small proportion of participants ([redacted]% in the RCT; [redacted]% in the OLE) received one as a concomitant medication. Our clinical experts have advised that around 70% of patients would be expected to receive an SGLT2 inhibitor as part of SoC. Additionally, sparsentan (a dual endothelin angiotensin-receptor antagonist) has recently been recommended by NICE and it is expected that it will replace RASi therapy. The NeflgARD Nef-301 trial provides data that informs the transition probabilities for the company's economic modelling of disease progression (link to Key Issue 2) and the Nef-301 OLE informs the proportion of patients being retreated with TRF-budesonide. It is unclear what impact, if any, the changes to SoC might have on effectiveness estimates from NeflgARD Nef-301 and the proportion of patients eligible for re-treatment. It is also unclear what impact the changes to SoC might have on when patients are retreated with TRF-budesonide.
What alternative approach has the EAG suggested?	None. This is a limitation of the available evidence.
What is the expected effect on the cost-effectiveness estimates?	The potential impact on the cost-effectiveness estimates is unknown. EAG exploratory analysis suggests that reduced rates of CKD progression with use of more effective treatments in standard care would reduce the relative cost-effectiveness of TRF-budesonide. However, this analysis is highly uncertain.
What additional evidence or analyses might help to resolve this key issue?	Discussion with clinical experts to discern their views on whether the changes to SoC (the use of SGLT2 inhibitors and sparsentan) that have occurred since the NeflgArd Nef-301 RCT was conducted could alter the relative efficacy of budesonide versus SoC and/or the proportion of patients eligible for re-treatment with a further course of TRF-budesonide after their initial course of treatment.

Issue 2 Re-treatment with TRF-budesonide

Report section	3.2.1.1.2, 3.2.2.2 and 3.2.6
Description of issue and why the EAG has identified it as important	The Nef-301 OLE provides evidence on the effects of re-treatment, but the study was rated by both the company and us as having an overall serious risk of bias. We are concerned about how generalisable the results are. Our concern about generalisability arises in part because there were 27 participants from the TRF-budesonide arm of the RCT who would have been eligible for the OLE but who were not screened (27 participants from the placebo arm of the trial were also not screened). It is not clear whether the 27 participants from the TRF-budesonide arm of the trial who did not take part differed in any way to the 45 participants who did take part. Additionally, there is a lack of long-term follow-up data for re-treatment because after the 9-month re-treatment period with TRF-budesonide ended, there was

	only a further 3-months of follow-up. There is also no evidence for any additional rounds of re-treatment. Finally, the changes to SoC described in Key Issue 1 apply to the data from the Nef-301 OLE and, as described in Key Issue 1, it is unclear what impact this might have on the proportion of participants eligible for re-treatment or when re-treatment might be received. Our clinical experts have advised that SGLT2 inhibitor use could impact on the proportion of patients eligible for retreatment (because of a reduced level of proteinuria). They also advised that when retreated, the response to re-treatment is potentially likely to be similar to the initial response.
What alternative approach has the EAG suggested?	None. This is a limitation of the available evidence.
What is the expected effect on the cost-effectiveness estimates?	The potential impact of the participants who would have been eligible for the OLE but were not screened on the cost-effectiveness estimates is unknown. The company conducted scenario analyses to explore the effects of increasing the number of rounds of re-treatment undertaken (scenarios for 3, 4, 5 or 6 rounds), varying the subsequent treatment effect (scenarios for 70%, 80% and 100%), varying the proportion eligible for re-treatment (scenarios for 25%, 33% and 50%) and altering the time between re-treatment cycles (scenarios for 20.75 months, 26.75 months and 32.75 months). In these scenarios the ICER £/QALY was either dominant or ranged from £15 to £11,532.
What additional evidence or analyses might help to resolve this key issue?	Further discussion with clinical experts about the extent to which the results of the Nef-301 OLE might be generalisable to the population of people with IgA nephropathy who would be considered for re-treatment with TRF-budesonide.

1.5 The cost-effectiveness evidence: summary of the EAG's key issues

Issue 3 High uncertainty about transition probabilities

Report section	4.2.6.1
Description of issue and why the EAG has identified it as important	There is high uncertainty about the transition probabilities that inform movement of patients between modelled disease stages CKD 1 to CKD 4 because of sparse data on observed transitions between these disease stages from the NeflgArd Nef-3 RCT. Additionally, the impact of changes to standard of care (see Key Issue 1) on transitions between disease stages is unknown.
What alternative approach has the EAG suggested?	This is a data availability issue. Additional analysis of comparative data from the trial is unlikely to reduce uncertainty.
What is the expected effect on the cost-effectiveness estimates?	The effect of uncertainty over relative treatment effects on transition probabilities is unknown. Simple exploratory analysis suggests that improvements in standard care may

	reduce the relative benefit of adding TRF-budesonide, but this is highly uncertain.
What additional evidence or analyses might help to resolve this key issue?	Modelling of background transition probabilities for CKD progression based on a large dataset reflective of current practice, with relative treatment effects estimated from the trial (e.g. Inker 2019, Barratt et al. 2024). However, it is not clear that this would reduce uncertainty.

Issue 4 Dosing and wastage for TRF-budesonide in NHS practice

Report section	4.2.10.1.1
Description of issue and why the EAG has identified it as important	There is a lack of clarity over when the two-week dose reduction to 8 mg per day should occur – after or within the full 9 month treatment course. This is not clearly described in the company's submission, and there is some inconsistency in how it is described in the clinical and economic sections of their report. The company commented on this issue in the factual accuracy check, confirming that the treatment course in the NefIgArd Nef-301 trial was 16 mg once daily for 9 months, followed by a further 2 weeks of treatment at a reduced dose of 8 mg once daily. This is inconsistent with the company's base case assumption for economic analysis (that the 2-week dose reduction occurs within the 9-month treatment period). The company noted that the SmPC wording on the timing of the dose reduction prior to treatment discontinuation is open to interpretation, and that they had reported 'an alternative plausible' scenario with the discontinuation dose reduction applied after 9 months of treatment at full dose. Assumptions regarding the timing of dose reductions prior to stopping treatment have implications for costing in the economic model. The cost-per-mg method used to cost TRF-budesonide over the treatment cycle in the company's submission does not account for wastage that is likely to occur when a full pack of 120 tablets is required to provide treatment at the reduced 8 mg dose for 2 weeks prior to discontinuation, or for the optional further reduction to 4 mg dose for 2 weeks. In the factual accuracy check, the company report that a smaller 28 x 4 mg tablet pack is now available, at a pro-rata price relative to the 120 tablet pack. This should help to reduce wastage.
What alternative approach has the EAG suggested?	TRF-budesonide costs in the economic model should reflect the full cost to the NHS of prescribing at the appropriate dose for the appropriate period of time, including any necessary wastage with the provision of full packs.
What is the expected effect on the cost-effectiveness estimates?	In the factual accuracy check, the company reported three estimates of additional costs due to wastage, assuming efficient prescribing of the 120 tablet and 28 tablet packs of TRF-budesonide: an additional [redacted] per patient if the pre-discontinuation dose reduction is used within the 9-month

	treatment (as in their base case analysis); [redacted] per patient if the reduced dose is used after 9 months of treatment; and a further [redacted] per patient if the optional two-week further dose reduction is used. We note some uncertainty over these estimates, but that these additional wastage costs are unlikely to change the cost-effectiveness results, unless combined with other more conservative assumptions.
What additional evidence or analyses might help to resolve this key issue?	Clarity on the appropriate timing of dose reduction(s) prior to discontinuation of TRF-budesonide, in relation to the 9 month full course of treatment, and when treatment is discontinued before this time.

1.6 Other issues: summary of the EAG's view

The NICE scope states that, if the evidence allows, the subgroup of people at risk of rapidly progressive immunoglobulin A (IgA) nephropathy (UPCR≥1.5 g/g) will be considered but this subgroup is not included in the company's decision problem. Some clinical effectiveness data are provided for this subgroup (Company submission [CS] Appendix C.1 and clarification response A1) and separate transition probabilities were calculated for subgroups of patients with UPCR <1.5g/g and UPCR ≥1.5g/g but this was not implemented in the model (clarification response B2). Although not requested in the NICE scope, we would have liked to see cost-effectiveness analysis for the subgroup with UPCR ≥ 0.8 g/g and < 1.5g/g for whom budesonide is not currently recommended. It might have been informative to see how cost-effectiveness estimates vary for this subgroup in comparison to the subgroup with UPCR≥1.5 g/g for which TRF-budesonide is already recommended (NICE TA937). However, we also recognise that the power of the trial evidence would be reduced and uncertainty around the results increased in a subgroup analysis. There is also a lack of information available for model parameters in addition to eGFR stratified by UPCR.

1.7 Summary of EAG's preferred assumptions and resulting ICER

Table 2 Cumulative change from company base case to results with EAG preferred assumptions (deterministic)

Scenario	Incremental cost	Incremental QALYs	INMB
Company's base case	[redacted]	[redacted]	£9,231
1. EAG correction of SoC drug cost (denominator)	[redacted]	[redacted]	£9,225
2. Cost of SGLT2i: 10 mg tablet to match daily dose	[redacted]	[redacted]	£9,439

Scenario	Incremental cost	Incremental QALYs	INMB
3. SMRs: UK RaDaR, with CKD 3a / 3b = CKD 2	[redacted]	[redacted]	£9,416
EAG's preferred base case	[redacted]	[redacted]	£9,416

Source: EAG using CS model with the respective changes
ICER, incremental cost-effectiveness ratio; Incr,, incremental; INMB, incremental net monetary benefit; LYs, life years gained; QALYs, quality-adjusted life years; SMRs, standardised mortality ratios; SGLT2i, Sodium/glucose cotransporter 2 inhibitor; SoC, standard of care; TRF, targeted-release formulation.

Modelling errors identified and corrected by the EAG are described in 5.3.1.1.2. For further details of the exploratory and sensitivity analyses done by the EAG, see 6.1.

2 INTRODUCTION AND BACKGROUND

2.1 Introduction

This report is a critique of the company's submission (CS) to NICE from Genus Pharmaceuticals on the clinical effectiveness and cost effectiveness of targeted release formulation (TRF)-budesonide budesonide (Kinpeygo) for treating adults with primary immunoglobulin A (IgA) nephropathy with a urine protein excretion ≥1.0 g/day or urine protein-to-creatinine ratio ≥ 0.8g/g. It identifies the strengths and weaknesses of the CS. Clinical experts were consulted to advise the external assessment group (EAG) and to help inform this report.

Clarification on some aspects of the CS was requested from the company by the EAG via NICE on 12 June 2025. A response from the company via NICE was received by the EAG on 3 July 2025 and this can be seen in the NICE committee papers for this appraisal.

2.2 Background

2.2.1 Background information on Immunoglobulin A nephropathy

IgA nephropathy is an autoimmune, primary glomerular disease; that is, it is a condition that affects the glomeruli in the kidney (the glomeruli filter waste and fluid from the bloodstream to produce urine).[1, 2] Its prevalence is highest among people of East Asian descent, with a relatively high prevalence also among people who are Caucasian.[1-3] It is rarer among people of sub-Saharan African descent.[1-3] It is estimated that around one in 50,000 people in the United Kingdom (UK) has IgA nephropathy,[4] with just over 18,000 people affected in England.[5]

IgA nephropathy is thought to be caused when galactose-deficient IgA1 (Gd-IgA1) is produced, which in turn prompts the production of anti-Gd-IgA1 antibodies.[2] Antigen-antibody complexes are formed and these can induce local inflammation and complement activation in the glomeruli of the kidney, which ultimately leads to glomerular injury (i.e. damage to the filtering units of the kidney).[2]

The clinical presentation of IgA nephropathy can be variable, but it is often characterised by either visible or invisible haematuria (blood in the urine).[1, 6] Sometimes proteinuria (a high level of protein in the urine) may also be present.[1, 6] More rarely, patients may already have established chronic kidney disease (CKD) or show a fast and significant increase in blood pressure (malignant hypertension) on presentation.[6] It is estimated that between 20% to 40% of patients with IgA nephropathy will develop end-stage renal disease (ESRD) between

10 to 20 years after they are diagnosed.[7] Risk factors for progression to ESRD include hypertension, persistent proteinuria (particularly if it is >1g/day), reduced glomerular filtration rate (GFR) and smoking.[1, 2]

2.2.2 Background information on targeted-release budesonide

TRF-budesonide is an oral glucocorticosteroid and its active component is released in the distal ileum, where it reduces Gd-IgA1 (CS Table 2, Fellström et al., 2017,[8] Liao et al., 2023[2] and Ouyang et al., 2025[9]). This then has an impact on subsequent steps in disease processes and through this mechanism is thought to reduce kidney inflammation and potentially reduce the pace of disease progression (CS Table 2).

TRF-budesonide initially had a marketing authorisation for the treatment of IgA nephropathy in adults who were at risk of rapid disease progression with a urine protein-to-creatinine ratio (UPCR) of ≥1.5 grams per gram (g/g) and was appraised by NICE within this full marketing authorisation indication as Technology Appraisal (TA) 937.[10] NICE recommended TRF-budesonide as an add-on to standard care in this population in December 2023. The company made a UK marketing authorisation application for the use of TRF-budesonide with an anticipated treatment indication of adults with primary IgA nephropathy with a urine protein excretion of ≥1.0g/day (or UPCR ≥0.8g/g) (CS Table 2).[11] The latter indication is the focus of this appraisal (CS section 1.1). When the company completed the factual accuracy check and confidential information check they stated that the marketing authorisation had been received.

TRF-budesonide is administered by oral capsule.[9, 11] The recommended dose is 16 mg once daily, taken as four 4 mg capsules in the morning, at least an hour prior to a meal (CS Table 2). It is recommended that TRF-budesonide is taken for nine months (CS Table 2). If the treatment needs to be discontinued, the dose is reduced to 8 mg once a day for two weeks, with an option to further reduce the dose to 4 mg once a day for an additional two weeks if considered necessary by the treating clinician (CS Table 2). Clinicians can consider at their discretion whether patients can undergo re-treatment with TRF-budesonide (CS Table 2).

2.2.3 The position of TRF-budesonide in the treatment pathway

Figure 1 is a reproduction of the company's depiction of the treatment pathway for IgA nephropathy which aims to simultaneously manage the i) consequences of IgA nephropathy-induced nephron loss and ii) the IgA nephropathy-specific drivers of nephron loss. This treatment pathway is sourced partly from: i) the Kidney Disease – Improving Global Outcomes (KDIGO) 2024 draft Clinical Practice Guideline for the management of immunoglobulin A nephropathy and immunoglobulin A vasculitis[12] (this is an update of a

2021 Guideline for the Management of Glomerular Diseases[13] which itself was an update of the original Clinical Practice Guideline for Glomerulonephritis published in 2012[14]), and ii) the existing NICE guidance for TRF-budesonide (TA937[10]). Managing the consequences of IgA nephropathy-induced nephron loss should include lifestyle advice (e.g. sodium restriction, smoking cessation, weight control, exercise); blood pressure control, use of renin-angiotensin system (RAS) inhibitors (RASi) and sodium-glucose cotransporter-2 (SGLT2) inhibitors (e.g. dapagliflozin and empagliflozin are both recommended by NICE for treating chronic kidney disease in TA1075[15] and TA942[16] respectively) to reduce glomerular hyperfiltration and proteinuria impact on the tubulointerstitium (the renal tubules and the surrounding interstitial tissue) and an assessment of cardiovascular risk plus interventions to reduce this if necessary.[17] Two classes of RAS inhibitors are relevant to this appraisal, angiotensin-converting enzyme inhibitors (ACEi) and angiotensin-receptor blockers (ARBs). Although not shown on CS Figure 7, NICE has recently recommended sparsentan (TA1074[18]), a dual endothelin angiotensin-receptor antagonist[19] which also acts to reduce proteinuria and can be used alongside lifestyle modification, SGLT2 inhibitors and TRF-budesonide.[18] If added to Figure 1, sparsentan would sit in the left hand box as one of the treatments to manage the generic response to IgA nephropathy induced nephron loss and it is expected that it will replace RASi therapy.[18] To manage the IgA nephropathy-specific drivers of nephron loss, as stated in section 2.2.2, TRF-budesonide has already been recommended by NICE for patients with a UPCR ≥1.5 g/g (TA937[10]) and the current submission would extend the use of TRF-budesonide to patients with a UPCR ≥0.8 g/g. The two clinical experts we consulted agreed that the company's depiction of the treatment pathway broadly matched what occurs in NHS practice (aside from the recent addition of sparsentan as noted above) but one expert also noted that most clinicians would have a lower threshold for starting disease-modifying therapy and modified release budesonide preparations formulated for inflammatory bowel disease may be used off label for this purpose. Clinicians know that reducing proteinuria has a long-term benefit and aim to reduce this as far as feasible.

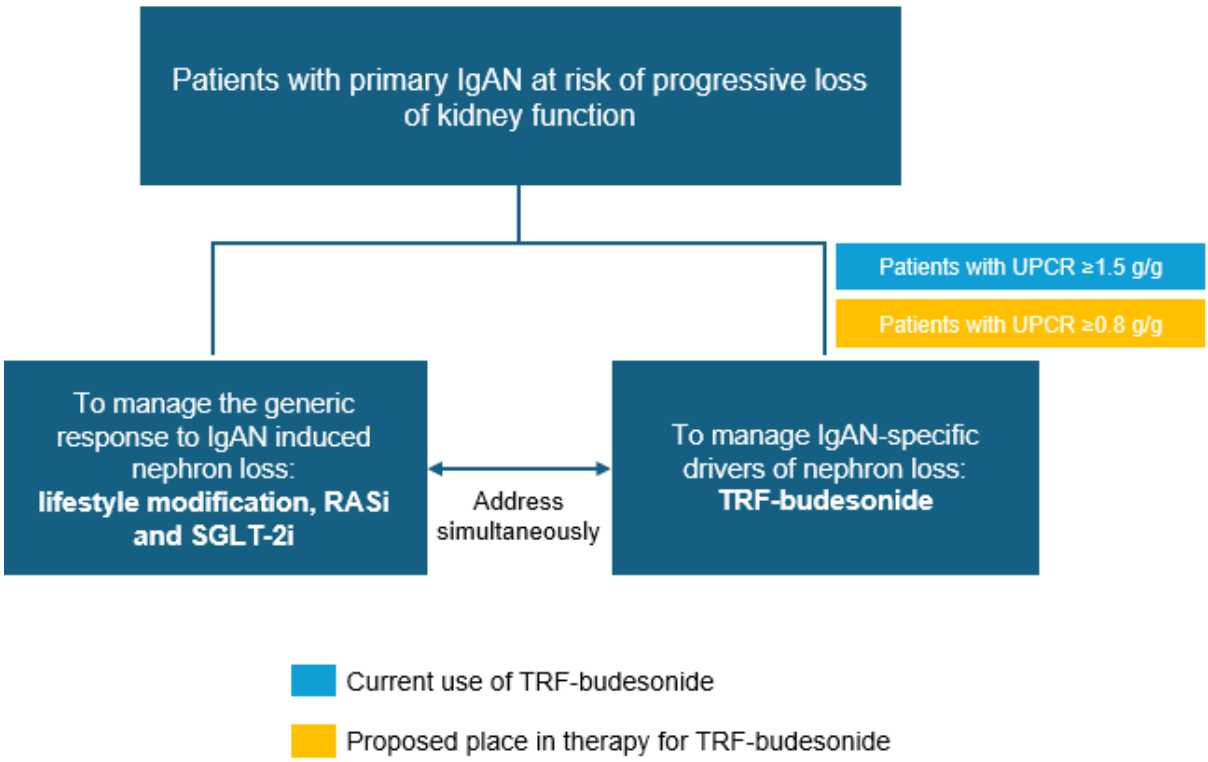

Figure 1 Treatment pathway for IgA nephropathy

Source: reproduction of CS Figure 7
IgAN, Immunoglobulin A nephropathy; RASi, renin-angiotensin system inhibitor; SGLT-2i, sodium glucose cotransporter 2 inhibitor; TRF, targeted-release formulation; UPCR, urine protein-creatinine ratio.

EAG comment

The company provide details about the pathogenesis, diagnosis, disease course and risk factors for progression of IgA nephropathy (CS section 1.3.1) as well as describing the epidemiology of IgA nephropathy (CS section 1.3.2). The clinical, humanistic and health care aspects of the burden of disease are also summarised (CS section 1.3.3). The anticipated place of TRF-budesonide for patients with IgA nephropathy and a UPCR of ≥0.8 g/g in the clinical pathway of care is described (CS section 1.3.4), in line with the anticipated expanded licenced indication. We note that sparsentan, which has recently been recommended by NICE (TA1074[18]), is not included in the company's depiction of the treatment pathway in CS Figure 7 and is not included as part of standard of care in the CS (at the time of submission TA1074 had not been published).

2.3 Critique of the company's definition of the decision problem

Table 3 summarises the decision problem addressed by the company in the CS in relation to the final scope issued by NICE and the EAG's comments on this. The company decision problem reflects the NICE scope with the exception that the company have not included a separate economic analysis for the subgroup of patients with a UPCR of 1.5g/g or more. Some clinical effectiveness data are provided for this subgroup in CS Appendix C.1 and clarification response A1, and the company's response to clarification question B2 indicates that separate transition probabilities were calculated for subgroups of patients with UPCR <1.5g/g and UPCR ≥1.5g/g but this was not implemented in the model (see section 4.2.3). Although NICE have already produced guidance for the subgroup with UPCR ≥1.5g/g in TA937[10] the recently updated marketing authorisation for TRF-budesonide is for an expanded population with primary IgA nephropathy and a urine protein excretion ≥1.0 g/day (or urine protein-to-creatinine ratio ≥0.8 g/g) and differences in transition probabilities between subgroups could affect cost-effectiveness in the subgroup with UPCR ≥0.8g/g to <1.5g/g for whom TRF-budesonide is currently not recommended.

Table 3 Summary of the decision problem

	Final scope issued by NICE	Company's decision problem	Rationale if different from the final NICE scope	EAG comments
Population	Adults with primary IgA nephropathy with a urine protein-to-creatinine ratio of 0.8 g/gram or more.	Adults with primary immunoglobulin A nephropathy (IgAN) with a urine protein excretion ≥1.0 g/day (or urine protein-to-creatinine ratio ≥0.8 g/g)	The population addressed in the company submission is aligned with the anticipated licensed indication for TRF-budesonide	In line with scope

	Final scope issued by NICE	Company's decision problem	Rationale if different from the final NICE scope	EAG comments
Intervention	Targeted-release budesonide as an add-on to standard care	As per scope	Not applicable[a]	In line with scope

Comparators	Individually optimised standard care without targeted-release budesonide: Standard care is defined as:
	• ACE inhibitors and ARBs at the maximum tolerated licensed doses, diuretics, and dietary and lifestyle modification, with or without:
	  • SGLT2 inhibitors
	  • Sparsentan (subject to NICE evaluation)
		As per scope	Not applicable[a]	In line with scope. At the time the CS was completed and received by us, the NICE guidance on sparsentan TA1074[18]) was not published and therefore sparsentan is not included as part of standard care.

Outcomes	The outcome measures to be considered include: • proteinuria (for example, change from baseline in urine protein creatine ratio) • kidney function (eGFR)	As per scope	Not applicable[a]	In line with scope

	Final scope issued by NICE	Company's decision problem	Rationale if different from the final NICE scope	EAG comments
	• disease progression (dialysis and/or transplant) • mortality • adverse effects of treatment • health-related quality of life			
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective.	This row of NICE scope not included in CS Table 1.	Not applicable[a]	The company's economic analysis adheres to the NICE reference case. CS Table 2 indicates that a simple discount has been agreed with NHS England, and this is applied in the economic evaluation (CS section 3.5.1.1 and CS Table 57).

	Final scope issued by NICE	Company's decision problem	Rationale if different from the final NICE scope	EAG comments
Subgroups	If the evidence allows the following subgroup will be considered: • People at risk of rapidly progressive IgA nephropathy (urine protein-to-creatinine ratio of 1.5g/gram or more)	Subgroup not included	The evidence for the clinical and cost effectiveness of TRF-budesonide for patients at risk of rapidly progressive IgA nephropathy (urine protein-to-creatinine ratio of 1.5g/gram or more) has previously been presented and accepted by NICE in TA937. The population considered within the submission is aligned with the anticipated marketing authorisation for TRF-budesonide, which will cover all patients with primary IgAN and a urine protein excretion ≥1.0	The company have not included a separate economic analysis for patients with a UPCR of 1.5g/gram or more. Results from Part B of the key trial are provided for some outcomes by baseline UPCR (<1.5g/gram or ≥1.5g/gram) in CS Appendix C.1 (see section 3.2.5.4). In response to clarification question A1 the company reiterated their rationale for not including the UPCR 1.5g/gram or more subgroup and indicated that in the Nef-301 OLE the number of patients in the subgroup with a UPCR of 1.5g/gram or more was [redacted]

	Final scope issued by NICE	Company's decision problem	Rationale if different from the final NICE scope	EAG comments
			g/day (or urine protein-to-creatinine ratio ≥0.8 g/g)	[redacted], limiting potential meaningful analysis. However, the company also indicate in response to clarification question B2 that they had calculated separate transition probabilities for subgroups by UPCR (<1.5g/g and ≥1.5g/g) but these had not been implemented in the model.
Special considerations including issues related to equity or equality	Guidance will only be issued in accordance with the marketing authorisation. Where the wording of the therapeutic indication does not include specific treatment combinations, guidance will be issued only in the context of the evidence that has underpinned the	This row of NICE scope not included in CS Table 1.	Not applicable[a]	No equity or equality issues were raised in the NICE scope and none have been identified by us or our experts

	Final scope issued by NICE	Company's decision problem	Rationale if different from the final NICE scope	EAG comments
	marketing authorisation granted by the regulator.			

Source: CS Table 1 with EAG comments added to the final column and minor changes as indicated in the footnotes.
ACE, Angiotensin-converting enzyme; ARB, Angiotensin-receptor blocker; CS, Company submission; eGFR, Estimated glomerular filtration rate; EAG, External Assessment Group; IgA, Immunoglobulin A; IgAN, Immunoglobulin A nephropathy; NA, Not applicable; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; OLE, open-label extension; SGLT2, Sodium/glucose cotransporter 2; TA, Technology Appraisal; TRF, Targeted-release formulation; UPCR, urine protein-to-creatinine ratio.
[a] Not applicable added by EAG, not included in CS Table 1

3 CLINICAL EFFECTIVENESS

3.1 Critique of the methods of review(s)

The company's systematic literature review was underpinned by a broad search to identify efficacy, safety and health-related quality of life (HRQoL) evidence for a population with primary IgA nephropathy treated either with TRF-budesonide or established treatments relevant to the NICE scope (CS Appendix B.1). Our detailed critique of the company's systematic review methods is provided in Appendix 1. We do not have any major concerns about how the review was conducted and it appears unlikely that any relevant evidence has been omitted.

3.2 Critique of studies of the technology of interest, the company's analysis and interpretation (and any standard meta-analyses of these)

3.2.1 Included studies

The company's systematic literature review found 65 records, plus one health technology assessment, that were included in the review which appear to represent 45 studies (41 identified from the original search plus 4 new studies identified by the update search). Of these, five publications representing a phase 2b RCT, a phase 3 RCT and the open-label extension for the phase 3 RCT provide evidence for TRF-budesonide in a population of adults with primary IgA nephropathy. The phase 3 RCT included a population with an estimated glomerular filtration rate (eGFR) of ≥35 and ≤90 mL/min per 1.73 m^2 and proteinuria ≥1 g/day or UPCR ≥0.8 g/g and its open label extension had mostly the same entry criteria except that the eGFR could be ≥30 mL/min per 1.73 m^2. The phase 2b RCT included a population with an eGFR ≥45 mL/min per 1.73 m^2 and a urine protein of ≥0.75 g/24-h or UPCR >0.5 g/g. These studies are summarised in CS Table 4 with additional information on their role in the CS and EAG comments about the studies in Table 4. In this report we focus on the phase 3 NeflgArd Nef-301 RCT and its open-label extension and signpost the reader to the CS for information on the phase 2b Nefigan Nef-202 RCT.

Table 4 Clinical effectiveness evidence and its role in the CS

Role in CS	EAG comments
NeflgArd Nef-301 (NCT03643965), Part A and Part B	
Part A: evaluated 9 months of treatment with TRF-budesonide 16 mg per day and 3 months of follow up for the first 201 participants randomised to the study. Results	When TA937 was conducted, the marketing authorisation for TRF-budesonide was for the treatment of primary IgA nephropathy in adults at risk

Role in CS	EAG comments
presented in CS Appendix J.2 but not used in the economic model. Part B: is the focus of the CS and contributes data to the economic model (informing baseline characteristics for the modelled population, transitions between CKD 1-4 health states between 0 and 24 months, adverse event rates and time to treatment discontinuation). Part B consisted of a one-year follow-up period from the end of Part A and no study treatment was given. Parts A and B therefore collectively evaluated 9 months of treatment and 15 months of follow up for all participants randomised to the study.	of rapid disease progression with a UPCR of ≥1.5g/g. The key evidence presented in the CS for TA937 came from Part A of the trial and focussed on the subgroup of participants that aligned with the licensed indication at the time. The full Part A results were presented in an appendix (CS for TA937 Appendix M). Part A results have now been superseded by the longer-term data from Part B. For the current submission the evidence presented covers the updated full anticipated marketing authorisation (adults with primary IgA nephropathy with a urine protein excretion ≥1.0g/day [or UPCR ≥0.8 g/g]) and all but two of the 366 randomised patients for the 9 month treatment period and the 15 month observational follow-up period (i.e. the participants randomised to the 'global study' part of the trial; see section 3.2.1.1.1).
Nef-301 OLE (NCT04541043)	
Results inform the proportion of patients eligible for re-treatment in the health economic model.	The proportion of patients eligible for re-treatment in the health economic model has been updated since TA937. In TA937 the proportion ([redacted]%) was obtained from those in CKD stages 1 to 3b who were still on treatment at the end of their initial treatment in Part A of the trial. In the current CS, the proportion eligible for re-treatment is [redacted]% based on those who met the criteria for inclusion in the OLE (OLE participants were in CKD stages 1 to 3b). The draft SmPC[11] states that re-treatment may be considered at the

Role in CS	EAG comments
	discretion of the treating physician. No specific eligibility criteria for re-treatment are provided.
Nefigan Nef-202 (NCT01738035)	
Summary provided in CS Appendix K. Results not used in economic model.	During TA937 the non-inclusion of data from this trial in the economic analysis was raised as a key issue. During technical engagement the company provided an analysis of pooled data from Nefigan Nef-202 and NeflgArd Nef-301 Part A for adults with primary IgA nephropathy at risk of rapid disease progression with a UPCR of ≥1.5g/g. The TA937 EAG agreed that the pooled results confirmed that the results from Nef-202 did not contradict the results from Nef-301. For this review of TA937 in a population of adults with primary IgA nephropathy and a urine protein excretion ≥1.0g/day (or UPCR ≥0.8 g/g) longer term data from NefligArd Nef-301 Part B are available and there is no equivalent longer term data from Nefigan Nef-202 that can be included.

Source: EAG created table
CKD, chronic kidney disease; CS, company submission; EAG, External Assessment Group; OLE, open-label extension; SmPC, Summary of product characteristics; TA, Technology Assessment; UPCR, Urine protein-to-creatinine ratio.

3.2.1.1 Study characteristics

3.2.1.1.1 NeflgArd Nef-301 (NCT03643965)

The NeflgArd Nef-301 trial was a phase 3, double-blind, multicentre RCT that evaluated the efficacy and safety of optimised RASi therapy plus TRF-budesonide 16 mg/day compared with optimised RASi therapy plus placebo in a population of adults with primary IgA nephropathy, who were at risk of progressing to ESRD despite receiving maximum tolerated

RASi treatment (CS Table 4 and CS section 2.3.1). Participants were included in the trial if they had an eGFR ≥35 and ≤90 mL/min per 1.73 m^2, a proteinuria ≥1 g/day or UPCR ≥0.8 g/g twice consecutively and were receiving a stable dose of RASi (ACE inhibitors and/or ARBs) at the maximum allowed or tolerated dose set out in the 2012 KDIGO guidelines for three months before randomisation (target systolic blood pressure <125 mmHg and diastolic blood pressure <75 mmHg recommended) (CS Table 5; please also see CS Table 5 for a full list of the trial's participant eligibility criteria). A total of 395 participants were randomised into the trial, which consisted of 366 participants in the 'global study', plus another 29 participants recruited in China (CS Appendix Figure 3). The trial was divided into two parts (Parts A and B):

- **Part A** assessed the efficacy and safety of TRF-budesonide (CS Table 4). After an initial screening period of up to 35 days, there was a nine-month blinded treatment period during which participants were randomised to either oral TRF-budesonide 16 mg/day administered via four 4 mg capsules once daily or matching placebo once daily. If clinically relevant adverse events occurred, the dose of the study drug could be reduced to two capsules once daily, but could not be increased again. Following the treatment period, there was a three-month observational follow-up period which consisted of two weeks during which the study treatment was tapered and then 10 weeks during which no study drug was administered (CS sections 2.3.1.3, 2.3.1.6 and CS Figure 8). However, we note CS section 3.2.3.1 states that the two weeks when study treatment was tapered occurred during the last month of the 9-month treatment period. Therefore there is a lack of clarity over when the two-week dose reduction should occur and this is an important consideration for the economic modelling (Key Issue 4). Optimised RASi was continued throughout Part A. In clarification response A4, the company stated that in addition to participants receiving optimised supportive care in the form of optimised RASi therapy, participants were encouraged at their screening visit to make and maintain healthy lifestyle choices, including weight management, stopping smoking, being physically active and consuming a low salt and low protein diet. Of the 395 participants who were randomised into the trial, 197 were allocated to TRF-budesonide and 198 to placebo (CS Appendix Figure 3).
- **Part B** assessed the longer-term impact of TRF-budesonide on renal function, and the drug's safety and tolerability (CS Table 4 and CS section 2.3.1). In this part of the trial optimised RASi was continued, but no other intervention was given (CS Table 4 and CS section 2.3.1.3). However, rescue medication (steroids and/or immunosuppressive treatment) was permitted, if needed, for participants with a proteinuria level of >1g per 24

hours. In Part B, participants were followed up for a period of 12 months (+14 to 35 days) after Part A had ended. Thus, this part of the trial, together with Part A, provided follow-up data for 25 months after participants received their first dose of the study drug or after participants were randomised in the case of those who did not receive the study drug. The Part B full analysis set (FAS) population, for which results are presented in the CS, consisted of 364 randomised participants (182 in each arm) (CS Appendix Figure 3).

The company state that Part A data are not used in their economic model for this appraisal, as Part A has been superseded by the longer-term follow-up data from Part B (CS Table 4).

The primary outcome of Part B was a time-weighted average of eGFR observations at measurement timepoints over the two-year follow-up period (CS Table 4 and CS section 2.3.1.8). The trial was conducted in 20 countries, including the UK. A total of [redacted] patients from the UK took part in Part B.[20] The trial is complete (CS Table 4).

The EAG has the following comments about the NeflgArd Nef-301 trial:

- It evaluated the anticipated marketing authorisation-recommended dose of TRF-budesonide, in the company's decision problem population and the anticipated extended marketing authorisation indication of patients with primary IgA nephropathy with a urine protein excretion ≥1.0g/day (or UPCR ≥0.8 g/g). Therefore, the whole trial population matches the population of interest in this appraisal.
- A clinical expert advised us that the participant eligibility criteria for the trial (CS Table 5) were generally representative of the patients they expect to receive TRF-budesonide in clinical practice, but that the blood pressure target is low and might not be achievable for all patients. This expert also did not expect that patients in clinical practice will have been in receipt of RASi therapy for three months prior to starting TRF-budesonide, as required in the trial; they expect patients will move onto TRF-budesonide more quickly and will be more likely to have been in receipt of RASi for around a month before starting TRF-budesonide.
- The standard care provided in the trial does not fully represent current standard care in clinical practice. We were advised by our clinical experts that, although standard care is currently in a state of flux, most patients will receive an ACE inhibitor or an ARB, a sodium/glucose cotransporter 2 (SGLT2) inhibitor (around 70% of patients) and lifestyle modification. In the trial, SGLT2 inhibitors do not appear to have been used as part of standard care (although were used by [redacted] of the participants in each trial arm as a concomitant medication; CS Table 8). The company acknowledges in CS section 2.13.2

that standard care has changed since the trial was conducted and that the SGLT2 inhibitor dapagliflozin is being increasingly used in the management of IgA nephropathy. The company also acknowledges that there are no data available on the effects of TRF-budesonide when used alongside standard care that includes SGLT2 inhibitors, but they state that clinical experts expect that SGLT2 inhibitors and TRF-budesonide would have an additive effect, as they work through different mechanisms of action. Both our clinical experts agreed that it is likely that the two drugs will have an additive effect. Additionally, since the company submitted the CS, NICE has recommended sparsentan for treating primary IgA nephropathy, which is expected to be used with current standard care, including SGLT2 inhibitors and TRF-budesonide, and is expected to replace RASi therapy.[18] We raise this as part of Key Issue 1.

- We received clinical expert advice that the rescue medication (steroids and/or immunosuppressive treatment) permitted for participants in Part B of the trial who had a proteinuria level of at least above 1g per 24 hour would not be used in clinical practice under this circumstance. We were advised that after a trial of budesonide, such patients would be offered standard of care or entry into a trial. We note that in the primary efficacy analyses of Part B, data affected by rescue medication were excluded so that the relative efficacy of budesonide versus placebo could be estimated free of the effects of rescue medication (CS section 2.6.1.1). A sensitivity analysis that included observed data from participants who had received rescue medication was also conducted (CS Appendix J.1.2).
- We received clinical expert advice that the dose reduction approach to managing adverse events related to the study drug in the trial was reasonable.
- A point was raised by the EAG in TA937 that the results of the NeflgArd Nef-301 trial may not have been generalisable to patients with IgA nephropathy who are not receiving RASi therapy in clinical practice. However, the committee noted that sometimes the maximally tolerated dose of RASi therapy will be no dose (a point also made by one of our clinical experts) and in this circumstance, TRF-budesonide would still be being used as an add-on to standard care.[10]

3.2.1.1.2 Nef-301 OLE (NCT04541043)

Participants who had completed the NeflgArd phase 3 trial and who had persistent proteinuria ≥1g/day or UPCR ≥0.8 g/g and eGFR ≥30 mL/min/1.73m^2 despite optimised RASi, could enter the Nef-301 open-label extension (OLE) (CS Table 4, CS Figure 9 and CS section 2.3.4.1). This was a phase 3b, single arm trial that evaluated the impact of 9 months

of treatment with TRF-budesonide 16 mg/day (administered via four 4mg capsules once a day) on UPCR and eGFR among participants originally randomised to either TRF-budesonide or placebo in the NeflgArd Nef-301 trial, who were receiving an optimised and stable dose of RASi (CS Table 4, CS Figure 9 and CS sections 2.3.4.1.1 and 2.3.4.1.5). All participants received open-label TRF-budesonide 16 mg/day. Thus, the trial evaluated the effects of re-treatment with TRF-budesonide among those who had originally been randomised to TRF-budesonide in the NeflgArd Nef-301 trial and the effects of a first course of TRF-budesonide among those who had originally been randomised to placebo (CS section 2.3.4.1.2). Although the OLE was open-label with all patients receiving TRF-budesonide, participants and investigators remained blinded to participants' originally randomised treatment in NeflgArd Nef-301 (CS section 2.3.4.1.2).

In the OLE, in line with the NeflgArd Nef-301 phase 3 trial, the dose of TRF-budesonide could be modified during the nine-month treatment period to 8 mg/day if adverse events considered to be related to the drug occurred (CS section 2.3.4.1.5). A two-week tapering period was also implemented at the end of the nine-month treatment period, where the dose of TRF-budesonide was reduced to two capsules once a day (CS section 2.3.4.1.5). The primary outcomes of the OLE were the ratios of eGFR and UPCR at 9 months versus the OLE baseline (CS Figure 9). The OLE also included a further follow-up at 12 months (CS Figure 9), which combined with the NeflgArd Nef-301 trial provides a total of three years of follow-up data from starting a first course of TRF-budesonide treatment or randomisation. If participants received rescue medication in the OLE (systemic steroids, immunosuppressive treatment, and/or dialysis), they had to be withdrawn from TRF-budesonide treatment, but continued to be followed-up up to 12 months (CS section 2.3.4.1.6). In the OLE, [redacted] and [redacted] of participants in the original TRF-budesonide and placebo arms, respectively, were in receipt of SGLT2 inhibitors as a concomitant medication (CS Table 12). We raise this as part of Key Issue 1.

A total of 234 participants from the NeflgArd Nef-301 trial met the eligibility criteria for the Nef-301 OLE (CS section 2.4.2.5 and clarification response A8). Of these 180 underwent screening for the OLE, while 54 did not. The reasons why 54 participants were not screened are unclear, because they are not provided in either the CS, clarification response A8 or the OLE clinical study report (CSR).[21] Of the 180 participants screened, 119 enrolled in the OLE and started TRF-budesonide treatment. Of the 119 enrolled participants, 45 were originally randomised to TRF-budesonide in NeflgArd Nef-301 and 74 were originally randomised to placebo. Forty-three participants originally randomised to TRF-budesonide and 62 originally

randomised to placebo completed the OLE treatment (CS section 2.4.2.5). The OLE trial completed in February 2023 (CS Table 4).

The EAG has the following comments about the Nef-301 OLE:

- As with the NeflgArd Nef-301 trial, the optimised standard care that participants received during the OLE does not fully reflect standard care in clinical practice, because it did not include SGLT2 inhibitors (Key Issue 1).
- It is unclear what impact use of SGLT2 inhibitors as part of standard care would have on the proportion of patients eligible for re-treatment with TRF-budesonide (the outcome from the OLE used in the company's economic model). In clarification response A10, the company provided clinical opinion indicating that it is not expected that use of SGLT2 inhibitors would impact on the proportion of patients eligible for re-treatment, but their use may delay when TRF-budesonide is first initiated. One of our clinical experts suggested that the impact of SGLT2 inhibitors on proteinuria, while not a large effect, may result in patients becoming ineligible for either initial or re-treatment with TRF-budesonide. Our other clinical expert concurred that an SGLT2 inhibitor will reduce proteinuria and this could impact on the proportion of patients eligible for re-treatment. However, as primary IgA nephropathy is a progressive disease, in the EAG's view it seems likely that patients would become eligible for TRF-budesonide treatment (or re-treatment) at some future point (Key Issue 1 and Key Issue 2).
- It is unclear why 54 participants from the NeflgArd Nef-301 trial who would have been eligible for the OLE were not screened. It is therefore unclear if these participants differed to those included in the OLE in a way that might have impacted the OLE results had they been screened and enrolled (that is, there is an unclear risk of selection bias). (Key Issue 2)
- The OLE findings about the effects of re-treatment are based on a small sample size of 45 participants who started re-treatment with TRF-budesonide, which results in a limited evidence-base and may limit the conclusions that can be drawn about the effectiveness of re-treatment. (Key Issue 2)
- The OLE only provided follow-up data for up to three months after TRF-budesonide re-treatment ended and therefore provides limited information about the longer-term effects of re-treatment. However, we received clinical expert advice that responses to re-treatment are potentially likely to be similar to that obtained with a first course of TRF-budesonide treatment. We were advised that it is expected that people will benefit again if proteinuria is not only due to scarring in the kidney. A response to TRF-budesonide,

with a reduction in proteinuria, suggests that there is ongoing IgA mediated inflammation. (Key Issue 2)

3.2.1.1.3 Nefigan Nef-202 (NCT01738035)

Nefigan Nef-202 was a phase 2b, double-blind, three-arm RCT of optimised RASi therapy plus TRF-budesonide 16 mg/day or TRF-budesonide 8mg/day or placebo, conducted in an adult population with a urine protein of ≥0.75 g/24-h or UPCR > 0.5g/g and eGFR ≥45 mL/min per 1.73 m² (i.e. a wider population than is of interest in this appraisal) (CS Table 4). Nine months of study treatment was provided, and participants were followed up for an additional three months. The study is summarised in CS Table 4 and an overview of the efficacy and safety results is provided in CS Appendix K. The company do not use the study in the economic model and instead use the longer-term data available from NeflgArd Nef-301 Part B (CS section 2.2). This appears reasonable.

3.2.1.2 Patients' baseline characteristics

In the NeflgArd Nef-301 Part B RCT baseline characteristics were generally balanced between the TRF-budesonide and placebo arms although we note that a higher proportion of the TRF-budesonide arm are described as being either diabetic or pre-diabetic at baseline (CS Table 6). One of our clinical experts agreed that diabetes was a significant comorbidity in this population and people with diabetes would be expected to have worse outcomes (we had not asked our other clinical expert about this). This might disadvantage the TRF-budesonide arm. The proportions of participants on either an ACEi or ARB therapy at baseline was high and [redacted] (CS Table 7). One of our clinical experts thought that in NHS practice the proportion of patients receiving either an ACEi or an ARB might be slightly lower because some patients, particularly younger patients, do not tolerate these medications. Our other expert thought the level of use was about right. Although there were some minor differences between the trial arms in terms of the proportions on either an ACEi or ARB alone and the proportions at different levels of RAS blockade (CS Table 7) these are not considered by the company to be clinically important. We note that during technical engagement for TA937 (in response to the EAG's key issue 6 for TA937) the company stated that differences in ACEi and ARB therapy use were not expected to affect outcomes and that clinical expert opinion obtained by the company had indicated that blood pressure was controlled in both trial arms at baseline. Following technical engagement, the EAG considered the possible selection bias key issue for TA937 resolved. The concomitant medications taken by trial participants are listed in CS Table 8. In addition to differences in ACEi and ARB medications, there are differences of [redacted] between the trial arms in HMG CoA reductase inhibitors (statins) ([redacted]% of the TRF-budesonide arm versus [redacted]% of the

placebo arm), in other lipid modifying agents ([redacted]% of the TRF-budesonide arm versus [redacted]% of the placebo arm), selective beta-blocking agents [redacted]% of the TRF-budesonide arm versus [redacted]% of the placebo arm), sulphonamides (plain, the CSR lists [redacted] as possible drugs in this group) ([redacted]% of the TRF-budesonide arm versus [redacted]% of the placebo arm), glucocorticoids ([redacted]% of the TRF-budesonide arm versus [redacted]% of the placebo arm) and corticosteroids ([redacted]% of the TRF-budesonide arm versus [redacted]% of the placebo arm). It's possible that the differences in statins and other lipid modifying agents may in part have been due to the differences between the trial arms in participants with diabetes or pre-diabetes. The company state that there were no clinically relevant differences in concomitant medication use between the trial arms. Our two clinical experts felt that it was not known or difficult to know if the differences in concomitant medication were clinically important or not. One of our clinical experts thought the differences between trial arms might be acceptable if blood pressures and overall proportions of ACEi and ARB use were similar between the two trial arms (we believe they are).

We have also compared the baseline characteristics for the NeflgArd Nef-301 Part B FAS with those of the Part A subgroup of patients with UPCR ≥1.5 g/g at baseline which informed TA937 and observe that they are similar. That subgroup was considered by the NICE committee to reflect the characteristics of the UK target population.

The OLE population was slightly older than the RCT population (as would be expected) and the age distribution was slightly different, suggesting that a greater proportion of patients in the ≥45 and <65 years age category was recruited to the OLE than in the <45 years age category (CS Table 10). Neither of our clinical experts thought that age would modify the effectiveness of TRF-budesonide. In the OLE the proportion of men receiving TRF-budesonide was greater than in the RCT, but it was accepted in TA937 (paragraph 3.8) that gender was not considered to be a factor that influences the effectiveness of TRF-budesonide. Participants in the OLE who entered from the TRF-budesonide arm of the RCT had similar OLE baseline median UPCR and median proteinuria as they had at the RCT baseline, whereas the participants in the OLE who entered from the placebo arm of the RCT had higher OLE baseline median UPCR and median proteinuria than had been the case at the RCT baseline, which is not unexpected. Patients recruited to the OLE from both arms of the RCT had baseline OLE median eGFR that was lower (indicating more advanced disease) than their baseline median eGFR for the RCT (CS Table 10). The use of RASi therapy during the OLE (CS Table 11) was broadly similar to what was observed in the RCT.

EAG comment on included studies

The CS included a phase 2b RCT, a phase 3 RCT and the open-label extension for the phase 3 RCT. The focus of the CS and the EAG report is the phase 3 RCT NeflgArd Nef-301 and its open-label extension Nef-301 OLE. Participants in the RCT had primary IgA nephropathy and were at risk of progressing to ESRD despite receiving the maximum tolerated RASi therapy. They were randomised to either TRF-budesonide 16mg/day or placebo. The participants are generally representative of the patients who would be expected to receive TRF-budesonide in the NHS. Participants in the OLE had completed the RCT and had persistent proteinuria and an eGFR ≥30 mL/min/1.73m^2 despite optimised RASi therapy. Not all the participants eligible for the OLE were screened for entry to it and the reasons for this are not clear. All 119 participants in the OLE received TRF-budesonide 16mg/day, either as a re-treatment (if they had received TRF-budesonide during the RCT) or for the first time (if they had received placebo in the RCT). A concern for both the RCT and the OLE is that standard care at the time these studies took place did not typically include SGLT2 inhibitors so the proportion of participants in receipt of SGLT2 inhibitors is lower than would be expected in current practice. The impact of this is unclear.

3.2.2 Risk of bias assessment

The company provided risk of bias assessments for NeflgArd Nef-301 and Nefigan Nef-202 in the CS (CS Table 16 and CS Appendix Table 4), and provided a risk of bias assessment for the Nef-301 OLE in response to clarification question A3. We do not discuss the Nefigan Nef-202 assessment here, because data from the trial are not used in the company's economic model.

3.2.2.1 NeflgArd Nef-301 trial

The company summarised their risk of bias assessment of the NeflgArd Nef-301 trial in CS Table 16, and presented the full assessment, that included reasons for their judgements, in CS Appendix Table 4. The company used the quality assessment criteria set out in NICE guidance to companies on preparing their STA submissions (CS section B.1.2).[22] These criteria are a standard set of criteria adapted from the Centre for Reviews and Dissemination.[23]

The company's and the EAG's independent risk of bias assessments of the NeflArd Nef-301 trial are shown in Table 21 in Appendix 2. Both the company and the EAG judged that there

was a low risk of detection, performance and reporting bias. However, our judgements about selection bias and attrition bias differed to the company's as follows:

- The company did not identify a risk of selection bias in their assessment, but we noted that proportionally more people with pre-diabetes or diabetes were randomised to TRF-budesonide than to placebo and we received clinical expert advice that such patients tend to have worse outcomes. We therefore considered that there was a risk of selection bias that might favour of placebo; that is, this baseline imbalance might have a conservative effect on the results from the TRF-budesonide arm.
- Regarding attrition bias, the company judged the trial to have not included an intention-to-treat analysis that had used appropriate methods to account for missing data (see Table 21 in Appendix 2 for their reasons), while we considered that it was unclear if one had been used. The trial results are presented in the CS for the FAS population and while this includes all but two of the participants randomised into the global study part of the trial, it is unclear from the information provided in CS Document B whether participants were analysed according to the treatment arms to which they were randomised (it is likely that they were [redacted] but this is not explicitly stated). Additionally, we noted that in all but one of the data analyses (that is, the analysis of the 2-year eGFR slope), data were either explicitly or implicitly imputed via multiple imputation and mixed model for repeated measures (MMRM), respectively, and both of these methods assume data are missing at random.[25, 26] However, it is unclear if the missing at random assumption was met. Additionally, the possibility that missingness in the outcome data might depend on its true value is raised by two of the reasons for missing data reported in clarification response A7: patients discontinuing early from the study and patients receiving rescue medication or prohibited immunosuppressive medicine. The company did conduct sensitivity analyses to assess the impact of missing data. Thus, overall, it was not possible to assess whether a true intention-to-treat analysis had been used and if appropriate methods were used to impute missing data. We therefore judged the trial to have an unclear risk of attrition bias.

3.2.2.2 Nef-301 OLE

The company provided a risk of bias assessment of the Nef-301 OLE using the ROBINS-I tool[27] in an Excel file that accompanied their clarification response. They appear to have used the original (2016) version of the tool. The company applied the assessment to the eGFR and UPCR ratio outcomes. The company and the EAG's independent risk of bias assessments are shown in Table 22 in Appendix 3. We agreed with the company's

judgements. The trial was rated by both the company and the EAG as having an overall serious risk of bias. The EAG considered there to be a serious risk of bias due to confounding in the OLE and a serious risk of selection bias due to not all eligible participants being screened for inclusion into the OLE.

3.2.3 Outcomes assessment

The outcomes that were assessed in the NeflgArd Nef-301 and Nef-301 OLE trials are shown in Table 5. The trials collectively measured all the NICE scope-specified outcomes and results for all the outcomes were reported in either the CS or trials' CSRs.[20, 21]

As stated in section 3.2.1.1.1, the primary outcome of the NeflgArd Nef-301 trial was a time-weighted average of eGFR measurements over two years. CS Table 4 states that this outcome and safety data from the trial informed the company's economic model.

None of the outcomes from the Nef-301 OLE appear to inform the model (CS Table 4). Re-treatment efficacy results from the OLE were not used in the model – a treatment effect waning assumption of 10% was applied instead (CS section 3.5.1.1.5). In the model, data from the OLE was only used to inform the percentage of patients who would be eligible for re-treatment (CS section 3.5.1.1.5).

We primarily discuss the outcomes included in the company's economic model here, but also provide some commentary where needed on other measured outcomes.

One of our clinical experts advised us that change in eGFR and a reduction in proteinuria are the most important and clinically meaningful outcomes from treatment in clinical practice for patients with primary IgA nephropathy. These outcomes were assessed in the NeflgArd Nef-301 trial and the Nef-301 OLE. Our other expert considered time to end stage kidney failure, tolerability of medications and pill burden to be the most important and clinically meaningful outcomes. Adverse events were measured in the trial, but not time to end stage kidney disease or pill burden.

Table 5 Outcomes assessed in the NefIgArd Nef-301 and Nef-301 trials

NICE scope-specified outcomes	NefIgArd Nef-301 (Part B) (type of outcome; where results are reported)	Nef-301 OLE (type of outcome; where results are reported)
Proteinuria (for example, change from baseline in urine protein creatine ratio)	• Ratio of UPCR compared with baseline averaged over time points between 12 and 24 months, inclusive, following the first dose of study drug (secondary outcome; results reported in CS section 2.6.1.4) • Ratio of UACR compared with baseline averaged over time points between 12 and 24 months, inclusive, following the first dose of study drug (secondary outcome; results reported in CS Appendix J.1.4)	• Ratio of UPCR at 9 months compared with baseline (primary outcome; results reported in CS section 2.6.2.2) • [redacted] results reported in CSR Table 14.2.4.2.1) [b] • [redacted] results reported in CSR Table 14.2.4.3.1) [b] • [redacted]; results reported in CSR Table 14.2.4.3.1) [b]
Kidney function (eGFR)	• Time-weighted average of eGFR over two years (primary outcome; results reported in CS section 2.6.1.1) • Two-year eGFR slope (supportive analysis of primary outcome; results reported in CS section 2.6.1.1.1) • Time to 30% reduction from baseline in eGFR (CKD-EPI) confirmed by a second value, with ≥4 weeks of separation between the 2 sampling time points (secondary outcome; results reported in CS section 2.6.1.3)	• Ratio of eGFR at 9 months compared with baseline, calculated using the CKD-EPI formula (primary outcome; results reported in CS section 2.6.2.1) • [redacted] reported in CSR Table 14.2.4.1.1) [b]

NICE scope-specified outcomes	NefIgArd Nef-301 (Part B) (type of outcome; where results are reported)	Nef-301 OLE (type of outcome; where results are reported)
	• Ratio of eGFR (CKD-EPI) compared with baseline averaged over time points between 12 and 24 months, inclusive, following the first dose of study drug (secondary outcome; results reported in CS section 2.6.1.2)	
Disease progression (dialysis and/or transplant)	[redacted] reported in CSR serious adverse events section 12.3.1.2	Proportion of patients on dialysis, undergoing kidney transplantation, or with eGFR <15 mL/min per 1.73 m^2 (secondary outcome; results reported in CS section 2.6.2.3)
Mortality	Deaths (reported in adverse events section of CS; CS section 2.11.1.1.2 and 2.11.1.1.3)	Deaths (reported in adverse events section of CS; CS section 2.11.1.2)
Adverse effects of treatment	• Treatment-emergent adverse events (results reported in CS section 2.11.1.1.2 and 2.11.1.1.3) • Adverse events of special interest (results reported in CS section 2.11.1.1.2 and 2.11.1.1.3)	• Treatment-emergent adverse events (results reported in CS section 2.11.1.2) • Adverse events leading to study drug discontinuation (results reported in CS section 2.11.1.2) • Adverse events of special interest (results reported in CS section 2.11.1.2)
Health-related quality of life	Short Form 36 assessment at 9 and 24 months (secondary outcome; results reported in CS section 2.6.1.5)	Short Form 36 assessment at 12 months compared with baseline (secondary outcome; results reported in CS section 2.6.2.4)

NICE scope-specified outcomes	NeflgArd Nef-301 (Part B) (type of outcome; where results are reported)	Nef-301 OLE (type of outcome; where results are reported)
Other outcomes (not specified in the NICE scope)	• Time from the first dose of study drug until receiving rescue medication (secondary outcome; results reported Appendix J.1.3) • [redacted] results reported in trial CSR section 11.1.2.6) [a] • Proportion of patients receiving rescue treatment ([redacted] results reported in CS Appendix J.1.3) [a]	• [redacted] results reported in trial CSR section 11.1.2.3) [b] • [redacted] results reported in trial CSR section 11.1.2.4) [b] • [redacted] results reported in trial CSR section 11.1.2.6) [b]

Source: Partly reproduced from CS Table 4 and CS section 2.3.1.9, with additional information included from the NeflgArd Nef-301 Part B analysis and Nef-301 OLE CSRs.[20, 21]

CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; CS, company submission; CSR, clinical study report; eGFR, estimated glomerular filtration rate; NICE, National Institute for Health and Care Excellence; OLE, open-label extension; UACR, urine albumin to creatinine ratio; UPCR, urine protein to creatinine ratio.

[a] Stated to be [redacted]* in the NeflgArd Nef-301 Part B analysis CSR,[20] but not in the CS.

[b] Stated to be [redacted] in the Nef-301 OLE[21] but not in the CS.

3.2.3.1 Efficacy outcome(s)

3.2.3.1.1 NeflgArd Nef-301

The efficacy outcomes measured in the NeflgArd Nef-301 trial are shown in Table 5. The primary outcome of Part B of the trial was a time-weighted average of eGFR over two years (CS section 2.3.1.8). We focus on describing this outcome (which informed the company's economic model) and the supportive analysis of the primary outcome of the 2-year eGFR slope here. We also provide some commentary on the measurement of disease progression outcomes, as this was an issue that was raised in TA937.

3.2.3.1.1.1 Time-weighted average of eGFR over two years

The CS states that for the time-weighted average endpoint, eGFR was calculated by a central laboratory at 3, 6, 9, 12, 18 and 24 months, with two measures of eGFR taken at both baseline and 24 months. The time-weighted average consisted 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"* (CS Table 17). The weight given to a measurement was in proportion to the length of time between that measurement point and the previous one (CS section 2.4.1.2). Measurements taken at 18 and 24 months were given twice the weighting (0.25 each) of those taken at the other measurement timepoints (0.125 each) (CS section 2.4.1.2 and Table 17. eGFR was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) [redacted].[20] In CS Document B, the company do not comment on how clinically meaningful this outcome is and what would constitute a clinically meaningful effect. Additionally, one of our clinical experts thought that a time-weighted average outcome is appropriate, but preferred a slope of GFR trends outcome (as was also measured in the trial; see section 3.2.3.1.1.2 below) because there can be variations in eGFR at single time points. Our other expert had some uncertainty about the methodology that had been used for the time-weighted average outcome, and thought that the eGFR slope is more relevant.

3.2.3.1.1.2 Supportive analysis of the primary outcome of the 2 year total eGFR slope

In Part B of the trial, the company carried out a supportive analysis of the primary outcome of the 2-year eGFR total slope, which shows the difference between groups in mean change in GFR over time.[28, 29] The GFR slope is an accepted surrogate endpoint for chronic kidney disease progression by the European Medicines Agency (EMA).[29] GFR decline is associated with later kidney failure.[28]

The company initially planned to carry out the analysis of the 2-year total eGFR slope using a random coefficients method that had been applied in Part A, but they argued that [redacted] that the method underestimates the relative treatment effect of TRF-budesonide and placebo (CS section 2.3.1.8.1 and trial Part B analysis CSR page 68[20]). [redacted][20] The company presents results from the primary supportive random coefficients analysis in CS Table 18 and presents results from two alternative analysis approaches in CS Appendix J.1.2 Table 24; a robust regression analysis and a random coefficients analysis including observed data from patients who received rescue medication. Results of a pre-specified linear spline mixed-effects analysis of the change in the 2-year total eGFR slope were provided in clarification response A6.

For the eGFR slope outcome, the company state that published[28] and revised[30] thresholds of 0.72 mL/min/1.73 m^2 per year and 1.23 mL/min/1.73 m^2 per year, respectively, are predictive of longer-term clinically meaningful benefits for patients (CS section 2.6.1.1.1). The revised threshold appears to be a NeflgArd Nef-301 trial-specific threshold that was calculated using trial data and statistical information from the published threshold paper (NeflgArd Nef-301 trial supplementary appendix[30]). We note that the 0.72 mL/min/1.73 m^2 per year threshold applies to the mean difference in total GFR slope over two years and is associated with a 97.5% probability of clinical benefit.[28] We received clinical expert advice that these thresholds are relevant.

3.2.3.1.1.3 Disease progression outcomes

The overall aim of treatment of IgA nephropathy is to prevent disease progression and ongoing decline in kidney function.[31] The EAG in TA937,[32] commented that the NeflgArd Nef-301 trial did not measure disease progression outcomes but focused on surrogate endpoints. We note that disease progression outcomes from Part B of the trial are not presented in the CS for the present appraisal, but as stated in Table 5, the [redacted] are reported from Part B in the trial's CSR serious adverse events section 12.3.1.2 (specifically, data on [redacted]). Therefore, again, in this appraisal, surrogate outcomes are relied on in the CS.

In TA937, the company argued in their clarification response that the surrogate endpoints measured in the NeflgArd Nef-301 trial (such as proteinuria and eGFR) are accepted endpoints by KDIGO, the European Medicines Agency and clinical experts for demonstrating

improved outcomes in people with IgA nephropathy, and that associations have been found in the literature between these endpoints and outcomes such as progression to end-stage renal disease/kidney failure and mortality.[32] In TA937, the EAG raised the non-inclusion of disease progression outcomes as a key issue.[32] In response, at the technical engagement stage of the appraisal, the company explained that measurement of disease progression outcomes such as dialysis and transplant would require trials over a longer time frame for statistical analyses of these outcomes to be sufficiently powered, given that, based on the trial's data, it was expected that placebo patients would progress to ESRD in 3 to 5 years.[10] The EAG accepted the company's explanation and considered the issue resolved. We agree that a long trial would likely be needed to adequately capture these outcomes and we consider that the use of surrogate outcomes is appropriate (also see section 3.2.3.1.2.1 below).

3.2.3.1.2 Nef-301 OLE

The efficacy outcomes measured in the Nef-301 OLE are shown in Table 5. We do not discuss the primary outcomes of the OLE further here, as they do not inform the company's economic model. We provide some commentary below about the data available for disease progression outcomes from the OLE, as the lack of data for these outcomes from the parent trial was raised as an issue in TA937.[32]

3.2.3.1.2.1 Disease progression outcomes

The OLE assessed disease progression outcomes as the proportion of patients on dialysis, undergoing kidney transplantation, or with a sustained eGFR <15 mL/min per 1.73 m^2 (CS sections 2.3.1.9 and 2.6.2.3. An eGFR <15 mL/min per 1.73 m^2 indicates end-stage renal disease[33] and we received advice from one of our clinical experts that this is an accepted definition of reaching end-stage kidney disease. The other expert advised that a GFR <15 mL/min per 1.73 m^2 indicates stage 5 kidney disease, while end stage kidney disease indicates that patients have started dialysis or have received a transplant. This expert commented that not all patients with a GFR <15 mL/min per 1.73 m^2 will have started dialysis. We note small numbers of participants were included in the OLE (45 from the original TRF-budesonide arm of the NeflgArd Nef-301 trial and 74 from the original placebo arm of the NeflgArd Nef-301 trial), with only two participants experiencing end-stage renal disease (CS Table 26), which limits the conclusions that may be drawn about the impact of TRF-budesonide treatment on disease progression outcomes. Additionally, the three-year follow-up period (from randomisation into the parent trial) provided by the OLE may not have been sufficient for capturing dialysis or kidney transplant outcomes, which, as discussed in section 3.2.3.1.1.3, might occur over a longer timeframe. We received clinical expert advice

that a small number of patients would reach end-stage kidney disease within three years of starting treatment (i.e. only those at the lower end of the GFR starting point). We also note that an analysis of a cohort of adults with IgA nephropathy and proteinuria >0.5 g/d or eGFR <60 ml/min per 1.73 m^2 (from the UK National Registry of Rare Kidney Diseases; RaDaR[34]) found that the mean average time to a first kidney failure or death event (reaching an eGFR <15 mL/min per 1.73 m^2, dialysis, transplant or death) was 6.6 years (standard deviation [SD] 6.6) (4.3 median years [Q1, Q3 1.8, 9.3]). These data suggest that these disease progression events are unlikely to be sufficiently captured in a three-year follow-up period.

3.2.3.2 HRQoL outcomes

In both NeflgArd Nef-301 and Nef-301 OLE, the Short Form 36 was used to measure quality of life. This is a validated, generic measure of quality of life.[35, 36] It measures four dimensions of functional status (physical functioning, social functioning, role limitations [physical problems], and role limitations [emotional problems]), and three dimensions of wellbeing (mental health, vitality and pain).[36] Dimension scores can range from 0 (indicating worst health) to 100 (indicating best health).[36] This outcome did not inform the company's economic model. The utilities used in the model were sourced from the literature (see section 4.2.9).

3.2.3.3 Safety outcomes

Table 5 outlines the safety outcomes assessed in NeflgArd Nef-301 and Nef-301 OLE. Treatment-emergent adverse event (TEAEs) occurring in ≥4% of patients in either arm of the FAS and treatment-emergent severe adverse events (TESAEs) occurring in ≥1 patient in either treatment group in the NeflgArd Nef-301 trial were included in the company's economic model (but as described in CS 3.3.2.4 we note that although the FAS was used to define the list of TEAEs to include in the model the data for those adverse events was drawn from the SAS because this was a larger sample of patients).

EAG comment on outcomes assessment

The efficacy outcomes measured in the NeflgArd Nef-301 and Nef-301 OLE trials are mainly surrogate endpoints but are appropriate. Some limited data on the proportion of patients on dialysis, undergoing kidney transplantation, or with an eGFR <15 mL/min per 1.73 m^2 are reported in the CS from the OLE, which provided three years of follow-up data from randomisation into the parent trial. Although the total three-year follow-up period collectively provided by the parent trial and OLE is a strength of the evidence, this timeframe was likely insufficient

to capture dialysis, kidney transplantation and kidney failure outcomes, given the nature of the disease.

3.2.4 Statistical methods of the included studies

The statistical methods of the RCT and its associated OLE are reported in CS section 2.4. We used this information, supplemented by additional details from the CSRs, protocol for the OLE and the responses to clarification questions to inform our summary and critique of the company's statistical methods (Table 6).

Table 6 Summary and critique of the statistical methods used in the NeflgArd Nef-301 RCT and the Nef-301 OLE

NeflgArd Nef-301 (NCT03643965), Part A and Part B	**Nef-301 OLE (NCT04541043)**
Analysis populations	
CS Table 13 defines three NeflgArd Nef-301 analysis populations: Part A FAS: n=199 (excludes 2 patients randomised in error). All patients regardless of whether they received study drug. Part B FAS: n=364. All patients randomised at completion of recruitment to the global part of the study. SAS: n=389. All patients who received at least 1 dose of study drug.	CS Table 14 defines two Nef-301 OLE analysis sets: FAS: n=119. All patients who received at least 1 dose of TRF-budesonide and had either a UPCR or eGFR efficacy measurement collected after dosing. SAS: n=119. All patients who had received at least 1 dose of study drug at the time of analysis.
EAG comment: Although there is no ITT population, we view the analysis populations as appropriate because the FAS represents 99.45% of those randomised. NeflgArd Nef-301: The SAS (n=389) includes 25 more participants than the Part B FAS (n=364). From the definitions provided in CS Table 13 and the participant flow diagram in CS Appendix B.2 Figure 3, the primary reason appears to be that the SAS includes participants from China (N=29 randomised, number who received at least 1 dose of study drug not reported in the CS) whereas the Part B FAS is based on those randomised in the Global Study (n=366) which does not include the participants from China. The reason for the exclusion of patients from China is not explained, but because these 29 participants represent approximately 7% of the total number randomised and are from a population likely to be less representative of patients treated in the NHS, we do not have any concerns about their exclusion from the Part B FAS. Although not explicitly stated, we believe the Part B FAS population also excludes the 2 patients randomised in error (as described for the Part A FAS population) thereby resulting in the Part B FAS of n=364 participants. Clinical effectiveness results presented in the CS focus on the Part B FAS data, results for the Part A FAS are presented in CS Appendix J.2.	

NeflgArd Nef-301 (NCT03643965), Part A and Part B	**Nef-301 OLE (NCT04541043)**
Nef-301 OLE: The FAS and SAS analysis sets include all participants enrolled in the OLE (shown in CS Table 15).	
Sample size calculations	
CS section B.2.4.1.3 provides details of sample size and power calculations. Part A: 200 participants required to provide >90% power to detect statistical significance with a 1-sided alpha level of 0.025 and assuming that TRF-budesonide treatment would lead to a 25% relative reduction in UPCR compared with placebo. Part B: 360 participants provide a 90% power to detect a statistically significant difference, again with a one-sided alpha of 0.025, assuming that the TRF-budesonide treatment effect relative to placebo would be a difference in mean eGFR at 2 years of 2.24 mL/min per 1.73 m^2.	CS section B.2.4.2.3 states that the total number of patients to be included was estimated to be approximately 250 based on the assumption that 75% of the patients who completed NeflgArd Nef-301 would enter the Nef-301 OLE. The publicly available protocol[37] and CS section B.2.4.2.2 indicate that no formal statistical hypothesis testing was planned or performed.
EAG comment: NeflgArd Nef-301: Part-A sample size calculations were critiqued as part of TA937. The use of a 1-sided test coupled with setting alpha to 0.025 (instead of the standard 0.05) was deemed unconventional but no practical problems were raised. Part-B calculations are also based on a one-sided alpha but we concur with the previous conclusion for TA937 that the risk of a type 1 error is alleviated by setting the alpha to 0.025. Nef-301 OLE: As no formal statistical hypothesis testing was planned, no formal sample size or power calculation was required. About 36% of the participants who completed the Part B follow-up actually enrolled in the OLE (119 of 326 participants) which is far less than the 75% assumed in the protocol. Of the 234 participants who had completed the parent trial and met the eligibility criteria for the OLE, 54 were not screened for inclusion in the OLE (CS Table 15 and clarification response A8) and the reasons for this are unclear. It is unclear why the company's estimate of the percentage of participants who would enter the OLE and the actual percentage who did, differ so substantially.	
Methods to account for multiplicity	
CS Figure 10 provides a summary of the hypothesis testing strategy. This and the text in CS section 2.4.1.3 show that the Part A primary analysis of UPCR at 9 months was to be tested at a one-sided significance level of 0.02. Because statistical significance was achieved for this analysis, the time-weighted average of eGFR over 2 years outcome for Part B was	Not applicable as no formal statistical hypothesis testing took place.

NeflgArd Nef-301 (NCT03643965), Part A and Part B	Nef-301 OLE (NCT04541043)
tested at a one-sided significance level of 0.025 (whereas, if the primary analysis of UPCR at 9 months had not achieved significance the final analysis of 2-year eGFR for Part B would have been analysed at a one-sided significance level of 0.005). The 2-year eGFR total slope was also tested at a one-sided significance level of 0.025 because statistical significance was achieved for the time-weighted average of eGFR over 2 years.	
EAG comment: The hierarchical testing procedure is explicitly described for NeflgArd Nef-301 and appears appropriate.	
Analysis of outcomes	
We summarise the statistical tests used in the analysis of the primary outcome and the primary supportive analysis of Part B of the trial (Part A has been critiqued previously as part of TA937). Primary outcome (Part B), time-weighted average of eGFR over 2 years: CS B.2.4.1.2 provides fuller details of the analysis for this outcome which was a multistep process. eGFR was calculated by a central laboratory at 3, 6, 9, 12, 18 and 24 months. Each timepoint was weighted with the final two timepoints having twice as much weight (timepoint weights were 0.125 for the 3, 6, 9 and 12 months and 0.25 for 18 and 24 months). For each timepoint, data were log-transformed before analysis and any missing data were imputed (see missing data below). To avoid the results being influenced by outlying data from a small subset of patients, the company used robust regression to analyse the time-weighted average of eGFR measurements. Robust regression had also been used for eGFR analysis conducted for TA937. Supportive analysis (Part B), 2-year eGFR slope: CS B.2.3.1.8.1 provides fuller	Descriptive statistics were used to summarise continuous variables. Categorical variables were tabulated using frequency and percent. For the eGFR and UPCR primary endpoints, two reference baseline timepoints were defined: the baseline for the OLE study and the baseline for the original NeflgARD Nef-301 RCT (CS 2.4.2.2). Primary outcome (OLE): ratio of UPCR at 9 months compared with OLE baseline: CS 2.4.2.2 provides fuller details. In brief, an MMRM with baseline UPCR as a covariate was used. Patient was included as a random effect and the within-patient correlation of data was modelled using an unstructured covariance matrix. Primary outcome (OLE): ratio of eGFR at 9 months compared with OLE baseline: CS 2.4.2.2 indicates a similar approach was used as for the ratio of UPCR at 9 months compared to OLE baseline analysis, but a robust regression model was used to derive the mean change in log(eGFR) from the

NefIgArd Nef-301 (NCT03643965), Part A and Part B	**Nef-301 OLE (NCT04541043)**
details. The methods to analyse this outcome were changed after analysis of the Part A eGFR data and were [redacted] Values from the robust regression analysis for eGFR at 2 years (used in the primary endpoint calculation) were also used to derive the mean change from baseline to 2 years. The 2-year eGFR total slope was then estimated as half of the between-arm difference in the mean change from baseline to 2 years.	OLE baseline and its confidence interval (CI).
EAG comment: The same method for eGFR analysis (robust regression) has been used for the Part B of the RCT and its associated OLE as was previously used for Part A of the RCT which contributed to TA937. Other analytical methods were also appropriate.	
Handling of missing data	
Primary outcome (Part B), time-weighted average of eGFR over 2 years: A multiple imputation method (described in CS B.2.4.1.2) was used to impute missing data before the time-weighted average was calculated. The imputation was conditional on previous outcomes observed for the same patient and the CSR[20] additionally states that imputation was based [redacted] Supportive analysis (Part B), 2-year eGFR slope: No missing data were imputed.	Primary outcome (OLE): ratio of eGFR at 9 months compared with OLE baseline: CS B.2.4.2.2 indicates that missing data were imputed in a similar way to Part B of the RCT (i.e. conditional on previous outcomes observed in the same patient). Primary outcome (OLE): ratio of UPCR at 9 months compared with OLE baseline: Although not explicitly stated in CS B.2.4.2.2 we would expect an MMRM analysis to be performed on observed data as it implicitly imputes missing data.
EAG comment: As stated in section 3.2.2.1 it is unclear if the missing at random assumption holds as no information is presented in the CS about this. Therefore there is some uncertainty about whether the handling of missing data is appropriate. Different assumptions about missing data have been explored (see Sensitivity and post-hoc analyses below).	
Sensitivity & post-hoc analyses	
For the Part B primary outcome of time-weighted average of eGFR over 2 years a sensitivity analysis using a MMRM was performed. A sensitivity analysis using different assumptions about missing data was also performed.	No sensitivity or post-hoc analyses are described in the CS. The CSR for the OLE[21] states that [redacted]

NeflgArd Nef-301 (NCT03643965), Part A and Part B	Nef-301 OLE (NCT04541043)
For the supportive 2-year eGFR slope outcome an analysis using a linear spline mixed-effects model was also pre-specified. The results were supplied in response to clarification question A6. Although not described in the summary of trial methodology (CS section 2.3) there is one post-hoc analysis reported in CS 2.6.1.3 for the secondary efficacy outcome of time to 30% reduction from baseline in eGFR or kidney failure.	
EAG comment: The sensitivity analyses for the RCT are appropriate and the results of these have been provided. One post-hoc analysis of the RCT was conducted. The CS does not describe sensitivity or post-hoc analyses for the OLE [redacted].[21]	

Source: EAG created table.
CS, company submission; CSR, clinical study report; EAG, External Assessment Group; eGFR, estimated glomerular filtration rate; FAS, full analysis set; ITT, intention-to-treat; Min, minute; mL, millilitre; MMRM, mixed model for repeated measures; NHS, National Health Service; OLE, open-label extension; RCT, randomised controlled trial; SAS, safety analysis set; TRF, targeted-release formulation; UPCR, urine protein to creatinine ratio.

EAG comment on study statistical methods

In alignment with the analysis of the NeflgArd Nef-301 Part-A analysis (critiqued as part of TA937), a 1-sided test with an alpha of 0.025 was used for the Part-B analysis. We agree with the conclusions of the EAG for TA937 that this is unconventional, but the alpha has been appropriately set at 0.025 and there is an appropriate hierarchical testing procedure for the trial. No formal statistical hypothesis testing took place for the Nef-301 OLE. We have no major concerns about the statistical methods used.

3.2.5 Efficacy results of the NeflgArd Nef-301 RCT Part B

3.2.5.1 Primary efficacy outcome (Part B): Time-weighted average of eGFR over 2 years

A statistically significant treatment benefit was observed in the TRF-budesonide arm of the NeflgArd Nef-301 trial in comparison to the placebo arm in terms of the time-weighted average of eGFR over 2 years for the primary analysis which excluded data impacted by recue medication use. CS Table 17 shows the mean time-weighted average change from

baseline in eGFR over 2 years was -2.47 mL/min/1.73 m^2 (95% CI -3.88 to -1.02) in the TRF-budesonide arm of the trial whereas in the placebo arm it was -7.52 mL/min/1.73 m^2 (95% CI -8.83 to -6.18) which corresponds to an average difference in eGFR over 2 years of 5.05 mL/min/1.73 m^2 (95% CI 3.24 to 7.38) between the study arms (one-sided p<0.0001). CS Table 17 also shows the results for the ratio of geometric LS mean time-weighted average of eGFR over 2 years demonstrating a 10% treatment benefit with TRF-budesonide when compared to placebo (ratio of geometric LS means 1.10 [95% CI 1.06 to 1.15]).

The company conducted four additional analyses of the time-weighted average of eGFR over 2 years (using the per protocol analysis set, using alternative assumptions for missing data due to patients who discontinued treatment early, including data recorded after receipt of rescue medication and a sensitivity analysis using MMRM instead of the robust regression analysis). These results, provided in CS Appendix J.1.1 Table 23 were all consistent with the primary analysis and all showed a statistically significant difference in favour of TRF-budesonide (p<0.0001 for all analyses).

CS Table 4 indicates that the time-weighted average of eGFR over 2 years outcome has been incorporated into the economic model. To do this, the eGFR patient level data were mapped to CKD stages and used to determine the likelihood of a patient transitioning from one CKD state to a different CKD stage after 24 months of treatment. This is described in greater detail in CS 3.3.2.1.1 and critiqued further in section 4.2.6.1 of this report.

The mean absolute change in eGFR from baseline, plotted for each trial arm through the 9-month treatment period and the subsequent 15-month follow-up period, can be seen in CS Figure 11. This shows that during the 15-month follow-up the eGFR benefit obtained from 9 months of TRF-budesonide (plus optimised RASi therapy) treatment over placebo (plus optimised RASi therapy) was maintained.

3.2.5.1.1 Primary supportive analysis of 2-year eGFR total slope

As stated in section 3.2.3.1.1, GFR slope has been accepted as a validated surrogate endpoint for CKD progression in RCTs by the EMA.[29] In Part B of the NeflgArd Nef-301 trial the eGFR 2-year total slope was -3.55 mL/min/1.73 m^2 (95% CI -4.48 to -2.62) in the TRF-budesonide arm and -5.37 mL/min/1.73 m^2 (95% CI -6.30 to -4.43). Thus the difference between the trial arms in 2-year eGFR total slope was 1.82 (95% CI 0.50 to 3.13, 1-sided p=0.0035). This difference exceeds a published threshold of 0.72 mL/min/1.73 m^2 per year for treatment effect to confer a 97.5% probability of a nonzero clinical benefit for a modest sized trial (defined in the Inker et al. publication[28] as an RCT with a standard error of the mean (SEM) of 0.4 [N roughly 720]). As the NeflgArd Nef-301 trial size was less than this,

the threshold is likely to be higher and this is bourne out by the revised threshold cited of 1.23 mL/min/1.73 m^2 per year. This was estimated specifically for the NeflgArd Nef-301 trial[30] based on information in the Inker et al. publication[28] and the difference in 2-year eGFR total slope between the trial arms also exceeds this threshold. The sensitivity and supplementary analyses of 2-year eGFR total slope reported in CS Appendix J.1.2 Table 24 also exceed the revised threshold of 1.23 mL/min/1.73 m^2 per year. The results of the analyses using the linear spline mixed-effects model also exceed the revised threshold (clarification response A6).

3.2.5.2 Secondary efficacy outcomes (Part B)

Three secondary outcomes from the NeflgArd Nef-301 Part B trial are reported in the CS but none contribute data to the economic model. These are the ratio of eGFR compared with baseline averaged over time points between 12 and 24 months (CS section 2.6.1.2), the time to 30% reduction from baseline in eGFR or kidney failure (CS section 2.6.1.3) and the change from baseline in UPCR (CS section 2.6.1.4). For each of these outcomes the difference between trial arms was in favour of TRF-budesonide.

3.2.5.3 HRQoL outcomes (Part B)

The CS reports on the eight health domains and the two composite scores for the SF-36v2 at baseline, Month 9 or Month 24 in CS Table 23. No differences between the TRF-budesonide and placebo arms of the trial were observed.

3.2.5.4 Subgroup analyses (Part B)

Subgroup analyses were conducted for four outcomes: time-weighted average of eGFR over 2 years (mL/min/1.73 m^2) using robust regression; 2-year eGFR total slope (mL/min/1.73 m^2 per year) using a linear spline mixed-effects model; ratio of UPCR (g/g) at 9 months compared with baseline using MMRM and ratio of UPCR (g/g) at 2 years compared with baseline using MMRM. The subgroups listed in CS section 2.8 and those actually reported in CS Appendix C.1 differ slightly. It seems likely that this is because subgroup levels with fewer than 20 participants exposed to TRF-budesonide were not assessed. The subgroups or subgroup levels listed in CS section 2.8 which are missing from CS Appendix C.1 are: age ≥65 years (CS Table 6 shows only 11 participants in this age category), black race (CS Table 6 shows there were no black participants), ethnicity (Hispanic/Latino versus not Hispanic/Latino (the trial CSR shows only [redacted] participants classified as Hispanic or Latino received TRF-budesonide) and region South America (the trial CSR shows only [redacted] participants in this region category). One subgroup, baseline hematuria (presence/absence)

is reported in CS Appendix C.1 but is not listed in CS section 2.8. The subgroups for which data are presented in CS Appendix C.1 are:

- By baseline demographic characteristics of age (<45 years, ≥45 to <65 years), sex (male or female), race (white or others) and region (North America, Europe or Asia Pacific)
- By the baseline disease status measures of proteinuria (<2 g/24 hours or ≥2 g/24 hours), eGFR (<60 ml/min/1.73 m^2 or ≥60 ml/min/1.73 m^2), hematuria (presence/absence) and UPCR (<1.5 g/gram or ≥1.5 g/gram)
- By baseline dose of RAS inhibitor therapy (<50% of maximum allowable dose, ≥50% and <80% of maximum allowable dose or ≥80% of maximum allowable dose)

The forest plots for the subgroup analyses of the four outcomes (CS Appendix C.1 Figures 4 to 7) demonstrate a consistent treatment effect in favour of TRF-budesonide. Although a small proportion of 95% confidence intervals cross the line of no effect the EAG has no concerns about this given the trial was not powered to detect subgroup differences and for some subgroups numbers contributing data are small.

The EAG also notes that one post-hoc subgroup analysis is reported in CS section 2.6.1.3 for the outcome of timed to a confirmed 30% eGFR reduction or kidney failure. The company report that this was similar for participants with a baseline UPCR <1.5 g/g and those with a baseline UPCR ≥1.5 g/g (HR 0.51 95% CI 0.21 to 1.12 and HR 0.42 95% CI 0.21 to 0.83 respectively).

3.2.5.5 Safety outcomes NeflgArd Nef-301 RCT

Adverse events from the NeflgArd Nef-301 RCT are reported in CS section 2.11.1.1 (with safety data from the phase 2 Nefigan Nef-202 study available in CS Appendix K). Exposure to TRF-budesonide 16mg/day or the blinded placebo dose was the same (median average daily dose received 15.9 mg during the 9-month treatment period) (CS Table 28).

Adverse events that occurred during the treatment period are summarised in CS Table 29. Most patients (78% in the overall FAS population) experienced a treatment emergent adverse event. The proportion of participants experiencing an adverse event considered to have been caused by the study treatment was higher in the TRF-budesonide arm than in the placebo arm of the trial ([redacted]% versus [redacted]% respectively in the SAS population) but in both the SAS and FAS populations most treatment-related adverse events ([redacted]% in the TRF-budesonide arm and [redacted]% in the placebo arm) were of mild or moderate severity. Treatment-emergent adverse events of special interest and serious adverse events occurred in a higher

proportion of the TRF-budesonide treated participants than the placebo arm participants (CS Table 29). One fatal coronavirus infection was considered unrelated to study treatment, this was the only death during the treatment phase of the study, and it occurred in the TRF-budesonide arm. During treatment, the events that occurred in >5% of patients in either treatment group and where the reported incidence was 5% greater or more in the TRF-budesonide arm than in the placebo arm were peripheral oedema, hypertension, muscle spasms, acne, face oedema and white blood cell count increased (SAS population; CS Table 31). TRF-budesonide-treated patients also experienced the events of weight increased, dyspepsia and arthralgia more than placebo participants (between [redacted]% and [redacted]% higher incidence).

Adverse events that occurred during the 15-month follow-up period are summarised in CS Table 30. Most patients (72% in the overall FAS population) experienced a treatment emergent adverse event and the incidence was similar between the two treatment arms. In comparison to the treatment period, the overall proportion was slightly lower (by [redacted]% in the SAS population 6.1% lower in the FAS population). The proportions of participants with an adverse event considered to have been caused by the study treatment was less than during the treatment period but remained higher in the TRF-budesonide arm than the placebo arm ([redacted]% versus [redacted]% respectively in the SAS population). There [redacted] severe event that was considered treatment-related [redacted] and all other treatment emergent events considered to be treatment-related were of mild or moderate severity. In the SAS population, a slightly [redacted] proportion of participants in the TRF-budesonide arm experienced a treatment emergent serious adverse event in comparison to the placebo arm ([redacted]% versus [redacted]% respectively) and [redacted] ([redacted]%) of these events in each arm [redacted] considered treatment-related. The proportions of participants experiencing an adverse event of special interest in the follow-up period followed a similar pattern to that observed in the treatment period ([redacted]% and [redacted]% in the budesonide and placebo arms respectively in the follow-up period versus [redacted]% and [redacted]% in the treatment period). There was one death in the TRF-budesonide arm during the follow-up period. During the follow-up period, the events that occurred in >3% of patients in either treatment group are reported in CS Table 32. Coronavirus infection was the most common treatment-emergent adverse [redacted]. For most of the events, the incidence was similar in the TRF-budesonide and placebo groups. The biggest differences in incidence were for hypertension, experienced by a greater proportion of the placebo arm (TRF-budesonide arm [redacted]% versus placebo arm [redacted]%), and diarrhoea, experienced by a greater proportion of the TRF-budesonide arm (TRF-budesonide arm [redacted]% versus placebo arm [redacted]%).

3.2.6 Efficacy results of the Nef-301 Open-label extension

During the OLE, participants who had already received TRF-budesonide 16 mg during the RCT, received a second course of TRF-budesonide in the extension phase. These participants are the TRF-budesonide-experienced group. Participants who had received placebo during the RCT received a first course of TRF-budesonide in the extension phase. These are the TRF-budesonide-naïve group.

3.2.6.1 Primary efficacy outcome (OLE): ratio of eGFR at 9 months compared with baseline

The TRF-budesonide-experienced group had an absolute change in eGFR at 9 months (in comparison to the OLE baseline) of -1.28 mL/min/1.73 m^2 (95% CI -3.20 to 0.72) (CS Table 24). The TRF-budesonide-naïve group had an absolute change in eGFR at 9 months of -1.53 mL/min/1.73 m^2 (95% CI -3.07 to 0.05). For both sets of participants the ratio of geometric least squares mean eGFR at 9 months, compared with the OLE baseline, was 0.97 with very similar confidence intervals (95% CI 0.94 to 1.01 for the experienced group or 0.94 to 1.00 for the naïve group) (CS Table 24). CS Figure 13 shows the mean absolute change in eGFR from the OLE baseline in the two groups of participants over the 9-month OLE treatment period. An increase in eGFR occurred from baseline to month 3 followed by a gradual decrease over the next 6 months in both groups.

3.2.6.2 Primary efficacy outcome (OLE): ratio of UPCR at 9 months compared with baseline

After receipt of TRF-budesonide in the OLE the ratio of geometric least squares mean UPCR at 9 months (compared with the OLE baseline) was 0.67 (95% CI 0.56 to 0.80) and 0.69 (95% CI 0.60 to 0.80) in the TRF-budesonide-experienced and TRF-budesonide-naïve groups respectively (CS Table 25). CS Figure 14 shows a very similar trajectory for percentage change in UPCR for both groups over the course of the OLE such that by 9-months the percent change from OLE baseline in UPCR was -33.3% (95% CI -44.4 to -19.9) in the TRF-budesonide-experienced group and -31.0% (95% CI -40.2 to -20.2) in the TRF-budesonide-naïve group.

3.2.6.3 Secondary efficacy outcome (OLE)

Only two participants, both from the TRF-budesonide-experienced group, had end-stage renal disease in the OLE (CS Table 26). Taking a broader approach and considering patients with end-stage renal disease or a confirmed 30% reduction in eGFR, [redacted] participants

([redacted]%) in the TRF-budesonide-experienced group and [redacted] participants ([redacted]%) in the TRF-budesonide-naïve group experienced this outcome (CS Table 26).

3.2.6.4 HRQoL outcomes (OLE)

Results for the SF-36v2 eight health domains and the two composite scores at baseline and at OLE month 12 are presented in CS Table 27 and the company states there were no meaningful changes from baseline to Month 12. In both the TRF-budesonide-experienced and TRF-budesonide-naïve groups the mean changes from baseline to month 12 were [redacted] (mean changes in the heath domains and composite scores ranging from [redacted] in the TRF-budesonide-experienced group and from [redacted] in the TRF-budesonide-naïve group.

3.2.6.5 Subgroup analyses (OLE)

No subgroup analyses for the OLE data are presented. It is the EAG's view that numbers of participants (n=45 in the TRF-budesonide-experienced group and n=74 in the TRF-budesonide-naïve group) are two low for any subgroup analyses to be meaningful.

3.2.6.6 Safety outcomes (OLE)

Adverse events from the NeflgArd Nef-301 open-label extension are reported in CS section 2.11.1.2. The median exposure to TRF-budesonide 16mg/day was 9.4 months reflecting the 9-month treatment period and subsequent tapering-off period (CS Table 33).

The treatment-emergent adverse events that occurred during the open-label extension are summarised in CS Table 34. Most patients (87% of the total OLE SAS) experienced a treatment emergent adverse event with the proportion slightly higher among the TRF-budesonide-experienced group than in the TRF-budesonide-naïve group (93.3% versus 83.8% respectively). The proportion experiencing any study treatment-related adverse event was similar between patients experienced and naïve to TRF-budesonide treatment (37.8% and 41.9% respectively). Only patients receiving TRF-budesonide for the first time experienced a treatment-emergent event of special interest (6.8%), with two of the five events (2.7%) considered related to study treatment. There were no serious adverse events considered related to study treatment but a greater proportion of the TRF-budesonide naïve group discontinued budesonide because of an adverse event (8.1% of the TRF-budesonide naïve group versus 2.2% of the TRF-budesonide experienced group). There were no deaths during the open-label study.

In common with the RCT phase of the study, the most commonly experienced treatment emergent adverse event during the open-label study was corona virus infection (26.7% in

the TRF-budesonide-experienced group and 17.6% in the TRF-budesonide-naïve group) (CS Table 35). Of the four other events which were reported by more than 10% in either group (hypertension, muscle spasms, peripheral oedema and weight increased), three (hypertension, muscle spasms and peripheral oedema) were events that had been observed in the RCT to occur in >5% of patients in either treatment group and with a reported incidence that was 5% greater or more in the TRF-budesonide arm than in the placebo arm.

3.2.7 Pairwise meta-analysis of intervention studies

We agree with the company (CS section B.2.9) that a meta-analysis is not required because NeflgArd Nef-301 is the only Phase 3 RCT which has assessed TRF-budesonide treatment with outcomes reported for a 2-year period (9th months treatment plus 15 months follow-up).

3.3 Critique of studies included in the indirect comparison and/or multiple treatment comparison

We are aware that the company included indirect treatment comparisons (ITCs) as part of their Technical Engagement response to a Key Issue that was raised by the EAG for TA937. One ITC was between TRF-budesonide and corticosteroids and immunosuppressants plus standard care. This is not relevant to this review of TA937 because the comparator description in the NICE scope has been revised and no longer mentions glucocorticoids. The second ITC was between TRF-budesonide and dapagliflozin plus standard care. The EAG for TA937 felt a key issue remained following technical engagement regarding the validity of the trial evidence in part because no evidence had been presented to show the effect of comparing TRF-budesonide plus standard care including an SGLT2 inhibitor versus standard care including an SGLT2 inhibitor. However, the company's ITC of TRF-budesonide and dapagliflozin plus standard care is not raised in TA937 section 3.9 and in TA937 section 3.3 the NICE committee seem to conclude that SGLT2 inhibitors would be included as part of standard care and had heard from clinical experts that they have a different mechanism of action to TRF-budesonide. We heard from our clinical experts that when dapagliflozin is used together with TRF-budesonide an additive effect could be expected, which agrees with information presented in the CS and aligns with the draft KDIGO guidelines practice point 2.3.2.2 to simultaneously prevent or reduce IgA immune complex formation and immune complex-mediated glomerular injury (i.e. use of TRF-budesonide) and manage the consequences of existing IgA nephropathy-induced nephron loss (i.e. lifestyle modification, RAS inhibitors, SGLT2 inhibitors and sparsentan) as shown in

Figure 3 of the draft KDIGO guidelines.[12] Therefore a comparison between TRF-budesonide and the SGLT2 inhibitor dapagliflozin is not required. However, it is still the case (as it was for TA937) that data are lacking for a comparison of TRF-budesonide + standard care without an SGLT2 inhibitor versus TRF-budesonide + standard care with an SGLT2 inhibitor. In Part B of the NeflgArd Nef-301 there were [redacted] participants ([redacted]%) in each trial arm taking SGLT2 inhibitors (CS Table 8) which is too few for a meaningful subgroup analysis to inform this. We asked our clinical experts if they would expect to see the same relative TRF-budesonide treatment effect if the trial were repeated with SGLT2 inhibitors being used as part of standard care in both arms. One clinical expert did expect to see the same relative benefit of TRF-budesonide whereas the other clinical expert would not because SGLT2 inhibitors will reduce the slope of GFR decline and proteinuria.

3.4 Conclusions on the clinical effectiveness evidence

The company's decision problem matches the NICE scope, except that no separate economic analysis was provided for the subgroup of people at risk of rapidly progressing IgA nephropathy (UPCR ≥ 1.5 g/g).

The company's key evidence is drawn from the NeflgArd Nef-301 phase 3 placebo-controlled RCT of TRF-budesonide 16 mg/day plus optimised RASi therapy versus placebo plus optimised RASi therapy and the open-label extension study, Nef-301 OLE, that followed this RCT. The participants in the RCT are representative of those who would be seen in clinical practice but the standard of care they received differs to the standard of care that is now in place as most patients would now be expected to receive an SGLT2 inhibitor and, in the future, sparsentan (which has recently been recommended by NICE) is expected to replace RASi therapy (Key Issue 1). We consider the RCT to be at a low risk detection, performance and reporting bias but believe there is a risk of selection bias that might favour the placebo arm and an unclear risk of attrition bias because it was unclear to us whether a true intention-to-treat analysis had been used and if appropriate methods were used to impute missing data. The OLE, which provides evidence on re-treatment, is considered by us and the company to have an overall serious risk of bias due to the serious risk of biases from confounding and selection of participants into the study.

A statistically significant treatment benefit was observed for the primary outcome of time-weighted average of eGFR over 2 years in the TRF-budesonide arm of the RCT in comparison to the placebo arm. The average difference in eGFR over 2 years between the study arms was 5.05 mL/min/1.73 m^2 (95% CI 3.24 to 7.38, one-sided $p<0.0001$). This effect was consistent in the four additional analyses (e.g. exploring alternative missing data

assumptions, using different analysis methods) conducted for this outcome. Data from this outcome informed the transition probabilities used in the economic model. The primary supportive analysis of 2-year eGFR total slope and three secondary outcomes also favour the TRF-budesonide arm of the trial. No differences in HRQoL were observed between the TRF-budesonide and placebo arms of the trial.

The Nef-301 OLE participants who were TRF-budesonide-experienced experienced a similar treatment effect in terms of the ratio of eGFR at 9 months compared with baseline and the ratio of UPCR at 9 months compared with baseline (the two primary OLE outcomes) as the TRF-budesonide-naïve participants. The only aspect of the OLE that informs the economic model is the proportion of patients eligible for re-treatment.

In the RCT during treatment a higher proportion of patients in the TRF-budesonide arm experienced an adverse event that was considered to have been caused by study treatment than in the placebo arm. The events that occurred during treatment in >5% in either trial arm and where the reported incidence was 5% greater or more in the TRF-budesonide arm than in the placebo arm were peripheral oedema, hypertension, muscle spasms, acne, face oedema and white blood cell count increased. Increased weight, dyspepsia and arthralgia were also experienced at a greater frequency by TRF-budesonide-treated participants than placebo participants. During the follow-up period of the RCT the proportions of participants with an adverse event considered to have been caused by study treatment were lower in both arms than during the treatment period but remained higher in the TRF-budesonide arm of the trial in comparison to the placebo arm. No new safety concerns arose during the Nef-301 OLE.

No pairwise meta-analysis or indirect comparison was conducted. As already stated, standard of care has changed since the RCT was conducted such that most patients would now be expected to receive an SGLT2 inhibitor. Data are lacking for a comparison of TRF-budesonide + standard care without an SGLT2 inhibitor versus TRF-budesonide + standard care with an SGLT2 inhibitor (linked to Key Issue 1).

4 COST EFFECTIVENESS

4.1 EAG comment on company's review of cost-effectiveness evidence

The company report a systematic literature review conducted to identify economic evaluations of targeted-release budesonide in comparison with established management of primary IgA nephropathy (CS section 3.1). The search strategy was broad, including an appropriate range of databases and supplementary sources searched from 2012 to January 2025, with limited exclusion criteria. The EAG consider that it is not likely that relevant references would have been missed.

Four non-UK publications were identified (Hiragi 2018, Ramjee 2022 and 2023 and Yaghoubi 2023)[38-41] in addition to the previous NICE appraisal of targeted-release budesonide for adults with primary IgA nephropathy at risk of rapid disease progression with UPCR ≥ 1.5 g/gram (TA937)[10]) (CS Appendix Table 6). In addition, since the company's submission, NICE have published guidance for sparsentan (TA1074).[42]

EAG comment on the company's review of cost-effectiveness evidence

The EAG consider that the search strategy for economic evaluations was appropriate, and it is not likely that relevant references would have been missed. We discuss the consistency of the company's economic evaluation with the modelling approach and NICE committee conclusions for TA937 and TA1074 in the sections below.

4.2 Summary and critique of the company's submitted economic evaluation

4.2.1 NICE reference case checklist

The company's economic evaluation is consistent with the NICE reference case (Table 7).[43]

Table 7 NICE reference case checklist

Element of health technology assessment	Reference case	EAG comment on company's submission
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers	Yes
Perspective on costs	NHS and PSS	Yes
Type of economic evaluation	Cost–utility analysis with fully incremental analysis	Yes
Time horizon	Long enough to reflect all important differences in	Yes (up to 100 years of age)

Element of health technology assessment	Reference case	EAG comment on company's submission
	costs or outcomes between the technologies being compared	
Synthesis of evidence on health effects	Based on systematic review	Yes
Measuring and valuing health effects	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of health-related quality of life in adults.	Yes
Source of data for measurement of health-related quality of life	Reported directly by patients and/or carers	Utilities were derived from EQ-5D-3L data from patients with CKD, specific values for people with IgA nephropathy were not identified (section 4.2.9)
Source of preference data for valuation of changes in health-related quality of life	Representative sample of the UK population	Yes
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	Yes. QALY severity modifiers are not applicable (see section 6.3)
Evidence on resource use and costs	Costs should relate to NHS and PSS resources and should be valued using the prices relevant to the NHS and PSS	Yes
Discounting	The same annual rate for both costs and health effects (currently 3.5%)	Yes

Source: Completed by the EAG based on information in the CS
NHS, National Health Service; PSS, personal social services

4.2.2 Model structure

4.2.2.1 Overview of the model structure

A cohort-level health state transition model was developed to assess the cost-effectiveness of TRF-budesonide with standard of care (SoC) compared with SoC alone for the treatment of primary IgA nephropathy (CS section 3.2.2). The model is implemented in Microsoft Excel, with a monthly cycle length, and a lifetime time horizon.

The model structure is described in CS section 3.2.2, and illustrated in CS Figure 15 (reproduced in Figure 2 below). It includes nine health states: six stages of chronic kidney disease (CKD 1, 2, 3a, 3b, 4 and 5, defined by ranges of eGFR), treatments for end-stage renal disease (dialysis and transplant) and death. The arrows show the allowable transitions in each model cycle.

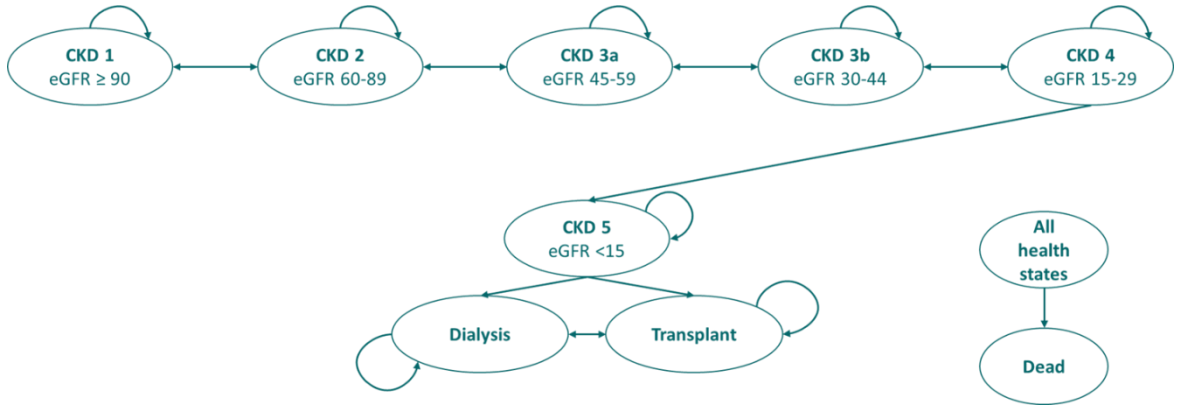

Figure 2 Health economic model structure

Source: Reproduced from CS Figure15
CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate

Assumptions and data sources for the model are described in CS sections 3.2 to 3.5.

- Key model features and assumptions are summarised in CS Tables 37 and 58.
- Transition probabilities between CKD 1 to 4 health states are shown in CS Table 39.
- A list of other base case input parameters is provided in CS Table 57.

The model structure and many of the assumptions and input parameters are consistent with the approach in TA937. We critique the model structure, assumptions and parameters, and highlight any differences with TA937 in the following sections.

4.2.2.2 EAG critique of the model structure

4.2.2.2.1 Health state definitions

The CKD stages in the model are defined by eGFR alone. The company state that this is consistent with the primary objective of the NefIgArd Nef-301 Part B trial, and with well-established precedent in cost-effectiveness modelling of CKD, including in the previous NICE appraisal of TRF-budesonide for people with primary IgA nephropathy (TA937).[10]

The numerical ranges of eGFR used to define the CKD stages in the model are consistent with the KDIGO classification for prognosis of CKD in adults, although the KDIGO

classification also includes a measure of albuminuria as a marker of risk.[17, 44] We note that the model in the recently-published NICE guidance for sparsentan in primary IgA nephropathy (TA1074) used composite health states, with eGFR stages 1-4 nested within UPCR categories.[18, 34] However, parameters for utility, mortality and health care costs were not stratified by UPCR in the final version of the TA1074 model with committee preferences. This suggests that stratification of health states by UPCR ranges would not improve the accuracy of the cost or QALY estimates.

4.2.2.2.2 Transitions between health states

In each one-month model cycle, patients in CKD stages 1-4 can stay in the same state or move to a neighbouring state, but jumps of more than one CKD stage are not allowed. The company justifies the inclusion of moves to a better CKD stage based on observed transitions in the NefIgArd Nef-301 study, the short model cycle length and precedent from previous appraisals (TA937, TA775).[10, 45] Overall, the disease is modelled to be progressive, as the monthly probabilities of progression are higher than the probabilities of regression (CS section 3.3.2.1).

Transitions from CKD stage 4 to 5 are governed by a risk of onset of end-stage renal disease (ESRD) (CS 3.3.2.2). Once people have reached CKD 5, it is assumed that they cannot revert to CKD 4. From CKD 5, patients can start renal replacement therapy (dialysis or transplant), and subsequent movements between dialysis and transplant are possible, due to transplant rejection and disease recurrence (CS 3.3.2.3). Deaths occur from any health state, with the risk increasing by CKD stage and with renal replacement therapy (RRT) (CS 3.3.2.5).

Clinical experts consulted by the EAG agreed that the above assumptions regarding health state transitions are reasonable.

EAG comment on model structure

The EAG considers that the model structure is appropriate. The use of CKD stage definitions based purely on eGFR is a reasonable simplification, consistent with the approach in TA937. We do not consider that stratification of eGFR-based health states by UPCR, as in the TA1074 model, would improve the accuracy of the cost-effectiveness results, given the lack of data to adjust utilities, mortality and costs for UPCR. Assumptions regarding transitions between the health states are also reasonable, given the available data and short model cycle length. We critique the validity of the model's predictions of disease progression in section 5.3.1 below.

4.2.3 Population and subgroups

The model is based on the NefIgArd Nef-301 Part B FAS population: adults with a diagnosis of primary IgA nephropathy, on stable RASi therapy at maximum tolerated or allowed dose, with eGFR ≥35 and ≤90 mL/min per 1.73 m^2 and proteinuria ≥1 g/day or UPCR ≥0.8 g/g. Data for this population are used to define baseline characteristics and transition probabilities in the company's base case analysis (CS Tables 36 and 39). Table 8 shows the baseline characteristics for the company's base case, and for scenarios with alternative baseline distributions of CKD stage (see CS Table 63).

Table 8 Baseline characteristics of the model population

Parameter	Base case	Scenario 1	Scenario 2	Scenario 3
Source	*NefIgArd Nef-301 Part B FAS*	*NefIgArd Nef-301 Part A FAS*	*UK RaDaR*	*UK RaDaR CKD 1-3*
Age (mean)	42.7 years	NR	NR	NR
Female (%)	34.1%	NR	NR	NR
Body weight	84.5 kg	NR	NR	NR
Distribution across eGFR defined CKD states				
CKD 1 (eGFR≥90)	2.2%	[redacted]	[redacted]	[redacted]
CKD 2 (eGFR 60-89)	38.5%	[redacted]	[redacted]	[redacted]
CKD 3a (eGFR 45-59)	37.1%	[redacted]	[redacted]	[redacted]
CKD 3b (eGFR 30-44)	22.3%	[redacted]	[redacted]	[redacted]
CKD 4 (eGFR 15-29)	0.0%	[redacted]	[redacted]	0.0%
CKD 5 (eGFR <15)	0.0%	[redacted]	[redacted]	0.0%
Total	**100%**	**100%**	**100%**	**100%**

Source: Adapted by the EAG from CS Table 36 and data on scenarios from the company's model
CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; FAS, full analysis set; RaDaR, National Registry of Rare Kidney Diseases; NR, not reported.

The NICE scope requested subgroup analysis for people at risk of rapidly progressing IgA nephropathy (UPCR ≥ 1.5 g/g), if the evidence allows. The company states that no subgroup analysis was performed (CS section 3.12). However, in response to clarification question B2, they report that separate transition probabilities were calculated for the categories UPCR <1.5g/g and UPCR ≥1.5g/g, but these results are not reported or implemented in the economic model.

EAG comment on model population and subgroups

We agree with the use of baseline characteristics from the NefIgArd Nef-301 trial population, as this aligns with the primary source of clinical data. The scenarios based on UK RaDaR registry data show the effect of assuming a higher initial proportion of patients at CKD stage 1, with or without the inclusion of patients at CKD stage 4. The view of a clinical expert advising the EAG is that, knowing the poor outcome in IgA

nephropathy, they would want to treat earlier to delay progression, almost regardless of eGFR (except <15). This suggests that the RaDaR scenario including patients at CKD stage 4 might be more representative of the patient population who might be offered treatment in clinical practice.

We would have liked to see cost-effectiveness analysis for the subgroup for whom TRF-budesonide is not currently recommended (UPCR ≥ 0.8 g/g and < 1.5g/g), as this might have helped to inform the decision over whether it is cost-effective to extend treatment to these patients. However, we acknowledge that subgroup analysis would reduce the power of the trial evidence, and hence increase uncertainty over the results. The lack of information to estimate other model parameters stratified by UPCR in addition to eGFR would also limit the discrimination of a subgroup analysis.

4.2.4 Interventions and comparators

4.2.4.1 Intervention

The model estimates the cost-effectiveness of treatment with TRF-budesonide as an add-on to standard care, which is consistent with the NICE scope and use in the NefIgArd Nef-301 trial (CS sections 3.2.3.1 and 3.5.1). The company make the following assumptions in their base case analysis:

Treatment initiation: TRF-budesonide is initiated in the first model cycle. Treatment is only started for patients in CKD stages 1 to 3b (in line with the NefIgArd Nef-301 Part B FAS population in Table 8 above). However, patients who progress to CKD stage 4 or 5 while on treatment are assumed to complete the full course.

Dosing: TRF-budesonide is self-administered at a fixed daily dose of 16 mg (four 4 mg tablets once daily), with a dose reduction to 8 mg daily assumed in the final two weeks of treatment before discontinuation, and an option to include a further dose reduction to 4 mg once a day for an additional two weeks (not included in the company's base case analysis). The company have noted in the factual accuracy check that the SmPC wording relating to the timing of the 2-week 8 mg discontinuation dose is open to interpretation, and that clinicians may include this within the 9-month treatment period or as an additional 2 weeks of treatment after 9 months at full dose.

For costing purposes, it is assumed that the two-week dose reduction to 8 mg daily occurs in the final two weeks of a full 9-month course of treatment. Whereas the standard treatment course in NefIgArd Nef-301 Part A was 9 months of treatment at the full dose of 16 mg daily,

followed by a further 2 weeks of treatment at a reduced dose of 8 mg. There is also some inconsistency in use of the term 'tapering period': in the economic chapters of the CS, only the final, optional 2-week period at 4 mg daily is referred to as the 'tapering period'.

Relative dose intensity: The cost of treatment is not adjusted for relative dose intensity, as it is expected that the cost for the full course of treatment will be incurred in practice. The company report a scenario with the acquisition cost for TRF-budesonide adjusted for the observed relative dose intensity in the NefIgArd Nef-301 study ([redacted]).

Treatment discontinuation: Kaplan-Meier (KM) data from the NefIgArd Nef-301 trial shows a [redacted] (CS Figure 20). The company note that patients were censored from the KM data at their final follow-up appointment, and it is stated in the model that the KM data excludes the tapering period. For the base case, the company use KM data to model discontinuation up to the start of the ninth month, patients still on treatment at that time are assumed to continue on treatment with the reduced dose in the final two weeks of month 9. All treatment is assumed to stop after 9 months.

Duration of treatment effect: The effect of TRF-budesonide is modelled using eGFR data collected over 24 months of follow-up in the NefIgArd Nef-301 trial (see CS sections 3.3.2.1 and 3.3.2.2). As there is no longer-term effectiveness evidence, the company assume that the effect of TRF-budesonide is lost at this time, and the SoC transition probabilities are applied to both arms from 24 months onwards.

Re-treatment: The MHRA Summary of product characteristics (SmPC) states that re-treatment may be considered at the discretion of the treating physician. Baseline assumptions regarding re-treatment were informed by the NefIgArd-OLE study (see CS B.3.5.1.1.5):

- *Number of re-treatment rounds*: assumed maximum of one round of re-treatment, which is likely to be conservative (increasing the number of rounds of re-treatment increases the incremental net benefit).
- *Time between treatment rounds*: 14.75 months based on time from completion of 9 months treatment in the RCT to OLE study entry (at 24 months from baseline).
- *Re-treatment eligibility*: [redacted]% ([redacted]/180) of patients from the RCT who were screened for the OLE study met the inclusion criteria for the study. Initiation of re-treatment is restricted to people in CKD stages 1-3b (as for the initial treatment).

- *Re-treatment effectiveness:* a 10% loss of treatment effect is assumed to apply to the transition probabilities and risk of ESRD during re-treatment. The company argue that this is conservative, as patients are not expected to develop resistance to TRF-budesonide.
- Other assumptions applied to re-treatment are the same as for the initial treatment period, including the duration of treatment effects, and rates of discontinuation.

4.2.4.2 Standard of care

The NICE scope specifies standard care as the comparator, defined as ACE inhibitors and ARBs at maximally tolerated licensed doses, diuretics, and dietary and lifestyle modification, with or without an SGLT2 inhibitor (NICE TA775, TA942 and TA1075) and sparsentan (which is now recommended as an option in NICE TA1074 guidance).[15, 16, 18, 45] We note that, although the uptake of new agents in the SoC basket of treatments will affect costs and outcomes in both treatment arms, these changes do not necessarily cancel out, due to the effect of TRF-budesonide on disease progression and survival.

The company state that the placebo arm of NefIgArd Nef-301 trial is a good proxy for SoC, as patients in both arms received optimised and stable RASi therapy (ACE inhibitor or ARB). However, few patients in the trial received an SGLT2 inhibitor and none received sparsentan, as these treatments were not recommended for primary IgA nephropathy at the time of the trial. The model includes costs for concomitant medications received by 10% or more of patients in either treatment arm of NefIgArd Nef-301 Part B FAS (CS Table 8). The company also assume that all patients would now be prescribed an SGLT2 inhibitor (dapagliflozin), and the cost of this was added to SoC in both treatment arms. However, the model does not include a treatment effect for SGLT2 inhibitors, or costs or treatment effects for sparsentan.

Clinical advice to the EAG is that most patients will now be on SGLT2 inhibitors, but that sparsentan is only recently approved so will take time to see how many people are started on it and how well tolerated it is in general population.

See section 4.2.10.1.2 for discussion on the potential for modelling the cost of sparsentan.

EAG comment on intervention and comparators

The company's assumptions regarding the use of TRF-budesonide are consistent with the analysis in TA937 and with clinical expert opinion regarding its use in practice.

We report an exploratory EAG scenario analysis applying a relative treatment effect to reduce disease progression in standard care (in both arms), to test the potential impact of more effective treatments, including the SGLT2 inhibitors, on the cost-effectiveness of TRF-budesonide. The company's base case model includes costs for SGLT2 inhibitors, but no effect on patient outcomes.

4.2.5 Perspective, time horizon and discounting

The analysis was conducted from an NHS and personal social services (PSS) perspective, with costs and benefits discounted at a rate of 3.5% per year. The model uses monthly cycles and a lifetime horizon.

4.2.6 Treatment effectiveness and extrapolation

Transition probabilities between health states CKD 1 to 4 are estimated from NefIgArd Nef-301 trial data, which the company considers to be the most relevant and representative dataset for the submission. Real-world evidence and data sourced from the published literature was used where trial data was not available (risk of ESRD, initiation of dialysis and transplant and mortality).

4.2.6.1 Transition probabilities (CKD 1-4)

4.2.6.1.1 Transitions from 0-24 months

The process for estimating transition probabilities between CKD stages 1-4 is described in CS section 3.3.2.1.1. A logistic regression model was fitted to baseline and 24-month individual patient data to estimate the probabilities of movement from CKD stages 1-3b to better or worse health states over this period. The log odds of disease progression and improvement, by CKD stage and treatment are reported in CS Table 38. The log odds were converted to 24-month probabilities, and then to monthly transition probabilities for use in the economic model. Uncertainty over the logistic regression coefficients is propagated though the probabilistic sensitivity analysis (PSA), with the logistic regression coefficients sampled from multivariate normal distributions.

The resulting monthly transition probability matrices are shown in CS Table 39. As there were no patients in CKD stage 4 at baseline, the company assumed that the probability of improvement from CDK stage 4 is the same as from CKD stage 3b. See section 4.2.6.2 below for methods used to estimate transitions from CKD stage 4 to 5. The company note that the TRF-budesonide matrix is applied to all patients in the intervention arm up to month 24, regardless of whether they have discontinued treatment. We agree that this is appropriate, as the TRF-budesonide coefficients were estimated from data that included

patients who discontinued treatment at or before 9 months. The use of constant transition probabilities throughout the first two years might not be realistic, but it is not evident that this would bias the cost-effectiveness results.

Further information about the estimation of CKD 1-4 transition probabilities is provided in the company's response to clarification question B1:

- The quantity of missing data was low: with [redacted] out of 182 observations missing in the TRF-budesonide arm, and [redacted] out of 182 missing in the SoC arm (clarification response Table 5). The company states that missing data were imputed using a last observation carried forwards (LOCF) approach, which we consider appropriate.
- The numbers of observations for some CKD stage transitions were very low: only 8 of 364 patients were in CKD stage 1 at baseline and none were in CKD stage 4 (CS Table 36); and data on improvement at 24 months were sparse, with [redacted] (clarification response Table 5). In this context, the use of one treatment effect coefficient in each of the two regression equations is reasonable, as this pools information across the CKD stages.
- Observed and predicted transitions from baseline to 9 and 24 months are reported in clarification response Tables 5 to 8 (see section 5.3.1.2 below for discussion).

The response to clarification question B2 reports on alternative specifications for the logistic regressions, including fitting the equations over different time intervals (Clarification response B2, Tables 9 to 11), and the addition of baseline UPCR as a covariate. The company state that separate transition probabilities were calculated for subgroups with UPCR <1.5g/g and UPCR ≥1.5g/g but were not implemented in the economic model, as they were not considered relevant to the decision problem. The subgroup transition probability matrices are not reported. As noted in section 4.2.3, we consider that this subgroup analysis is potentially relevant, as it could affect the cost-effectiveness results for the lower-risk subgroup who are not included in the current NICE recommendation for TRF-budesonide.

4.2.6.1.2 Transitions beyond 24 months

The company assume that the effect of TRF-budesonide lasts for a maximum of 24 months from the start of treatment, reflecting the lack of clinical evidence beyond this time (CS section 3.3.2.1.2). In the absence of re-treatment, the SoC transition matrix is applied to both arms from 24 months onwards. The company argue that this is conservative, citing clinical opinion from an advisory board, arguments relating to the mechanism of action, and a modelling study that predicted a persistent effect (Barratt et al. 2024).[46-48] Barratt et al. used

the 24-month effect of TRF-budesonide on the eGFR slope (from NefIgArd Nef-301 Part B) as a surrogate to estimate time to a clinical outcome of kidney failure, eGFR < 15 ml/min/1.73 m^2 or sustained doubling of serum creatinine. The analysis used the formula estimated by Inker et al. (2019).[28] to model the relationship between eGFR slope and the clinical outcome, and a background risk of progression with standard care from a matched cohort study of patients from the Leicester General hospital registry.[46]

4.2.6.2 Transitions to CKD stage 5

The numbers of patients progressing to CKD stage 5 or end stage renal disease (ESRD) in the NefIgArd Nef-301 trial and OLE were low, and do not provide data on the relative treatment effect on this outcome (clarification response B12). The company therefore used alternative sources to estimate the probability of transition from CKD stage 4 to 5 in the economic model, as described in CS section 3.3.2.2. This entailed first modelling the background risk of transition to CKD 5 under standard care using UK RaDaR registry data, and then adjusting for the relative effect of TRF-budesonide based on a surrogate outcome of change in eGFR and the method reported by Inker et al. (2019).[28] We discuss these steps below.

4.2.6.2.1 SoC arm

The risk of transition to CKD 5 is estimated from UK RaDaR registry data for patients with IgA nephropathy, UPCR ≥ 0.8 g/g and eGFR in the range used to define the CKD 4 health state in the model (15-29 mL/min/1.73 m²). The KM curve for time to diagnosis of ESRD in this cohort is shown in CS Figure 16.[49] The company note that for the model, it is assumed that the outcome ESRD is equivalent to CKD 5. They also note that the number of patients at risk in the KM curve diminishes from year 4, so the tail of the curve might not reflect clinical practice.

The KM curve was digitised to produce pseudo patient level data (CS Figure 16), to which parametric survival curves were fitted (CS Figure 17). Measures of the fit of the parametric curves to the KM data are reported in CS Table 40. The exponential curve has the best fit based on the BIC statistic, and the log-normal and Weibull have the best fit based on the AIC statistic (lower values of these statistics indicate a better fit, but small differences are not meaningful). We show these three curves with digitised KM data in Figure 3, over a shorter timeframe (10 years), which shows that the exponential has a poor visual fit in the initial period up to about 2 years, underestimating progression. Conversely, the log-normal has a good initial fit to the KM, but then appears to overestimate progression. As noted by the

company, the later KM results are unreliable due to the small number of patients remaining at risk ([redacted] at 2 years, and [redacted] at 4 years).

Regarding long-term predictions, CS Figure 17 shows that the exponential distribution (constant hazard), predicts the highest rate of progression to CKD 5. This indicates that all other parametric distributions predict diminishing hazards over time.

The company chose the exponential model for their base case analysis: on the basis that it has the best statistical (based on BIC); but also, because a constant hazard is consistent with the varying durations of CKD in the RaDaR dataset and memoryless nature of the Markov decision model. This is a reasonable argument, although in relation to the economic model's long time horizon, the assumption of a constant hazard of progression to CKD 5 might not be realistic. An expert advising the EAG noted that the risk of CKD progression is related to age and to comorbidities such as diabetes mellitus and hypertension, which might suggest an increasing risk with age, although comorbidities progress at different rates and there are other factors that influence progression.

There is therefore uncertainty over the assumption of a constant risk of progression to CKD 5, although we note that this is a conservative assumption: cost-effectiveness is better (higher incremental net monetary benefit [INMB]) than with the other parametric extrapolations (see Appendix 4).

Figure 3 Digitised KM and fitted extrapolations for time from CKD4 to CKD5

Source: Produced by the EAG from the company's economic model
KM, Kaplan Meier; CKD, chronic kidney disease; SoC, standard of care

4.2.6.2.2 TRF-budesonide

The rate of progression from CKD stage 4 to 5 in the TRF-budesonide treatment arm is estimated by applying a relative treatment effect (HR) to the modelled rate in the standard care arm for the assumed duration of treatment effect (2 years in the base case). After this time, the risk of progression is assumed equal to that of standard care, except when another round of treatment is used. This same 2-year duration of effect is applied in retreatment.

The model uses an estimated HR of 0.38 (95% CI 0.21-0.63) reported by Barratt et al. (2024).[46] This is estimated based on: a difference in 2-year eGFR total slope with TRF-budesonide compared to placebo estimated from the NefIgArd Nef-301 trial for patients of 2.78 mL/min/1.73 m^2 per year (95% CI 1.39-4.17) (Barratt et al. 2024).[46] And the Inker et al. (2019)[28] estimate of the relationship between the mean difference in eGFR total slope and the hazard ratio for progression to CKD5 or ESRD over two years (CS Figure 18). These calculations are explained in CS section 3.3.2.2.2. We also discuss this supportive analysis of 2-year eGFR total slope in sections 3.2.3.1.1.2 and 3.2.5.1.1 above.

We report exploratory EAG analysis to investigate the effect of uncertainty over the estimated HR for the risk of CKD progression, using the 95% confidence limits reported by Barratt et al. (see section 6.1)

4.2.6.3 Renal replacement therapy (CKD 5, dialysis and transplant)

Data on the probability of transition between the health states of CKD5 (without renal replacement therapy), dialysis and transplant were not available from the NefIgArd Nef-301 trial, because recruitment was restricted to CKD stages 1-3b, and few patients progressed to stage 5 within the 2-year follow-up. The company therefore used estimates from the DAPA-CKD trial reported by Sugrue et al. (2019) which were used in NICE TA775.[45, 50] The monthly probabilities are reported in CS Table 41. The same were used in both arms, with the assumption of no lasting effect of TRF-budesonide after progression to CKD stage 5. The company report a scenario analysis with a 6% monthly probability of transition from CKD 5 to dialysis, to align with an EAG scenario in TA937.

EAG comment on the estimated transition probabilities

Use of 'hybrid data', with clinical trial data used to estimate transition probabilities between CKD stages 1-4 and registry data to estimate the risk of progression to CKD 5, is consistent with TA937 and the TA1074 committee preferences.

Methods used to estimate the transition probabilities for CKD 1-4 are appropriate, although we note high uncertainty due to sparse data for some transitions. In addition, the trial data do not reflect current practice, as they omit the effects of SGLT2 inhibitors, which were only used by a few patients in the clinical trial. We report a simple exploratory analysis to illustrate the effect of improvements in the effectiveness of standard care that apply to both arms; see section 6.1.

We would have liked to see results from the company's subgroup analysis of transition probabilities for UPCR <1.5g/g and UPCR ≥1.5g/g referred to in the response to clarification question B3, and the impact of this on cost-effectiveness results, although we acknowledge that this would reduce the effective sample size.

There is also some uncertainty over the estimated risks of progression to CKD 5. The rate of transition with standard care is estimated from UK RaDaR data, but the sample size and length of follow up for the population of interest are modest. However, although there is uncertainty over the extrapolation of these data, the company's selection of the exponential (constant hazard) extrapolation is conservative compared with the other parametric extrapolations, which predict diminishing hazards. The hazard ratio used to

estimate the treatment effect of TRF-budesonide on progression to CKD 5 relies on a surrogate relationship with eGFR. We conduct additional scenario analysis to test the sensitivity of cost-effectiveness results to the reported confidence interval for the hazard ratio (section 6.1).

4.2.7 Mortality

Mortality was modelled relative to general population risk, by age and sex (ONS 2021-23).[51] Mortality in CKD stage 1 was assumed equal to that in the general population, and standardised mortality ratios (SMRs) were used to adjust the risk for CKD stages 2-5 and for people on renal replacement therapy. For the base case, SMRs were estimated from 10-year survival estimates for an IgA nephropathy cohort from the UK RaDaR registry (CS Table 43). See Table 9 for the base case SMRs and estimates from three alternative sources used for scenario analysis.

The base case SMRs are the same as in the previous NICE appraisal for TRF-budesonide (TA937), and we agree that the UK RaDaR IgA nephropathy cohort with all patients included is still the most appropriate data source for use in the model. Estimates for the UPCR ≥ 0.8g/g subgroup from RaDaR are not plausible, as for several CKD stages the SMRs predict a mortality risk that is considerably lower than in the general population. This is likely to be an artefact due to the small sample size of the subgroup. Hastings et al. reported survival data for a US cohort (n=251) with long follow up, however it may not be representative of the UK population or current practice.[52] Greene et al. simulated survival from eGFR trajectories from 47 randomised treatment comparisons, estimating the mortality hazard rate as a linear function of eGFR.[53]

Table 9 Standardised mortality ratios by CKD stage

Health state	UK RaDaR [49]		Hastings 2018 [52]	Greene 2019 [53]
	All patients	UPCR ≥ 0.8g/g		
CKD 1	[redacted]	[redacted]	[redacted]	[redacted]
CKD 2	[redacted]	[redacted]	[redacted]	[redacted]
CKD 3a	[redacted]	[redacted]	[redacted]	[redacted]
CKD 3b	[redacted]	[redacted]	[redacted]	[redacted]
CKD 4	[redacted]	[redacted]	[redacted]	[redacted]
CKD 5	[redacted]	[redacted]	[redacted]	[redacted]
RRT	[redacted]	[redacted]	[redacted]	[redacted]

Source: Adapted from CS Table 43 by the EAG, using additional data from the company's model
CKD, chronic kidney disease; RRT, renal replacement therapy; SMR, standardised mortality ratio

The company also report scenarios with adjustments to the base case UK RaDaR SMRs to avoid lower SMRs (better survival) for CKD stages 3a and 3b than for stage 2 (CS section 3.3.2.5 and the company's response to clarification question B4).

EAG comment on the mortality estimates

For EAG analysis, we prefer the SMR estimates based on the UK RaDaR dataset (with all patients), but with SMRs for CKD stages 3a and 3b set equal to the value for CKD stage 2 ([redacted]). This provides a gradation of SMRs across the CKD stages, with higher mortality in more advanced disease. The results are also reasonably consistent with the Greene et al. estimates, which are obtained from a linear function of eGFR using simulated data.[53]

4.2.8 Adverse events

The model includes estimated costs and disutilities associated with treatment-related adverse events that occurred in ≥4% of patients in either arm of the NefIgArd Nef-301 Part B SAS (CSR Table 37) and all treatment emergent severe adverse events that occurred for more than one patient in the SAS and Part B FAS (CSR Table 43).

- The adverse event (AE) rates used in the model are shown in CS Table 42.
- The estimated duration of the modelled AEs, the disutility experienced during this time and resulting QALY loss are shown in CS Tables 46, 47 and 48 respectively (CS section 3.4.4).
- Costs associated with the modelled AEs are estimated using assumptions and unit cost data from the NHS National Schedule 2023/24 (see CS Table 56).

The mean QALY loss and cost are applied in the first model cycle for both arms, and for the TRF-budesonide in the first cycle of each retreatment round. The overall impacts of the AEs are estimated to be small (CS Appendix Tables 18 and 19). For the company's base case, AEs are associated with [redacted]

EAG comment on AE disutility and costs

The EAG has no concerns over the methods used to model the impact of AEs.

4.2.9 Health related quality of life

Methods used to estimate the effects of TRF-budesonide on health state utilities are described in CS section 3.4.2. The EQ-5D questionnaire was not used in the NefIgArd Nef-301 Part B trial or OLE study, although HRQoL data was collected from patients using the

SF-36 (see section 3.2.3.2 above). The company report that no between-group differences were observed in SF-36 domain scores over 9 or 12 months of follow-up in the NefIgArd Nef-301 Part B trial (CS section 2.6.1.5), or over 12 months of follow-up in the OLE study (CS section 2.6.2.4). However, these results, do not necessarily reflect the overall impact on 'utility', which is required to estimate QALYs for economic evaluation. SF-36 data could be used to calculate preference-based SF-6D utility scores, which are suitable for QALY calculations, but this is not NICE's preferred method for measuring and valuing the effect of interventions on HRQoL for economic analysis.[43] We therefore agree with the company, that health state utility estimates from the literature based on EQ-5D data are a better source of utility estimates for use in the model.

The company updated the SLR conducted in 2022 for the previous NICE appraisal of TRF-budesonide (CS section 3.4.3 and Appendix F). The updated review identified one study (Zhou et al. 2024) that reported utility values for people with IgAn.[54] However, this used a vignette approach with time trade-off valuations derived from members of the general public, which is not consistent with the NICE reference case.[43] The company therefore decided to use EQ-5D utility values from UK general CKD populations (not specific to IgAN) reported from an SLR by Cooper et al. (2020), with scenarios based on utilities reported by Zhou et al. and a US time trade off analysis by Gorodetskaya et al. 2005 (see Table 10).[54-56]

Table 10 Utility values by health state

	Cooper et al. 2020 [a]	Zhou et al. 2024	Gorodetskaya et al. 2005
CKD 1	0.85	0.71	0.90
CKD 2	0.85	0.71	0.90
CKD 3a	0.80	0.61	0.87
CKD 3b	0.80	0.61	0.87
CKD 4	0.74	0.49	0.85
CKD 5	0.73	0.42	0.85
Haemodialysis	0.44	-	-
Peritoneal dialysis	0.53	-	-
Post transplant	0.71	-	-

Source: Adapted by the EAG from CS Table 44
[a] Reported in systematic literature review by Cooper et al. (2020): CKD stages 1 to 5 Jesky et al. (2016); haemodialysis, peritoneal dialysis and post-transplant from Lee et al (2005).[55, 57, 58]

EAG comment on HRQoL

We agree with the company's decision to use base case health state utilities, from studies by Jeskey et al. (2016) and Lee et al. (2005), as reported by Cooper et al. (2020). Although these utilities are derived from CKD populations, and are not specific for people with IgAN, they are consistent with the NICE reference case and have been used in previous NICE appraisals for an IgAN (TA937 and TA1074), as well for CKD (TA775, TA942 and TA1075).

4.2.10 Resources and costs

4.2.10.1 Drug acquisition costs

4.2.10.1.1 TRF-budesonide

TRF-budesonide is available in packs containing 120 4 mg tablets, at a list price of £4,681.24, or [redacted] with a [redacted] confidential Patient Access Scheme (PAS) discount applied. One pack provides 30 days of treatment at the full daily dose of 16 mg. Methods and assumptions used to cost TRF-budesonide are described in CS section 3.5.1.1.1.

4.2.10.1.1.1 Dosing and wastage assumptions

We summarise dosing assumptions used in the economic model in section 4.2.4.1 above. This includes the assumption that the 2-week period at the 8 mg reduced dose occurs in the final two weeks of treatment – before the end of month 9. The optional further dose reduction to 4 mg daily for an additional two weeks is not included in the base case, but is reported as a scenario.

The company use a per mg method to estimate the cost of TRF-budesonide and other drugs in the economic model, with an assumption that the exact dose required will be dispensed, with no wastage. As the model uses a monthly cycle length of 30.4375 days (one twelfth of a year), the cost per cycle of TRF-budesonide at the full daily dose of 16 mg dose is estimated at [redacted]. The estimated cost for the final cycle (accounting for 16 mg dosing before the patient switches to the reduced dose of 8 mg for the final two weeks) is [redacted], and the cost for the additional 2-week tapering period at 4 mg is [redacted]. These costs are likely to be under-estimated, as wastage is likely in practice.

In the factual accuracy check, the company report that a 'tapering pack' containing 28, 4 mg tablets is now available at a pro rata price, relative to the 120 tablet pack, of £1,092.29, or [redacted] with the [redacted] PAS discount applied. They estimate an additional of cost of [redacted] per patient for wastage in the base case analysis with the reduced 8 mg daily dose in the final

two weeks of the 9 month treatment period: assuming efficient prescribing of 8 x 120 tablet packs and 4 x 28 tablet packs (4 tablets wasted). The additional cost of wastage if the two-week 8 mg dose is used after 9 months of treatment at the full dose is estimated at [redacted] assuming 9 x 120 tablet packs and 2 x 28 tablet packs (12 tablets wasted).

The cost for the optional 2-week tapering period at 4 mg assuming no wastage is [redacted] The model includes an option to assume wastage of the remaining tablets in the tapering pack, which brings the cost of the additional, optional tapering period to [redacted]. The company submission reports scenarios including tapering, with and without the tapering pack cost.

We note that the above wastage scenarios are subject to various uncertainties relating to prescribing practice and the implementation of reduced and tapered dosing. They do not include potential wastage related to early discontinuation or adjusted dose intensity, which would tend to reduce overall treatment costs. But additional wastage costs will be incurred for patients who have retreatment.

The base case analysis assumes that costs for prescribing the full 16 mg daily dose, the 8 mg reduced dose, and the 4 mg tapered dose (when applied) are incurred with no other adjustment for relative dose intensity (RDI). The company report a scenario with cost adjustment based on the observed RDI in the NefIgArd Nef-301 trial.

4.2.10.1.1.2 Time to treatment discontinuation

The KM curve for the observed time to treatment discontinuation from the NefIgArd Nef-301 trial is shown in CS Figure 20. This shows a gradual rate of discontinuation, with a sharp decline in the final 2 weeks of the 9-month treatment period and a period of continuing treatment into month 10. The company note that patients were censored from the KM at the final follow up appointment, and suggest that this explains the sharp drop in treatment before the end of month 9. The company assume that all patients on treatment at the start of month 9 receive the reduced dose for 2 weeks, and that all treatment stops at the end of month 9.

4.2.10.1.1.3 Retreatment assumptions

Retreatment assumptions are summarised in CS section 3.5.1.1.5. The base case assumes that [redacted]% of patients in CKD stages 1 to 3b have one round of retreatment, 14.75 months after the end of the first round (approximately 24 months from baseline): based on the experience of transition from the end of NefIgArd Nef-301 to the start of the OLE study. The company states that the assumption of one retreatment round is considered to be conservative. They assume 10% waning of the treatment effect in subsequent treatment

rounds, applied to transition probabilities between CKD stages 1-3 and the risk of CKD. Other costs and effects of retreatment are assumed to be the same as for the initial round of treatment. These assumptions are varied in scenario analysis.

4.2.10.1.2 Standard of care

CS Table 52 summarises the estimated drug costs for SoC. Further detail is provided in CS Appendix Table 22 and in an Excel file "Data on file. SoC costs for NICE", provided in the CS reference pack.

Included drug classes

Costs were included for concomitant medications used by at least 10% of patients in either arm of the NefIgArd Nef-301 Part B FAS population (CS Table 8). This includes ARBs and ACE inhibitors, which were specified in the NICE scope, and other drugs not specified in the scope (other classes of antihypertensives; lipid lowering medicines; preventive treatments for renal stones and osteodystrophy; glucocorticoids; paracetamol; proton pump inhibitors and a sulphonamide antibiotic). Viral vaccines and herbal and traditional medicines which met the 10% threshold were excluded, as they were not considered relevant.

The company also assumed 100% use of an SGLT2 inhibitor (dapagliflozin), despite very low use in the trial, based on TA775.[45] Other drugs specified in the scope but not used in the trial (sparsentan and empagliflozin) were not included in the SoC cost, as they were not recommended by NICE at the time of the company submission.

Weightings for drug classes

We note a minor error in the calculation of the weighted monthly cost of SoC in the company's base case (CS Table 52). Costs were weighted across the drug classes based on the proportion of patients using a medication in that class between the first dose of study medication and the end of follow up (month 20), with data pooled across the treatment arms (N=364; CS Table 8). However, the calculations in the submitted Excel file use a denominator of 374 (Concomitant medications CSR! G5:G19). See Table 11 for the corrected weightings, which are consistent with concomitant medication use in CSR Table 14.1.5.4.[20] The correction causes a small increase in the total monthly SoC cost: from £80.18 to £80.74.

Calculation of the cost per month

Drug costs are based on list prices from the drugs and pharmaceutical electronic market information tool (eMIT), or the British National Formulary (BNF) for dapagliflozin which is not listed in eMIT (CS Appendix Table 22).[59, 60]

Costs for each drug class are calculated as a simple unweighted mean of list prices for the included medicines and formulations based on a maximum daily dose and cost per mg, with adjustment for the one-month model cycle length (30.4375 days) (CS 3.5.1.2). This method produces some anomalies, with unrealistic fractions of tablets assumed for some formulations, but we think it is a reasonable simplification given the low total cost of SoC drugs excluding dapagliflozin (£21.08 per month in our corrected analysis). However, we consider that the company's estimated cost for dapagliflozin (£59.66 per month) is unrealistic as this assumes 50:50 use of 5mg and 10mg tablets, which cost the same (£36.59 per 28 days), and an assumed daily dose of 10mg. We therefore we consider it more appropriate to cost dapagliflozin based on the 10mg tablet (£39.78 per month).

Table 11 EAG-corrected drug acquisition costs for SoC

Drug class	Weighting (EAG) [a]	Monthly cost [b]	Weighted monthly cost
Drugs specified in NICE scope			
ARBs (irbesartan, losartan)	[redacted]	£3.17	£1.67
ACEIs (captopril, lisinopril, ramipril)	[redacted]	£2.32	£1.01
Other blood pressure lowering			
Dihydropyridine derivatives (CCBs)	[redacted]	£17.57	£6.95
Beta blockers	[redacted]	£3.51	£0.60
Alpha-adrenoreceptor antagonists	[redacted]	£1.78	£0.21
Lipid modification			
HMG CoA reductase inhibitors (statins)	[redacted]	£0.82	£0.38
Other lipid modifying agents (ezetimibe)	[redacted]	£1.70	£0.35
Prevention of renal complications			
Uric acid inhibition (renal stones)	[redacted]	£2.14	£0.69
Vitamin D & analogues (renal osteodystrophy)	[redacted]	£5.10	£1.46
Other medications			
Glucocorticoids (immune suppression)	[redacted]	£23.96	£4.61
Analides (paracetamol)	[redacted]	£6.71	£2.14
Proton pump inhibitors (gastric protection)	[redacted]	£1.64	£0.28
Sulfonamides (antibiotic)	[redacted]	£3.64	£0.74
Weighted average cost for SoC			
Total weighted monthly cost excluding SGLT2i			£21.08
Including 100% SGLT2i at £59.66 per month (50:50 5mg and 10mg) [c]			£80.74
Including 100% SGLT2i at £39.78 per month (10mg only) [c]			£60.86

Source: Adapted from CS Table 52 by the EAG
ACEIs, angiotensin-converting enzyme inhibitors, ARBs, angiotensin-receptor blockers; CCBs, calcium channel blockers; EAG, External Assessment Group; HMG CoA, 3-hydroxy-3-methylglutaryl-CoA; SGLT2i, Sodium/glucose cotransporter 2 inhibitor, SoC, standard of care;
[a] Percentage of patients in NefIgArd Nef-301 Part B FAS with concomitant medication in ATC class, with EAG correction to total sample size (N=362)
[b] Cost per class calculated as unweighted mean of included medications and formulations, based on the cost per mg at list price and maximum daily dose, adjusted for monthly cycle (30.4375 days).
[c] Assumption that all patients would be prescribed dapagliflozin

Costs for recent NICE recommendations

NICE recommended empaglifozin for treating chronic kidney disease in 2023 (TA942). Since publication of the final scope for the current appraisal, guidance for dapagliflozin for treating chronic kidney disease has been updated in a cost comparison with empagliflozin (TA1075).[15, 16] Both SGLT2 inhibitors are now recommended as options with the same conditions for access, and advice to use the least expensive option as they have similar clinical effects. The list prices for dapagliflozin and empaglifozin are currently the same, so there is no need investigate the effect of the uptake of empagliflozin, as an alternative to dapagliflozin, on the cost of SoC.

Sparsentan was included in the NICE scope for the current appraisal, subject to NICE evaluation. Since publication of the scope, NICE has recommended sparsentan as an option to treat primary IgA nephropathy. (TA1074).[18] Sparsentan is therefore now available as a potential replacement for RASi therapy in standard care, but is not included in the company's model. The EAG considered conducting a scenario analysis with the cost for sparsentan included for a proportion of patients in the SoC arm. However, a clinical expert has advised that, as the NICE recommendation for sparsentan is so recent, it is not known how many people will be started on sparsentan in clinical practice, or how well it will be tolerated. Furthermore, the NICE recommendation for sparsentan includes a 'stopping rule': that treatment should be discontinued after 36 weeks if the UPCR is 1.76 g/g or more and has not reduced by 20% or more. We therefore conclude that it is not feasible to model the cost or effects of sparsentan.

4.2.10.2 Drug administration costs

The model does not include any costs for administration of TRF-budesonide or other drugs used for standard care, as they are oral medications that are self-administered.

4.2.10.3 Healthcare resource use and costs

Sources and assumptions used to estimate healthcare resource use and costs for the model health states are summarised in CS section 3.5.2.

CKD stages 1-5: The base case uses micro-costings for hospital care (including all hospital admissions, routine dialysis treatment and day case and outpatient care) by CKD stage are reported by Kent et al. 2015, uprated to 2024 prices using PSSRU inflation indices (see CS Table 55). These costs were estimated from resource use data for a large international cohort of patients with moderate to severe kidney disease (not specific to IgAN). Kent et al reported costs for patients from Europe, Australasia or North America, using UK unit costs at 2011 prices, which the company uprated to 2023/24 prices using an Inflation index (PSSRU). This source is consistent with the committee's preferred approach in TA937 and TA1074. The company also report scenarios with alternative sources of costs by CKD stage (Pollock et al. 2022 and Baxter et al. 2024).[61-63]

Primary care: As Kent et al. did not include costs for primary care, these were estimated separately based on assumed numbers of GP visits and blood tests (twice per year for CKD stage 1-3b, and quarterly for CKD 4 and 5), with unit costs taken from the PSSRU and NHS National Cost collection 2023/24, respectively.

Dialysis: Costs for dialysis were estimated as a weighted sum of NHS National Cost Collection 2023/24 unit costs for different types of dialysis (CS Table 53), weighted by the frequency of use in England and Wales, from the UKRR 26th Annual report.[64, 65] Other costs included for dialysis are the cost of transport for people receiving hospital and satellite haemodialysis, nephrologist outpatient appointments, blood tests and hospital admissions.

Transplants: Costs for transplants included a one-off cost (including pre-assessment, the procedure and post-transplant follow up) and ongoing costs (including outpatient appointments with a nephrologist, blood tests and immunosuppressive therapy (tacrolimus).

End of life: A cost for end-of-life care was included, based on a study by Kerr et al. (2017), inflated to 2023/24 prices.

EAG comment on resources and costs

The cost-per-mg method used to cost TRF-budesonide over the treatment cycle does not account for wastage that is likely to occur in practice. The company has provided estimates of the additional costs of wastage based on efficient use of the 120 tablet and 28 tablet packs of TRF-budesonide. The overall estimated costs of wastage are modest, and it is unlikely that they would change the cost-effectiveness conclusions, unless combined with other more conservative assumptions.

Use of the cost-per-mg approach to cost standard care drugs also requires some unrealistic assumptions about use of fractions of tablets, although we understand that it is a reasonable simplification given the low total cost of most standard care drugs. However, we consider the company's estimate of £59.66 per month for dapagliflozin to be unrealistic, as it assumes 50:50 use of 5mg and 10mg tablets (at the same cost per tablet), to deliver a daily dose of 10mg. We therefore consider it more appropriate to cost dapagliflozin based on the 10mg tablet (£39.78 per month).

Methods used to estimate costs for healthcare resource use by CKD stage and for dialysis and transplant are reasonable, and consistent with other NICE appraisals for IgaN and CKD. We agree with the use of hospital cost estimates reported by Kent et al. (2015).

5 COST EFFECTIVENESS RESULTS

5.1 Company's base case cost effectiveness results

In this section we summarise the company's results, as reported in CS sections B.3.10 and B.3.11, which are based on the version of the company's model dated 22 May 2025, (*ID6485 budesonide Company CE model v1.0 22052025 JE [CON]*). Results are reported with a confidential PAS discounted price for TRF-budesonide and other drugs at list price (no other confidential price discounts are currently available). To aid comparison when one treatment option is dominant (and the ICER statistic is not informative), we report an Incremental Net Monetary Benefit (INMB) statistic with QALYs valued at the £30,000 per QALY gained threshold.

The company reported the deterministic results for the base case analysis in CS Table 59. In response to clarification question C3, the company acknowledged that the incremental life years and incremental QALY columns in Table 59 had been mislabelled, and they provided a revised version (clarification response Table 14). It is not clear why the total cost and total QALY results in the revised table differ from those in CS Table 59 (which is consistent with base case results in the company's submitted model).

We report the company's base case results in Table 12, including the deterministic results from CS Table 59 (with correct labelling of the incremental QALYs), and probabilistic results replicated from CS Table 61. In the deterministic analysis, TRF-budesonide is estimated to be dominant compared with SoC alone, as it has lower costs and higher QALYs. The probabilistic results are slightly less favourable, with an ICER of £1,211 per QALY gained.

Table 12 Company's base case results (TRF-budesonide at PAS price)

Treatment	Total costs (£)	Total QALYs	Incr. costs	Incr. QALYs	ICER £/QALY	INMB, at £30k/QALY
Deterministic						
TRF-budesonide	[redacted]	[redacted]	-	-	-	-
SoC alone	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	£9,231
Probabilistic						
TRF-budesonide	[redacted]	[redacted]	-	-	-	-
SoC	[redacted]	[redacted]	[redacted]	[redacted]	£1,211	£8,022

Source: Partly reproduced from the CS Table 59 and 61
Abbreviations: ICER, incremental cost-effectiveness ratio; Incr,, incremental; INMB, incremental net monetary benefit at £30,000 per QALY threshold; LYs, life years gained; PAS, patient access scheme confidential discount price; QALYs, quality-adjusted life years; SoC, standard of care; TRF, targeted-release formulation.

5.2 Company's sensitivity analyses

5.2.1 Probabilistic sensitivity analysis

The company reports a probabilistic ICER estimate of £1,211 QALY gained based on 1,000 Monte Carlo iterations (CS Table 61, replicated in Table 12 above). To test the stability of the probabilistic results, we re-ran the PSA with 10,000 iterations, see Table 13. This confirms that there is a small difference between the deterministic and probabilistic base case results, although this does not change the conclusion that TRF-budesonide appears to be very cost-effective (dominant or with a low ICER).

We further discuss the stability of the probabilistic results in section 5.3.1.1.1.

Table 13 Company base case results: probabilistic analysis with 10,000 iterations

Treatments	Total costs (£)	Total QALYs	Incr. costs	Incr. QALYs	ICER £/QALY	INMB at £30k/QALY
TRF-budesonide	[redacted]	[redacted]	-	-	-	-
SoC	[redacted]	[redacted]	[redacted]	[redacted]	£520	£8,393

Source: Produced by the EAG using the company's submitted model
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years; SoC, standard of care; TRF, targeted-release formulation.

5.2.2 Deterministic sensitivity analyses

In the one-way sensitivity analyses, the company used variations in input parameters based on an assumed standard error of 10% of the base case value. Table 62 in CS section 3.11.2 shows the 10 variables with the most influence on the INMB. The model is most sensitive to the utility value associated with CKD stage 2, with baseline age the second most influential parameter. Utility values for CKD stages 3a and 3b, as well as for haemodialysis and post-transplant care were also parameters to which the model was sensitive. Unit costs for LD06A, LD05A (informing the costs of satellite haemodialysis) and LD02A (informing the costs of hospital haemodialysis) were also influential parameters.

5.2.3 Scenario analysis

The CS includes 53 scenario analyses listed in CS Table 62. The results of these analyses are presented in CS Table 63 and reproduced in Appendix 4 (Table 23) below, with incremental costs and QALYs and INMB (at , calculated with QALYs valued at the £30,000 per QALY gained threshold, added by the EAG.

All scenarios show that TRF-budesonide is cost effective compared to SoC. The scenarios with the lowest INMB values (indicating less favourable cost-effectiveness results) were:

- CKD stage distribution at baseline: RaDaR data assuming no patients in CKD 4
- Risk of ESRD (RaDaR data for UPCR ≥0.8 g/g and on ACEi/ARB; Leicester General Hospital data)
- Changes to the SMR by CKD stage; same SMR for stages CKD 1-3b; SMR based on Greene et al. 2019 and Hastings et al. 2018.
- Various assumptions around TRF-budesonide dose management (no dose reduction; with tapering to 4mg included; with tapering to 4mg and cost of the tapering pack included);
- Various re-treatment assumptions (no re-treatment; effectiveness of the subsequent treatment at 70% and 80%; proportion of patients eligible for re-treatment
- Sources to inform hospital care costs (Kent et al. 2015 and Baxter et al. 2024).

5.3 Model validation and face validity check

5.3.1 EAG validation

5.3.1.1 EAG model checks

We conducted a number of tests on the submitted model to verify model inputs, calculations and outputs. This included:

- Cross-checking model input parameters against values reported in the CS and in the cited sources.
- Checking all model outputs against results reported in the CS.
- Scenarios were run manually, and model outputs checked against results reported in the CS for the deterministic sensitivity analyses and scenario analyses.
- Checking of the individual equations and formulae within the model.
- Applying a range of extreme value and logic tests to check the plausibility of changes in results when parameters are changed.

5.3.1.1.1 Stability of PSA results

As reported in section 5.2.1, there are small differences between the deterministic and probabilistic results from the company's cost-effectiveness model. We therefore checked the stability of the probabilistic results to assess whether this difference was due to running an insufficient number of iterations of the probabilistic sensitivity analysis (PSA). Figure 4 below

shows how the probabilistic ICER changes with an increasing number of PSA iterations (using non-seeded random numbers). This shows that convergence is achieved after approximately 2000 iterations.

Figure 4 Cumulative mean ICER over 5000 iterations (PSA convergence)

Source: Produced by the EAG from the company's model
Abbreviations: ICER, incremental cost-effectiveness ratio

5.3.1.1.2 EAG corrections to the company model

We identified a small error in the calculation of SoC costs (wrong denominator used to calculate weightings of drug classes from trial data on concomitant medication use), see section 4.2.10.1.2 above. This increases the monthly cost of SoC medication from £80.18 in the company's base case (CS Table 52) to £80.74 (Table 11 above). We correct this error in additional EAG analysis presented in Chapter 6.

5.3.1.2 Internal validation: comparison of results from model and trial

Figure 5 summarises information provided by the company in response to clarification question Table 5-8. It shows that the economic model produces good predictions of the distribution of patients by CKD stage at 24 months from baseline, in comparison with observed results at this timepoint from the NefIgArd Nef-301 Part B. However, the model predictions at 9 months are less good, as the proportion of patients at CKD stage 3b in both arms is higher than was observed in the trial. This is not surprising, as the logistic regression analyses used to estimate transition probabilities for CKD 1-4 were fitted to baseline and 24-month data only, and applied at a constant rate to in model cycles between these times (4.2.6.1.1).

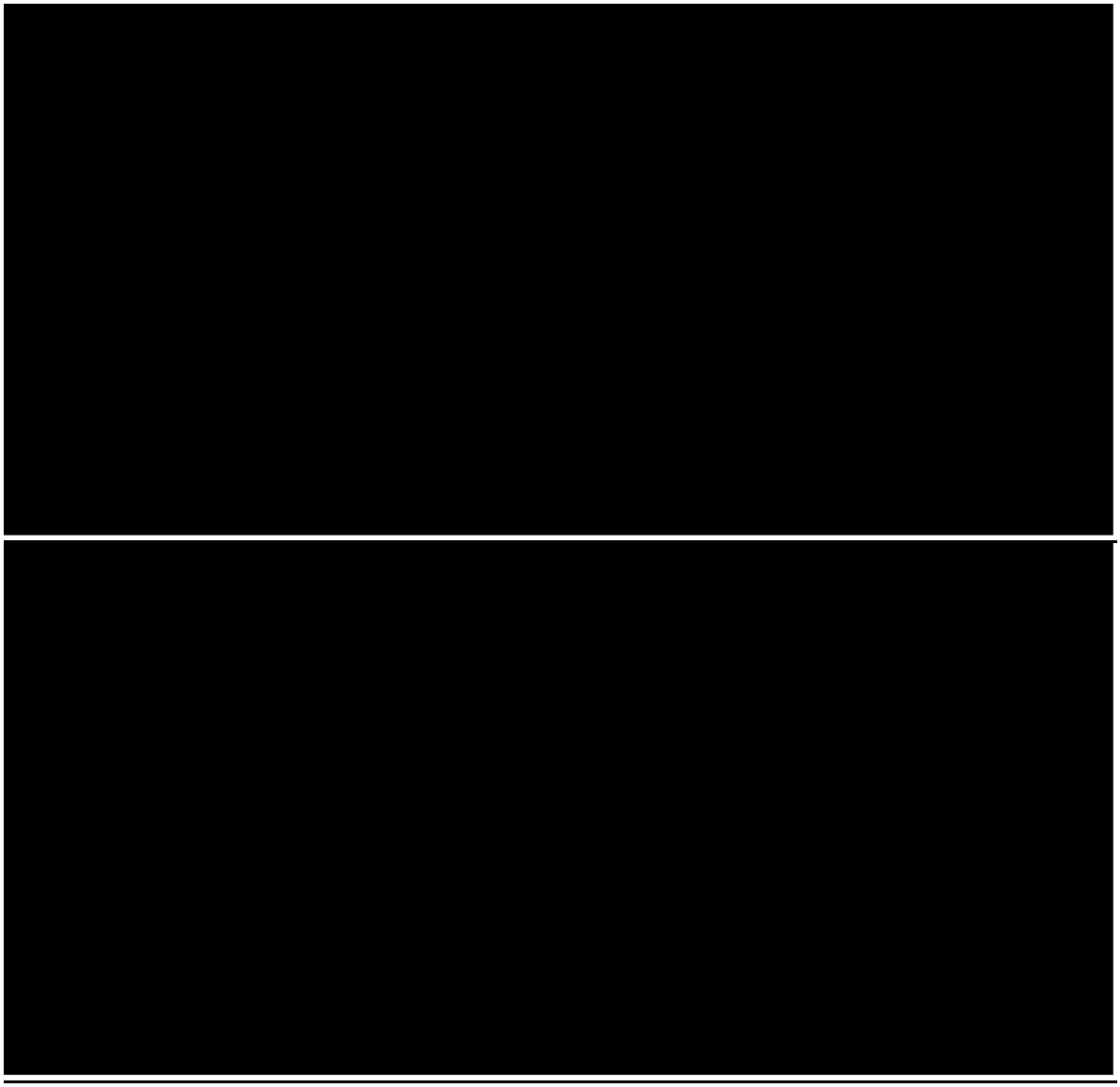

Figure 5 Observed and predicted CKD distributions at 0, 9 and 12 months

Source: Produced by the EAG with data from the company's response to clarification question
CKD, chronic kidney disease; ESRD, end stage renal disease; SoC, standard of care

5.3.2 EAG summary of key issues and additional analyses

Key issues for economics

- Uncertainty over the transition probabilities for CKD stages 1-4, due to sparse data from the NefIgArd Nef-301 trial.
- The transition probabilities do not reflect the treatment effect of SGLT2 inhibitors, which were not part of standard care in the NefIgArd Nef-301 trial but are now routinely used in practice. This suggests that the transition probabilities for standard care are likely over-estimate the rates of CKD progression (in both the intervention and comparator arm).

EAG additional analysis

- Exploratory analysis to illustrate the effect of reduced disease progression due to the use of more effective treatments in standard care, including SGLT2 inhibitors. See section 6.1 below for further information.
- We conducted an additional scenario analysis to investigate the impact of uncertainty over the estimated treatment effect of TRF-budesonide on the risk of progression to CKD, using a confidence interval for the HR estimated by Barratt et al. (2024).

EAG preferred assumptions

- Correction to cost of SoC drug treatments (see 4.2.10.1.2)
- Cost of SGLT2i 10 mg tablet to match daily dose (4.2.10.1.2)
- SMRs: UK RaDaR, with CKD 3a / 3b = CKD 2 (4.2.7)

6 EAG'S ADDITIONAL ANALYSES

6.1 EAG's exploratory analyses using the company's base case

Progression multiplier: To illustrate the sensitivity of cost-effectiveness results to changes in SoC effectiveness which apply to both arms in the economic model. The company base case assumes 100% use of SGLT2 inhibitors, but they were not part of standard care in the trial and few patients received them. A relative risk of 0.49 (0.32, 0.74) has been estimated for the effect of of SGLT2 inhibitors on CKD progression for people with IgA nephropathy.66 However, this is cannot be applied direction to transition probabilities in the economic model. We therefore applied a simple multiplier to the monthly probabilities of progression from CKD stages 1, 2, 3a and 3b (both arms). Effects on progression from CKD 4 to 5 are not modelled, as the risk of progression to CKD5 is estimated from registry data (UK RaDaR), which is likely to include some level of SGLT2 inhibitor use. We report threshold values for the progression multiplier to illustrate what level of improvement in clinical effectiveness would be required for the TRF-budesonide ICER to increase to the NICE £20,000 and £30,000 per QALY thresholds.

HR for risk of CKD 5: The model uses an estimated treatment effect on the risk of progression to CKD based on the surrogate outcome of change in eGFR total slope, reported by Barratt et al. (2024), using results from the NefIgArd Nef-301 trial and the Inker et al. (2019) formula.[28, 46] Barrett et al. report a confidence interval for the HR 0.38 (95% CI 0.21-0.63), but this is not used in the company sensitivity or scenario analysis. We therefore test the impact of this in EAG exploratory analysis.

Table 14 EAG exploratory scenarios

Company base case assumption	EAG scenario	Justification for EAG assumption	Section in EAG report
No adjustment for effects of SGLT2i	Multiplier applied to progression probabilities from CKD stages 1-3b	To illustrate the impact of reduced progression with use of SGLT2i in SoC (assumed 100% use in company base case)	4.2.4.2 and 4.2.6.1
HR for risk of CKD5 = 0.38	95% confidence limits reported by Barratt et al. (0.21-0.63)	To test sensitivity to uncertainty over the estimated HR	4.2.6.2.2

CKD, chronic kidney disease; EAG, External Assessment Group; HR, hazard ratio; SGLT2i, Sodium/glucose cotransporter 2 inhibitor, SoC, standard of care.

Table 15 Results of EAG exploratory scenario: effect of SGLT2i (deterministic)

Scenario	Incr. cost	Incr. QALYs	ICER £/QALY	INMB at £30k/QALY
Company base-case	[redacted]	[redacted]	Dominant	£9,231
1. Multiplier for probability of progression from CKD stages 1-3b (base case 1.00)				
EAG progression multiplier = 0.90	[redacted]	[redacted]	£3,387	£7,985
EAG progression multiplier = 0.68	[redacted]	[redacted]	£19,024	£2,937
EAG progression multiplier = 0.61	[redacted]	[redacted]	£29,192	£198
EAG progression multiplier = 0.55	[redacted]	[redacted]	£42,494	-£2,730
2. Uncertainty over the HR for the risk of progression to CKD 5 (base case 0.38)				
Lower 95% confidence limit = 0.21	[redacted]	[redacted]	Dominant	£10,361
Lower 95% confidence limit = 0.63	[redacted]	[redacted]	£3,620	£7,728

Source: EAG using CS model with the respective changes
CKD, chronic kidney disease; EAG, External Assessment Group; HR, hazard ratio; ICER, incremental cost-effectiveness ratio; Incr, incremental; INMB, incremental net monetary benefit; QALYs, quality-adjusted life years; SGLT2i, Sodium/glucose cotransporter 2 inhibitor,

6.2 EAG's preferred assumptions

We make three changes to the company's base case:

- EAG correction to SoC drug cost weightings (see section Table 11)
- Cost of SGLT2 inhibitors: 10 mg tablet to match daily dose, same price for dapagliflozin and empagliflozin (no need to add empagliflozin to the model) (see 4.2.10.1.2)
- SMRs based on UK RaDaR IgA nephropathy data including all patients, with CKD stages 3a and 3b set equal to the value for CKD stage 2 ([redacted]).

Table 16 Cumulative results with EAG preferred assumptions (deterministic)

Preferred assumptions	EAR section	Incr. cost	Incr. QALYs	ICER £/QALY	INMB at 30k/QALY
Company base-case	Table 12	[redacted]	[redacted]	Dominant	£9,231
1. EAG correction of SoC drug cost (denominator)	Table 11	[redacted]	[redacted]	Dominant	£9,225
2. Cost of SGLT2i: 10 mg tablet to match daily dose	4.2.10.1.2 Table 11	[redacted]	[redacted]	Dominant	£9,439
3. SMRs: UK RaDaR, with CKD 3a / 3b = CKD 2	4.2.10.1.2 Table 11	[redacted]	[redacted]	Dominant	£9,416

Source: EAG using CS model with the respective changes
ICER, incremental cost-effectiveness ratio; Incr,, incremental; INMB, incremental net monetary benefit; LYs, life years gained; QALYs, quality-adjusted life years; SMRs, standardised mortality ratios; SGLT2i, Sodium/glucose cotransporter 2 inhibitor; SoC, standard of care; TRF, targeted-release formulation.

Table 17 Full results for the EAG's preferred analysis (TRF-budesonide at PAS price)

Treatment	Total costs (£)	Total QALYs	Incr. costs	Incr. QALYs	ICER £/QALY	INMB, at £30k/QALY
Deterministic						
TRF-budesonide	[redacted]	[redacted]				
SoC alone	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	£9,416
Probabilistic (3,000 iterations)						
TRF-budesonide	[redacted]	[redacted]				
SoC	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	£8,088

Source: Partly reproduced from the CS Table 59 and 61
Abbreviations: ICER, incremental cost-effectiveness ratio; Incr,, incremental; INMB, incremental net monetary benefit at £30,000 per QALY threshold; LYs, life years gained; PAS, patient access scheme confidential discount price; QALYs, quality-adjusted life years; SoC, standard of care; TRF, targeted-release formulation.

Table 18 Results of scenario analyses applied to EAG base case (deterministic)

Scenario analysis	Incr. costs	Incr. QALYs	ICER £/QALY	INMB at £30k/QALY
EAG's Preferred analysis	[redacted]	[redacted]	Dominant	£9,416
CKD stage distribution at baseline (base case NefIgArd Part B FAS population)				
UK RaDaR population	[redacted]	[redacted]	Dominant	£18,172
UK RaDaR excluding CKD 4	[redacted]	[redacted]	Dominant	£8,676
Risk of ESRD (base case UK RADAR data UPCR ≥0.8 g/g, exponential extrapolation)				
UK RaDaR UPCR≥0.8g/g on ACEi/ARB	[redacted]	[redacted]	Dominant	£9,008
Log-normal extrapolation	[redacted]	[redacted]	Dominant	£15,195
Weibull extrapolation	[redacted]	[redacted]	Dominant	£10,452
Leicester cohort with HR applied [a]	[redacted]	[redacted]	£3,580	£7,456
Reduced progression with standard care, TP multiplier from CKD 1-3b (base case =1)				
EAG progression multiplier = 0.90	[redacted]	[redacted]	£1,950	£8,123
EAG progression multiplier = 0.65	[redacted]	[redacted]	£22,730	£1,800
EAG progression multiplier = 0.60	[redacted]	[redacted]	£31,430	-£330
EAG progression multiplier = 0.55	[redacted]	[redacted]	£43,447	-£2,817
Duration of TRF-budesonide treatment effect (base case 2 years)				
Effect duration 3 years	[redacted]	[redacted]	Dominant	£9,416
Effect duration: 5 years	[redacted]	[redacted]	Dominant	£17,607
Uncertainty over the HR for the risk of progression to CKD 5 (base case 0.38)				
Lower 95% confidence limit = 0.21	[redacted]	[redacted]	Dominant	£10,552
Lower 95% confidence limit = 0.63	[redacted]	[redacted]	£2,094	£7,904

Scenario analysis	Incr. costs	Incr. QALYs	ICER £/QALY	INMB at £30k/QALY
Retreatment assumptions (base case: [redacted] 1 round after 14.75 months, 90% effect)				
TRF-budesonide: no re-treatment	[redacted]	[redacted]	Dominant	£6,340
TRF-budesonide: 3 rounds of treatment	[redacted]	[redacted]	Dominant	£11,645
CKD 1–3b re-treatment: 25%	[redacted]	[redacted]	Dominant	£8,017
CKD 1–3b re-treatment: 75%	[redacted]	[redacted]	Dominant	£10,944
Retreatment gap: 20.75 months	[redacted]	[redacted]	Dominant	£9,785
Retreatment gap: 26.75 months	[redacted]	[redacted]	Dominant	£10,060
Retreatment gap: 32.75 months	[redacted]	[redacted]	Dominant	£10,248
Subsequent treatment effect: 55%	[redacted]	[redacted]	£29,491	£104
Subsequent treatment effect: 60%	[redacted]	[redacted]	£21,259	£1,949
Subsequent treatment effect: 80%	[redacted]	[redacted]	£3,184	£7,405
Mortality by CKD stage: SMR relative to CKD 1 (base case UK RaDaR all patients)				
SMR same for CKD 1-3b	[redacted]	[redacted]	Dominant	£9,513
SMR source Greene et al. 2019	[redacted]	[redacted]	£9,443	£5,466
SMR source Hastings et al. 2018	[redacted]	[redacted]	Dominant	£8,327
Utility data source (Base case: Cooper et al. 2020)				
CKD utility: Gorodetskaya et al. 2005	[redacted]	[redacted]	Dominant	£10,810
CKD utility: Zhou et al. 2024	[redacted]	[redacted]	Dominant	£5,512
TRF-budesonide use and costing (9 months standard dose with 2-week reduced dose)				
Include tapering (2 weeks at 4mg)	[redacted]	[redacted]	Dominant	£9,349
Include cost for tapering pack	[redacted]	[redacted]	Dominant	£9,283
Treatment stopping, use TTD curve	[redacted]	[redacted]	Dominant	£9,411
Relative dose intensity: Included	[redacted]	[redacted]	Dominant	£10,392
Other cost assumptions				
Cost of dapagliflozin excluded	[redacted]	[redacted]	Dominant	£9,840
Hospital care cost: Pollock et al. 2022	[redacted]	[redacted]	£3,800	£7,747
Hospital care cost: Baxter et al. 2024	[redacted]	[redacted]	£6,113	£7,063

Source: Partly reproduced from the CS. Incremental ICERs and INMBs added by EAG from the company's model.
Abbreviations: CKD, chronic kidney disease; CSR, clinical study report; FAS, full analysis set; ICER, incremental cost-effectiveness ratio; INMB, incremental net monetary benefit (calculated at the £30,000 per QALY cost-effectiveness threshold value); QALY, quality-adjusted life year; SMR, standardised mortality ratio; SoC, standard of care; TP, transition probability; TRF- targeted-release formulation; TTD, time to treatment discontinuation.
[a] Source Barratt et al. (2024)[46] – HR mapped from change in eGFR slope, Leicester cohort.

6.3 QALY weighting for severity

The company does not apply a QALY weighting for severity (CS section 3.6). The EAG agrees that this is not applicable based on the criteria in section 6.2.12 of the NICE health technology evaluations manual (2022).[43] Table 19 summarises the results of the QALY shortfall calculations for the company's base case and the EAG's base case, produced by the EAG using the QALY shortfall calculator (Schneider et al. 2021).[67]

Table 19 Summary of company and EAG base case QALY shortfall analysis

Base case	Expected QALYs for general population [a]	Expected QALYs with primary IgA nephropathy [b]	Absolute QALY shortfall	Proportional QALY shortfall	Preferred QALY weight
Company	17.86	[redacted]	[redacted]	[redacted]	1.00
EAG	17.86	[redacted]	[redacted]	[redacted]	1.00

Source: Produced by the EAG using the QALY shortfall calculator (Schneider et al. 2021)[67]
EAG, evidence assessment group; IgA, immunoglobulin A; QALY, quality adjusted life years
[a] QALYs (discounted at 3.5% per year) for people of age 43 years, 34% female (CS Table 36). Reference case for general population QALYs MVH value set + HSE 2014 ALDVMM model (Hernandez Alava et al. 2017)[68]
[b] Remaining QALYs (discounted at 3.5% per year) for population with standard of care.

6.4 Conclusions on the cost effectiveness evidence

The company's model structure and many of the model assumptions and input parameters are consistent with the approach in TA937. The EAG agrees that the use of a model structure with CKD stage definitions based purely on eGFR is a reasonable simplification. Stratification of eGFR-based health states by UPCR, as in the TA1074 model, would not improve the accuracy of the cost-effectiveness results, given the lack of data to adjust other model parameters. Assumptions regarding transitions between the health states are also reasonable, given the available data and short model cycle length.

Methods used to estimate the transition probabilities for CKD 1-4 are appropriate, although we note high uncertainty due to sparse data for some transitions. In addition, the trial data do not reflect current practice, as they omit the effects of SGLT2 inhibitors, which were only used by a few patients in the clinical trial. We report a simple exploratory analysis to illustrate the effect of improvements in the effectiveness of standard care that apply to both arms.

We agree with the approach of estimating the risks of progression to CKD 5 based on UK RaDaR data for standard care, with a treatment effect estimated using eGFR results from the NefIgArd Nef-301 trial.[28, 46] There is uncertainty over use of a constant hazard to

extrapolate KM data, but we note this is conservative compared with the other parametric extrapolations, which predict diminishing hazards.

For the EAG analysis, we prefer the SMR estimates based on the UK RaDaR dataset (with all patients), but with SMRs for CKD stages 3a and 3b set equal to the value for CKD stage 2. This provides a gradation of SMRs across the CKD stages, with higher mortality in more advanced disease.

We agree with the company's choice of utility values for the economic model, which are consistent with preferred in previous NICE appraisals for an IgAN population (TA937 and TA1074), as well as for CKD (TA775, TA942 and TA1075). And methods used to estimate costs for healthcare resource use by CKD stage and for dialysis and transplant are reasonable, and consistent with other NICE appraisals for IgaN and CKD.

However, we do have some concerns over the cost-per-mg method used to cost TRF-budesonide over the treatment cycle, as this does not account for wastage that is likely to occur when a full pack of 120 tablets is required to provide treatment at the reduced 8 mg dose for 2 weeks prior to discontinuation, or for the 4 mg dose for the 2-week tapering period. Estimates of additional costs for wastage of TRF-budesonide have been provided with the company's factual accuracy check. These estimates are subject to uncertainty, but we consider that they are unlikely to change the overall cost-effectiveness conclusions, unless implemented alongside other more conservative assumptions.

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8 APPENDICES

Appendix 1 EAG appraisal of systematic review methods

Table 20 EAG appraisal of systematic review methods

Systematic review components and processes	EAG Response (Yes, No, Unclear)	EAG comments
Was the review question clearly defined using the PICOD framework or an alternative?	Yes	CS Appendix B.1 states why the review was conducted and the PICOD framework is presented in CS Appendix B.1.2.
Were appropriate sources of literature searched?	Yes	The Ovid platform was used to search Medline (including In-Process), Embase, EBM Reviews including CENTRAL, CDSR, DARE, HTA database, NHS EED and others. The INAHTA database, reference list of eligible studies, global HTA bodies and trial registries were also searched. Conference proceedings were searched via Embase if indexed there and 5 non-indexed kidney/renal specific conferences were also searched on-line.
What time period did the searches span and was this appropriate?	Yes	Database inception to 3rd November 2022 with update searches overlapping from 2022 to 8 January 2025 (CS Appendix B.1). Conferences last 3 years.
Were appropriate search terms used and combined correctly?	Yes	Search strategies were appropriately constructed and are reported in CS Appendices B.1.1.2 and B.1.1.3
Were inclusion and exclusion criteria specified? If so, were these criteria appropriate and relevant to the decision problem?	Yes	Study selection criteria provided in CS Appendix B.1.2 are relevant to the decision problem and would be expected to return a broader set of studies than specified by the decision problem e.g. the population was people with primary IgA nephropathy with no restriction by urine protein-to-creatinine ratio.
Were study selection criteria applied by two or more reviewers independently?	Yes	CS Appendix B.1.2 states two independent analysts screened records for inclusion or exclusion.

Systematic review components and processes	EAG Response (Yes, No, Unclear)	EAG comments
Was data extraction performed by two or more reviewers independently?	Yes	CS Appendix B.1.2 states two independent analysts conducted data extraction.
Was a risk of bias assessment or a quality assessment of the included studies undertaken? If so, which tool was used?	Yes, in part	CS Appendix 1.2 states that assessments used the tool recommended by NICE[22] The results of the assessment for parallel group RCTs are provided in Appendix B.3. No assessment of the Nef-301 OLE is reported in the CS but this was provided in response to clarification question A3 using the ROBINS-I tool.[27]
Was risk of bias assessment (or other study quality assessment) conducted by two or more reviewers independently?	No	The CS did not state how risk of bias assessments were conducted. In response to clarification question A2 the company stated that assessments were conducted by one reviewer and checked by a second reviewer with any discrepancies resolved either through discussion or with input from a third reviewer.
Is sufficient detail on the individual studies presented?	Yes	Details for the key phase 3 RCT are provided in the following sections: CS 2.3.1 – trial methodology CS 2.3.2 – baseline characteristics CS 2.3.4 – OLE methodology including baseline characteristics for participants CS 2.4 statistical analysis for trial and OLE CS 2.6 results CS Appendix K provides a summary of the earlier phase 2b RCT which does not inform the economic model.
If statistical evidence synthesis (e.g. pairwise meta-analysis, ITC, NMA) was undertaken, were appropriate methods used?	NA	No meta-analyses or ITCs were undertaken.

Source: EAG created table
CDSR, Cochrane Database of Systematic Reviews; CENTRAL, Cochrane Central Register of Controlled Trials; CS, company submission; DARE, Database of Abstracts of Reviews of Effects; EBM, Evidence-based Medicine; HTA, Health Technology Assessment; INAHTA, International Network of Agencies for Health Technology Assessment; ITC, indirect treatment comparison; NA, not applicable; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; NMA, network meta-analysis; OLE, open-label extension; PICOD, population, intervention, comparator, outcomes, and study design; ROBINS-I, Risk Of Bias In Non-randomised Studies – of Interventions; RCT, randomised controlled trial

Appendix 2 Critical appraisal of the NeflgArd Nef-301 trial

Table 21 Comparison of the company and the EAG's critical appraisal of the NeflgArd Nef-301 trial

Question	Company response	Company comments	EAG response	EAG comments
Was randomisation carried out appropriately?	Yes	Using Interactive Response Technology System	Yes	An Interactive Response Technology System was used.
Was the concealment of treatment allocation adequate?	Yes	To ensure the success of the double-blinding and maintenance of treatment masking, both TRF-budesonide and placebo capsules were matched in taste, smell, and appearance. Masking was rigorously maintained until completion of the full 2-year trial. Treatment assignment was unmasked at local sites for individual patients in the event of a potential medical emergency, which was monitored by sponsor personnel. Overall, unmasking occurred for three patients.	Yes	An Interactive Response Technology System was used to randomise participants and it is likely that this adequately concealed forthcoming treatment allocations from investigators enrolling participants into the trial. The EAG notes that the company's response to this risk of bias assessment question pertains to study blinding rather than treatment allocation concealment.
Were the groups similar at the outset of the study in	Yes	Similar baseline values reported between treatment groups	No	A greater proportion of participants treated with TRF-budesonide had

Question	Company response	Company comments	EAG response	EAG comments
terms of prognostic factors?				diabetes or pre-diabetes at baseline (diabetes: 8.8% versus 4.4%; pre-diabetes: 39.0% versus 27.5%; CS Table 6). We received clinical expert advice that patients with diabetes may have worse outcomes from treatment than those without diabetes, so the imbalance in these characteristics in the trial would be conservative to TRF-budesonide.
Were the care providers, participants and outcome assessors blind to treatment allocation?	Yes	Double-blind trial design	Yes	Double-blind study. Patients, investigators and site staff remained blinded to treatment allocation throughout the trial (CS section 2.3.1.4). The company state above that the TRF-budesonide and placebo capsules were matched in taste, smell and appearance to preserve blinding.

Question	Company response	Company comments	EAG response	EAG comments
Were there any unexpected imbalances in drop-outs between groups?	No	Similar number of patients lost to follow-up and discontinued treatment in both arms	No	There were no unexpected imbalances between the trial arms in the proportions of patients completing the Part A treatment period or entering into or completing the long-term follow-up period (Part B) (CS Appendix Figure 3)
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	All outcomes listed in methodology reported	No	Results are reported for all measured outcomes either in the CS or the trial CSR.[20]
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	No	FAS/PP analysis used; included all patients who had been followed for 9 months by data cutoff and safety analysis which included all patients dosed by the time of the data cut-off	Unclear	In the CS, the trial results are presented for the FAS population, which included all but two participants who were randomised to the global part of the trial (FAS N = 364/366 [99.45%] randomised participants) (CS Table 13). The two excluded participants were randomised in error (CS Table 13). The CS does not state if data from

Question	Company response	Company comments	EAG response	EAG comments
				participants in the FAS population were analysed according to their randomised treatment allocation (it is likely that they were because the protocol for the study states the primary analysis will use the intent-to-treat principle,[24] but this is not explicitly stated). Multiple imputation was used to impute missing data for the primary endpoint of Part B of the trial (CS section B.2.4.1.4). No missing data were imputed for the primary supportive analysis of the two-year eGFR slope (CS section B.2.4.1.4). Multiple imputation and the MMRM analysis that was used to analyse continuous endpoints (CS section B.2.4.1.4 both assume that data are missing at random.[25, 26] No information is provided in CS Document B about the extent of

Question	Company response	Company comments	EAG response	EAG comments
				missing data nor about whether the missing at random assumption held. Clarification response A7 shows the proportions of missing data were similar between trial arms, but by month 24 around 20% of participants in each arm had missing outcome data. The reasons for missing data (patients discontinuing early from the study and patients receiving rescue medication or prohibited immunosuppressive medicine, clarification response A7) raise the possibility that missingness of outcome data might depend on its true value. The company did conduct sensitivity analyses to assess the impact of missing data. Overall, it is unclear if the FAS analyses represent true ITT analyses and if appropriate

Question	Company response	Company comments	EAG response	EAG comments
				methods were used to impute missing data. To the left, the company mention that per protocol analysis was used – this has been used for a sensitivity analysis (CS Appendix J.1.1 Table 23).

Source: Reproduced from CS Appendix Table 4 with added EAG comments.
CS, company submission; CSR, clinical study report; EAG, External Assessment Group; eGFR, estimated glomerular filtration rate; FAS, full analysis set; ITT, intention-to-treat analysis; MMRM, mixed model for repeated measures; PP, per protocol; TRF, targeted-release formulation.

Appendix 3 Critical appraisal of the Nef-301 OLE

Table 22 Comparison of the company and the EAG's critical appraisal of the Nef-301 OLE

Bias domain	Company response	EAG response
Bias due to confounding	Serious	Serious
Bias in selection of participants into the study	Serious	Serious
Bias in classification of interventions	Low	Low
Bias due to deviations from intended interventions	Low	Low
Bias due to missing data	Low	Low
Bias in measurement of outcomes	Low	Low
Bias in selection of the reported result	Low	Low
Overall bias	Domain 1 and 2 flagged 'serious' risk of bias concerns	Serious risk of bias

Source: Partly reproduced from the Company's Excel file entitled 'ID6485 ROBINS-I ROB_OLE-v1' provided with their clarification response. The Cochrane ROBINS-I tool was used to carry out risk of bias assessment.[27]
EAG; External Assessment group; OLE, open-label extension

Appendix 4 Company scenarios analyses

Table 23 Results of the company's scenario analyses

Scenario analysis	Incr. costs	Incr. QALYs	ICER £/QALY	INMB at £30k/QALY
Company's base case	[redacted]	[redacted]	**Dominant**	**£9,231**
Time horizon: 20 years	[redacted]	[redacted]	Dominant	£9,519
Time horizon: 30 years	[redacted]	[redacted]	Dominant	£9,541
Time horizon: 40 years	[redacted]	[redacted]	Dominant	£9,253
Time horizon: 50 years	[redacted]	[redacted]	Dominant	£9,231
Distribution of CKD at baseline: Part A NefIgArd Nef-301	[redacted]	[redacted]	Dominant	£9,536
Distribution of CKD at baseline: UK RaDaR data	[redacted]	[redacted]	Dominant	£17,908
Distribution of CKD at baseline: UK RaDaR data - excluding CKD 4	[redacted]	[redacted]	£1,498	£8,491
Risk of ESRD: UK RaDaR UPCR ≥0.8 g/g and on ACEi/ARB	[redacted]	[redacted]	£836	£8,834
Risk of ESRD: Leicester General Hospital data with HR applied	[redacted]	[redacted]	£4,969	£7,320
Time to CKD 5: Log-normal	[redacted]	[redacted]	Dominant	£15,141
Time to CKD 5: Gen. gamma	[redacted]	[redacted]	Dominant	£13,958
Time to CKD 5: Gompertz	[redacted]	[redacted]	Dominant	£19,313
Time to CKD 5: Log-logistic	[redacted]	[redacted]	Dominant	£16,659
Time to CKD 5: Gamma	[redacted]	[redacted]	Dominant	£9,460
Time to CKD 5: Weibull	[redacted]	[redacted]	Dominant	£10,297
SoC acquisition costs: £0	[redacted]	[redacted]	Dominant	£10,096
Time to no effect: 2.5 years	[redacted]	[redacted]	Dominant	£9,231
Time to no effect: 5 years	[redacted]	[redacted]	Dominant	£17,398
Time to no effect: time horizon	[redacted]	[redacted]	Dominant	£75,979
SMR: same for CKD 1-3b	[redacted]	[redacted]	£343	£9,303
SMR: UK RaDaR data: UPCR ≥0.8g/g	[redacted]	[redacted]	Dominant	£11,824
SMR: Greene et al. 2019	[redacted]	[redacted]	£10,120	£5,286
SMR: Hastings et al. 2018	[redacted]	[redacted]	£539	£8,131
CKD utility: Gorodetskaya et al. 2005	[redacted]	[redacted]	Dominant	£10,649
CKD utility: Zhou et al. 2024	[redacted]	[redacted]	Dominant	£5,267
Age-adjusted utilities excluded	[redacted]	[redacted]	Dominant	£9,709

Scenario analysis	Incr. costs	Incr. QALYs	ICER £/QALY	INMB at £30k/QALY
Company's base case	[redacted]	[redacted]	**Dominant**	**£9,231**
TRF-budesonide: no dose reduction	[redacted]	[redacted]	£226	£9,097
TRF-budesonide: tapering included	[redacted]	[redacted]	£6	£9,164
TRF-budesonide: tapering included with cost for tapering pack	[redacted]	[redacted]	£225	£9,098
Treatment stopping: use TTD curve	[redacted]	[redacted]	Dominant	£9,226
Societal costs: Included	[redacted]	[redacted]	Dominant	£10,359
TRF-budesonide: 3 rounds of treatment	[redacted]	[redacted]	Dominant	£11,418
TRF-budesonide: 4 rounds of treatment	[redacted]	[redacted]	Dominant	£14,414
TRF-budesonide: 5 rounds of treatment	[redacted]	[redacted]	Dominant	£18,389
TRF-budesonide: 6 rounds of treatment	[redacted]	[redacted]	Dominant	£22,727
TRF-budesonide: no re-treatment	[redacted]	[redacted]	£1,469	£6,209
Subsequent treatment effect: 70%	[redacted]	[redacted]	£11,532	£4,816
Subsequent treatment effect: 80%	[redacted]	[redacted]	£4,661	£7,229
Subsequent treatment effect: 100%	[redacted]	[redacted]	Dominant	£10,945
Utility for CKD 1–3b: CKD 1 value	[redacted]	[redacted]	Dominant	£10,000
Utility for CKD 1–4: CKD 1 value	[redacted]	[redacted]	Dominant	£9,939
Dispensing (admin) charge: £10.00	[redacted]	[redacted]	£533	
Relative dose intensity: Included	[redacted]	[redacted]	Dominant	£10,207
CKD 1–3b eligible for retreatment: 25%	[redacted]	[redacted]	£234	£7,858
CKD 1–3b eligible for retreatment: 33%	[redacted]	[redacted]	£15	£8,374
CKD 1–3b eligible for retreatment: 50%	[redacted]	[redacted]	Dominant	£9,359
Time between retreatment cycles: 20.75 months	[redacted]	[redacted]	Dominant	£9,602
Time between retreatment cycles: 26.75 months	[redacted]	[redacted]	Dominant	£9,880
Time between retreatment cycles: 32.75 months	[redacted]	[redacted]	Dominant	£10,071
Monthly transition probability from CKD 5 to dialysis: 6%	[redacted]	[redacted]	Dominant	£9,593
Cost of dapagliflozin excluded	[redacted]	[redacted]	Dominant	£9,875
Hospital care cost: Pollock et al. 2015	[redacted]	[redacted]	£5,284	£7,552
Hospital care cost: Baxter et al. 2024	[redacted]	[redacted]	£8,198	£6,662

Source: Partly reproduced from the CS. Incremental ICERs and INMBs added by EAG from the company's model.
Abbreviations: CKD, chronic kidney disease; CSR, clinical study report; FAS, full analysis set; ICER, incremental cost-effectiveness ratio; INMB, incremental net monetary benefit (calculated at the

£30,000 per QALY cost-effectiveness threshold value); QALY, quality-adjusted life year; SMR, standardised mortality ratio; SoC, standard of care- TRF- targeted-release formulation; TTD, time to treatment discontinuation.

Single Technology Appraisal

Targeted-release budesonide for treating primary IgA nephropathy (review of TA937) [ID6485]

EAG report – factual accuracy check and confidential information check

"Data owners may be asked to check that confidential information is correctly marked in documents created by others in the evaluation before release." (Section 5.4.9, NICE health technology evaluations: the manual).

You are asked to check the EAG report to ensure there are no factual inaccuracies or errors in the marking of confidential information contained within it. The document should act as a method of detailing any inaccuracies found and how they should be corrected.

If you do identify any factual inaccuracies or errors in the marking of confidential information, you must inform NICE by **5pm on Friday 8 August 2025** using the below comments table.

All factual errors will be highlighted in a report and presented to the appraisal committee and will subsequently be published on the NICE website with the committee papers.

Please underline all confidential information, and information that is submitted as 'confidential' should be highlighted in turquoise and all information submitted as 'depersonalised data' in pink.

Issue 1 EAG Issue 4: TRF-budesonide dosing

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Issue 4 dose reduction in the following sections: • **Table 1, pg 1** • **Tabulated Issue 4, pg 5** • **Section 4.2.4.1, pg 56** The EAG pointed to a lack of clarity over timing of dose reductions and how these are referred to.	The company have provided clarification here and request the EAG consider rewording the elements of their report identified, based on the clarifications provided, as considered appropriate.	**Clarifications:** The treatment course in the NeflgArd Nef-301 trial was 16 mg once daily for 9 months, followed by a further 2 weeks of treatment at a reduced dose of 8 mg once daily. The SmPC states that "The recommended dose is 16 mg once daily in the morning, at least one hour before a meal, for an initial duration of 9 months. When treatment is to be discontinued, the dose should be reduced to 8 mg once daily for 2 weeks of therapy". The timing of the 2-week 8 mg discontinuation dose is open to interpretation, such that clinicians may either incorporate this into the 9-month treatment period or add this on as an additional 2 weeks of treatment. The company base case assumed that the discontinuation dose-reduction to 8 mg once daily would be implemented for the last 2 weeks of the 9-month	Thank you for these clarifications. It is helpful to have confirmation that the SmPC wording regarding the timing of the recommended dose reduction to 8 mg daily prior to discontinuation is open to clinical interpretation. We note that the interpretation used in the company's base case (that the dose reduction occurs in the final two weeks of the 9-month treatment period) is not consistent with treatment course in the NeflgArd New-301 trial, which provides the clinical effectiveness evidence for the economic model (dose reduction after the 9-month treatment period). We have commented on the clarification in this FAC response in the EAR: see Issue 4 (page 5) and section 4.2.4.1 (page 57).

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
		treatment period, for an overall treatment duration of 9 months. An alternative plausible scenario would be for the 8 mg discontinuation dose-reduction to be implemented from the end of the 9-month treatment period, resulting in an overall treatment duration of 9 months and 2 weeks. The SmPC also states that “the dose may be reduced to 4 mg once daily for an additional 2 weeks, at the discretion of the treating physician.” In clinical practice this would involve an additional dose reduction from 8 mg to 4 mg and being at the clinicians discretion would likely not happen for all patients. This optional dose reduction was described as the “treatment tapering period” for the purposes of the model in the company submission. This was excluded from the company base case, in line with the original NICE appraisal, TA937.	

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
		The impact of these considerations on drug cost is discussed below, in relation to drug wastage.	
Issue 4 drug wastage in the following sections: • **Table 1, pg 1** • **Tabulated Issue 4, pg 5** • **Section 4.2.10.1.1.1, pg 67** • **Section 4.2.10.3, pg 72** The EAG noted that the cost-per-mg method does not account for wastage that is likely to occur when a full pack of 120 tablets is required to provide treatment at reduced dosing	The company request the EAG to consider rewording the elements of their report identified, based on the clarifications provided here	**Clarifications:** Wastage is anticipated to be minimal, relative to the overall cost of TRF-budesonide over a 9-month treatment course, when using the 120 x 4 mg tablet pack. A smaller 28 x 4 mg tablet pack is now available (as of 1st August 2025; priced pro-rata to 120-tablet pack, including PAS), which should minimise the impact of wastage further. **2-week discontinuation dose of 8 mg incorporated into 9 month treatment period; total treatment duration 9 months (company base case assumption):** When considering the full 9-month treatment period (16 mg daily, except for the last 2 weeks where 8 mg daily is taken), assuming that any wastage occurs at the end of the 9-month treatment period, a basic calculation of	Thank you for confirming that the 28 x 4 mg pack is now available. We agree that this will reduce potential wastage. Based on the PAS discounted price of [redacted] for the 120 tablet pack, the pro-rata PAS price for the new 28 tablet pack would be [redacted]. The company reports three wastage scenarios, assuming efficient prescribing of 120 tablet and 28 tablet packs: 1. **Reduced dose within 9 months** 8x120 tablet packs and 4x28 tablet packs provide a total of 1072 tablets. For 9 months (274 days) of treatment (260 days on full dose and 14 days on half dose) a total of 1068 4 mg tablets are required, thus 4 tablets are wasted, at a cost of about [redacted] 2. **Reduced dose after 9 months**

		drug costs based on the number of tablets needed shows that an optimal combination of 8 x 120 tablet packs and 4 x 28 tablet packs would come to a total cost of treatment of [redacted], including a wastage of 4 tablets at a cost of [redacted] **2-week discontinuation dose of 8 mg added to end of 9 month treatment period; total treatment duration 9 months and 2 weeks (alternate scenario):** A dosing scenario where patients are on the full dose (16 mg daily) for 9 months before they then go on to the reduced dose (8 mg daily) for 2 weeks may be preferred by some clinicians. Assuming that any wastage occurs at the end of the treatment period, a basic calculation based on the number of tablets needed shows that an optimal combination of 9 x 120 tablet packs and 2 x 28 tablet packs would come to a total cost of treatment of [redacted], including a wastage of 12 tablets at a cost [redacted] **Additional tapering scenario (as provided in company submission;**	9 x 120 tablet packs and 2 x 28 tablet packs provide a total of 1136 4 mg tablets. With 274 days at full dose plus 14 days at half dose, 1124 tablets are needed, thus 12 tablets would be wasted at an estimated cost of [redacted]. 3. **Additional tapering** Wastage costs are more uncertain for patients who are prescribed the additional reduction to 4 mg per day for a further 14 days. The company assume that 14 tablets would be wasted (half a 28 tablet pack). However, patients offered the additional tapered dose should have already undergone the 2-week reduced dose, and so may already have some left over tablets. After scenario 1, only 4 tablets would be left, so an additional 28 tablet pack would still be required. But after scenario 2, with 12 remaining tablets, clinicians may decide not to prescribe another pack. The above wastage scenarios are subject to various uncertainties relating to prescribing practice and the implementation of reduced and tapered dosing. They do not include potential wastage related to early discontinuation

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
		optional additional taper to 4 mg for 2 weeks): In the company submission a scenario was provided in which the optional additional 2-week taper to 4 mg daily was included. Only 14 tablets are required for this 2-week period; assuming wastage of the remaining 14 tablets in the 28-tablet pack, this would equate to drug wastage to the value of [redacted]	or adjusted dose intensity, which would tend to reduce overall treatment costs. But additional wastage costs will be incurred for patients who have retreatment. We conclude that, with the new 28 tablet pack, the overall costs of wastage are modest, and it is unlikely that they would change the cost-effectiveness conclusions, unless combined with other more conservative assumptions. We have added comments on these clarifications and wastage costings in the EAR: Issue 4 (page 5), section 4.2.10.1.1.1, (pages 69-70), section 4.2.10.3 (page 74) and section 6.4 (page 87).

Issue 2 Error on description of TRF-budesonide costs

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Text Page 68 As the model uses a monthly cycle length (one twelfth of a year) the cost per month at the full daily dose of 16 mg dose is estimated at [redacted]. The estimated cost for 2 weeks at the reduced dose of 8 mg is [redacted], and the cost for the additional 2-week tapering period at 4 mg is [redacted]. These costs are likely to be under-estimated, as wastage is likely in practice.	The company suggests the revised wording below: As the model uses a monthly cycle length of 30.4375 days, the cost per cycle at the full daily dose of 16 mg is estimated at [redacted] The estimated cost for the final cycle (accounting for 16 mg dosing before the patient switches to the reduced dose of 8 mg for the final 2 weeks) is [redacted]. The cost for the additional, optional 2-week tapering period at 4 mg assuming no wastage is [redacted]. The model provides the option of assuming wastage of the remaining tablets which brings the cost of the additional, optional tapering period to [redacted].	[redacted] was provided as the cost of the full final month of treatment. This cost for the final cycle included the full 16 mg dose taken for 30.4375 minus 14 days, before the patient switched to the reduced 8 mg dose for the remaining 14 days of the final cycle. Furthermore, the optional, additional 2-week taper to the 4 mg dose can be costed using the new 28 x 4 mg pack, and can be included either in a no wastage scenario (14 tablets) or in a wastage scenario (full pack, 28 tablets)	Thank you, we agree with these corrections, and have added them in section 4.2.10.1.1. of the EAR (page 69).

Issue 3 Interpretation of safety data

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 3.2.5.5, pg 44/45 Coronavirus infection was the most common treatment-emergent adverse event in both groups [redacted] (CS Table 32).	The text should be moved to the next paragraph (EAG report, pg 45, paragraph 2), which describes adverse events that occurred during the 15-month follow-up period	This text is included in a paragraph of the EAG report that describes adverse events occurring during the treatment period. However, CS table 32 refers to adverse events that occurred during the follow up period. Coronavirus infection was the most common adverse event during the follow-up period.	We have moved this text to the next paragraph as suggested.

Location of incorrect marking	Description of incorrect marking	Amended marking	EAG response
Tabulated Issue 4, pg 5 [redacted]	The company can confirm that the tapering pack (28 x 4mg tablets) is now available (as of 1st August 2025), and as such confidential mark	Please remove confidential marking, and consider revision to text in italics: The company state that a tapering pack *containing* 28 4 mg tablets is expected to be launched in the latter half of 2025. *The company have now*	Confidential marking removed, and wording amended.

Location of incorrect marking	Description of incorrect marking	Amended marking	EAG response
	up is no longer necessary.	*confirmed that this is now available at pro-rata price to the 120 tablet pack. The availability of this taper pack would help to avoid wastage.*	
Tabulated Issue 4, pg 5 [redacted]		Please remove confidential marking from paragraph below, and consider if removal or rewording is appropriate: Further information about the availability of a tapering pack, and a clear explanation of the impact on costs to the NHS.	This text has been deleted.
Section 2.1, pg 7 …clinical effectiveness and cost effectiveness of targeted release formulation (TRF)-budesonide budesonide (Kinpeygo) for treating [redacted]	The company can confirm that UK marketing authorisation has now been granted. Confidential mark up can therefore be removed.	Please remove confidential marking to following text: …clinical effectiveness and cost effectiveness of targeted release formulation (TRF)-budesonide budesonide (Kinpeygo) for treating adults with primary immunoglobulin A (IgA) nephropathy with a urine protein excretion ≥1.0 g/day or urine protein-to-creatinine ratio ≥ 0.8g/g	Confidential marking has been removed.

Location of incorrect marking	Description of incorrect marking	Amended marking	EAG response
Section 2.2.2, pg 8 The company has now made a UK marketing authorisation application for the use of TRF-budesonide with an anticipated treatment indication of [redacted]		Please remove confidential marking to following text and consider if rewording is appropriate: The company has now made a UK marketing authorisation application for the use of TRF-budesonide with an anticipated treatment indication of adults with primary IgA nephropathy with a urine protein excretion of ≥1.0g/day (or UPCR ≥0.8g/g)	Confidential marking has been removed and the text updated so that it now reads: "The company made a UK marketing authorisation application for the use of TRF-budesonide with an anticipated treatment indication of adults with primary IgA nephropathy with a urine protein excretion of ≥1.0g/day (or UPCR ≥0.8g/g) (CS Table 2).[11] The latter indication is the focus of this appraisal (CS section 1.1). When the company completed the factual accuracy check and confidential information check they stated that the marketing authorisation had been received."
Section 2.2.2, pg 8		Please remove confidential marking to following text and consider if removal or rewording is appropriate:	Text in section 2.2.2, page 8 has been updated as described in the row above.

Location of incorrect marking	Description of incorrect marking	Amended marking	EAG response
It is expected that the marketing authorisation will be received in [redacted]		It is expected that the marketing authorisation will be received in July/August 2025	
Section 2.3, pg 11 Although NICE have already produced guidance for the subgroup with UPCR ≥1.5g/g in TA937[10] the anticipated marketing authorisation for TRF-budesonide is for [redacted]		Please remove confidential marking to following text and consider if rewording is appropriate: Although NICE have already produced guidance for the subgroup with UPCR ≥1.5g/g in TA937[10] the anticipated marketing authorisation for TRF-budesonide is for an expanded population with primary IgA nephropathy and a urine protein excretion ≥1.0 g/day (or urine protein-to-creatinine ratio ≥0.8 g/g)	Confidential marking has been removed and the text slightly updated so that it now reads: "Although NICE have already produced guidance for the subgroup with UPCR ≥1.5g/g in TA937[10] the recently updated marketing authorisation for TRF-budesonide is for an expanded population with primary IgA nephropathy and a urine protein excretion ≥1.0 g/day (or urine protein-to-creatinine ratio ≥0.8 g/g)"
Section 2.3, pg 11 …could affect cost-effectiveness in the subgroup with UPCR [redacted] <1.5g/g for		Please remove confidential marking to following text and consider if rewording is appropriate: …could affect cost-effectiveness in the subgroup with UPCR ≥0.8g/g to	Confidential marking has been removed.

Location of incorrect marking	Description of incorrect marking	Amended marking	EAG response
whom TRF-budesonide is currently not recommended.		<1.5g/g for whom TRF-budesonide is currently not recommended.	
Table 3, pg 11 [redacted]		Please remove confidential marking to following text: Adults with primary immunoglobulin A nephropathy (IgAN) with a urine protein excretion ≥1.0 g/day (or urine protein-to-creatinine ratio ≥0.8 g/g)	Confidential marking has been removed.
Table 4, pg 18 For the current submission the evidence presented covers the updated full anticipated marketing authorisation [redacted]		Please remove confidential marking to following text and consider if rewording is appropriate: For the current submission the evidence presented covers the updated full anticipated marketing authorisation (adults with primary IgA nephropathy with a urine protein excretion ≥1.0g/day [or UPCR ≥0.8 g/g])	Confidential marking has been removed.
Table 4, pg 18 The draft SmPC[11] states that [redacted]		Please remove confidential marking to following text and consider if rewording is appropriate: The SmPC[11] states that re-treatment may be considered at the discretion	Confidential marking has been removed.

Location of incorrect marking	Description of incorrect marking	Amended marking	EAG response
		of the treating physician. No specific eligibility criteria for re-treatment are provided.	
Table 4, pg 19 For this review of TA937 in a population of [redacted]		Please remove confidential marking to following text: For this review of TA937 in a population of adults with primary IgA nephropathy and a urine protein excretion ≥1.0g/day (or UPCR ≥0.8 g/g)	Confidential marking has been removed.
Section 3.2.1.1.1, pg 21 It evaluated the [redacted]		Please remove confidential marking to following text and consider if rewording is appropriate: It evaluated the anticipated marketing authorisation-recommended dose of TRF-budesonide, in the company's decision problem population and the anticipated extended marketing authorisation indication of patients with primary IgA nephropathy with a urine protein excretion ≥1.0g/day (or UPCR ≥0.8 g/g).	Confidential marking has been removed.

Location of incorrect marking	Description of incorrect marking	Amended marking	EAG response
Section 4.2.4.1, pg 57 The draft MHRA Summary of product characteristics (SmPC) states that [redacted]		Please remove confidential marking to following text and consider if rewording is appropriate: The MHRA Summary of product characteristics (SmPC) states that re-treatment may be considered at the discretion of the treating physician.	Confidential marking has been removed and 'draft' deleted from the text as suggested.
Section 4.2.10.1.1.1, pg 68 [redacted]	The company can confirm that the tapering pack (28 x 4mg tablets) is now available (as of 1st August 2025), and as such confidential mark up is no longer necessary on its availability. PAS price however must remain confidential.	Please amend confidential marking to following text: The company state that a tapering pack containing 28 4 mg is expected to be launched in the latter half of 2025. This increases the cost for the additional 2-week tapering period at 4 mg per day to £[redacted]. The company reports scenarios including tapering, with and without the tapering pack cost.	Confidential marking has been removed except for the PAS price.