NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Targeted-release budesonide for treating primary IgA nephropathy [ID1434]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Targeted-release budesonide for treating primary IgA nephropathy [ID1434]

Contents:

The following documents are made available to stakeholders:

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

Pre-technical engagement documents

1. **Company submission** from Britannia Pharmaceuticals
2. **Company summary of information for patients (SIP)** from Britannia Pharmaceuticals
3. **Clarification questions and company responses**
4. **Patient group, professional group and NHS organisation submissions** from:
   a. Kidney Research UK
5. **External Assessment Report** prepared by Kleijnen Systematic Reviews (KSR)
6. **External Assessment Report – factual accuracy check**

Post-technical engagement documents

7. **Technical engagement response from company**
8. **Technical engagement responses and statements from experts:**
   a. Benjamin Stokes – patient expert, nominated by Kidney Research UK
   b. Guy Hill – patient expert, nominated by Kidney Care UK
   c. Professor Jonathan Barratt, The Mayer Professor of Renal Medicine – clinical expert, nominated by Britannia Pharmaceuticals (company)
9. **Technical engagement responses from stakeholders:**
   a. UK Kidney Association
   b. NHS England
   c. Novartis
10. **External Assessment Report critique of company response to technical engagement** prepared by Kleijnen Systematic Reviews (KSR):
    a. Main critique
    b. Addendum

c. Addendum 2 on PSA issues

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 [ID1434]

Document B

Company evidence submission

April 2023

File name	Version	Contains confidential information	Date
ID11434_TRF-budesonide for IgAN_Doc B_ACIC redacted_240423	**1.0**	**Yes**	**24 April 2023**

Contents

Abbreviations

ACE	Angiotensin converting enzyme
AE	Adverse events
AESI	Adverse events of special interest
AIC	Akaike information criterion
AJKD	American Journal of Kidney Disease
ARB	Angiotensin receptor blockers
AUC	Area under the curve
BL	Baseline
BIC	Bayesian information criterion
BMI	Body-mass index
BP	Blood pressure
CEM	Cost effectiveness model
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CKD	Chronic kidney disease
CKD-EPI	Chronic kidney disease epidemiology collaboration equation
CS	Corticosteroid
CSR	Clinical study report
CVD	Cardiovascular disease
DBP	Diastolic blood pressure
DCO	Data cut-off
DM	Diabetes mellitus
DSA	Deterministic sensitivity analysis
eGFR	Estimated glomerular filtration rate
EMA	European Medicines Agency
eMIT	Electronic market information tool
ERG	Evidence Review Group
ESKD	End-stage kidney disease
ESRD	End-stage renal disease
FAS	Full analysis set
gd-IgA	Galactose-deficient immunoglobulin A
GI	Gastrointestinal
GP	General practitioner
HD	Haemodialysis
HR	Hazard ratio
HRQoL	Health-related quality of life

HRG	Health resource group
HSUV	Health state utility value
HTA	Health technology assessment
ICER	Incremental cost-effectiveness ratio
IgA	Immunoglobulin A
IgAN	Immunoglobulin A nephropathy
IQR	Interquartile range
ITC	Indirect treatment comparison
IV	Intravenous
KDIGO	Kidney Disease Improving Global Outcomes
LS	Least squares
LY	Life year
Max	Maximum
MCS	Mental component score
MHRA	Medicines and Healthcare Products Regulatory Agency
MEST	Mesangial and endocapillary hypercellularity, segmental sclerosis, interstitial fibrosis/tubular atrophy, and crescents
Min	Minimum
MMF	Mycophenolate mofetil
MMRM	Mixed-Effects Model for Repeated Measures
MRU	Medical resource use
N/A	Not applicable
MTD	Maximum tolerated dose
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NMB	Net monetary benefit
OD	Once daily
OLE	Open-label extension
ONS	Office for National Statistics
PCS	Physical component score
PD	Peritoneal dialysis
PLD	Patient level data
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
QoL	Quality of life

R	Randomisation
RaDaR	UK National Registry of Rare Kidney Diseases
RAS	Renin-angiotensin system
RCT	Randomised controlled trial
RDI	Relative dose intensity
Ref	Reference
RRT	Renal replacement therapy
SAE	Serious adverse events
SAS	Safety analysis set
SBP	Systolic blood pressure
SD	Standard deviation
SE	Standard error
SF-36	Short-form 36
SGLT2i	Sodium-glucose cotransporter-2 inhibitor
SLR	Systematic literature review
SmPC	Summary of product characteristics
SMR	Standardised mortality rate
SoC	Standard of care
TA-PCR	Time-average protein to creatinine ratio
TEAE	Treatment-emergent adverse event
TESAE	Treatment-emergent serious adverse event
TLR	Toll-Like Receptor
TRF	Targeted-release formulation
TTD	Time to treatment discontinuation
Tx	Treatment
UACR	Urine albumin to creatinine ratio
UK	United Kingdom
UKRR	United Kingdom Renal Registry
UPCR	Urine protein to creatinine ratio
US	United States
UTI	Urinary tract infection

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

B.1.1 Decision problem

This submission covers the full marketing authorisation for targeted-release formulation (TRF)-budesonide, which is indicated for the treatment of primary immunoglobulin A nephropathy (IgAN) in adults at risk of rapid disease progression with a urine protein to creatinine ratio (UPCR) ≥1.5 g/g (1).

Calliditas is the original developer of TRF-budesonide, STADA have the license to market the product in Europe, and Britannia Pharmaceuticals (STADA group) is the United Kingdom (UK) affiliate of STADA responsible for marketing the product in the UK and the UK marketing authorisation holder.

Table 1 summarises the decision problem addressed by the company submission.

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	People with primary IgA nephropathy	Adult patients with primary IgAN who: • are on a stable dose of maximally-tolerated RAS inhibitor therapy, and • are at risk of rapid disease progression with a UPCR ≥1.5 g/g	The population addressed in the company submission is in line with the licence of TRF-budesonide
Intervention	Targeted-release budesonide	As per scope	
Comparator(s)	Established clinical management without targeted-release budesonide, including ACE inhibitors and ARBs at the maximum tolerated licensed doses, diuretics and dietary and lifestyle modification, with or without: • Glucocorticoids • SGLT2is	Standard of care: • Blood pressure management; maximally tolerated dose of ACEi/ARB; lifestyle modification; and addressing cardiovascular risk • SGLT2is are given to patients with IgAN as part of SoC for cardiovascular protection (2)	The comparators selected are in line with SoC for patients with IgAN (2, 3) • The KDIGO guideline and UK clinical expert opinion indicated that SoC includes lifestyle modification, blood pressure management, and maximum-tolerated RAS blockade (ACEi or ARBs) (2, 3) • Dapagliflozin has received NICE approval for the treatment of CKD (TA775) (4) and is also anticipated to be used as part of SoC in patients with IgAN, as indicated by clinical expert opinion (2) • The KDIGO guidelines state that CS and immunosuppressants are only recommended if a clinical trial is not accessible and the risk/benefit profile is considered to be acceptable (3). UK clinical experts reported that in practice, CS are used sparingly/only in severe patients with kidney disease

			(i.e. patients with nephrotic syndrome or rapidly progressive glomerulonephritis) (2) • MMF is recommended in Chinese patients only, where it can be used as a glucocorticoid-sparing agent (3). In clinical practice in England, MMF may be administered to Caucasian as well as Asian patients with IgAN due to the lack of other available treatment options (2). Due to a lack of clinical evidence showing benefit of MFF in Caucasians, it is not considered a relevant comparator for TRF-budesonide (2) No UK/NICE guidelines for the management of IgAN have been published to date.
Outcomes	The outcome measures to be considered include: • proteinuria (for example, change from baseline in urine protein creatine ratio) • disease progression (dialysis and/or transplant) • mortality • adverse effects of treatment • health-related quality of life	As per scope	

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. The availability of any commercial arrangements for the intervention, comparator and subsequent treatment technologies will be taken into account.	As per scope	

Abbreviations: ACE, angiotensin converting enzyme; ARB, angiotensin receptor blockers; IgAN, immunoglobulin nephropathy A; CKD, chronic kidney disease; CS, corticosteroids; KDIGO, Kidney Disease Improving Global Outcomes; MMF, mycophenolate mofetil; NICE, National Institute for Health and Care Excellence; NHS, National Health Service; RAS, renin-angiotensin system; SGLT2i, sodium-glucose cotransporter-2 inhibitor; SoC, standard of care; UPCR, urine protein to creatinine ratio.

B.1.2 Description of the technology being evaluated

TRF-budesonide is the first and only approved treatment specifically designed for patients with IgAN. It has been specifically 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) (5). Here, its anti-inflammatory action is expected to provide a disease-modifying effect by decreasing the secretion of gd-IgAs, preventing downstream effects manifesting as kidney inflammation and loss of renal function (5-7).

The summary of product characteristics (SmPC) and UK public assessment report for TRF-budesonide (1) are presented in Appendix C.

Table 2: Technology being evaluated

UK approved name and brand name	Generic name: TRF-budesonide Brand name: Kinpeygo®
Mechanism of action	The intended action of TRF-budesonide is the suppression of mucosal B-cells, located in the Peyer's patches in the ileum, and inhibition of their proliferation and differentiation into plasma cells that produce mucosal gd-IgA1 antibodies. Consequently, it is expected that the occurrence of gd-IgA1 antibodies and formation of immune complexes in the systemic circulation will be suppressed, therefore preventing the downstream effects of glomerular mesangial deposition of immune complexes containing gd-IgA1, manifesting as glomerulonephritis and loss of renal function.
Marketing authorisation/CE mark status	The CHMP recommended the granting of a conditional marketing authorisation for TRF-budesonide on 19 May 2022 (8). Marketing authorisation was granted by the European Commission on the 15th July 2022 (9). Marketing authorisation by the MHRA on 01 February 2023 (1).
Indications and any restriction(s) as described in the summary of product characteristics (SmPC)	TRF-budesonide is indicated for the treatment of primary IgAN in adults at risk of rapid disease progression with a UPCR ≥1.5 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	List price: [redacted]
Patient access scheme (if applicable)	[redacted]

Abbreviations: CHMP, Committee for Medicinal Products for Human Use; gd-IgA1, galactose-deficient IgA1, IgAN, immunoglobulin A nephropathy; MHRA, Medicines and Healthcare Products Regulatory Agency; TRF, targeted-release formulation; UPCR, urine protein to creatinine ratio.
Source: MHRA. TRF-budesonide SmPC. 2023 (1).

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

Overview of IgAN

- IgAN is a progressive chronic kidney disease (CKD) with an orphan designation, which is estimated to affect 14,372 people in England (10, 11)
- 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 inflammatory events, causing inflammation and fibrosis which can lead to a decline in kidney function and CKD (3, 7, 12-14)
- Patients with IgAN in England are typically diagnosed at 41 (standard deviation [SD]: 15) years of age and the majority of patients progress to end-stage renal disease (ESRD) within 10–15 years from diagnosis (15)
- Within the IgAN population, those with elevated time-average protein to creatinine ratio have been reported to have a significantly greater risk of progression to ESRD and death; >50% of patients with UPCR >1.76 g/g progress to ESRD by 5 years from diagnosis (15)
- Patients with IgAN face an average 10-year reduction in life expectancy, a mortality rate approximately twice that of the general population (16, 17), a high risk of comorbidities (18), and may suffer from a broad range of symptoms which can cause physical limitations and restrict daily activities (19-23)

IgAN treatment pathway

- There are currently no therapies licensed specifically for patients with IgAN
- Treatment guidelines for IgAN focus on optimised supportive care, which includes lifestyle modification, blood pressure management, maximum-tolerated renin-angiotensin system (RAS) blockade, and sodium-glucose cotransporter-2 (SGLT2) inhibitors to provide cardiovascular protection (2, 3, 7)
- For patients with IgAN who remain at high risk of progressive CKD despite maximal supportive care, guidelines and UK clinical experts recommend participation in a clinical trial, if possible (2, 3, 7)

- If a clinical trial is not accessible, systemic corticosteroid (CS) therapy is cautiously recommended due to an uncertain benefit-to-risk ratio and associated significant toxicity (2, 3, 7, 24-26). In clinical practice in England, the use of CSs in people with IgAN is avoided due to associated serious adverse events (AEs) and may only be considered in patients with nephrotic syndrome (2)

- For patients with IgAN who progress to ESRD, treatment options are limited to dialysis or kidney transplantation, which substantially increase disease burden and associated treatment costs (3, 7, 20, 27-29)

- Due to the risk of disease progression and limited treatment choices, there remains a high unmet need for safe and effective therapies which target the underlying mechanisms of IgAN

TRF-budesonide

- TRF-budesonide is the first approved treatment specifically designed for patients with IgAN; the anticipated indication for TRF-budesonide is for the treatment of primary IgAN in adults at risk of rapid disease progression with a UPCR ≥1.5 g/g

- Formulated to release the active component in the distal ileum, TRF-budesonide is expected to exert an anti-inflammatory effect at a primary site of gd-IgA production, the Peyer's patches (5)

- By reducing the levels of immune complexes circulating in the blood, it is anticipated that TRF-budesonide will provide a disease-modifying effect by preventing the downstream effects of their deposition in the kidneys, such as kidney inflammation, damage, and loss of function (1, 5)

B.1.3.1 Overview

Immunoglobulin A nephropathy is a progressive, chronic disease of the kidney that occurs when IgA antibody complexes deposit in the kidney, causing inflammation and fibrosis, which can lead to kidney failure (7, 13, 14). Disease progression in patients with IgAN is defined by estimated glomerular filtration rate (eGFR)-based CKD stages (30).

In line with the indication for TRF-budesonide, this submission focuses on primary IgAN, in which there is no obvious initiating or underlying cause of disease.

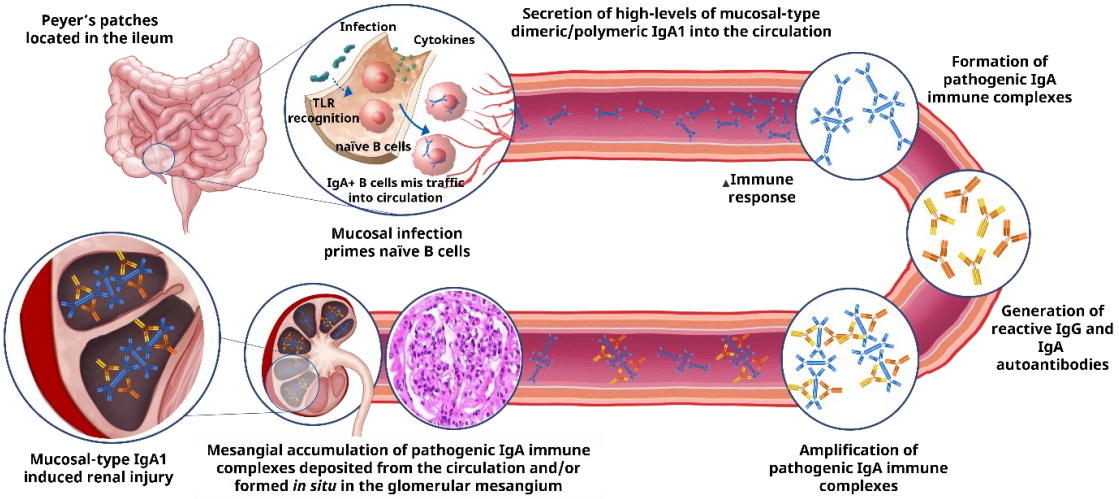
B.1.3.1.1 Aetiology and pathogenesis

The aetiology and pathogenesis of IgAN are not entirely understood and the processes that initiate disease activity and underlie disease susceptibility remain an area of investigation (7, 14). Genetic and environmental factors have been reported to contribute to dysregulation of the normal physiological process of IgA production in patients with IgAN (7, 14, 23). Proposed contributing factors include the triggering of increased production of gd-IgAs due to hereditary causes, or by an initial trauma such as mucosal infection (e.g. tonsillitis), stress, or exposure to toxins (7, 14).

The steps involved in the pathogenesis of IgAN, illustrated in Figure 1, can be described by the “four-hit hypothesis,” which includes:

1. Increased levels of circulating gd-IgAs which are produced by IgA1-producing cells, including those in the Peyer’s patches at the distal ileum, a primary site of IgA production (5, 7, 31)
2. IgG and IgA autoantibodies are generated and directed against gd-IgAs (7, 31)
3. Autoantibodies and gd-IgAs form immune complexes (31)
4. The IgA-containing immune complexes deposit in the glomerular mesangium and initiate inflammatory and fibrotic processes in the kidney which lead to renal injury (7, 31)

Figure 1: Pathophysiology of IgAN



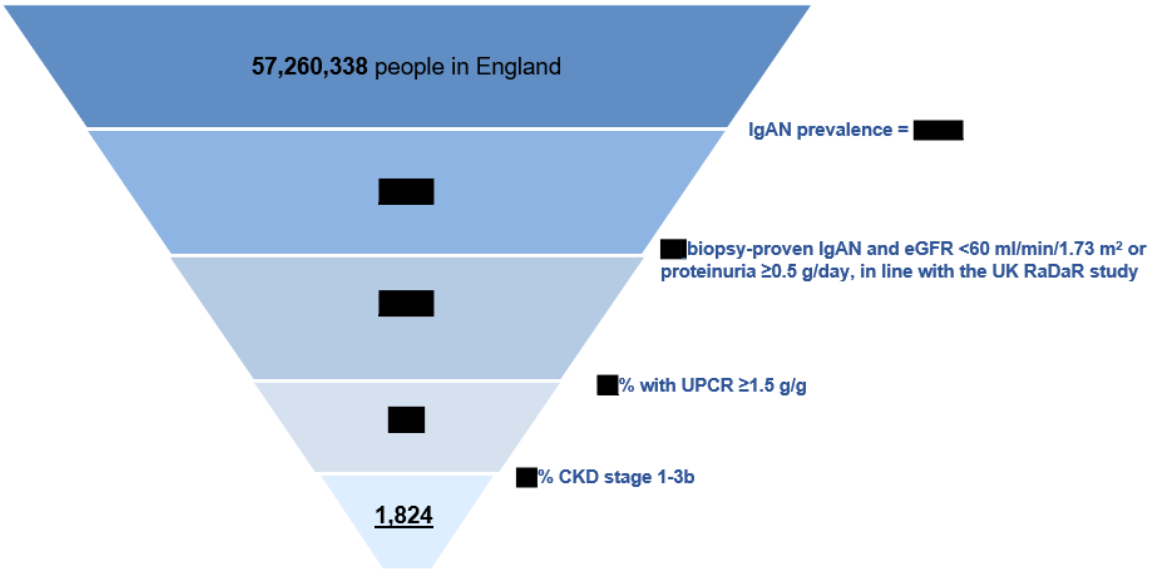
Abbreviations: IgA, immunoglobulin A; IgAN, immunoglobulin A nephropathy; IgG, immunoglobulin G; TLR, Toll-Like Receptor.
Adapted from Boyd et al. 2012 (32).

B.1.3.1.2 Epidemiology

IgAN is an orphan disease with a worldwide annual incidence of at least 2.5 per 100,000 people (33). In the UK, the incidence of IgAN has been reported to be [redacted] per 10,000 people (34). Although IgAN is the most common cause of glomeruli inflammation, the rates of IgAN diagnosis vary widely between countries, likely due to differences in screening and biopsy practices which may contribute to an underestimation of disease burden (7, 23, 35). It is estimated that there are [redacted] people with IgAN in England (11). Literature data relating to the proportion of patients with IgAN at risk of rapid disease progression is scarce. Although, the UK National Registry of Rare Kidney Diseases (RaDaR) study (the largest UK study of people with IgAN [2,299 adults, 140 children]) could not identify whether included patients were at risk of rapid disease progression, it is estimated that [redacted] of patients (2) would be considered at risk of rapid, based on the estimated proportion of patients with proteinuria biopsy-proven IgAN and eGFR <60 mL/min/1.73 m^2 or 24-hour proteinuria ≥0.5 g (i.e. with disease severity captured in UK RaDaR). This assumption was validated by clinical expert opinion (2). UK RaDaR data estimates that [redacted] of these patients have UPCR ≥1.5 g/g and [redacted] are CKD 1–3b (36). Based on these proportions, the number of people estimated to be eligible for treatment with TRF-budesonide in England is 1,824 (Figure 2) (11).

IgAN can present at any age; the mean age at diagnosis in the UK has been reported to be 41 (15) years (15). IgAN is more frequently diagnosed in males than females, with ratios ranging from less than 2:1 in East Asia to as high as 6:1 in Northern Europe and the United States (US) (22, 37). Caucasian and Asian populations are more prone to developing IgAN compared with Black populations (22).

Figure 2: Patient population covered by the company submission



Abbreviations: IgA, immunoglobulin A; UPCR, urine protein to creatinine ratio.
Source: Britannia Pharmaceuticals LTD. IgAN epidemiology calculations. Data on file. 2023 (11).

B.1.3.1.3 Diagnosis

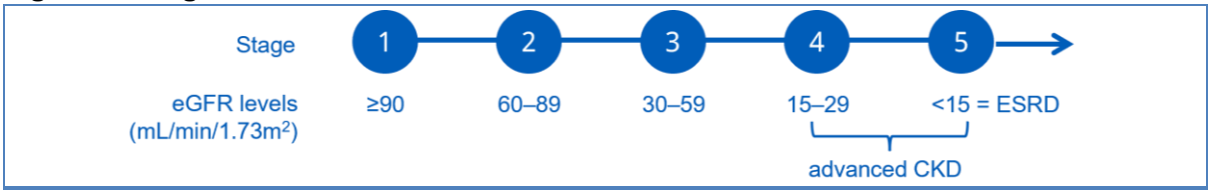
The first step towards a diagnosis of IgAN typically includes a urine test to check for a urine infection and to measure protein levels (38, 39). A blood test to measure serum creatinine can also be conducted to assess kidney function (38, 39). A definitive diagnosis of IgAN requires a renal biopsy with immunofluorescence or immunoperoxidase to detect IgA deposition (3, 7, 40). As IgAN is 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) (41). 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]) (3). There are no validated diagnostic serum or urine biomarkers for IgAN (3).

B.1.3.1.4 Disease course and risk factors for progression

IgAN causes a chronic decline in kidney function, the extent of which is defined based on eGFR levels (Figure 3) (7, 14, 30). Disease progression can lead to kidney failure (ESRD; CKD stage 5), where patients require renal replacement therapy (RRT) in the form of a kidney transplant or chronic dialysis (3, 23, 28, 42).

Figure 3: Stages of CKD based on eGFR levels

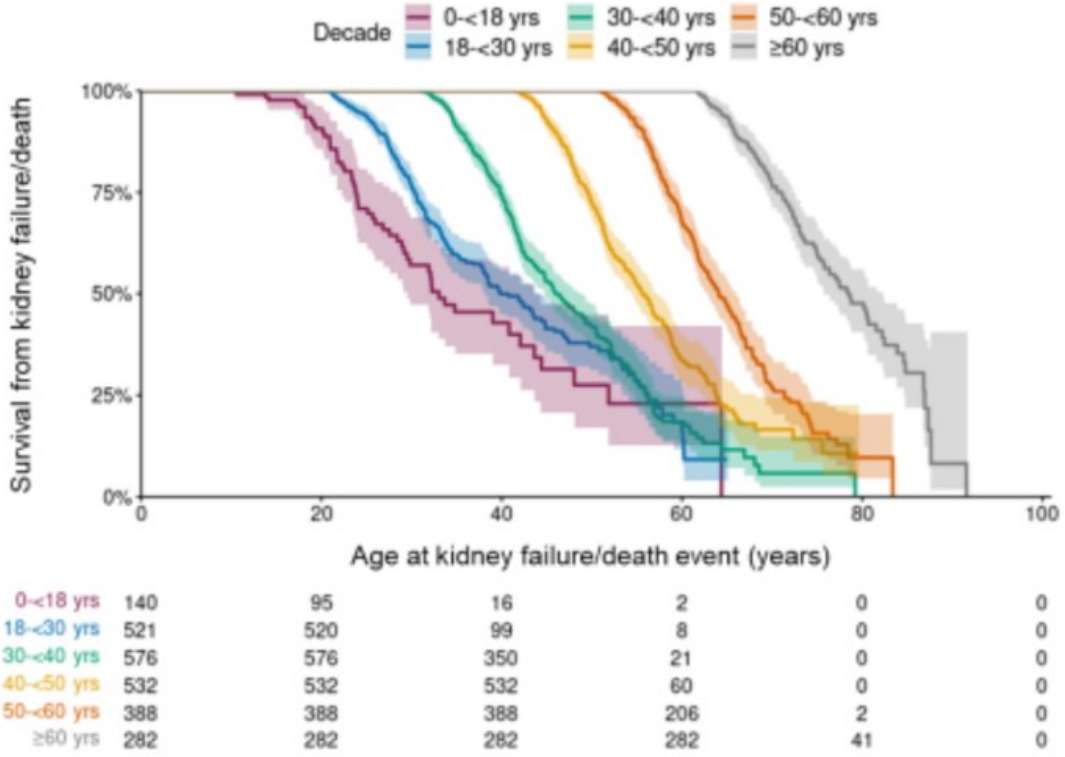


Stage	Description	eGFR levels (mL/min/1.73 m²)†
1	Kidney damage‡ with normal or increased eGFR	≥90
2	Kidney damage‡ with mildly decreased eGFR	60 to 89
3	Moderate decreased eGFR	30 to 59
4	Severe decreased eGFR	15 to 29
5	Kidney failure (ESRD)	<15 or dialysis

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) (30).

People with IgAN typically progress to ESRD or death at a substantially earlier age than patients with CKD, although disease course and rate of progression of IgAN are variable (15, 43). In a study of patients from the UK RaDaR IgAN cohort (2,299 adults, 140 children), 50% of patients reached kidney failure or died during the study period (median [Q1, Q3] follow-up: 5.9 [3.0, 10.5] years) (15). The mean age at kidney failure/death was 48 years and most patients progressed to kidney failure within 10–15 years from diagnosis (Figure 4) (15). The median age of kidney replacement therapy among patients with CKD in the European Renal Association Registry age was 67.9 years (43).

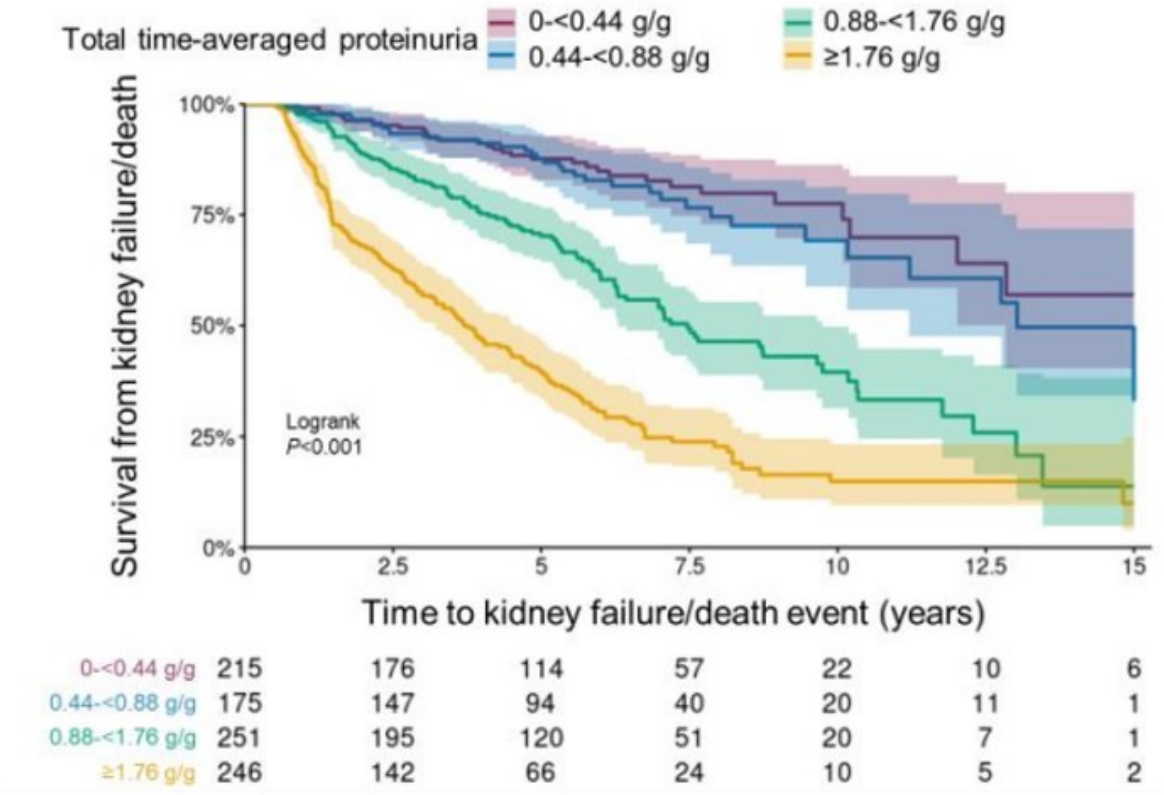
Figure 4: Kaplan-Meier survival curves (95% CI) of time to kidney failure/death event based on age at diagnosis for patients from the UK RaDaR IgAN cohort



Abbreviations: CI, confidence interval; IgAN, immunoglobulin A nephropathy; UK RaDaR, United Kingdom National Registry of Rare Kidney Diseases.
Source: Pitcher et al. 2023 (15).

Disease progression in IgAN is faster in specific patient groups at risk of rapid progression. 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 greater proteinuria (7, 14, 23). 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) were likely to progress to kidney failure or death more quickly than patients with time-averaged proteinuria <0.88g/g (Figure 2) (15). Patients with low proteinuria of <0.88 g/g UPCR (n=390) had a median time to ESRD or death of >15 years <0.88g/g. However, this decreased to approximately 7.5 years in patients with UPCR 0.88 to <1.76 g/g (n=251), and further decreased to ~3 years in patients with UPCR ≥1.76 g/g (n=246) (15).

Figure 5: Kaplan-Meier survival curves (95% CI) of time to kidney failure/death event in the UK RaDaR IgAN cohort

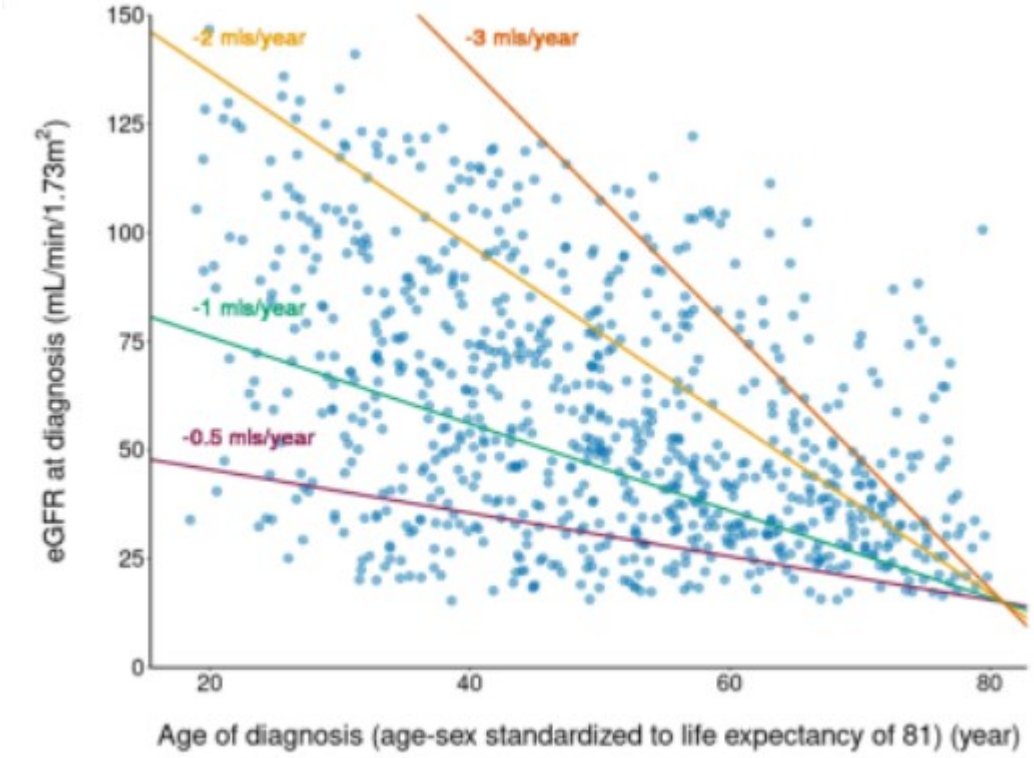


Abbreviations: CI, confidence interval; IgAN, immunoglobulin A nephropathy; UK RaDaR, United Kingdom National Registry of Rare Kidney Diseases.
Source: Pitcher et al. 2023 (15).

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, 44). 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) (44). The majority of people with IgAN in the UK RaDaR cohort were shown to be at risk of progression to kidney failure within their expected lifetime, unless a rate of eGFR loss ≤1 ml/min/1.73 m^2/year could be maintained (15) (Figure 6). 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 kidney failure (15). A decline of as little as 1 mL/min/1.73 m^2/year would result in ~40% of people diagnosed before 50 years of age reaching kidney failure (15). This implies that a decline in eGFR of <1 mL/min/year is required to avoid risk of progression ESRD (15).

Figure 6: 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 (15).

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 (45-48).

B.1.3.1.5 Cardiovascular risk in patients with IgAN

Proteinuria (3, 49, 50) and low levels of eGFR (51) are also risk factors for cardiovascular disease (CVD), which is a leading cause of death in patients with IgAN (16, 52) and CKD (28). 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) (49). 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 levels (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]) (51).

B.1.3.1.6 Survival and mortality in IgAN

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). The cause of death was not available for all patients but included ischaemic heart disease, vascular disease, sepsis, and malignancy (53). Cardiovascular disease has been reported to be a leading cause of death in patients with IgAN (16, 52).

B.1.3.1.7 Clinical burden

The clinical manifestations of IgAN at presentation typically 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 (23, 40, 54). A broad range of other clinical manifestations may also present and can vary as IgAN progresses (7, 23). These can include progressive CKD and infections leading to acute care events, including hospitalisation or emergency department visits (7, 23, 55). Patients with IgAN can experience tiredness and fatigue which limit physical activity and result in low stamina (19). A

high risk of certain comorbidities has also been reported for patients with IgAN, including an 86% increased risk of future ischaemic heart disease compared with the general population (18).

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 (20, 28, 56). If left untreated, kidney failure ultimately leads to death (28). Therefore, RRT is needed for people with kidney failure, either in the form of chronic dialysis or kidney transplantation (20, 28). However, dialysis is associated with a debilitating emotional and physical burden (Section B.1.3.1.8) as well as multiple unpleasant symptoms frequently reported to include fatigue, muscle weakness, itching, and sleep problems (56-59). Kidney transplantation is associated with a risk of transplant failure, disease recurrence, iatrogenic infection, and the requirement for lifelong immunosuppressive therapy (27, 60-62).

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 (56); O'Connor 2012 (20); Voskamp et al. 2019 (63).

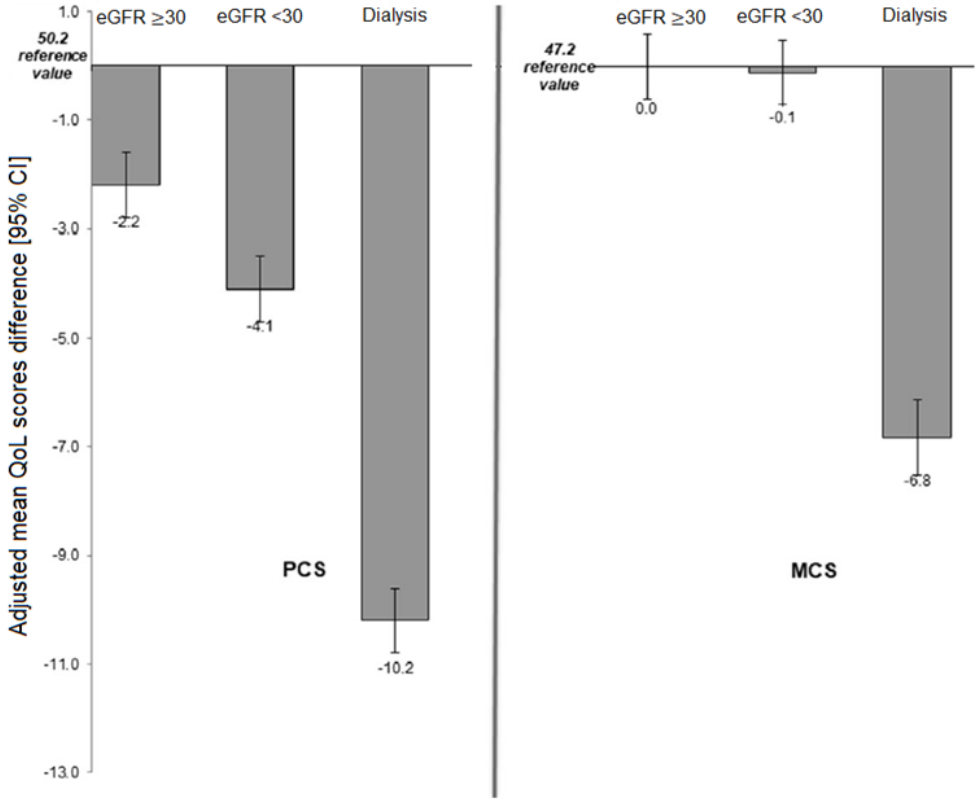
B.1.3.1.8 Humanistic burden

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 (19-21). 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, 7, 19, 64). Patients with IgAN suffer from anxiety, depression, and fear of progression to ESRD (19, 21).

The considerable physical and mental health burden of IgAN increases with disease progression, particularly when dialysis becomes necessary (21). A diagnosis of CKD often causes trauma and distress, with uncertainty about the future prompting patients to re-evaluate their lives (65). 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 (56, 66-69). 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 (30, 59, 70-73). 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 7) (66, 72, 74, 75).

Figure 7: 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 (66).

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 (19, 65, 76). Carers of patients with CKD can be impacted by depressive symptoms or anxiety, with some caregivers reporting battling an unrelenting and debilitating burden (65).

B.1.3.1.9 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 (40, 77). However, limited published evidence of the economic and healthcare burden of IgAN is available (21); 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 (78-81). Costs increase substantially with progression of CKD, even at early stages (79, 82). 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 (79). ESRD is the most expensive stage of CKD (79, 82). The largest direct cost drivers in CKD and ESRD are hospitalisation and medication costs (83-85). Indirect cost drivers include productivity loss and years lost due to absenteeism or presenteeism of patients and/or caregivers, and disability/sick leave (79, 83, 86).

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 with CKD stages 4–5 without dialysis in a population-based cohort study of the Swedish national healthcare system (29). 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 (87). Cost drivers for dialysis relate to the procedure itself, hospitalisations, outpatient care, transportation, and drug costs (29, 88-92).

B.1.3.2 Clinical pathway of care

B.1.3.2.1 Current pathway of care

There is currently no cure for IgAN, and no guidance for the management of the condition have been published by the National Institute for Health and Care Excellence (NICE). Published NICE Guidelines for the assessment and management of CKD (NG203) (93) do not contain specific information on the treatment of patients with IgAN.

Clinical experts have reported that in England, the Kidney Disease Improving Global Outcomes (KDIGO) guidelines (3) are widely used in the management of patients with IgAN. Hypertension and proteinuria are major risk factors for progression to ESRD (3). Therefore, the goal of treatment in IgAN is to control blood pressure and

reduce proteinuria, in order to slow the rate of renal function decline in IgAN, prevent or delay dialysis, and/or improve cardiovascular risk (3, 23, 28).

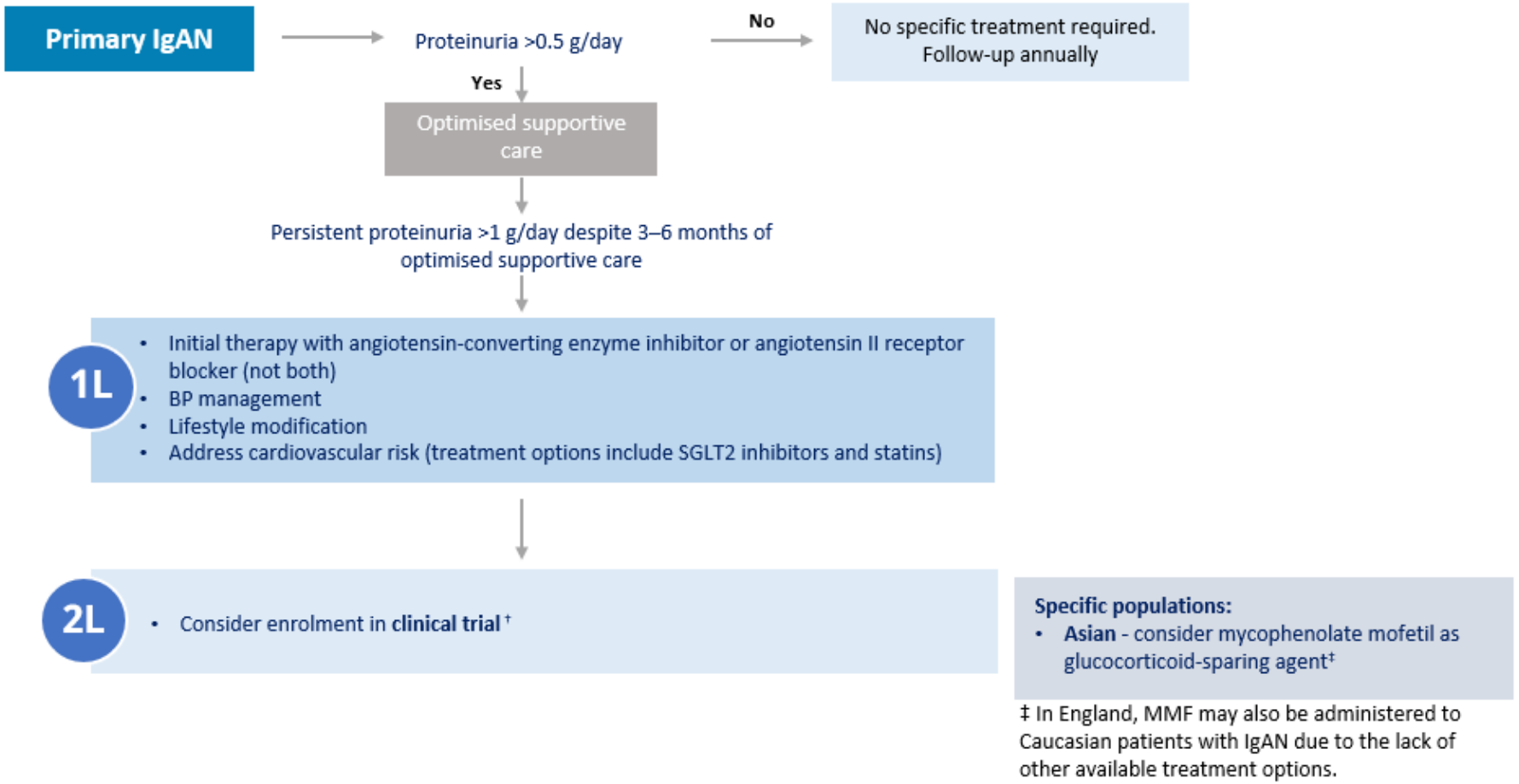
Current treatment of IgAN in the UK is focused on optimised supportive care, which includes lifestyle modification, blood pressure management, and maximum-tolerated RAS blockade (angiotensin-converting enzyme inhibitors [ACEi] or angiotensin receptor blockers [ARB]) (Figure 8) (2, 3). In clinical practice in England, patients with IgAN are also treated with SLGT2 inhibitors as part of standard of care (SoC) to provide cardiovascular protection (2). For example dapagliflozin, which has received NICE approval for the treatment of CKD (TA775) (4), is also anticipated to be used in patients with IgAN (2).

For patients with IgAN at high risk of progression to ESRD despite optimised supportive care, available treatment options are limited and indicated for specific populations only (3). Due to uncertainty relating to the safety and efficacy of existing immunosuppressive treatment choices, all patients who remain at high risk of progressive CKD despite maximal supportive care should be offered the opportunity to take part in a clinical trial (3). If a clinical trial is not accessible, the KDIGO guidelines cautiously recommend CS therapy for patients who remain at high risk of progressive CKD despite maximal supportive care due to the uncertain benefit relative to AE profile, e.g. higher risk of infections (3). The KDIGO guidelines stipulate that a detailed discussion of the risks and benefits of each drug should be undertaken with the patient recognising that AEs are more likely in patients with an eGFR <50 ml/min/1.73 m^2 (3). In addition, patient risk should be continuously monitored, as decisions regarding immunosuppression may change (3). In line with the KDIGO guidelines, clinical experts have also reported that in England, CS are prescribed sparingly as a result of their uncertain benefit to risk ratio and significant toxicity (2). Mycophenolate mofetil (MMF) is recommended in Chinese patients only, where it can be used as a glucocorticoid-sparing agent (3). Experts reported that in clinical practice in England, MMF may be administered to Caucasian as well as Asian patients with IgAN as a glucocorticoid-sparing agent due to the lack of other available treatment options and despite a lack of clinical evidence showing benefit in Caucasians (2). Clinical experts reported that in England, the use of

immunosuppressive agents (CS and MMF) is avoided due to associated serious AEs and may only be considered in patients with nephrotic syndrome (2).

In patients who have progressed to ESRD, the only treatment option is RRT, either in the form of a kidney transplant or chronic dialysis (3, 28).

Figure 8: Current treatment pathway for IgAN in England



Abbreviations: BP, blood pressure; eGFR, estimated glomerular filtration rate; IgAN, Immunoglobulin A nephropathy; MMF, mycophenolate mofetil; SGLT2, sodium-glucose cotransporter-2.
† Based on the KDIGO 2021 guidelines (3), high risk of progression in IgAN is currently defined as proteinuria >0.75–1 g/d despite ≥90 days of optimised supportive care. Although CSs are included in the KDIGO 2021 treatment pathway (3), UK clinical experts indicated that the use of CSs in people with IgAN is avoided due to associated serious adverse events (AEs) and may only be considered in patients with nephrotic syndrome (2). CSs have therefore not been included in the treatment pathway diagram.
Source: KDIGO, 2021 (3) and Britannia Pharmaceuticals TRF-budesonide UK advisory board report 2023 (2).

B.1.3.2.2 TRF-budesonide: place in the treatment pathway

TRF-budesonide is the first and only approved treatment specifically designed for patients with IgAN. It has been formulated to release the active component, budesonide, in the distal ileum where it is expected to exert a disease-modifying anti-inflammatory effect at a primary site of gd-IgA production, the Peyer's patches (Figure 9) (5).

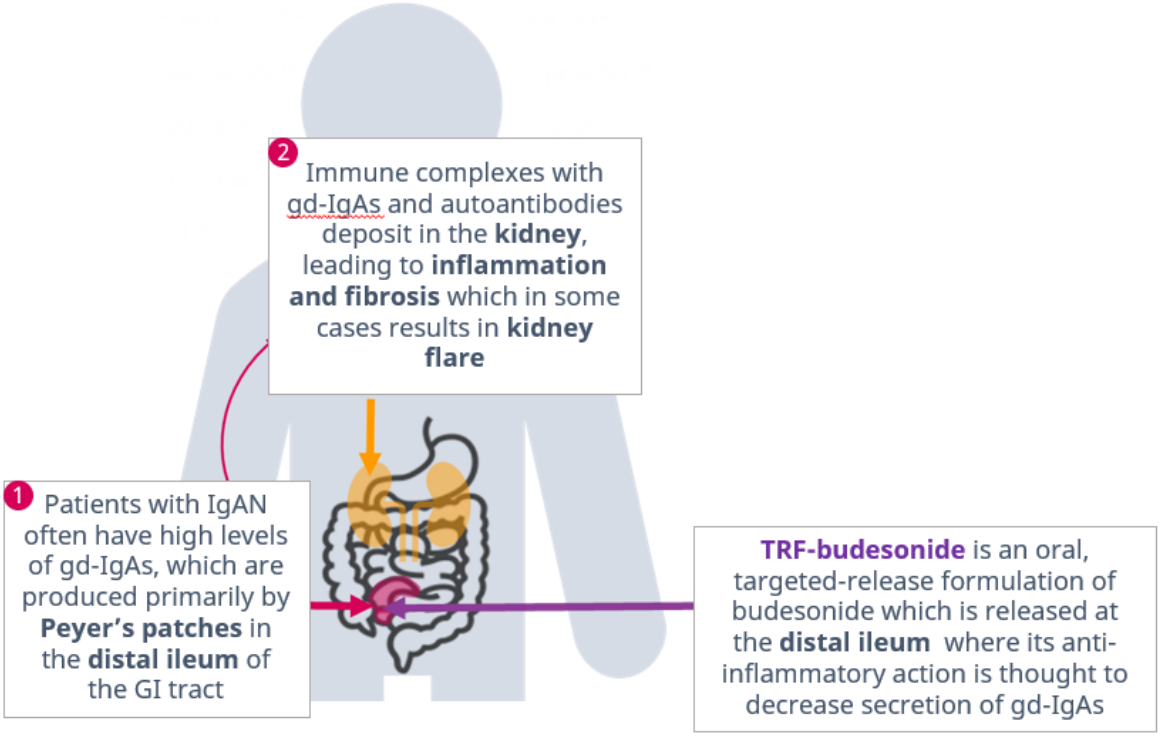
The mechanism of action of TRF-budesonide was investigated in an exploratory analyses of patient serum samples from the phase 2b Nef-202 study, where systemic levels of gd-IgA1 and of IgA containing immune complexes were significantly reduced by treatment with TRF-budesonide in a dose-dependent manner (94). TRF-budesonide treatment also positively modulated levels of gut-relevant biomarkers, with decreases in the serum levels of secretory IgA and IgA specific for casein A and gliadin reported (95). A treatment-related reduction in serum levels of fatty acid-binding protein 2, a marker of gut permeability, was also observed (95). In addition, TRF-budesonide treatment was associated with a decrease in serum PRO-C6, a marker of collagen type VI formation, and increase in urinary C3M/creatinine, a marker of collagen type III degradation, indicating a positive effect on interstitial fibrosis (96). Levels of serum BAFF and circulating soluble BCMA and TACI, which are markers of B cell homeostasis, were reported to be significantly lower following treatment with TRF-budesonide ($p<0.05$), representing changes in T cell independent B cell maturation in the gut in response to treatment (97).

Overall, these effects suggest that TRF-budesonide may contribute to the long-term preservation of renal function in patients with IgAN. By reducing the levels of immune complexes circulating in the blood, it is anticipated that TRF-budesonide will have a disease-modifying effect, preventing the downstream effects of their deposition in the kidneys, such as kidney inflammation, damage, and loss of function (1, 5).

It is anticipated that TRF-budesonide will be used in adult patients with primary IgAN who (Figure 10):

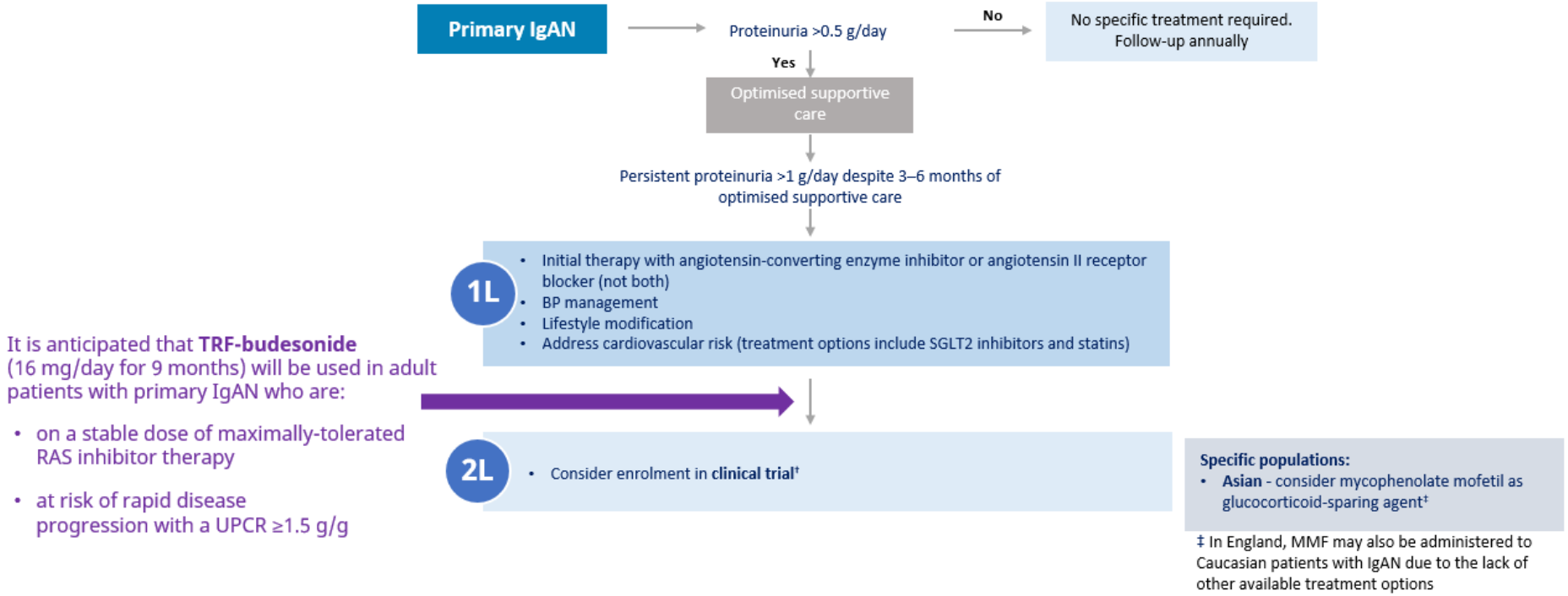
- are on a stable dose of maximally-tolerated RAS inhibitor therapy
- are at risk of rapid disease progression with a UPCR ≥1.5 g/g (1)

Figure 9: 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 (7); Suzuki et al. 2011 (13); Del Vecchio et al. 2021 (5); Fellström et al. 2017 (6).

Figure 10: Anticipated place in treatment pathway for TRF-budesonide



Abbreviations: BP, blood pressure; eGFR, estimated glomerular filtration rate; IgAN, Immunoglobulin A nephropathy; MMF, mycophenolate mofetil; RAS, renin-angiotensin system; SGLT2, sodium-glucose cotransporter-2; UPCR, urine protein to creatinine ratio.
† Based on the KDIGO 2021 guidelines (3), high risk of progression in IgAN is currently defined as proteinuria >0.75–1 g/d despite ≥90 days of optimised supportive care. Although CSs are included in the KDIGO 2021 treatment pathway (3), UK clinical experts indicated that the use of CSs in people with IgAN is avoided due to associated serious adverse events (AEs) and may only be considered in patients with nephrotic syndrome (2). CSs have therefore not been included in the treatment pathway diagram.
Source: KDIGO, 2021 (3) and Britannia Pharmaceuticals TRF-budesonide UK advisory board report 2023 (2).

B.1.3.3 Unmet need

Current treatment options for the management of IgAN are limited, with no therapies licensed specifically for patients with IgAN (27, 98, 99). Therefore, guidelines and clinical experts recommend that patients with IgAN who remain at high risk of progressive CKD despite maximal supportive care should be offered the opportunity to take part in a clinical trial (2, 3, 7). If a clinical trial is not accessible, systemic CS therapy is cautiously recommended for patients at high risk of progression despite maximal supportive care (3, 7). However, CSs are associated with an uncertain benefit-to-risk ratio and significant toxicity (3, 7, 24-26) and data supporting the efficacy or reduced toxicity of alternate-day glucocorticoid regimens or dose-reduced protocols are limited (3).

In the TESTING (26) clinical trial comparing patients with IgAN receiving CSs plus supportive care with those receiving supportive care alone, CSs were associated with higher rates of serious adverse events (SAEs; 28 vs 4 events; p=0.001), particularly serious infections (13 vs 0 events; p<0.001). The increased risk of SAEs led to modification of the TESTING trial to assess a reduced dose of CS (0.6–0.8 mg/kg per day reduced to 0.4 mg/kg per day) (26, 100). Although a lower incidence of serious adverse events was observed in the reduced-dose group after these changes were made, safety concerns including excess hospitalisations and serious infections were reported (100). In the STOP-IgAN study of the effect of immunosuppressive therapy in addition to SoC in people with IgAN, a greater number of infection events were reported in the immunosuppression plus supportive care group vs supportive care alone (174 vs 111; p=0.07), of which 25% were considered by the investigators to be related to the study treatment (24). There was no significant difference in the annual decline in eGFR between the two groups (24).

Due to the moderate-quality evidence available, clinical guidelines present a weak and cautious recommendation for use of CSs in patients with IgAN at high risk of progression to ESRD (3, 7). Clinical experts indicated that in clinical practice in England, CS use is reserved for people with nephrotic syndrome (2). Additional immunosuppression has not been reported to convey significant clinical improvements in patients with IgAN, with the exception of MMF in patients of Asian descent (99).

For patients with IgAN who progress to ESRD, treatment options are limited to dialysis or kidney transplantation, which substantially increase disease burden (Section B.1.3.1.7 to B.1.3.1.9) (3, 7, 20, 27, 28). Dialysis is associated with physical limitations, reductions in quality of life, and a high economic burden (29, 56-59, 70). Transplantation is associated with a risk of transplant failure, iatrogenic infection, and disease recurrence, estimated to occur in ~30% of recipients (27, 60, 61, 101).

Due to the high risk of lifetime progression to ESRD (Section B.1.3.1.4) and limited treatment choices, there remains a significant unmet need for safe and effective therapies which target the underlying mechanisms of IgAN. As a therapeutic option specifically developed to inhibit the pathogenetic process of IgA nephropathy at its source, while avoiding the toxicity of systemic glucocorticoids, the introduction of TRF-budesonide may address this unmet need.

B.1.4 Equality considerations

As presented in Section B.1.3.1.2, IgAN is more frequently diagnosed in males than females and in Caucasian and Asian populations compared with Black populations (22, 37). While the epidemiology of IgAN will affect the demographics of patients eligible for treatment with TRF-budesonide, the use of TRF-budesonide is not expected to raise any equality issues.

B.2 Clinical effectiveness

Overview

- NefIgArd Nef-301 is 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, and is presented in this submission
    - **Part B** completed in February 2023 and evaluated the effect of TRF-budesonide on long-term renal function preservation (data analyses expected to be completed in Q3/4 2023)
- This submission focuses on adult patients with primary IgAN with a baseline UPCR ≥1.5 g/g (a subpopulation of the NefIgArd Nef-301 trial), in line with the licensed indication of TRF-budesonide (1) and the decision problem defined in Section B.1.1

Clinical efficacy summary

- The results of the NefIgArd Nef-301 trial confirmed the efficacy of TRF-budesonide in significantly reducing proteinuria and slowing the decline in eGFR in patients with primary IgAN and a baseline UPCR ≥1.5 g/g who were already receiving optimised and stable RAS blockade
- Treatment with TRF-budesonide 16 mg/day provided statistically significant and clinically-relevant improvements in the primary efficacy endpoint, with a [redacted] reduction in UPCR after 9 months of treatment compared with placebo (95% CI: [redacted]; p=[redacted])
    - Published meta-analyses have demonstrated consistent associations between early reductions in proteinuria and lower risk of kidney function loss, progression to ESRD and mortality in patients with IgAN and CKD (102-106)
    - Proteinuria continued to improve during 3 months of untreated follow-up, with a [redacted] reduction in UPCR (95% CI: [redacted]; p=[redacted]) in patients who had received TRF-budesonide 16 mg/day compared with placebo

- Administration of TRF-budesonide 16 mg/day maintained kidney function during 9 months of treatment ([redacted]% eGFR decrease from baseline at 9 months; [redacted] mL/min/1.73 m^2 decrease), whereas patients receiving placebo experienced a [redacted]% deterioration in eGFR ([redacted] mL/min/1.73 m^2 decrease versus baseline; p=[redacted])
    - Of note, at 9 months of treatment with TRF-budesonide 16 mg/day, the absolute change from baseline in eGFR following 9 months was [redacted] mL/min/1.73 m^2 (in comparison to [redacted] for the placebo arm). This further demonstrates that treatment with TRF-budesonide may slow the progression to kidney failure
    - This eGFR treatment effect was maintained during the 3-month follow-up period after stopping TRF-budesonide 16 mg/day. A [redacted]% eGFR treatment benefit (p=[redacted]) vs placebo was observed at 12 months, highlighting a significant delay in the progression of kidney disease
- Results for the subgroup of patients with a baseline UPCR ≥1.5 g/g were generally consistent with the full trial population

Clinical safety summary

- The majority of AEs reported by patients who received TRF-budesonide 16 mg/day were mild to moderate ([redacted] in the TRF-budesonide 16 mg/day group and [redacted] in the placebo group experienced a severe treatment-emergent AE [TEAE]) and were in-line with the known safety profile of an oral budesonide product
- Importantly, no severe infections – which occur frequently during treatment with the use of systemic CSs (3, 7, 24-26) – were reported during treatment with TRF-budesonide, and there was no increase in overall infections compared with placebo ([redacted]% patients in the TRF-budesonide group vs [redacted]% patients in the placebo group experienced an infection)
- In total, [redacted] in the TRF-budesonide 16 mg group with a baseline UPCR ≥1.5 g/g and [redacted] in the placebo group discontinued study treatment due to a TEAE (up until 14 days after the last dose of study treatment). There were no deaths during the trial

B.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 D. A total of 51 individual publications were included in the SLR; of these, two studies were identified which provided relevant information on TRF-budesonide in patients with IgAN (6, 107, 108).

B.2.2 List of relevant clinical effectiveness evidence

The efficacy and safety of TRF-budesonide is being investigated in an ongoing clinical development program in patients with IgAN, a summary of which is provided in Table 4.

Results from Part A of the NefIgArd Nef-301 pivotal phase 3 study provides the efficacy and safety evidence relevant to the current submission and used to inform the economic model. Details of the ongoing studies of TRF-budesonide in patients with IgAN are provided in Section B.2.11.

Table 4: Clinical effectiveness evidence

Study	NefIgArd Nef-301 (NCT03643965)				NefIgArd-OLE (NCT04541043)		Nefigan Nef-202 (NCT01738035)		Phase 2a (NCT00767221)	
	Part A		Part B							
Primary sources	CSR (107), Barratt et al. 2023 (108)				Study protocol (109)		Fellström et al. 2017 (6)		Smerud et al. 2011 (110)	
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		Open-label, uncontrolled proof-of-concept study	
	Part A evaluated the efficacy and safety of TRF-budesonide		Part B is evaluating TRF-budesonide for long-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		• ≥18 years biopsy-confirmed primary IgAN • eGFR ≥45 mL/min per 1·73 m² • UPCR >0.5 g/g or urine protein ≥0.75 g/24-h		• >18 years • U-albumin >500 mg/day • S-creatinine <200 µmol/L	
Intervention(s)	Optimised RASi therapy plus TRF-budesonide 16 mg/day		No intervention		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)		Optimised RASi therapy plus TRF-budesonide 8 mg/day	
Comparator(s)	Optimised RASi therapy plus placebo									
Status	Completed		Completed February 2023. Data analyses expected to complete Q3/4 2023.		Ongoing (end date: May 2024)		Completed		Completed	
Indicate if study supports application for marketing authorisation	Yes	*X*	Yes		Yes		Yes	*X*	Yes	
	No		No	X	No	X	No		No	X

Study	NefIgArd Nef-301 (NCT03643965)				NefIgArd-OLE (NCT04541043)		Nefigan Nef-202 (NCT01738035)		Phase 2a (NCT00767221)	
	Part A		Part B							
Indicate if study used in the economic model	Yes	*X*	Yes		Yes		Yes		Yes	
	No		No	X	No	X	No	X	No	X
Rationale if study not used in model	Not applicable		Study ongoing – data not available		Study ongoing – data not available		Phase 2 study		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 2years (analysis to be performed when the last patient randomised has complete Visit 17b)		• 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		• Change in 24-h urine albumin excretion	
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		• 2-year eGFR slope • Time to 30% reduction from baseline in eGFR • Time to rescue medication • Ratio of UPCR, UACR, and eGFR compared with baseline averaged over time points between 12 and 24 months, inclusive • Proportion of patients without microhaematuria in at least two time points • Proportion of patients receiving rescue treatment • SF-36 at 9 and 24 months		• 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		• Changes in serum creatinine, eGFR and serum concentrations of IgA and IgA antibodies against gliadin • Safety endpoints	

Study	NefIgArd Nef-301 (NCT03643965)		NefIgArd-OLE (NCT04541043)	Nefigan Nef-202 (NCT01738035)	Phase 2a (NCT00767221)
	Part A	**Part B**			
	time points up to 12 months • 1-year eGFR slope • Safety variables	• Exploratory analyses on blood and urine Safety variables			

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: Calliditas Therapeutics AB. Data on file. Clinical study report Nef-301. 2021 (107); Calliditas Therapeutics AB. Data on file. Clinical study report Nef-301-OLE. (109); Fellström et al. 2017 (6); Smerud et al. 2011 (110).

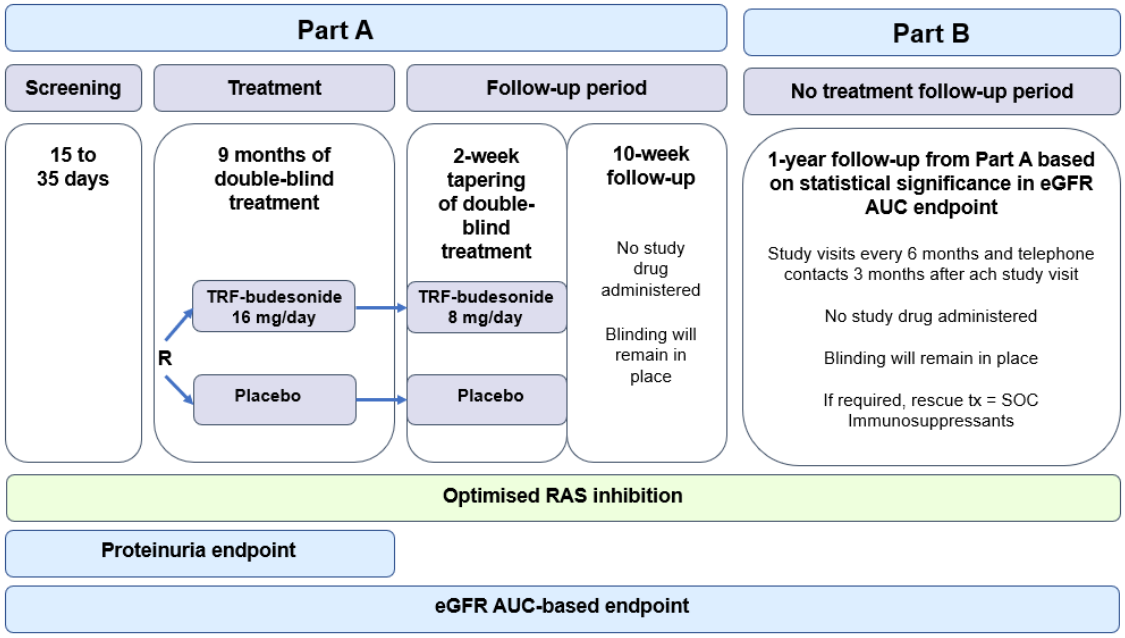
B.2.3 Summary of methodology of the relevant clinical effectiveness evidence: NefIgArd Nef-301

B.2.3.1 Summary of trial methodology

NefIgArd Nef-301 is a multinational, randomised, double-blind, placebo-controlled, multicentre clinical trial (NCT03643965) with a two-part design (Figure 11) (107). The aim was to evaluate the efficacy, safety, and tolerability of oral TRF-budesonide 16 mg/day compared with placebo in patients with primary IgAN treated with optimised RAS inhibition therapy. A placebo comparator was selected due to the lack of approved treatments for patients with IgAN at risk of progressing to ESRD.

The methodology of NefIgArd Nef-301 Part A, which constitutes the key evidence supporting this submission, is provided in Table 5. The trial included adult patients with primary IgAN, however, this submission focuses on adult patients with primary IgAN with a UPCR ≥1.5 g/g in line with the licensed indication (1).

Figure 11: NefIgArd Nef-301 phase 3 trial design



Abbreviations: AUC, area under the curve; eGFR, estimated glomerular filtration rate; R, randomisation; RAS, renin-angiotensin system; SoC, standard of care; TRF, targeted-release formulation; tx, treatment.
Source: Adapted form Calliditas Therapeutics AB. Data on file. Clinical study report Nef-301. 2021 (107).

Table 5: Summary of NefIgArd Nef-301 (NCT03643965) Part A methodology

Study	NefIgArd Nef-301 (NCT03643965) Part A
Study objective	The primary objective of Part A of NefIgArd Nef-301 was to assess the effect of TRF-budesonide 16 mg/day treatment on urine UPCR over 9 months compared with placebo.
Trial design	Multinational, randomised, double-blind, placebo-controlled, multicentre clinical trial.
Duration of study	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 5 October 2020; the Part A DCO was scheduled to occur once the first 201 randomised patients had had the opportunity to complete their 9-month visit.
Method of randomisation	Patients were randomised 1:1, 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).
Method of blinding (care provider, patient, and outcome assessor)	Double blinded study, i.e. the patients, investigators, and site staff conducting study procedures, evaluating patients, entering study data, and/or evaluating study data were blinded to treatment assignment
Eligibility criteria for participants	**Key inclusion 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 **Key exclusion criteria** • Other causes of mesangial IgA deposition, other glomerulopathies, nephrotic syndrome • Recipients of a kidney transplant

Study	NefIgArd Nef-301 (NCT03643965) Part A
	• 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 CSs 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 • 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
Settings and locations where the data were collected	NefIgArd Nef-301 is being conducted across 155 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.
Trial drugs (the interventions for each group with sufficient details to allow replication, including how and when they were administered) Intervention(s) (n=[x]) and comparator(s) (n=[x])	**Study 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). 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). **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.

Study	NefIgArd Nef-301 (NCT03643965) Part A
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 CSs 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 Excluded medications: • Systemic immunosuppressive drugs (including CSs), 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 - patients were also instructed to avoid grapefruit and grapefruit juice • Patients were to avoid starting new medications and making changes to existing medications
Primary outcomes (including scoring methods and timings of assessments)	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, and 12 months to describe the time course of effect.
Other outcomes used in the economic model/specified in the scope	• Ratio of eGFR at 3, 6, 9, and 12 months compared with baseline calculated using the CKD-EPI formula • Ratio of UACR at 3, 6, 9, and 12 months compared with baseline • 1-year eGFR slope • Treatment-emergent adverse events assessed at all visits • Adverse events of special interest assessed at all visits • SF-36 quality of life assessment at 9 months

Study	NefIgArd Nef-301 (NCT03643965) Part A
Pre-planned subgroups	The pre-defined subgroups for the Part A primary endpoint and eGFR at 9 months were: • Age (<45 years, or ≥45 and <65 years) • Gender (male or female) • Region (Europe or North America) • Baseline proteinuria (<2 g/24 hours or ≥2 g/24 hours) • Baseline eGFR (<60 mL/min/1.73 m^2 or ≥60 mL/min/1.73 m^2) • Dose of RAS inhibitor therapy (ACEis and/or ARBs) with patients split into three groups: <50%, ≥50% to <80% and ≥80% of the maximum allowed dose • Subgroup analyses of eGFR according to weight (<85 kg or ≥85 kg) and baseline UPCR (<1.5 g/g or ≥1.5 g/g) were added post hoc.

Abbreviations: ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CKD-EPI, chronic kidney disease epidemiology collaboration equation; DBP, diastolic blood pressure; DCO, data cut-off; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; CS, corticosteroid; GI, gastrointestinal; IgA, immunoglobulin A; IgAN, immunoglobulin A nephropathy, KDIGO, Kidney Disease: Improving Global Outcomes; MTD, maximum tolerated dose, RAS, renin-angiotensin system; SBP, systolic blood pressure; SF-36, Short Form 36; TRF, targeted-release formulation; UACR, urine albumin to creatinine ratio; UK, United Kingdom; UPCR, urine protein to creatinine ratio; US, United States; 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 MTD according to the 2012 KDIGO guideline were permitted if an attempt to reach the maximum allowed dose or MTD had been performed or if such attempt was deemed unsafe for the patient by the Investigator.
Source: Calliditas Therapeutics AB. Data on file. Clinical study report Nef-301. 2021 (107).

B.2.3.2 Appropriateness of the efficacy outcomes assessed

Assessing the efficacy of treatments for IgAN is complicated by the long-term nature of disease progression in the majority of patients (102, 103). The evaluation of treatment efficacy therefore relies on the use of surrogate endpoints (3, 102, 106).

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 (2, 3, 102, 106). 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 (102, 103, 105, 106, 111). 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% (111). 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 (103). A study by Inker et al. 2021 (104) 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.

Glomerular filtration rate is generally considered the most useful overall measure of kidney function, with CKD stages defined by eGFR levels (2, 106). 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, 44, 112, 113). As a severe reduction in eGFR is defined as kidney failure, by definition, a decline in eGFR is representative of progression to kidney failure (106). 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 (3, 106, 114). In addition, in a meta-analysis of 13 IgAN clinical trials, 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 (115). The study reported that a sustained effect on eGFR slope provided a clear indication of a disease-modifying treatment effect (115).

As UPCR and eGFR are considered to be suitable markers of long term clinical benefit, it is assumed that the treatment effects in Part A of NefIgArd Nef-301 will not only translate into improvements in later clinical endpoints, but will also translate into a statistically significant and clinically meaningful improvement for the Part B primary endpoint. This has been confirmed, with a statistically significant ($p<0.0001$) benefit over placebo in eGFR observed over the 2-year period of 9-months of treatment with TRF-budesonide or placebo and 15-months of follow-up off drug in initial analyses of Part B of NefIgArd Nef-301 (116).

B.2.3.3 Baseline characteristics and demographics

The baseline patient demographics, disease, and treatment characteristics for patients with UPCR ≥1.5 g/g at baseline are presented in Table 6.

Demographic and disease characteristics were balanced between treatment groups. The proportion of men ([redacted]%) and women ([redacted]%) was consistent with that expected for a predominately White ([redacted]%) IgAN patient population (117, 118), with half ([redacted]%) of all patients aged <45 years. Median UPCR at baseline was [redacted] g/g; [redacted]% of patients had baseline proteinuria of ≥2 g/day, and kidney function was mildly-to-moderately impaired overall (median eGFR: [redacted] ml/min/1.73 m^2). In addition, most patients ([redacted]%) had micro-haematuria at baseline, detected by dipstick.

Table 6: Baseline characteristics of patients with UPCR ≥1.5 g/g at baseline in NefIgArd Nef-301 Part A

Characteristic	TRF-budesonide 16 mg (n=[redacted])	Placebo (n=[redacted])	Total (n=[redacted]
Median age (range), years	[redacted]	[redacted]	[redacted]
Age distribution, n (%)			
<45 years	[redacted]	[redacted]	[redacted]
≥45 and <65 years	[redacted]	[redacted]	[redacted]
≥65 years	[redacted]	[redacted]	[redacted]
Sex, n (%)			
Male	[redacted]	[redacted]	[redacted]
Female	[redacted]	[redacted]	[redacted]
Childbearing potential (female only), n (%)			
n[†]	[redacted]	[redacted]	[redacted]
Yes	[redacted]	[redacted]	[redacted]
No	[redacted]	[redacted]	[redacted]
Race, n (%)			
White	[redacted]	[redacted]	[redacted]
Asian	[redacted]	[redacted]	[redacted]
Black or African American	[redacted]	[redacted]	[redacted]
Other	[redacted]	[redacted]	[redacted]
Weight, kg			
Median (IQR)	[redacted]	[redacted]	[redacted]
Min, max	[redacted]	[redacted]	[redacted]
BMI, kg/m^2			
Median (IQR)	[redacted]	[redacted]	[redacted]
Min, max	[redacted]	[redacted]	[redacted]
SBP, mmHg			
Median (IQR)	[redacted]	[redacted]	[redacted]
Min, max	[redacted]	[redacted]	[redacted]
DBP, mmHg			
Median (IQR)	[redacted]	[redacted]	[redacted]
Min, max	[redacted]	[redacted]	[redacted]
UPCR (g/g), median (IQR)	[redacted]	[redacted]	[redacted]
UACR (g/g), median (IQR)	[redacted]	[redacted]	[redacted]
Proteinuria, g/day, median (IQR)	[redacted]	[redacted]	[redacted]
Proteinuria, n (%)			

Characteristic	TRF-budesonide 16 mg (n=[redacted])	Placebo (n=[redacted])	Total (n=[redacted]
<2 g/day	[redacted]	[redacted]	[redacted]
≥2 and ≤3.5 g/day	[redacted]	[redacted]	[redacted]
>3.5 g/day	[redacted]	[redacted]	[redacted]
eGFR (CKD-EPI), mL/min/1.73 m^2			
eGFR (CKD-EPI), mL/min/1.73 m^2, median (IQR)	[redacted]	[redacted]	[redacted]
Time from IgAN diagnosis to trial entry, years			
n†	[redacted]	[redacted]	[redacted]
Median (IQR)	[redacted]	[redacted]	[redacted]
Patients with prior CS or immunosuppressive use, n (%)	[redacted]	[redacted]	[redacted]
Use of any RAS inhibitor therapy, n (%)			
Patients on either ACEi or ARB	[redacted]	[redacted]	[redacted]
Patients on ACEi alone	[redacted]	[redacted]	[redacted]
Patients on ARB alone	[redacted]	[redacted]	[redacted]
Patients on both ACEi and ARB	[redacted]	[redacted]	[redacted]

Abbreviations: ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin II type I receptor blocker; BMI, body-mass index; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; FAS, full analysis set; CS, corticosteroid; IgAN, immunoglobulin A nephropathy; IQR, interquartile range; max, maximum; min, minimum; RAS, renin-angiotensin system; SAS, safety analysis set; SBP, systolic blood pressure; TRF, targeted-release formulation; UACR, urine albumin to creatinine ratio.
† Number of participants recorded if different from the full sets for the subgroup.
Baseline was defined as the last measurement prior to the first dose of study drug. Baseline for SBP and DBP was defined as the arithmetic mean of all measurements prior to the first dose of study drug. Baseline proteinuria and eGFR, were calculated as the geometric mean of the two consecutive measurements prior to randomisation.
Source: Calliditas Therapeutics AB. Data on file. Additional data from NefIgArd for baseline UPCR ≥1.5 g/g subgroup. Table 14.1.3.2d.2022 (119).

B.2.3.4 Expert elicitation/opinion

UK clinical and health economic expert opinion was sought to support the submission for TRF-budesonide for the treatment of patients with IgAN, with expert opinion collected at an advisory board meeting in February 2023. Six experts participated (3 clinicians and 3 health economic experts). The criteria for selecting suitable experts were expertise and experience of treating IgAN in the UK (clinician) and specialised technical expertise in economic evaluation and health technology assessment (HTA; health economic expert).

Experts were provided with pre-read material prior to the advisory board which contained an overview of IgAN and the current UK treatment landscape, TRF-budesonide clinical trial data, and TRF-budesonide health economic model information. The objective of the advisory board was to discuss the robustness of the clinical data and assumptions informing economic modelling to ensure the models and supporting evidence are appropriate for submission to UK HTA agencies. The goals were as follows:

- Assess the clinical evidence and clinical positioning of TRF-budesonide in the treatment pathway for IgAN in England (TRF-budesonide clinical evidence and treatment positioning)
- Validate the cost-effectiveness model, model inputs and test model assumptions (Cost-effectiveness model validation)

Topics for which further clarification was required were followed-up via email communication with the relevant attendee.

For full details of the advisory board refer to the relevant Britannia Pharmaceuticals report (data on file (2)).

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

B.2.4.1 Populations analysed

The following analysis sets were defined for the NefIgArd Nef-301 study Part A:

- The Part A full analysis set (FAS, n=197), which included all patients who had received at least one dose of study drug, provided an evaluation of efficacy and safety in a population of patients who had the opportunity to receive the full 9-month treatment regimen
- The Part A safety analysis set (SAS, n=294), which included all randomised patients who had received at least one dose of study drug as of the data cut-off (DCO), was presented for completeness
- The Part A per protocol set included all data from patients in the FAS for whom no protocol deviations occurred during the study period that were considered to

have the potential to impact the efficacy evaluation. The Part A Per Protocol Set was determined through blinded review prior to Part A database lock

The evaluation of the efficacy of TRF-budesonide in patients with a baseline UPCR of ≥1.5 g/g was a subgroup analysis in the NefIgArd Nef-301 study. The TRF-budesonide indication is for the treatment of adult patients with primary IgAN at risk of rapid disease progression with a UPCR ≥1.5 g/g (1), the results for this patient population are presented in the main body of this submission. A summary of the results for the FAS is presented in Appendix D.

In all efficacy analyses, any data impacted by rescue medication were excluded.

B.2.4.2 Statistical analysis

Based on the NefIgArd NEF-202 study (phase 2b, double-blind, randomised controlled trial [RCT]), 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%.

All statistical analyses were performed in SAS™. All efficacy endpoints, apart from eGFR 1-year slope, were log-transformed prior to analysis. UPCR and UACR were analysed using a mixed-effect model for repeated measures, including baseline, 3-, 6-, 9-, and 12-month data. Baseline UPCR was included as a covariate and was calculated as the geometric mean of the 2 pre-randomisation UPCR measurements and log-transformed prior to inclusion in the analysis model. The model also included terms for treatment group, visit, log(baseline)-by-visit, and visit-by-treatment group interaction. A common unstructured covariance structure was used to model the within-patient errors. The Kenward-Roger's degrees of freedom adjustment was used. Restricted maximum likelihood was used to obtain parameter estimates.

eGFR analyses at 9 and 12 months were performed using robust regression with Huber weights and a cut-off value of 2 with sequentially multiply imputed missing data. The imputation model for eGFR included treatment, baseline eGFR, and the 3, 6, 9, and 12-month eGFR values.

B.2.4.3 Sample size and power calculation

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. 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 (107).

B.2.4.4 Sensitivity analyses and other supportive analyses

Pre-defined sensitivity analyses were performed for the FAS dataset to assess the robustness of the analysis of UPCR at 9 months; results presented in Appendix M. No sensitivity analyses were performed for the sub population with a baseline UPCR ≥1.5 g/g, which is the focus of this submission.

B.2.4.5 Data management and 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 was documented in the electronic case report form. If a patient withdrew prematurely from the study, study staff were to make every effort to complete an Early Termination Visit if the patient discontinued prior to completion of Study Visit 11, or an End of Study Visit if the patient discontinued after completion of Study Visit 11 but prior to completion of Part B.

For continuous endpoints to be analysed using the Mixed-Effects Model for Repeated Measures (MMRM), no explicit imputation of missing data was needed, as the MMRM analysis was performed on observed cases and implicitly imputes missing data.

B.2.4.6 Participant flow in the relevant randomised controlled trials

In total, of patients with a baseline UPCR of ≥1.5 g/g, [redacted] treated with TRF-budesonide and [redacted] treated with placebo completed the 9-month treatment period and 3-month follow-up period. For further details, please refer to Appendix M.

B.2.5 Critical appraisal of the relevant clinical effectiveness evidence

NefIgArd Nef-301 was performed in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines, under the auspices of an independent data and safety monitoring committee (107).

A complete quality assessment of NefIgArd Nef-301 in accordance with the NICE-recommended checklist for the assessment of bias in RCTs is presented in Table 7. The risk of bias in the NefIgArd Nef-301 study is confirmed as being low.

Table 7: Quality assessment results for NefIgArd Nef-301

Trial name	NefIgArd Nef-301
Was randomisation carried out appropriately?	Yes
Was the concealment of treatment allocation adequate?	Unclear
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 drop-outs 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).

B.2.6 Clinical effectiveness results of the relevant studies

B.2.6.1 NefIgArd Nef-301

The indication for TRF-budesonide is for the treatment of adult patients with primary IgAN at risk of rapid disease progression with a UPCR ≥1.5 g/g (1). Therefore, the results for this patient population are presented in the main body of this submission. A summary of the results for the FAS patient population is presented in Appendix M.

B.2.6.1.1 Change in UPCR from baseline

After 9 months of treatment, the ratio of UPCR compared with baseline was [redacted] for patients with a baseline UPCR ≥1.5 g/g treated with TRF-budesonide 16 mg/day and [redacted] for those who received placebo (Table 8). This equated to a statistically significant and clinically-relevant [redacted]% reduction in UPCR for patients treated with TRF-budesonide 16 mg/day compared with placebo (95% CI: [redacted]; p=[redacted]).

A reduction of UPCR from baseline with TRF-budesonide 16 mg/day was seen at all timepoints, including during 3-months of untreated follow-up (Table 9; Figure 12). At the 12-month timepoint (after 3 months of observational follow-up following the 9-month treatment period), UPCR was [redacted]% lower with TRF-budesonide 16 mg/day compared with placebo (95% CI: [redacted]; p=[redacted]). The reduction in UPCR compared with placebo observed following treatment with TRF-budesonide may translate to a delay in the progression of CKD, as a reduction in proteinuria has been consistently associated with corresponding beneficial effects on progression to ESRD and mortality in patients with IgAN (102, 103, 105, 106, 111).

Table 8: Analysis of the UPCR (g/g) at 9 months compared with baseline in patients with a baseline UPCR ≥1.5 g/g in NeflgArd Nef-301 Part A

	TRF-budesonide 16 mg/day† n=	Placebo† n=
Ratio of geometric LS mean UPCR at 9 months compared with baseline (95% CI)		
Corresponding % reduction (95% CI)		
TRF-budesonide vs placebo		
Ratio of geometric LS mean UPCR at 9 months compared with baseline (95% CI)		
Corresponding % reduction (95% CI)		
p value		

Abbreviations: CI, confidence interval; LS, least squares; RAS, renin-angiotensin system; TRF, targeted-release formulation; UPCR, urine protein to creatinine ratio.
† Treatment in addition to RAS inhibition.
Source: Calliditas Therapeutics AB. Data on file. Additional data from NeflgArd for baseline UPCR ≥1.5 g/g subgroup. Table 2.7.3.3.1a.2022 (119).

Table 9: Analysis of UPCR (g/g) at 3, 6, 9, and 12 months using MMRM for patients with a baseline UPCR ≥1.5 g/g in NeflgArd Nef-301 Part A

Timescale	Ratio of geometric LS mean UPCR compared with baseline (95% CI)		Comparison of TRF-budesonide 16 mg/day† vs placebo†; ratio of geometric LS means (95% CI); p value	Corresponding % change‡
	TRF-budesonide (n=)	Placebo (n=)		
3 months				
6 months				
9 months				
12 months				

Abbreviations: CI, confidence interval; LS, least squares; MMRM, mixed-effects model for repeated measures; RAS, renin-angiotensin system; TRF, targeted-release formulation; UPCR, urine protein to creatinine ratio.
† Treatment in addition to RAS inhibition.
‡ Calculated as (1 – ratio) of LS means * 100.
Source: Calliditas Therapeutics AB. Data on file. Additional data from NeflgArd for baseline UPCR ≥1.5 g/g subgroup. Table 2.7.3.3.1a.2022 (119).

Figure 12: Percentage change in UPCR (g/g) from baseline in patients with a baseline UPCR ≥1.5 g/g in NeflgArd Nef-301 Part A

Abbreviations: TRF, targeted-release formulation; UPCR, urine protein to creatinine ratio.
Source: Calliditas Therapeutics AB. Data on file. Additional data from NeflgArd for baseline UPCR ≥1.5 g/g subgroup. Figure 2.7.3.3.1a. 2022 (119).

B.2.6.1.2 Change in UACR compared with baseline

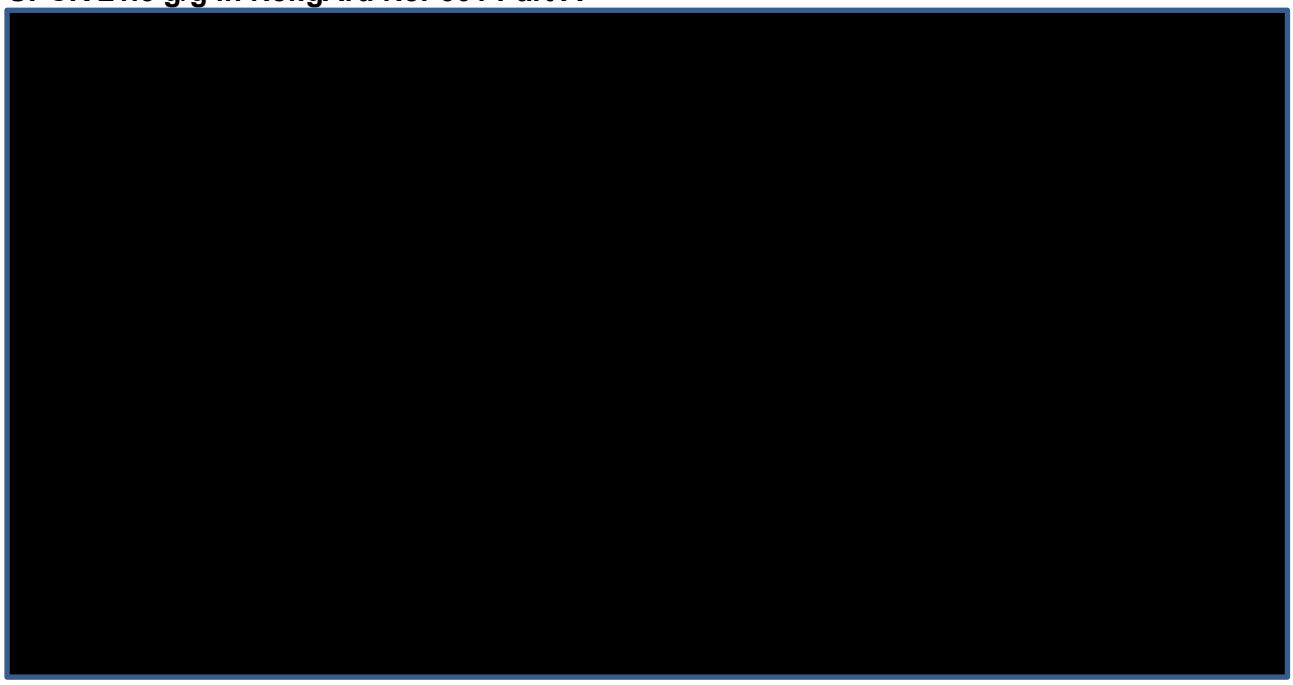
UACR, like UPCR, is a measure of proteinuria - a surrogate endpoint for improved outcomes in IgAN (2, 3, 102, 106). Consistent with the primary endpoint, after 9 months of treatment, patients with a baseline UPCR ≥1.5 g/g treated with TRF-budesonide 16 mg per day showed a statistically significant and clinically-relevant [redacted]% reduction in UACR compared with placebo (95% CI: [redacted]; p=[redacted]; Table 10; Figure 12), demonstrating a delay in disease progression. After 3 months of observational follow-up, a [redacted]% reduction in UACR with TRF-budesonide 16 mg was observed at 1 year compared with placebo (p=[redacted]; Table 10).

Table 10: Analysis of UACR (g/g) at 3, 6, 9, and 12 months compared with baseline using MMRM in patients with a baseline UPCR ≥1.5 g/g in NeflgArd Nef-301 Part A

Timescale	Ratio of geometric LS mean UACR at 9 months compared with baseline (95% CI)		Comparison of TRF-budesonide 16 mg/day† vs placebo†; ratio of geometric LS means (95% CI); p value	Corresponding % change‡
	TRF-budesonide (n=[redacted])	Placebo (n=[redacted])		
3 months	[redacted]	[redacted]	[redacted]	[redacted]
6 months	[redacted]	[redacted]	[redacted]	[redacted]
9 months	[redacted]	[redacted]	[redacted]	[redacted]
12 months	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CI, confidence interval; FAS, full analysis set; LS, least squares; MMRM, mixed-effects model for repeated measures; RAS, renin-angiotensin system; TRF, targeted-release formulation; UACR, urine albumin to creatinine ratio; UPCR, urine protein to creatinine ratio.
† Treatment in addition to RAS inhibition.
‡ Calculated as (1 – ratio) of LS means * 100.
Source: Calliditas Therapeutics AB. Data on file. Additional data from NeflgArd for baseline UPCR ≥1.5 g/g subgroup. Table 2.7.3.3.5g.2022 (119).

Figure 13: Percentage change in UACR (g/g) from baseline in patients with a baseline UPCR ≥1.5 g/g in NeflgArd Nef-301 Part A



Abbreviations: TRF, targeted-release formulation; UACR, urine albumin to creatinine ratio; UPCR, urine protein to creatinine ratio.
Source: Calliditas Therapeutics AB. Data on file. Additional data from NeflgArd for baseline UPCR ≥1.5 g/g subgroup. Figure 14.2.2.5.3f.2022 (119).

B.2.6.1.3 Ratio of eGFR compared with baseline

After 9 months of treatment, a statistically significant and clinically-relevant benefit on eGFR was observed with TRF-budesonide 16 mg/day compared with placebo for patients with a baseline UPCR of ≥1.5 g/g (Table 11). Kidney function changed very little in patients who received TRF-budesonide 16 mg/day ([redacted]% eGFR decrease from baseline at 9 months; [redacted] mL/min/1.73 m^2 decrease), demonstrating a statistically significant delay in the progression of kidney disease compared with patients who received placebo ([redacted]% eGFR decrease from baseline at 9 months; [redacted] mL/min/1.73 m^2 decrease versus baseline; p=[redacted]).

The eGFR treatment benefit for TRF-budesonide 16 mg/day versus placebo continued after 3 months of non-treated follow-up; the estimated difference in absolute change in eGFR from baseline for TRF-budesonide vs placebo was [redacted] mL/min/1.73 m^2 at the 12 month timepoint (Table 12; Figure 14).

Table 11: Analysis of the ratio of eGFR (mL/min/1.73 m^2) at 9 months in patients with a baseline UPCR ≥1.5 g/g in NeflgArd Nef-301 Part A

	TRF-budesonide 16 mg/day† n=	Placebo† n=
Ratio of geometric LS mean eGFR at 9 months compared with baseline (95% CI)		
Corresponding % change (95% CI)		
Estimated absolute change from baseline (mL/min/1.73 m^2)		
TRF-budesonide vs placebo		
Ratio of geometric LS mean eGFR at 9 months compared with baseline (95% CI)		
p value		
Estimated difference in absolute change (mL/min/1.73 m^2)		

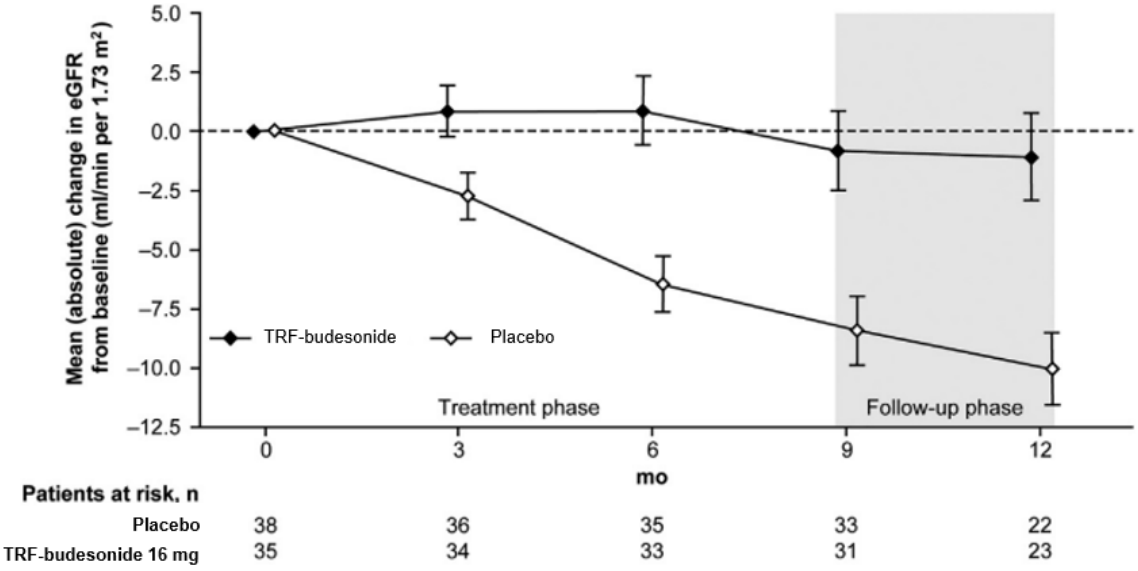
Abbreviations: CI, confidence interval; eGFR, estimated glomerular filtration rate; FAS, full analysis set; LS, least squares; RAS, renin-angiotensin system; TRF, targeted-release formulation.
† Treatment in addition to RAS inhibition.
Source: Calliditas Therapeutics AB. Data on file. Additional data from NeflgArd for baseline UPCR ≥1.5 g/g subgroup. Table 2.7.3.3.3h.2022 (119).

Table 12: Analysis of the ratio of eGFR (CKD-EPI) (mL/min/1.73 m^2) at 3, 6, 9, and 12 months compared with placebo using robust regression in patients with a baseline UPCR ≥1.5 g/g in NeflgArd Nef-301 Part A

Timepoint	Comparison of TRF-budesonide 16 mg/day† vs placebo†		
	Ratio of geometric LS means (95% CI); p value	Corresponding % change‡	Difference in absolute change (mL/min/1.73 m^2)
3 months			
6 months			
9 months			
12 months			

Abbreviations: CI, confidence interval; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; eGFR, estimated glomerular filtration rate; FAS, full analysis set; LS, least squares; RAS, renin-angiotensin system; TRF, targeted-release formulation.
† Treatment in addition to RAS inhibition.
‡ Calculated as (1 – ratio) of LS means * 100.
Source: Calliditas Therapeutics AB. Data on file. Additional data from NeflgArd for baseline UPCR ≥1.5 g/g subgroup. Table 2.7.3.3.3h.2022 (119).

Figure 14: Percentage change in eGFR (CKD-EPI) (mL/min/1.73 m^2) from baseline in patients with a baseline UPCR ≥1.5 g/g in NefIgArd Nef-301 Part A



Abbreviations: BL, baseline; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; eGFR, estimate glomerular filtration rate; od, once daily; TRF, targeted-release formulation; UPCR, urine protein to creatinine ratio.
Note: Baseline was defined as the geometric mean of the two consecutive measurements prior to randomisation. Mean changes ± standard error of eGFR (CKD-EPI) were estimated from robust regression analysis back transforming log-transformed post-baseline to baseline ratios at 3, 6, 9, and 12 months.
Source: Barratt et al. 2023 (108).

B.2.6.1.4 Decline in eGFR at 1-year eGFR (total slope)

The results of the supportive analysis of 1-year eGFR total slope for patients with baseline UPCR ≥1.5 g/g are presented in Table 13. Treatment with TRF-budesonide 16 mg/day provided an improvement in slope of [redacted] mL/min/1.73 m^2 per year compared with placebo (95% CI: [redacted]; p=[redacted]). This corresponded to a least squares mean 1-year eGFR slope of [redacted] mL/min/1.73 m^2 per year in the TRF-budesonide 16 mg/day group and of [redacted] mL/min/1.73 m^2 in the placebo group. As a treatment effect on 1-year eGFR slope has been demonstrated to be a major, independent predictor of treatment effect on long-term clinical outcomes in IgAN (115), the results presented indicate that TRF-budesonide provided a disease-modifying treatment effect.

Table 13: Supportive analysis of 1-year eGFR (CKD-EPI) (mL/min/1.73 m^2 per year) total slope for the of patients with baseline UPCR ≥1.5 g/g

1-year eGFR slope	TRF-budesonide 16 mg/day† n=[redacted]	Placebo† n=[redacted]
LS mean	[redacted]	[redacted]
95% CI LS mean	[redacted]	[redacted]
TRF-budesonide vs placebo		
Difference in LS means vs placebo	[redacted]	
95% CI difference in LS means vs placebo	[redacted]	
p value vs placebo	[redacted]	

Abbreviations: CI, confidence interval; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; eGFR, estimated glomerular filtration rate; FAS, full analysis set; LS, least squares; RAS, renin-angiotensin system; TRF, targeted-release formulation.
† Treatment in addition to RAS inhibition.
Source: Calliditas Therapeutics AB. Data on file. Additional data from NefIgArd for baseline UPCR ≥1.5 g/g subgroup. Table 2.7.3.3.7f.2022 (119).

B.2.6.1.5 TRF-budesonide humanistic value

No improvements in health-related quality of life (HRQoL), assessed using the short form 36 (SF-36) tool, were observed in either the TRF-budesonide or placebo groups following the 9-month treatment period, when compared with baseline (Table 14). However, it should be noted that the SF-36 is a generic HRQoL measure without any domains specific to kidney disease, as opposed to tool specific to people with kidney disease, which may be more sensitive to potential changes in response to therapy.

As outlined in Section B.1.3.1.8, the humanistic burden of IgAN is typically observed in late-stage kidney disease (56, 66-69); the physical and mental health burden of IgAN increases with disease progression, particularly when dialysis becomes necessary (21). It is anticipated that the clinical benefits of TRF-budesonide in significantly reducing proteinuria and slowing the decline in eGFR (outlined in the above sections) would in turn reduce the risk of HRQoL decline associated with ESRD and dialysis in patients with primary IgAN and a baseline UPCR ≥1.5 g/g.

Table 14: Analysis summary of SF-36v2 scores for the of patients with baseline UPCR ≥1.5 g/g

Subscale		TRF-budesonide 16 mg/day† (n=[redacted])	Placebo† (n=[redacted])
Bodily Pain	Baseline, mean (SD)	[redacted]	[redacted]
	Month 9, mean (SD)	[redacted]	[redacted]
	Change from baseline, mean (SD)	[redacted]	[redacted]
General Health	Baseline, mean (SD)	[redacted]	[redacted]
	Month 9, mean (SD)	[redacted]	[redacted]
	Change from baseline, mean (SD)	[redacted]	[redacted]
Mental Health Summary Measure	Baseline, mean (SD)	[redacted]	[redacted]
	Month 9, mean (SD)	[redacted]	[redacted]
	Change from baseline, mean (SD)	[redacted]	[redacted]
Mental Health Norm-Based Score	Baseline, mean (SD)	[redacted]	[redacted]
	Month 9, mean (SD)	[redacted]	[redacted]
	Change from baseline, mean (SD)	[redacted]	[redacted]
Physical Health Summary Measure	Baseline, mean (SD)	[redacted]	[redacted]
	Month 9, mean (SD)	[redacted]	[redacted]
	Change from baseline, mean (SD)	[redacted]	[redacted]
Physical Function	Baseline, mean (SD)	[redacted]	[redacted]
	Month 9, mean (SD)	[redacted]	[redacted]
	Change from baseline, mean (SD)	[redacted]	[redacted]
Role-Emotional	Baseline, mean (SD)	[redacted]	[redacted]
	Month 9, mean (SD)	[redacted]	[redacted]
	Change from baseline, mean (SD)	[redacted]	[redacted]
Role-Physical	Baseline, mean (SD)	[redacted]	[redacted]
	Month 9, mean (SD)	[redacted]	[redacted]
	Change from baseline, mean (SD)	[redacted]	[redacted]
Social Function	Baseline, mean (SD)	[redacted]	[redacted]
	Month 9, mean (SD)	[redacted]	[redacted]
	Change from baseline, mean (SD)	[redacted]	[redacted]
Vitality	Baseline, mean (SD)	[redacted]	[redacted]

Subscale		TRF-budesonide 16 mg/day† (n=[redacted])	Placebo† (n=[redacted])
	Month 9, mean (SD)	[redacted]	[redacted]
	Change from baseline, mean (SD)	[redacted]	[redacted]

Abbreviations: SD, standard deviation; TRF, targeted-release formulation; UPCR, urine protein to creatinine ratio.
† Treatment in addition to RAS inhibition.
Source: Calliditas Therapeutics AB. Data on file. Additional data from NeflgArd for baseline UPCR ≥1.5 g/g subgroup. Table 14.2.1.4.1a.2022 (119).

B.2.7 Subgroup analysis

Subgroup analyses of patients with a baseline UPCR ≥1.5 g/g were not conducted.

B.2.8 Meta-analysis

No meta-analysis has been conducted as results from only one study (107, 108) are included in this submission.

B.2.9 Indirect and mixed treatment comparisons

As outlined in section B.1.1, the comparator considered relevant for this submission is current SoC for IgAN, which includes: blood pressure management, maximally tolerated dose of ACEi/ARB, lifestyle modification, and addressing cardiovascular risk.

Part A of the NefIgArd Nef-301 study compared the efficacy, safety, and tolerability of oral TRF-budesonide with placebo (i.e. SoC) in patients with primary IgAN treated with optimised RAS inhibition therapy (107, 108). It provides sufficient comparative evidence vs SoC; as such, an indirect treatment comparison (ITC) was not deemed necessary.

As described in the above sections (section B.1.3.2), patients with IgAN may also receive SLGT2 inhibitors as part of their SoC regimen for cardiovascular protection (2). Specifically, dapagliflozin, which has received NICE approval for the treatment of CKD (TA775) (4), is also anticipated to be used in patients with IgAN (2). The findings of the DAPA-CKD study (120) suggest that dapagliflozin treatment in patients with IgAN (N=270) did not have a statistically significant impact on eGFR over 36 months compared with placebo. The least mean squares eGFR slopes from baseline to end of treatment in the dapagliflozin and placebo groups were -3.5 (standard error [SE], 0.5) and -4.7 (SE, 0.5) mL/min/1.73 m^2 per year, respectively, resulting in an insignificant between-group difference of 1.2 mL/min/1.73 m^2 per year (95% CI: -0.12, 2.51 mL/min/1.73 m^2 per year). Based on this, it can be inferred that the efficacy of SoC is not impacted by the inclusion of SGLT2 inhibitors in this population; therefore, conducting an ITC of TRF-budesonide vs SoC including dapagliflozin was not relevant.

Immunosuppressive agents were not considered to be relevant comparators for TRF-budesonide, and an ITC was not considered to be relevant to this submission. This was based on clinical expert opinion indicating that in England, the use of immunosuppressive agents (CSs and MMF) is not advised due to their uncertain benefit-to-risk ratio (2).

B.2.10 Adverse reactions

B.2.10.1 Overview of safety in NeflgArd Nef-301

Overall, the 9-month treatment regimen of TRF-budesonide was well tolerated (119). Of the patients with a baseline UPCR ≥1.5 g/g, [redacted] of [redacted] ([redacted]%) patients in the TRF-budesonide 16 mg/day group and [redacted] of [redacted] ([redacted]%) patients in the placebo group reported TEAEs, up until 14 days after the last dose of study treatment (Table 15). The TEAE incidence rates were slightly lower in the SAS with baseline UPCR ≥1.5 g/g; [redacted] of [redacted] ([redacted]%) patients in the TRF-budesonide 16 mg/day group and [redacted] of [redacted] ([redacted]%) patients in the placebo group reported AEs.

The majority of TEAEs were of mild or moderate severity and reversible (Table 15). [redacted] in the TRF-budesonide 16 mg group and [redacted] in the placebo group experienced an AE graded severe. The frequencies of TEAEs in patients with baseline UPCR ≥1.5 g/g considered likely to be study treatment-related by the Investigator were higher in the TRF-budesonide 16 mg/day group compared with the placebo group ([redacted] with TRF-budesonide 16 mg/day, [redacted] with placebo).

The most commonly reported TEAEs with a >5% greater incidence were peripheral oedema, hypertension, headache, muscle spasms, nausea, increased weight, cushingoid, dermatitis, vomiting and increased white blood cell count. Notably, no severe infections were reported during treatment with TRF-budesonide and there was no increased incidence of infections with TRF-budesonide 16 mg/day ([redacted]) versus placebo ([redacted]).

The AE profile of TRF-budesonide was consistent between patients with baseline UPCR ≥1.5 g/g and the full trial population (Table 15).

B.2.10.2 Serious AEs in patients with a baseline UPCR ≥1.5 g/g

Of the patients with a baseline UPCR ≥1.5 g/g, [redacted] patients reported [redacted] treatment-emergent SAEs: [redacted] patients in the TRF-budesonide 16 mg/day group and [redacted] patients in the placebo group.

B.2.10.3 Discontinuations and deaths in patients with a baseline UPCR ≥1.5 g/g

In total, [redacted] in the TRF-budesonide 16 mg group with a baseline UPCR ≥1.5 g/g and [redacted] in the placebo group discontinued study treatment due to a TEAE (up until 14 days after the last dose of study treatment; Table 15). There were no deaths during the trial.

Adverse events of special interest (AESIs) identified prior to the trial included severe infection requiring hospitalisation, new onset of diabetes mellitus, confirmed fracture, new osteonecrosis, gastrointestinal bleeding that required hospitalisation, cataract formation and onset of glaucoma. During the 9-month treatment period (up until 14 days after the last dose of study treatment), [redacted] patients in the TRF-budesonide 16 mg group and [redacted] in the placebo group reported an AESI.

Table 15: Overview of AEs in NefIgArd Nef-301

Adverse events, n (%)	Baseline UPCR ≥1.5 g/g				Nef-301 full study population			
	FAS		SAS		FAS		SAS	
	TRF-budesonide 16 mg† n=[redacted]	Placebo† n=[redacted]	TRF-budesonide 16 mg† n=[redacted]	Placebo† n=[redacted]	TRF-budesonide 16 mg† n=97	Placebo† n=100	TRF-budesonide 16 mg† n=[redacted]	Placebo† n=[redacted]
Any TEAE	[redacted]	[redacted]	[redacted]	[redacted]	84 (86.6)	73 (73.0)	[redacted]	[redacted]
Maximum severity of TEAEs								
Mild	[redacted]	[redacted]	[redacted]	[redacted]	49 (50.5)	46 (46.0)	[redacted]	[redacted]
Moderate	[redacted]	[redacted]	[redacted]	[redacted]	31 (32.0)	26 (26.0)	[redacted]	[redacted]
Severe	[redacted]	[redacted]	[redacted]	[redacted]	4 (4.1)	1 (1.0)	[redacted]	[redacted]
Maximum severity of study treatment-related TEAEs								
Mild	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Moderate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Severe	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Any AESI	[redacted]	[redacted]	[redacted]	[redacted]	2 (2.1)	0 (0.0)	[redacted]	[redacted]
Any SAE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Any study treatment-related TEAE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Any study treatment-related TESAE	[redacted]	[redacted]	[redacted]	[redacted]	2 (2.1)	2 (2.0)	[redacted]	[redacted]
Any AE leading to death	[redacted]	[redacted]	[redacted]	[redacted]	0 (0.0)	0 (0.0)	[redacted]	[redacted]
Any TEAE leading to discontinuation of study treatment	[redacted]	[redacted]	[redacted]	[redacted]	9 (9.3)	1 (1.0)	[redacted]	[redacted]

Abbreviations: AE, adverse event; AESI, adverse event of special interest; FAS, full analysis set; RAS, renin-angiotensin system; SAE, serious adverse event; SAS, safety analysis set; TEAE, treatment-emergent adverse event; TESAE, treatment-emergent serious adverse event; TRF, targeted-release formulation. † Treatment in addition to RAS inhibition.
TEAEs were defined as AEs that occurred for the first time after dosing with study treatment or existed before but worsened in severity or relationship to study treatment after dosing. Study treatment-related TEAEs were those assessed by the Investigator to have a reasonable possibility that the event may have been caused by the study treatment. If the relationship was missing, then it was considered as study treatment-related. AEs that started >14 days after the last dose of study treatment were excluded from the summary. The last dose was defined as the last dose the patient received, including the tapering period, regardless of the duration of treatment.
Source: Calliditas Therapeutics AB. Data on file. Additional data from NefIgArd for baseline UPCR ≥1.5 g/g subgroup. Table 2.7.3.3.1a. 2022 (119); Barratt et al. 2023 (108).

B.2.10.4 Additional studies

In addition to the phase 3 Part A trial, the phase 2b study also investigated the safety of TRF-budesonide in patients with IgAN; results from this are presented in Appendix F.

B.2.11 Ongoing studies

Part B of the NefIgArd Nef-301 study is a further 12-month observational follow-up period, during which the study blinding will remain in place, to assess the effect of treatment on eGFR. The study completed in February 2023 and data analyses are expected to complete in Q3/4 2023. Preliminary data analyses from Part B of NefIgArd Nef-301 demonstrate that the UPCR reductions observed during Part A were durable during the 15-month follow-up period off treatment (116). In addition, a highly statistically significant benefit in eGFR was observed for TRF-budesonide compared with placebo ($p<0.0001$) over the 2-year study period (9-months of treatment with TRF-budesonide or placebo and 15-months of follow-up off) (116). Supportive analyses of the 2-year eGFR slope also demonstrated a statistically significant and clinically-meaningful treatment benefit (116). Of note, the eGFR benefit was observed across the entire study NefIgArd Nef-301 population, irrespective of UPCR at baseline (116).

The NefIgArd-OLE open-label extension (OLE) study is an ongoing phase 3b, multicentre, open-label, single-arm extension trial to evaluate the efficacy and safety of TRF-budesonide 16 mg/day treatment in patients with IgAN who have completed the phase 3 NefIgArd Nef-301 trial. All patients will receive TRF-budesonide 16 mg/day for 9 months (including those who received NefIgArd and were previously treatment naïve to TRF-budesonide), as well a stable dose of RAS inhibitor therapy. The TRF-budesonide dose may be reduced if clinically-relevant AEs develop that the Investigator considers related to the trial drug and that mandate dose reduction. Trial completion is due in May 2024.

B.2.12 Interpretation of clinical effectiveness and safety evidence

B.2.12.1 Principal 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 with a baseline UPCR ≥1.5 g/g already receiving optimised and stable RAS blockade. Results for the FAS support those reported for the indicated population and are presented in Appendix M.

In the population with a baseline UPCR of ≥1.5 g/g, the focus of this submission, patients receiving TRF-budesonide 16 mg/day showed a statistically significant and clinically-relevant [redacted]% reduction in UPCR compared with placebo following 9 months of treatment (95% CI: [redacted]; p=[redacted]). The reduction in UPCR with TRF-budesonide 16 mg/day increased over time compared with placebo; after 3 months of observational follow-up, a [redacted]% reduction with TRF-budesonide 16 mg/day was observed compared with placebo (95% CI: [redacted]; p=[redacted]). A reduction in proteinuria has been consistently associated with corresponding beneficial effects on progression to ESRD and mortality in patients with IgAN (Section B.2.3.2) (102, 103, 105, 106, 111). As such, these results support the potential clinical benefit of TRF-budesonide in delaying the progression of CKD in this population. It is also anticipated that the use of TRF-budesonide could reduce the risk of HRQoL decline associated with ESRD and dialysis in patients with primary IgAN and a baseline UPCR ≥1.5 g/g (Section B.1.3.1.8).

The secondary efficacy endpoint of eGFR (CKD-EPI), a validated surrogate endpoint for CKD progression that can be used to demonstrate disease-modifying treatment effects (Section B.2.3.2) (3, 106, 114, 115), was supportive of the primary efficacy endpoint. TRF-budesonide 16 mg/day provided a statistically significant and clinically-relevant [redacted]% benefit on eGFR (CKD-EPI), compared with placebo (p=[redacted]), after 9 months of treatment. The eGFR treatment benefit for TRF-budesonide 16 mg/day versus placebo was consistent at all time points. After 3 months of observational follow-up, the treatment benefit at 1 year was maintained

at [redacted]% (p=[redacted]). A supportive analysis of 1-year eGFR slope was statistically significant (p=[redacted]), showing an improvement in total slope of [redacted] mL/min/1.73 m^2 per year with TRF-budesonide 16 mg/day compared with placebo. Preliminary data analyses from Part B of NefIgArd Nef-301 demonstrate a statistically significant benefit in eGFR for TRF-budesonide compared with placebo (p<0.0001) over the 2-year study period (116). Supportive analyses of the 2-year eGFR slope also demonstrated a statistically significant and clinically meaningful treatment benefit (116).

In accordance with the above treatment effects, TRF-budesonide 16 mg/day also provided a statistically significant and clinically-relevant [redacted]% reduction in UACR, compared with placebo, after 9 months of treatment (95% CI: [redacted]; p=[redacted]). After 3 months of observational follow-up, a [redacted]% reduction in UACR with TRF-budesonide 16 mg/day was observed at 1 year compared with placebo (p=[redacted]).

Importantly, the clinical benefits of TRF-budesonide were achieved safely. The 9-month treatment regimen of TRF-budesonide was well tolerated in patients with a baseline UPCR ≥1.5 g/g; AEs were generally mild or moderate in severity and reversible. Of the patients with a baseline UPCR ≥1.5 g/g, [redacted] of [redacted] ([redacted]%) patients in the TRF-budesonide 16 mg group and [redacted] of [redacted] patients in the placebo group reported TEAEs. Glucocorticoid-related AEs were as expected for an oral budesonide treatment and without the serious side effects associated with systemic glucocorticoids, which can be long-lasting and life-altering (26, 121). In addition, treatment with TRF-budesonide 16 mg/day over 9 months did not increase the risk of infection [redacted]% TRF-budesonide vs [redacted]% placebo), and in particular, no severe infections were reported. This is in marked contrast to results of recent studies using systemic glucocorticoids (STOP- IgAN and TESTING) for IgAN (Section B.1.3.3) (24, 26, 100). The safety profile of TRF-budesonide was consistent across the indicated population, the FAS, and subgroups assessed. The consistency of the safety results provide reassurance that the incidence rates observed in Part A of NefIgArd Nef-301 are a reliable estimate of the true incidence of a 9-month treatment regimen.

The efficacy and safety results available to date suggest that TRF-budesonide would have a favourable benefit-risk profile for the treatment of primary IgAN in adults at

risk of rapid disease progression (UPCR ≥1.5 g/g) and highlight the potential to improve the treatment landscape for patients for which no therapies are currently approved.

B.2.12.2 Strengths and limitations of the clinical evidence base for the technology

The design of the NefIgArd Nef-301 trial represents a novel approach to study new treatments for IgAN that originated from a collaboration between the US Food and Drug Administration and the American Society of Nephrology's Kidney Health Initiative (108). The primary endpoint of Part A, proteinuria reduction, is an accepted surrogate for long-term clinical outcomes in IgAN (3, 102, 106). This approval was based on the expectation that 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 that there is a strong association between treatment effects on UPCR and subsequent changes in the rate of eGFR decline and the risk of development of kidney failure (102-104, 122, 123). Based on two meta-analyses (122, 124), the magnitude of the treatment effects observed on UPCR and eGFR at 1 year in Part A of the NefIgArd Nef-301 trial is highly likely to predict, with >97.5% confidence, clinical benefit on long-term preservation of kidney function.

The NefIgArd Nef-301 study has been and is continuing to be conducted at high quality, with oversight by the Data and Safety Monitoring Board. There has been a low discontinuation rate, high compliance, and a small number of patients for whom data were excluded from the primary analysis of the FAS due to rescue treatment. The number of patients with data recorded at 12 months was lower than at 9 months because not all patients in the Part A FAS had reached the 12-month time point by the data cut-off, not due to study discontinuations. Data continued to be collected for any patients who discontinued study treatment early, thus minimising the amount of missing data.

The majority of patients ([redacted]%) in the NefIgArd Nef-301 were Caucasian, which is in line with the expected characteristics of people with IgAN in England (2). 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 or required for entry into the study, 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 (125). However, exploratory biomarker analyses indicate that TRF-budesonide has a positive effect on the levels of immune complexes involved in the pathogenesis of IgAN (50, 51), interstitial fibrosis (52), and B cell homeostasis (53) (Section B.1.3.2.2)A further potential limitation was the use of SF-36 to assess the quality of life of participants, as opposed to tool specific to people with kidney disease, which may be more sensitive to potential changes in response to therapy.

Prolonged administration of TRF-budesonide (beyond 9 months) was not tested in Part A of NefIgArd Nef-301. However, the efficacy of additional treatment cycles and the effects of long-term exposure to TRF-budesonide have been investigated in Part B and the ongoing OLE study (Section B.2.11).

B.2.12.3 Overall conclusion

In conclusion, the NefIgArd Nef-301 study, a multinational, randomised, double-blind, placebo-controlled, multicentre phase 3 clinical trial, has shown that 9 months of treatment with TRF-budesonide, in addition to optimised and stable RAS blockade, was well tolerated and resulted in clinically-important improvements in UPCR, UACR, and eGFR compared with optimised supportive care alone. As changes in proteinuria (UPCR and UACR) and eGFR can be used as surrogate endpoints for progression to ESRD and mortality in patients with CKD (3, 16, 44, 102, 103, 105, 106, 111-113), the improvements observed to date in patients treated with TRF-budesonide in NefIgArd Nef-301 provide support for a disease-modifying treatment effect which may delay progression to ESRD in patients with IgAN. This is the first phase 3 randomised controlled trial to show treatment benefits of this magnitude with a drug that may target the underlying pathophysiology of IgAN.

B.3 Cost effectiveness

Overview

- A cost-utility model was developed to assess the cost-effectiveness of TRF-budesonide in patients with primary IgAN at risk of rapid disease progression with a UPCR ≥1.5 g/g
- The model was a Markov cohort model with health states CKD stages 1, 2, 3a, 3b, 4 and 5 and the need for dialysis or kidney transplant (renal replacement therapy)
- Baseline characteristics were informed by data from Part A of NefIgArd Nef-301 to reflect the patient population observed in UK clinical practice. Clinical evidence for the efficacy of TRF-budesonide and SoC were derived directly from Part A of the NefIgArd Nef-301 study and applied in the cost-effectiveness model as transition probabilities between CKD 1 to 4 health states and AE rates. Transitions to the dialysis and transplant health state were informed by values from the literature. Real-world evidence obtained from UK RaDaR was used to inform the risk of CKD 5 and mortality
- In the absence of utility data from Part A of the NefIgArd Nef-301 study, an alternative published study in CKD was identified as a source of health state utility values in the economic model. Clinical event disutility values were also derived from values in the literature
- The analysis was consistent with the NICE reference case and took a National Health Service (NHS) and Personal Social Services (PSS) perspective. Costs and benefits were discounted at a rate of 3.5%, a lifetime time 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 (+0.102 years), increased quality-adjusted life years (QALYs; [redacted] per patient), and an incremental cost of [redacted] per patient. As a result, TRF-budesonide was considered cost-effective compared with SoC at a threshold of £20,000 to £30,000 per QALY, with an incremental cost-effectiveness ratio (ICER) of £18,643/QALY gained

- The probabilistic cost-effectiveness analysis results further demonstrated TRF-budesonide's cost-effectiveness. The probabilistic sensitivity analysis showed the probabilities of cost-effectiveness for TRF-budesonide at a willingness-to-pay thresholds of £20,000/QALY and £30,000/QALY gained were 66.1% and 75.1%
- The key driver of the deterministic sensitivity analysis were the time point from where no treatment effect for TRF-budesonide is assumed and the health state utility values
- The scenario analyses also demonstrated the cost-effectiveness analysis to be robust and TRF-budesonide remained cost-effective in 85% of scenarios. The scenarios that altered the time from where no treatment effect for TFR-budesonide is assumed had the largest impact on the ICER
- In summary, 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

B.3.1 Published cost-effectiveness studies

The economic SLR conducted at initial model development did not identify any UK cost-effectiveness analyses for IgAN. Therefore, for this submission, it was necessary to develop a *de novo* economic model to determine the cost-effectiveness of TRF-budesonide versus relevant comparators for the treatment of people with IgAN at risk of rapid disease progression with a UPCR ≥1.5 g/g from the perspective of the UK NHS and Personal Social Services (PSS). To inform the model structure, functionality, assumptions and data sources, previous NICE technology appraisals for the treatment of CKD were used. In total, 45 HTA submissions were identified in the non-clinical searches, of which 19 were deemed relevant for further consideration. Of these, eight were submissions to NICE; seven to the Scottish Medicines Consortium; one to Haute Autorité de santé; one to Institute for Quality and Efficiency in Health Care; and 2 to the Pharmaceutical Benefits Scheme. A summary of key features of the submissions is reported in Table 16. NG203 is not presented in the table as no economic modelling was undertaken.

The methods used in the *de novo* model 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 (126).

Table 16: Summary list of previous NICE technology appraisals in CKD

Study	Modelling approach	Time horizon	Cycle length	Source of utilities	Source of costs
TA809 – Imlifidase for desensitisation treatment before kidney transplant in people with CKD (127)	Standard, cohort-simulation, Markov model including three health states: Dialysis (HD/PD), functioning graft, and death	Lifetime (57 years)	6-months (half-cycle correction applied); 114 cycles	EQ-5D-3L and EQ-5D-5L data collected from UK-specific study of dialysis and kidney transplant patients (128, 129). A systematic review of published studies reporting health utility scores. [No specific utility data were available for imlifidase or the specific population considered].	NHS reference costs, eMiT, BNF, published literature and UK clinical expert opinion
TA807 – Roxadustat for treating symptomatic anaemia in CKD (associated with SMC2461 submission) (130)	De novo model including eight health states to reflect anaemia status based on different ranges of Hb levels: Hb <7, Hb 7.00 to 7.99, Hb 8.00 to 8.99, Hb 9.00 to 9.99, Hb 10.00 to 10.99, Hb 11.00 to 11.99, Hb 12.00 to 12.99, Hb ≥13.00	Lifetime (25 years)	3-months	EQ-5D-5L data collected from Yarnoff et al. 2016 (131) and mapped to EQ-5D-3L. A systematic review of published studies reporting health utility scores in the relevant patient population. Scenario analysis sourced patient preference data and a DCE was performed to elicit preferences (to estimate the utility gains associated with moving from subcutaneous injections at home once every two weeks (reference case) to alternative modes of administration.	NHS reference costs, BNF, PSSRU, published literature and UK clinical expert opinion
TA775 - Dapagliflozin for treating CKD (associated with SMC2428 submission) (4)	Markov cohort model including health states based on CKD stages 1, 2, 3a, 3b, 4 and 5 (defined by eGFR levels); need for dialysis or kidney transplant (renal	Lifetime (data in confidence)	Monthly (304 cycles)	EQ-5D-5L data collected from the DAPA-CKD study and mapped to EQ-5D-3L. A systematic review of published studies reporting health utility	NHS reference costs, eMIT, PSSRU, and published literature

Study	Modelling approach	Time horizon	Cycle length	Source of utilities	Source of costs
	replacement therapy); hospitalisation for heart failure, acute kidney injury; adverse events (volume depletion, major hypoglycaemic events, bone fractures, diabetic ketoacidosis, amputation, genital infection, urinary tract infection); and death			scores in the relevant patient population.	
TA599 - Sodium zirconium cyclosilicate for treating hyperkalaemia (associated with SMC2288 submission) (132)	Patient level simulation model [details in confidence]	Lifetime [suggested changes by the ERG reduced the time horizon in the emergency setting to 52 weeks]	Unclear [4-week cycle in the maintenance phase]	EQ-5D data identified through a systematic review of published studies (133).	Unclear [data in confidence]; scenario analysis in the emergency setting included NHS reference costs
TA623 – Patiromer for treating hyperkalaemia† (134)	Markov model including CKD health states: CKD stage 3 to 4 with mild hyperkalaemia, CKD progression to ESRD, hyperkalaemia (moderate or severe), cardiovascular events, and death	Lifetime (35 years; mean life span in the model 7.5 years)	1-month (30.44 days)	A systematic review of published studies reporting health utility scores in the relevant patient population.	NHS reference costs, PSSRU, BNF, published literature and UK clinical expert opinion
TA117 – Cinacalcet for the treatment of secondary hyperparathyroidism in patients with ESRD on	Markov (state transition) model including health states reflecting patients' status in relation to adverse events associated with secondary hyperparathyroidism	Unclear [data in confidence]	Unclear [data in confidence]	A systematic review of published studies reporting preference-based health state and utility scores in the relevant patient population.	NHS reference costs

Study	Modelling approach	Time horizon	Cycle length	Source of utilities	Source of costs
maintenance dialysis therapy (135)					
NG28 - Type 2 diabetes in adults: management (136)	Decision-analytic model using a microsimulation approach, capturing renal health states: CKD stages 1, 2, 3A, 3B, 4, and 5 prior to dialysis, receiving dialysis, and post renal transplant; and health states relating to MI, stroke, hospitalisation for heart failure and death	10 years	26-weeks	A systematic review of published studies reporting utility values for DKD health states and DK-related cardiovascular events.	NHS reference costs, BNF, PSSRU, and published literature and UK clinical expert opinion

Abbreviations: BNF, British National Formulary; CKD, chronic kidney disease; DKD, diabetic kidney disease; ERG, Evidence Review Group; ESRD, end-stage renal disease; Hb, haemoglobin; HD, haemodialysis; ICER, incremental cost-effectiveness ratio; NHS, National Health Service; PD, peritoneal dialysis; PSSRU, Personal Social Services Research Unit; QALYs, quality-adjusted life years; UK, United Kingdom.

B.3.2 Economic analysis

As no published cost-effectiveness studies in IgAN were identified at the time of initial model development, a *de novo* economic model was necessary for this submission.

The objective of the economic evaluation was to assess the cost-effectiveness of TRF-budesonide in patients with primary IgAN at risk of rapid disease progression with a UPCR ≥1.5 g/g.

B.3.2.1 Patient population

The Medicines and Healthcare Products Regulatory Agency (MHRA) license approved TRF-budesonide for the treatment of primary IgAN in adults at risk of rapid disease progression with a UPCR ≥1.5 g/g (1).

This is reflected in the NICE scope and company decision problem, which specify the following patient population:

- Adults with primary IgAN at risk of rapid disease progression with a UPCR ≥1.5 g/g

The economic evaluation includes data from NefIgArd Nef-301 Part A study. The entry criteria for NefIgArd NEF-301 included patients with a UPCR ≥0.8 g/g or proteinuria ≥1 g/day. The results from NefIgArd Nef-301 Part A used in the cost-effectiveness analysis include subgroup patient characteristics and clinical effectiveness data for patients with a baseline UPCR ≥1.5 g/g, the patient population relevant to this submission.

B.3.2.2 Patient characteristics

Baseline characteristics for patients with IgAN with UPCR ≥1.5 g/g were derived from NefIgArd Nef-301 Part A study. 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. The baseline patient characteristics used in the model are summarised in Table 17.

Table 17: Baseline patient characteristics used in the economic model

Parameter	Mean	DSA (Low; high values) †	Source
Age	[redacted]	[redacted]	NefIgArd Part A data from NefIgArd for baseline UPCR ≥1.5 g/g subgroup 2022 (119)
Proportion female	[redacted]	[redacted]	
Average weight	[redacted]	[redacted]	

Abbreviations: CSR, clinical study report; DSA, deterministic sensitivity analysis.

† Low and high values for age were sourced directly from the NefIgArd Part A study. In the absence of data, low, high values are calculated as ±10% of mean value.

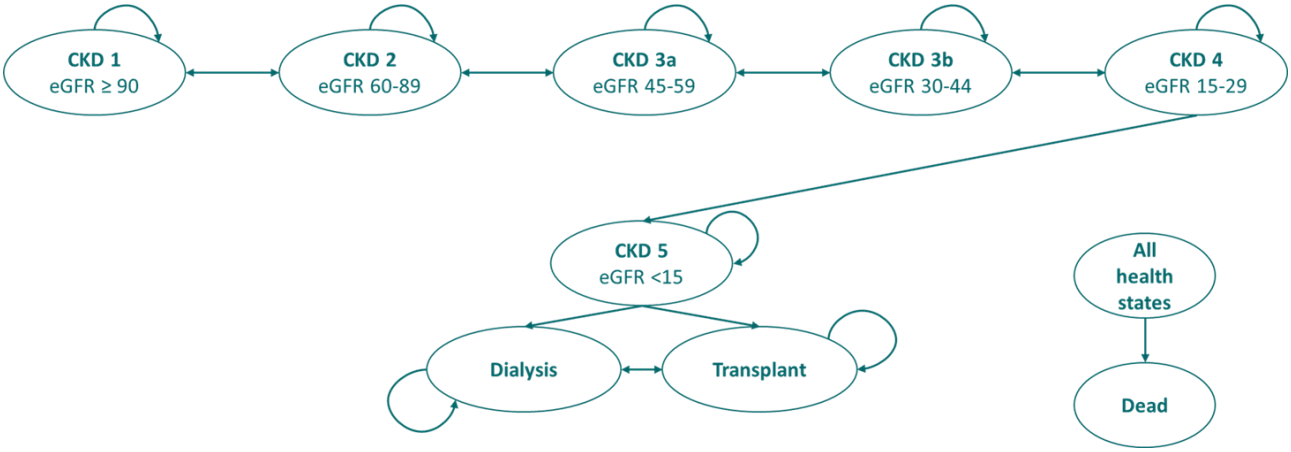
B.3.2.3 Model structure

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.

Due to the lack of published cost-effectiveness analyses specific to IgAN, the relative strengths of patient-level and cohort-level approaches to the decision problem were considered. Despite the reduced flexibility, it was agreed that a cohort-level approach would be optimal as it requires fewer data inputs than a patient-level simulation approach. Therefore, given the limited IgAN data identified in the SLR, a cohort-level approach was considered preferential. A cohort-level approach was also the most commonly used structure in CKD submissions identified in the economic SLR, which was considered by clinicians to be a good proxy for patients with IgAN.

The chosen CEM structure is captured in Figure 15. Aspects of the model structure used in the single technology appraisal NICE submission (TA775) (4) were utilised in the model structure. As per the TA775 submission, the model's health states are mostly defined by CKD state; that is, by eGFR levels. Though eGFR was a secondary endpoint in NefIgArd Nef-301 Part A study and UPCR was the primary endpoint, the published cost-effectiveness precedent in CKD has linked CKD health states to patient utility, health resource use, and transition probability data. Furthermore, there is no such precedent for UPCR-defined states in CKD, and as noted, no identified published CEM precedent is specific to IgAN. Therefore, defining health states by eGFR was deemed most appropriate to 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).

Within the model there are eight health states and an absorbing mortality state. An identical cohort enters each treatment arm of the model, distributed across the CKD health states in a manner that reflects the baseline distribution of CKD states in the NefIgArd Nef-301 Part A study. The arrows in Figure 15 represent the permitted transitions between health states.

Reflecting the observed patient movements in the NefIgArd Nef-301 Part A study, clinician feedback, and given the relatively short monthly CEM time cycle for a chronic disease, movements between CKD states are assumed to be restricted to immediate neighbouring states at each cycle, except for movements to CKD 5 (further detail described in Section B.3.3.2). As indicated by Figure 15, the CEM assumes it is not possible to move from CKD 5 to an improved CKD state. Similarly, 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 (4).

As indicated by 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 Part A study and due to the relatively low mortality risk in early CKD stages,

no mortality data from NefIgArd Nef-301 were available to directly inform the CEM. Therefore, the CEM relies on real-world evidence from the national registry of rare kidney diseases (UK RaDaR) to inform the risk of death from all health states (further described in Section B.3.3.5).

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.

The model structure presented in Figure 15 was validated by expert opinion gathered at an advisory board held in February 2023 (2) (Section B.2.3.4).

B.3.2.3.1 Time horizon and cycle length

At the end of each monthly cycle, the distribution of the cohort in each model arm changes based on state transition probability data (further detail described in Sections B.3.3.1 and B.3.3.2). The model uses a half-cycle correction to account for the fact that events and transitions may occur at any point during the cycle.

B.3.2.3.2 Perspective and discounting

The base-case analysis takes the perspective of the NHS and PSS in the UK. An annual discount rate of 3.5% is applied for both costs and outcomes, as per the NICE reference case.

B.3.2.3.3 Features of the economic analysis

A summary of the features of the economic analysis is presented in Table 18.

Table 18: Features of the economic analysis

Factor	Chosen values	Reference in submission	Justification
Time horizon	Lifetime horizon (56 years) (Up to 70 years)	Section B.3.2.3.1	In concordance with the NICE scope which recommends a lifetime horizon (137)
Cycle length	Monthly (30.4375 days)	Section B.3.2.3.1	IgAN is a chronic disease and therefore a monthly cycle length is appropriate. Cycle length was validated by KOLs
Model structure	Cohort state-transition model	Section B.3.2.3	A cohort state-transition model requires fewer data

Factor	Chosen values	Reference in submission	Justification
			assumptions than a patient-level approach. Cohort state-transition model have also been used in previous CKD submissions.
Source of efficacy	NefIgArd Nef-301 Part A trial subgroup data for UPCR ≥1.5 g/g	Section B.3.3	In accordance with NICE guidance
Source of AE rates	NefIgArd Nef-301 Part A study	Section B.3.3.4	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 (138)	Section B.3.4.2	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 Schedule of Reference Costs 2021–2022 (139) and sources from the literature	Section B.3.5.1	In accordance with NICE guidance
Source of standard care treatment cost	eMIT (140) and BNF (141)	Section B.3.5.1	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 (82), NHS Schedule of Reference Costs 2021–2022 (139)	Section B.3.5.2	Most recently published and reliable data source available

Abbreviations: AE, adverse event; CKD, chronic kidney disease; eMIT, electronic market information tool; HSUV, health state utility values; KOL, key opinion leader; NHS, Nation Health Service; NICE, National Institute of Health and Care Excellence; SoC, standard of care; TRF, targeted-release formulation; UPCR, urine protein creatinine ratio.

B.3.2.4 Intervention technology and comparators

B.3.2.4.1 TRF-budesonide

In line with the NefIgArd Nef-301 Part A study, and the MHRA license wording (1), the CEM assumes TRF-budesonide is self-administered as four 4 mg tablets once daily for 9 months. Before discontinuation, the dose should be reduced to 8 mg once daily for 2 weeks (subsequent to 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.

The MHRA license states the TRF-budesonide dose may be reduced to 4 mg once daily for an additional 2 weeks, at the discretion of the treating physician (1). The model includes functionality to include treatment tapering but is excluded from the base case analysis and explored only in scenario analysis.

B.3.2.4.1.1 Retreatment

The MHRA license states that re-treatment may be considered at the discretion of the treating physician (1), therefore the CEM includes the functionality to explore cost-effectiveness projections for TRF-budesonide retreatment scenarios. At the point of assumed retreatment, retreatment-eligible patients are assumed to follow the same cost, relative clinical effectiveness versus SoC, and patient utility pathways as used for the starting treatment with TRF-budesonide. When retreatment is allowed, the time between on-treatment periods is assumed to be 14.75 months. In the absence of available data to inform the duration between retreatment cycles, 14.75 months was based on the time between completion of 9 months of treatment in Part A of the NefIgArd Nef-301 trial and the start of the NefIgArd-OLE study. In the OLE study, eligible patients from both arms enrolled in NefIgArd would receive TRF-budesonide over a 9-month period, starting at the visit scheduled at approximately 24 months from the NefIgArd Nef-301 Part A baseline. The retreatment scenarios in the CEM are confined to several assumptions and limitations as follows:

- 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 Part A eligibility criteria (eGFR ≥35 mL/min/1.73m^2). Of these patients, the model assumes only patients that were still on treatment at the end of their initial treatment period will be retreated. Therefore, the base case assumes [redacted] of TRF-budesonide patients will undergo retreatment. This assumption is made to prevent patients that discontinued TRF-budesonide during the initial treatment period from being retreated with TRF-budesonide
- Transition probabilities: Patients are assumed to follow the 0–12-month TRF-budesonide transition probabilities in the initial 12 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 12+ month TRF-budesonide CKD stage transition probabilities are applied dependent on the

selected duration of the TRF-budesonide treatment effect (further details in Section B.3.3.1.2)

- 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 HR 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 (TTD): The proportion of patients on treatment, as defined by the TTD curve observed in the NefIgArd Nef-301 Part A trial, is applied to all eligible patients from the start of each retreatment round. TTD is described further in Section B.3.5.1.1.5

The base case model results include one retreatment round (two rounds of treatment in total). A range of retreatment scenarios are further explored in more detail in Section B.3.11.3.13.

B.3.2.4.2 Comparators

The model includes one comparator: SoC. The placebo arm of NefIgArd Nef-301 is assumed to be a good proxy for SoC in reflecting optimised supportive care, as described in Chapter 2 of the KDIGO 2021 Clinical Practice Guideline for the Management of Glomerular Diseases (3). Patients in both treatment arms of NefIgArd Nef-301 received optimised and stable RAS blockade (108), which is assumed to represent optimised supportive care. KDIGO 2021 describes optimised supportive care as: blood pressure management; maximally tolerated dose of ACEi/ARB; lifestyle modification; and addressing cardiovascular risk (3).

The decision to exclude glucocorticoids as a component of SoC was based on opinions from clinical experts gathered at an advisory board held in February 2023 (2). The clinical experts confirmed they would not use glucocorticoids in clinical practice to treat people with IgAN with a UPCR ≥1.5 g/g due to the poor risk-benefit profile of glucocorticoids demonstrated in the STOP-IgAN (24, 142) and TESTING (26) studies and severe toxicity. For this reason, clinical experts choose to limit the use of glucocorticoids for patients with nephrotic syndrome (2).

SGLT2 inhibitors were expected by clinical experts to be included as a component of SoC in clinical practice and as such, the cost of such treatments were included within SoC costs.

The NefIgArd Nef-301 trial data used to inform the model did not include patients on SGLT2 inhibitors as at the time of recruitment this was not deemed to be part of SoC. In the CEM, SoC data from the NefIgArd Nef-301 trial was not adjusted to account for the inclusion of SGLT2 inhibitors. This is based on the findings of the DAPA-CKD study (120) which reported that dapagliflozin treatment in patients with IgAN (N=270) did not have a statistically significant impact on eGFR over 36 months compared with placebo. The least mean squares eGFR slopes from baseline to end of treatment in the dapagliflozin and placebo groups were -3.5 (SE 0.5) and -4.7 (SE 0.5) mL/min/1.73 m^2 per year, respectively, resulting in an insignificant between-group difference of 1.2 mL/min/1.73 m^2 per year (95% CI: -0.12, 2.51 mL/min/1.73 m^2 per year). Since the transition probability matrices included in the model are based on changes in eGFR values, the inclusion of SGLT2 inhibitors was deemed not to improve the clinical impact of the model's patient population.

B.3.3 Clinical parameters and variables

B.3.3.1 CKD 1–4 health state transition matrices

B.3.3.1.1 Transitions between 0–12 months

Transition probabilities between CKD 1–4 health states 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)(143). eGFR values were mapped to CKD stages at baseline and after 9 months of treatment. Patients are considered to have 'transitioned' if they were in a different CKD stage after 9 months of treatment compared with baseline, with the likelihood of transitioning evaluated by treatment arm and baseline CKD stage. To account for the bias of small changes in eGFR readings around threshold values, transitions to better health states (observed in the trial) were also incorporated.

The output of the logistic regression produced log odds ratios for each coefficient (CKD stage at baseline and treatment arm) is presented in Table 19.

Table 19: NeflgArd 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]
Placebo	3a	[redacted]
TRF-budesonide		[redacted]

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

The log odds in Table 19 were converted to 9-month probabilities as follows:

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

Where p is the 9-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 9-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 9-month probability and t is time-period (9 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 20.

Table 20: NeflgArd Nef-301-informed cycle transition probabilities (0–12 months)

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

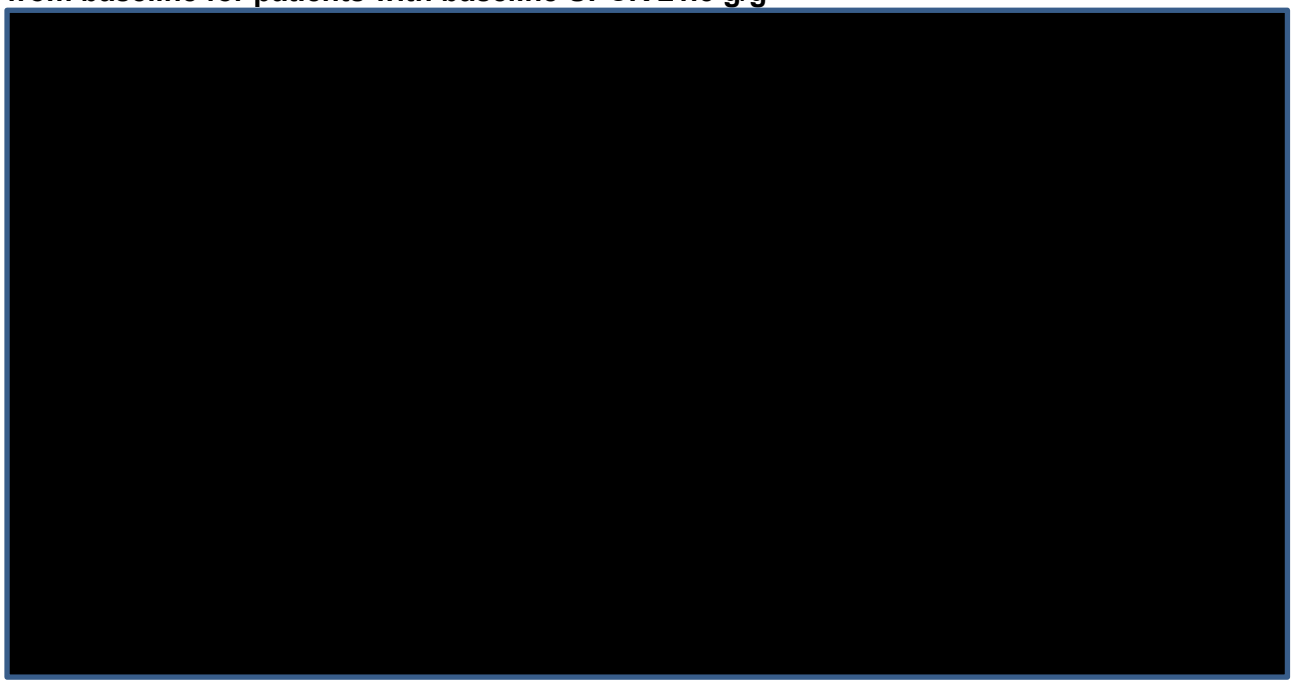
Abbreviations: CKD, chronic kidney disease; SoC, standard of care; TRF, targeted-release formulation.

Note: There were no patients with CKD stage 4 at baseline, therefore transitions are assumed equal to CKD stage 3b.

Patients that discontinue treatment still incur the TRF-budesonide transition probabilities presented in Table 20. This implicitly assumes that the transition probabilities from the trial data included patients that discontinued before 9 months and therefore the transition probabilities also account for the disease progression of patients that discontinued.

Although the transitions presented in Table 20 were calculated using data up to 9 months, these transitions were assumed to be applicable for up to 12 months. This is because the treatment effect of TRF-budesonide observed during the 9-month treatment period was maintained during the 3-month observational follow-up (9–12 months from baseline) in Part A of the NeflgArd Nef-301 study for this sub-population. The eGFR data shown in Figure 16 provide evidence to support an ongoing treatment effect of TRF-budesonide, with the treatment benefit maintained at 12 months following 3 months of off-treatment observational follow up.

Figure 16: Ad hoc analysis of NefIgArd Nef-301 Part A percentage change in eGFR from baseline for patients with baseline UPCR ≥1.5 g/g



Abbreviations: eGFR, estimated glomerular filtration rate; FAS, full analysis set; UPCR, urine protein creatinine ratio
Source: Calliditas Therapeutics AB. Data on file. Additional data from NefIgArd for baseline UPCR ≥1.5 g/g subgroup. Figure 2.7.3.3.2.1h (119).

B.3.3.1.2 Transitions beyond 12 months

No data from NefIgArd Nef-301 Part A beyond 12 months from baseline were available at the time of submission. As such, the transition probabilities beyond 12 months in the SoC arm are assumed equivalent to observed transition probabilities in the NefIgArd Nef-301 SoC arm, as presented in Section B.3.3.1 (107).

The transition probabilities in the NefIgArd Nef-301 TRF-budesonide arm are only applied up until the treatment effect duration, which in the base case is 1 year, after which point the beyond 12-month transition probabilities are assumed equivalent to observed transition probabilities in the NefIgArd Nef-301 SoC arm, as presented in Section B.3.3.1. This is in line with the NefIgArd Nef-301 Part B where the change in eGFR of the TRF-budesonide arm from month 12 to month 24 was not significantly different to that of the placebo arm for the full trial population. Therefore, the model base case assumes concordant results for the UPCR ≥1.5 g/g IgAN population.

B.3.3.2 Risk of CKD 5 (eGFR <15 mL/min/1.73m^2)

B.3.3.2.1 SoC arm

As per the model structure in Figure 15, only patients with CKD 4 can transition to CKD 5. In the model base case, the risk of CKD 5 is informed by real world evidence from patients with IgAN and UPCR ≥1.5 g/g collected in the UK RaDaR database (36). Figure 2 presents the Kaplan-Meier (KM) curve which estimates the probability of progressing to ESRD or mortality over time. The model assumes ESRD is equivalent to CKD 5.

Figure 17: UK RaDaR KM curve estimating time to diagnosis of ESRD or mortality

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 2023 (36).

The KM curve presented in Figure 17 was digitalised using Engauge Digitizer 12.1 software (144). Pseudo patient level data (PLD) was generated from the digitised data using the R packages (145) “MASS” and “splines”. As data were only available for up to 4 years, parametric survival modelling was fitted to these data to extrapolate to estimated data completion, using the R packages (145) “survival” and “flexsurv”. Figure 18 presents the extrapolated and digitalised KM data with seven parametric extrapolations fitted.

Figure 18: 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.

The Akaike information criterion (AIC) and Bayesian information criterion (BIC) both rank gamma as the parametric model that best fits the observed data, as presented in Table 21. The gamma model is used in the base case since it provides the numerically best fit according to both AIC and BIC statistics. Alternative model extrapolations are explored in scenario analyses.

Table 21: AIC and BIC statistics for time to CKD 5 models

Model	AIC	AIC rank	BIC	BIC rank
Exponential	181.20	4	183.35	3
Generalised gamma	180.18	3	186.61	6
Gompertz	181.39	6	185.67	5
Log-logistic	181.38	5	185.67	4
Log-normal	184.03	7	188.31	7
Weibull	178.37	2	182.66	2
Gamma	178.20	1	182.48	1

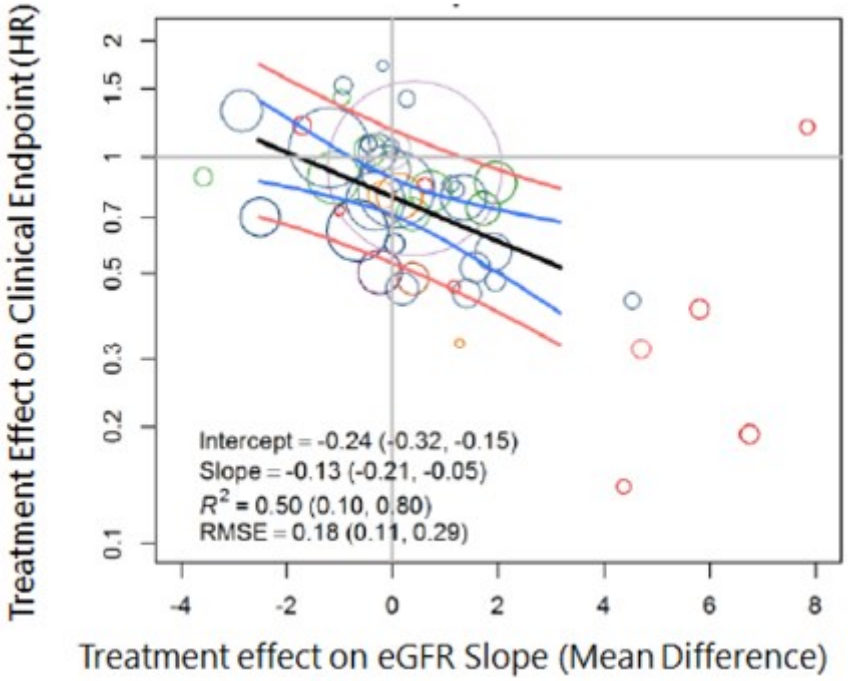
Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion; CKD, chronic kidney disease.

B.3.3.2.2 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 (described in Section B.3.3.2.1).

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 [redacted] to the extrapolated KM data presented in Figure 18. Published meta-analyses (124) were 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 1-year eGFR slope and the relationship between endpoints. The observed treatment effect on 1-year eGFR total slope in the sub-population of patients with baseline UPCR ≥1.5 g/g of [redacted] mL/min/1.73 m^2 per year (95% CI:[redacted]) in Nef-301 predicts a HR of [redacted] for the clinical outcome.

Figure 19: Relationship between treatment effect on 1-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 (124). The meta-analysis of 47 trials in chronic kidney disease (Inker et al. 2019 supplement eFigure5) relating treatment effects on 1-year eGFR total slope to long-term clinical outcomes in IgAN was used to predict the HR associated with the treatment effect on 1-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 19 and the observed treatment effect on 1-year eGFR total slope of [redacted] mL/min/1.73 m^2 per year is presented below:

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

$$HR = e^{(-0.24+[-0.13\times 8.98])} = [redacted]$$

Figure 20 presents the risk of transitioning to the CKD 5 health state while receiving TRF-budesonide by applying the HR of [redacted] to the digitised KM data and fitted survival models in Figure 18.

Figure 20: Digitised UK RaDaR KM data with fitted gamma extrapolation and HR of [redacted] 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 [redacted] 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 1-year (further detail in Section B.3.3.1). 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. The treatment effect is also assumed to be the same for retreatments.

B.3.3.3 Transitions from CKD 5, dialysis, and kidney transplant health states

Transitions between CKD 5, dialysis, and transplant health states are sourced from NICE TA775 (4); 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 a systematic literature review by Sugrue et al. 2019 (146). 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 22 presents the monthly transition probabilities from CKD 5, dialysis, and transplant used in the model.

Table 22: 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

B.3.3.4 Adverse reactions

The adverse events rates for both the TRF-budesonide and SoC arm were sourced from the NefIgArdNef-301 CSR Pooled Dataset (Safety Analysis Set) (107). All treatment-related AEs occurring in ≥4% of patients in either treatment arm of the safety analysis set were included in the model. Additionally, treatment-emergent severe adverse events (TESAEs) occurring in more than one patient were also included in the analysis. The AEs included in the model are presented in Table 23.

Table 23: Adverse event rates by treatment

Treatment-emergent AE	TRF-budesonide 16 mg (N=[redacted]) n (%)	Placebo (N=[redacted]) n (%)
Acne	[redacted]	[redacted]
Cushingoid	[redacted]	[redacted]
Dyspepsia	[redacted]	[redacted]
Oedema peripheral	[redacted]	[redacted]
Face oedema	[redacted]	[redacted]
Headache	[redacted]	[redacted]

Treatment-emergent AE	TRF-budesonide 16 mg (N=[redacted]) n (%)	Placebo (N=[redacted]) n (%)
Hirsutism	[redacted]	[redacted]
Hypertension	[redacted]	[redacted]
Mood swings	[redacted]	[redacted]
Upper respiratory tract infection	[redacted]	[redacted]
Weight increase	[redacted]	[redacted]
Treatment emergent SAEs		
Pulmonary embolism	[redacted]	[redacted]
Renal impairment	[redacted]	[redacted]

Abbreviations: AE, adverse event; 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.
Source: Calliditas Therapeutics AB. Data on file. Clinical study report Nef-301. 2021 (107).

B.3.3.5 Mortality

As no long-term survival data were available from the NefIgArd Nef-301 clinical trial and due to the relatively low mortality risk in early CKD stages, no NefIgArd Nef-301 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 risk of death was greater for the general population compared with the modelled population using any mortality source described in Sections B.3.3.5.1 and B.1.1, 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) life tables (147).

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

B.3.3.5.1 Risk of death from CKD 1-5, dialysis, and transplant health states

Data from UK RaDaR was used to inform the risk of mortality from CKD stages 1–5 and dialysis (36). The standardised mortality rates from the UK RaDaR data were calculated by building a cox regression model with age, sex, and CKD stage as

factors. The 10-year survival rates were used to calculate the standardised mortality ratios (SMR). The SMR weights used in the CEM for the CKD stages and dialysis health states are presented in Table 24.

Table 24: Standard mortality ratios

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

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

B.3.4 Measurement and valuation of health effects

B.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, this would only inform CKD 1 to CKD 4 health states in the model. 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.

B.3.4.2 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.

No UK-specific EQ-5D studies were identified in the economic SLR for patients with IgAN. Instead, the references listed in recent CKD submissions to NICE were cross-checked. Cooper et al. 2020 (138) was included in the TA775 NICE HTA submission reference list (4). Cooper et al. 2020 (138), report a systematic literature review of HRQoL utility weights for CKD stages used in economic evaluations. 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 some of the 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. These values were used to inform the following health states; CKD stages 1, 2, 3a, 3b, 5, haemodialysis, peritoneal dialysis, and transplant. In the CEM, CKD stage 4 is informed by the EQ-5D-3L analysis of data from the US as no UK value was available. Utility values derived from the EQ-5D-3L questionnaire were selected for use in the model. The utility values from Cooper et al. 2020 (138) are presented in Table 25.

Table 25: Summary of utility values from Cooper et al. 2020 (138)

Health state	Utility value	Standard error	Reference
CKD 1	0.85	0.08	Cooper et al. 2020 (138)
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 patient utility in the dialysis and transplant health states, utility values were also sourced from Cooper et al. 2020 (138). Patients in the dialysis health state are assumed to receive either haemodialysis (86.5%) or peritoneal dialysis (13.5%) based on the distribution reported in the United Kingdom Renal Registry (UKRR) 24th Annual report (148). 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 24th Annual report.

Table 26: Summary of utility values for the dialysis and transplant health states from Cooper et al. 2020 (138).

Health state	Utility value	Standard error	Reference
Haemodialysis	0.44	0.032	Cooper et al. 2020 (138)
Peritoneal dialysis	0.53	0.066	
Post transplant	0.71	0.019	

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

A key limitation of the approach to patient utility in the model was that Cooper et al. 2020 (138) did not contain data from patient groups with characteristics matched to NefIgArd Nef-301 patient characteristics. While this is 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.

B.3.4.3 Mapping

Not applicable.

B.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 duration and disutility of AEs captured in the CEM were informed by literature sources obtained from a targeted literature review. Where data were not identified in the literature, a simplifying assumption of no associated disutility was assumed. Additionally, where data were not available to inform AE duration, a simplifying assumption of a one-week duration was made.

The disutility and duration assumptions applied for each AE are presented in Table 27 and Table 28.

Table 27: Adverse event rates duration

Treatment-emergent AE	Duration (days)	Source
Acne	7.00	Assumption
Cushingoid	7.00	Assumption
Dyspepsia	7.00	Assumption
Oedema peripheral	7.00	Assumption
Face oedema	7.00	Assumption
Headache	7.00	Assumption
Hirsutism	7.00	Assumption
Hypertension	7.00	Assumption
Mood swings	7.00	Assumption
Upper respiratory tract infection	6.61	NHS ref 17/18: Total HRG's - weighted average non-elective length of stay CB02A, CB02B, CB02C, CB02D, CB02E, CB02F (149)
Weight increase	7.00	Assumption
Treatment-emergent SAE		
Pulmonary embolism	6.61	NHS ref 17/18: Total HRGs - weighted average non-elective length of stay DZ09J, DZ09K, DZ09L, DZ09M, DZ09N, DZ09P, DZ09Q (149)
Renal impairment	6.29	NHS ref 17/18: Total HRGs - weighted average non-elective length of stay LA09J, LA09K, LA09L, LA09M, LA09N, LA09P, LA09Q (149)

Abbreviations: AE, adverse event.

Table 28: Adverse event rates disutility value

Treatment-emergent AE	Disutility	Source
Acne	-0.00	Assumption
Cushingoid	-0.16	Sullivan et al. (2011) (150)
Dyspepsia	-0.04	Sullivan et al. (2011)
Oedema peripheral	-0.16	Assumed same as cushingoid
Face oedema	-0.16	Assumed same as cushingoid
Headache	-0.04	Sullivan et al. (2011) (150)
Hirsutism	-0.00	Sullivan et al. (2011) (150)
Hypertension	-0.05	Sullivan et al. (2011) (150)
Mood swings	-0.13	Sullivan et al. (2011) (150)
Upper respiratory tract infection	-0.00	Sullivan et al. 2006 (151)
Weight increase	-0.00	Assumption
Treatment-emergent SAE		
Pulmonary embolism	-0.00	Assumption
Renal impairment	-0.00	Assumption

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

Data in Table 27 and Table 28 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 23, to estimate the total AE-attributable QALYs lost per treatment arm. These QALY loss estimates, presented in Table 29, were then applied as one-off QALY decrements in the first model cycle of their respective treatment arm.

Table 29: 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	0.0000000	[redacted]	[redacted]
Cushingoid	-0.0907646	[redacted]	[redacted]
Dyspepsia	-0.0255127	[redacted]	[redacted]
Oedema peripheral	-0.0907646	[redacted]	[redacted]
Face oedema	-0.0907646	[redacted]	[redacted]
Headache	-0.0255782	[redacted]	[redacted]
Hirsutism	-0.0006961	[redacted]	[redacted]
Hypertension	-0.0268552	[redacted]	[redacted]
Mood swings	-0.0740310	[redacted]	[redacted]
Upper respiratory tract infection	0.0000000	[redacted]	[redacted]
Weight increase	0.0000000	[redacted]	[redacted]
Treatment-emergent SAE			
Pulmonary embolism	0.0000000	[redacted]	[redacted]
Renal impairment	0.0000000	[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 QALY 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).

B.3.4.5 Age-adjusted general-population mortality

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 (152). 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 aging. The linear regression model used to estimate the general population utility was:

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

B.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 TSD 12.1 (153).

The health state utility values and the clinical event disutilities applied in the base case cost effectiveness analysis are summarised in Table 30.

Table 30: 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 (138)
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 (138)
Peritoneal dialysis	0.53	0.066	
Post transplant	0.71	0.019	
AEs			
Acne	-0.00	0.00	Assumption
Cushingoid	-0.16	0.04	Sullivan et al. (2011) (150)
Dyspepsia	-0.04	0.01	Sullivan et al. (2011) (150)
Oedema peripheral	-0.16	0.04	Assumed same as cushingoid
Face oedema	-0.16	0.04	Assumed same as cushingoid

	Mean utility value	Standard error	Reference
Headache	-0.04	0.01	Sullivan et al. (2011) (150)
Hirsutism	-0.00	0.01	Sullivan et al. (2011)
Hypertension	-0.05	0.00	Sullivan et al. (2011)
Mood swings	-0.13	0.01	Sullivan et al. (2011) (150)
Upper respiratory tract infection	-0.00	0.00	Sullivan et al. 2006 (151)
Weight increase	-0.00	0.00	Assumption
Pulmonary embolism	-0.00	0.00	Assumption
Renal impairment	-0.00	0.00	Assumption

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

B.3.5 Cost and healthcare resource use identification, measurement and valuation

B.3.5.1 Intervention and comparators' costs and resource use

B.3.5.1.1 TRF-budesonide treatment costs

As described in Section B.3.2.4 and in line with the Part A of NefIgArd Nef-301 study and MHRA license wording (1), TRF-budesonide is self-administered as four 4 mg tablets once daily for nine months within the CEM. The cost per pack of TRF-budesonide used in the model was [redacted]. As TRF-budesonide is self-administered orally, the cost of TRF-budesonide administration is assumed to be zero in the CEM.

B.3.5.1.1.1 Dose reduction and dose tapering

The 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 (1). The model functionality applies dose reduction for 2 weeks after 9 months of treatment. The MHRA license wording also describes an optional dose 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 expert clinical opinion (data on file (2)), only the dose reduction period of the first 2 weeks subsequent to the 9-month treatment period was included in the base case model results, in line with the NefIgArd Nef-301 study protocol. The tapering period of 4 mg once daily for an

additional 2 weeks was explored as a scenario analysis. The cost of a reduced dose of TRF-budesonide was applied in month 10 of the model.

Table 31 presents the monthly treatment costs for TRF-budesonide for a reduced dose model cycle.

Table 31: 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§	Admin cost per dose	Treatment cost with reduced dose per cycle
TRF-budesonide	8 mg	2 weeks	14	112.00	0.23	£0	[redacted]

Abbreviations: TRF, targeted-release formulation.

† Equal to the model cycle length divided by the reduced dose frequency (7 days / 2 weeks)

‡ Full-dose frequency equal to model cycle length minus the reduce dose frequency per cycle (30.4375 – 15.20835)

§ Packs per cycle calculated as total dose per cycle divided by table size (4 mg) divided by the pack size (120).

Figures presented in the table are rounded to two significant figures.

B.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.

[redacted] 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 32.

Table 32: TRF-budesonide cost per mg

Treatment	Tablet size	Pack size	Cost per pack	Cost per mg†
TRF-budesonide	4 mg	120	[redacted]	[redacted]

†Cost per mg calculated as the cost per pack divided by the pack size, divided by tablet size ([redacted])

B.3.5.1.1.3 Relative dose intensity

Relative dose intensity (RDI) was not captured by the CEM. While RDI was recorded in the Part A of 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.

B.3.5.1.1.4 Retreatment

The proportion of retreatment eligible patients assumed to be on treatment were applied to the 9-month cost of TRF-budesonide treatment.

B.3.5.1.1.5 Time to treatment discontinuation

As per the MHRA license, which requires a daily dose of 16 mg for 9 months (1), 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 A of the NefIgArd Nef-301 study. This data was digitalised and is presented in Figure 21.

Figure 21: 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 21 does not include patients that received a reduced dose for 2 weeks after 9 months of treatment. Therefore, it is assumed that all patients on treatment at the start of the month 9 will receive a reduced dose.

B.3.5.1.2 Treatment costs for standard of care

In order 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 receiving treatment in both the TRF-budesonide and SoC arm in the CEM. As shown in Table 33, SoC costs comprised of ACEi or ARBs, i.e. treatments that have an indication in renal disease, including treatments indicated for renal disease in adult patients with hypertension and type 2 diabetes mellitus. Dapagliflozin was also

included in the cost of SoC based on feedback received from clinical experts (2). For each SoC treatment, the number of tablets required per day was calculated by dividing the maximum daily dose by the tablet size. This was multiplied by the cost per tablet (calculated as the pack price divided by the number of tablets per pack) to determine the cost per day. The cost per month per SoC treatment was calculated by multiplying the cost per day by the model cycle length (30.4375 days).

Table 33: Unit costs associated with the SoC in the economic model

Items	Maximum daily dose	Daily tablets required for maximum dose[†]	Pack price	Cost per table[‡]	Cost per day[§]	Cost per month[¶]	Source
ACEi							
Captopril 12.5 mg tablets/ Pack size 56	150 mg	12.0	£0.58	£0.01	£0.13	£3.81	EMC (154-156); eMIT (140)
Captopril 25 mg tablets / Pack size 56		6.0	£0.61	£0.01	£0.07	£1.99	
Captopril 50 mg tablets / Pack size 56		3.0	£0.77	£0.01	£0.04	£1.25	
Average cost of Captopril						**£2.35**	
Lisinopril 10 mg / Hydrochlorothiazide 12.5 mg tablets / Pack size 28	40 mg	4.0	£1.15	£0.04	£0.16	£5.01	
Lisinopril 10 mg tablets / Pack size 28		4.0	£0.38	£0.01	£0.05	£1.67	
Lisinopril 2.5 mg tablets / Pack size 28		16.0	£0.94	£0.03	£0.53	£16.28	
Lisinopril 20 mg / Hydrochlorothiazide 12.5mg tablets / Pack size 28		2.0	£2.19	£0.08	£0.16	£4.76	
Lisinopril 20 mg tablets / Pack size 28		2.0	£1.09	£0.04	£0.08	£2.37	
Lisinopril 5 mg tablets / Pack size 28		8.0	£0.93	£0.03	£0.27	£8.10	
Average cost of Lisinopril						**£6.37**	
Ramipril 1.25 mg capsules / Pack size 28	10 mg	8.0	£0.41	£0.01	£0.12	£3.58	
Ramipril 10 mg capsules / Pack size 28		1.0	£0.39	£0.01	£0.01	£0.43	
Ramipril 2.5 mg capsules / Pack size 28		4.0	£0.42	£0.01	£0.06	£1.82	
Ramipril 5 mg capsules / Pack size 28		2.0	£0.33	£0.01	£0.02	£0.72	
Average cost of Ramipril						**£1.64**	
Average cost of ACEi						**£3.45**	

Items	Maximum daily dose	Daily tablets required for maximum dose†	Pack price	Cost per table‡	Cost per day§	Cost per month¶	Source
ARB							
Irbesartan 150 mg / Hydrochlorothiazide 12.5 mg tablets (Co-aprovel or eqv) / Pack size 28	300 mg	2.0	£6.30	£0.22	£0.45	£13.69	EMC (157); eMIT (140)
Irbesartan 150 mg tablets / Pack size 28		2.0	£0.99	£0.04	£0.07	£2.15	
Irbesartan 300 mg / Hydrochlorothiazide 12.5 mg tablets (Co-aprovel or eqv) / Pack size 28		1.0	£6.11	£0.22	£0.22	£6.65	
Irbesartan 300 mg / Hydrochlorothiazide 25 mg tablets (Co-aprovel or eqv) / Pack size 28		1.0	£4.40	£0.16	£0.16	£4.78	
Irbesartan 300 mg tablets / Pack size 28		1.0	£1.51	£0.05	£0.05	£1.64	
Irbesartan 75 mg tablets / Pack size 28		4.0	£0.58	£0.02	£0.08	£2.53	
Average cost of Irbesartan						**£5.24**	
Losartan 100 mg tablets / Pack size 28	150 mg	1.5	£1.55	£0.06	£0.08	£2.54	EMC (158); eMIT (140)
Losartan 25 mg tablets / Pack size 28		6.0	£0.85	£0.03	£0.18	£5.53	
Average cost of Losartan						**£4.03**	
Average cost of ARB						**£4.64**	
Dapagliflozin							
Forxiga 5 mg tablets / Pack size 28	10 mg	2.0	£36.59	£1.31	£2.61	£79.55	BNF (141); EMC (159)
Forxiga 10 mg tablets / Pack size 28		1.0	£36.59	£1.31	£1.31	£39.78	
Average cost of dapagliflozin						**£59.66**	

Abbreviations: ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker.
† Calculated as the maximum daily dose divided by the tablet size; ‡ Calculate as the pack price divided by the pack size; § Calculated as the cost per tablet multiplied by the number of daily tables required for maximum dose; ¶ Calculated as the cost per day multiplied by 30.4375 days.

The average monthly cost of each SoC treatment class was weighted by the proportion of patients that receive each treatment class to produce a total SoC monthly cost of £63.71, as shown in Table 34.

Table 34: Weighted average monthly cost of SoC

Treatment	Weighting	Monthly cost	Weighted average cost
ACEi	50%	£3.45	£1.73
ARB	50%	£4.64	£2.32
SGLT2i	100%	£59.66	£59.66
Weighted average cost of SoC			**£63.71**

Abbreviations: ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; SGLT2i, sodium-glucose cotransporter-.

B.3.5.1.3 Treatment costs used in the economic model

Table 35 presents the unit cost associated with a full 16 mg dose for TRF-budesonide and SoC.

Table 35: Unit costs associated with the TRF-budesonide and SoC in the economic model

Items	TRF-budesonide	Source	SoC	Source
Cost per pack	[redacted]	Data on file	N/A	Assumption
Administration cost	£0.00		£0.00	
Total cost per monthly cycle	[redacted]	Data on file	£63.71	
Total cost per reduced dose monthly cycle	[redacted]	Assumes 8 mg per day for 2-weeks after 9 months of treatment	N/A	

Abbreviations: N/A, not applicable; SoC, standard of care; TRF, targeted-release formulation.
SoC, standard of care multiplied by the cost per pack (£4,838.58) to calculate the total cost per monthly cycle

The total monthly cycle cost for TRF-budesonide was calculated by multiplying the daily dose of 16 mg by 30.4375 to determine the monthly dose. This was then used to calculate the number of packs required each month.

B.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 to 5, the cost of MRU was sourced from Kent et al. 2015 (82), 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. Kent et al. 2015 (82) costs were inflated to 2021 costs using Personal Social Services Research Unit (PSSRU) inflation indices (160).

As Kent et al. 2015 (82) reports costs by health state for secondary costs, the CEM also included the cost of primary care. Primary care costs in the CEM comprise GP appointments and blood tests. The cost of a GP appointment was sourced from the PSSRU (160), with the cost of blood tests obtained from the NHS National Cost Collection 2021/22 (139). The model assumes GP appointments and blood tests occur twice a year for CKD stages 1 to 3b and quarterly throughout the year for CKD 4 and CKD 5.

MRU unit costs for dialysis were sourced from the NHS National Cost Collection 2021/22 (139). Patients in the dialysis health state are assumed to receive either haemodialysis (86.5%) or peritoneal dialysis (13.5%) based on the proportions reported in the UKRR 24th Annual report (148). Patients receiving haemodialysis were then further distributed by the modalities: hospital haemodialysis (35.4%), satellite haemodialysis (58.9%) and home haemodialysis (5.7%), also sourced from the UKRR 24th Annual report (148). The unit costs for haemodialysis were calculated as weighted averages of the healthcare resource groups (HRG) codes outlined in Table 36.

Patients receiving hospital and satellite haemodialysis were also assigned a transportation cost sourced from Liu et al. 2015 (81), 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.

The CEM applies the costs of nephrologist outpatient appointments, blood tests and hospitalisations to patients receiving dialysis. In the model base case, nephrology appointments and blood tests were assumed to occur quarterly, with one hospitalisation per year for 50% of all dialysis patients also assumed and validated by clinical opinion.

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 (161). The guidance in TA481 suggests that in practice, patients may require a combination of immunosuppressive therapy (161). However, as this is considered on a case-by-case basis, the CEM utilised 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 (161)) 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 2021/22 (139) as presented in Table 36. Hospitalisations were assumed to occur once annually for 50% of patients in the transplant health state, as validated by clinical expert opinion.

The MRU unit costs assumed in the model and their respective sources are summarised in Table 36. The sources for the frequency of each MRU type per health state are summarised in Table 37.

Table 36: MRU unit costs

Resource use	Unit cost	Source
GP appointment	£28.00	PSSRU: Unit Costs of Health and Social Care 2021 . General Practitioner. Cost per surgery consultation lasting 9.22 minutes, excluding direct medical costs, without qualification costs (160).
Blood tests	£2.96	National Schedule of NHS costs – Year 2021-22 – NHS trust and NHS foundation trusts. Total HRGs – DAPS05: Haematology (139)
Nephrologist visits	£196.88	National Schedule of NHS costs – Year 2021-22 – NHS trust and NHS foundation trusts. Total Outpatient Attendance – Service code 361 (139)
Hospital haemodialysis	£187.86	National Schedule of NHS costs – Year 2021-22: Total HRG's – weighted average LD01A, LD02A, LD03A, LD04A (139)
Satellite haemodialysis	£163.51	National Schedule of NHS costs – Year 2021-22 – NHS trust and NHS foundation trusts. Total HRGs – weighted average LD01A, LD02A, LD03A, LD04A (139)
Home haemodialysis	£218.76	National Schedule of NHS costs – Year 2021-22 – NHS trust and NHS foundation trusts. Total HRGs – weighted average LD05A, LD06A, LD07A, LD08A (139)
Haemodialysis transport	£12.94	National Schedule of NHS costs – Year 2021-22 – NHS trust and NHS foundation trusts. Total HRGs – weighted average LD09A, LD10A (139)
Peritoneal dialysis	£82.83	National Schedule of NHS costs – Year 2021-22 – NHS trust and NHS foundation trusts. Total HRGs – weighted average LD11A, LD12A, LD13A (139)

Resource use	Unit cost	Source
Transplantation pre-assessment	£414.76	National Schedule of NHS costs – Year 2021-22 – NHS trust and NHS foundation trusts. Total HRGs – weighted average LA11Z, LA12A (139)
Transplantation procedure cost	£17,838.14	National Schedule of NHS costs – Year 2021-22 – NHS trust and NHS foundation trusts. Total HRGs – weighted average LA01A, LA02A, LA03A (139)
Transplantation post-transplant assessment	£290.94	National Schedule of NHS costs – Year 2021-22 – NHS trust and NHS foundation trusts. Total HRGs – weighted average LA13A, LA14Z (139)
Tacrolimus	£42.92	BNF: Adaport 0.5mg capsule, pack size 50 (162)
Hospitalisation	£775.55	National Schedule of NHS costs – Year 2021-22 – NHS trust and NHS foundation trusts. Non elective short stay – weighted average LA08G, LA08H, LA08J, LA08K, LA08L, LA08M, LA08N, LA08P (139)

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

Table 37: Frequency of MRU annually, by health state

Annual frequency of MRU	CKD stages 1 to 3a	CKD 4 & CKD 5	HD	PD	Transplant	Source
GP appointment	2	4	0	0	2	Assumption
Blood tests	2	4	4	4	4	
Nephrologist visits	0	0	4	4	2	
Hospital haemodialysis	-	-	156†	-	-	NHS website (73)
Satellite haemodialysis	-	-	156†	-	-	
Home haemodialysis	-	-	156†	-	-	
Haemodialysis transport	-	-	156‡	-	-	NHS survey (163)
Peritoneal dialysis	-	-	-	365.25	-	NHS website (73)
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 38 presents the total costs applied per cycle for each health state, in addition to the one-off costs of transplantation.

Table 38: MRU costs per cycle by health state

Health state	Total cost per health state
CKD 1	£110.86
CKD 2	£110.86
CKD 3a	£110.86
CKD 3b	£110.86
CKD 4	£380.41
CKD 5	£1,307.94
Dialysis	£2,547.29
Transplant (Transplantation maintenance)	£1,366.27
One-off transplantation cost	
Transplantation procedural costs	£18,543.84†

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.

B.3.5.3 End of life costs

End of life care costs were sourced from Kerr et al. 2017 (85), 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 (85) 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. The 30-day value is chosen to inform the CEM base case in order to avoid potential double-counting with MRU costs. The Kerr et al. 2017 (85) cost for hospital care from 30 days to death was inflated to 2021 prices using PSSRU inflation indices (160). The inflated end of life cost implemented in the CEM is £3,222.10, which is applied upon transition to the death state prices using PSSRU inflation indices (160). The inflated end of life cost implemented in the CEM is £3,222.10, which is applied upon transition to the death state.

B.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 2021/22 (139). The cost per AE was calculated as the weighted average of HRG codes presented in Costs associated with the resolution of AEs are sourced

from the NHS national cost collection 2021/22 (139). The cost per AE was calculated as the weighted average of HRG codes presented in Table 39.

Table 39: List of adverse reactions and summary of costs in the economic model

Treatment-emergent AE	Cost	Source
Acne	£0.00	Assumption
Cushingoid	£197.59	NHS ref 21/22: Total Outpatient Attendance - Service code 302, Endocrinology (139)
Dyspepsia	£148.93	NHS ref 21/22: Total Outpatient Attendance - Service code 301, Gastroenterology (139)
Oedema peripheral	£0.00	Assumption
Face oedema	£0.00	Assumption
Headache	£0.19	eMIT: Paracetamol 500mg tablets, pack size 16 (140)
Hirsutism	£0.00	Assumption
Hypertension	£196.88	NHS ref 21/22: Total Outpatient Attendance - Service code 361, Nephrology (139)
Mood swings	£0.00	Assumption
Upper respiratory tract infection	£1,273.39	NHS ref 21/22 : Total HRG's - weighted average CB02A, CB02B, CB02C, CB02D, CB02E, CB02F (139)
Weight increase	£0.00	Assumption
Treatment emergent SAE		
Pulmonary embolism	£1,905.92	NHS ref 21/22: Total HRGs - weighted average DZ09J, DZ09K, DZ09L, DZ09M, DZ09N, DZ09P, DZ09Q (139)
Renal impairment	£1,757.91	NHS ref 21/22: Total HRGs - weighted average LA09J, LA09K, LA09L, LA09M, LA09N, LA09P, LA09Q (139)

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.

B.3.5.5 Miscellaneous unit costs and resource use

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

B.3.6 Severity

Not applicable.

B.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.

B.3.7.1 Uncertainty in clinical inputs

The rare nature of IgAN places substantial limitations on the ability to collect efficacy data, as the only available phase 3 data for patients with UPCR ≥1.5 g/g comes from the NefIgArd Nef-301 trial. The small sample size of this trial is a key source of uncertainty, particularly as there was only one patient with CKD 1 at baseline. Furthermore, at the time of submission, there was only data available for patients with UPCR ≥1.5 g/g up to 9 months of treatment which meant assumptions regarding TRF-budesonide's treatment effect beyond 9 months had to be made. Whilst there is evidence to suggest TRF-budesonide's effect lasts up to 12 months (as described in Section B.3.3.1.1), there is less evidence to support the assumption that TRF-budesonide's treatment effect extends beyond 12 months. Therefore, the model makes the conservative assumption that treatment effect stops after 1-year 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.

B.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 MHRA license wording indicates that retreatment may be considered at the discretion of the treating

physician (1). 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. As such, assumptions regarding the efficacy of retreatment have been made which increase the level of uncertainty regarding retreatment.

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 (1). Although tapering was excluded from the model base case based on clinician feedback (2), the impact tapering would have on the ICER is explored in the scenario analysis.

B.3.8 Managed access proposal

Not applicable.

B.3.9 Summary of base-case analysis inputs and assumptions

B.3.9.1 Summary of base-case analysis inputs

The base-case inputs for the economic model are summarised in Table 40.

Table 40: Summary of variables applied in the economic model

Variable	Value	Measurement of uncertainty (distribution)	Reference to section in submission
Model setup parameters			
Time horizon	56 years	Fixed	Section B.3.2.3
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	[redacted]	Normal	Section B.3.2.2
Proportion female	[redacted]	Beta	
Average weight	[redacted]	Normal	

Variable	Value	Measurement of uncertainty (distribution)	Reference to section in submission
Distribution across CKD stages at baseline			
CKD 1	[redacted]	Dirichlet	Section B.3.2.2
CKD 2	[redacted]	Dirichlet	
CKD 3a	[redacted]	Dirichlet	
CKD 3b	[redacted]	Dirichlet	
CKD 4	[redacted]	Dirichlet	
TRF-budesonide treatment effect			
HR applied to SoC risk of CKD 5	[redacted]	Log-normal	Section B.3.3
Time point from where no treatment effect is assumed	1 year	Normal	
Health utility values			
CKD 1	0.85	Beta	Section B.3.4
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	0.00	Beta	Section B.3.4.4
Cushingoid	0.05	Beta	
Dyspepsia	0.05	Beta	
Oedema peripheral	0.11	Beta	
Face oedema	0.00	Beta	
Headache	0.03	Beta	
Hirsutism	0.05	Beta	
Hypertension	0.03	Beta	
Mood swings	0.02	Beta	
Upper respiratory tract infection	0.00	Beta	
Weight increase	0.00	Beta	
Pulmonary embolism	0.00	Beta	
Renal impairment	0.00	Beta	
Adverse event rate duration (days)			

Variable	Value	Measurement of uncertainty (distribution)	Reference to section in submission
Acne	7.00	Normal	Section B.3.4.4
Cushingoid	7.00	Normal	
Dyspepsia	7.00	Normal	
Oedema peripheral	7.00	Normal	
Face oedema	7.00	Normal	
Headache	7.00	Normal	
Hirsutism	7.00	Normal	
Hypertension	7.00	Normal	
Mood swings	7.00	Normal	
Upper respiratory tract infection	3.48	Normal	
Weight increase	7.00	Normal	
Pulmonary embolism	6.61	Normal	
Renal impairment	6.29	Normal	
Adverse event rates – TRF-budesonide			
Acne	[redacted]	Normal	Section B.3.3.4
Cushingoid	[redacted]	Normal	
Dyspepsia	[redacted]	Normal	
Oedema peripheral	[redacted]	Normal	
Face oedema	[redacted]	Normal	
Headache	[redacted]	Normal	
Hirsutism	[redacted]	Normal	
Hypertension	[redacted]	Normal	
Mood swings	[redacted]	Normal	
Upper respiratory tract infection	[redacted]	Normal	
Weight increase	[redacted]	Normal	
Pulmonary embolism	[redacted]	Normal	
Renal impairment	[redacted]	Normal	
Adverse event rates – SoC			
Acne	[redacted]	Normal	Section B.3.3.4
Cushingoid	[redacted]	Normal	
Dyspepsia	[redacted]	Normal	
Oedema peripheral	[redacted]	Normal	
Face oedema	[redacted]	Normal	
Headache	[redacted]	Normal	
Hirsutism	[redacted]	Normal	

Variable	Value	Measurement of uncertainty (distribution)	Reference to section in submission
Hypertension	[redacted]	Normal	
Mood swings	[redacted]	Normal	
Upper respiratory tract infection	[redacted]	Normal	
Weight increase	[redacted]	Normal	
Pulmonary embolism	[redacted]	Normal	
Renal impairment	[redacted]	Normal	
TRF-budesonide treatment costs			
Full dose monthly cost	[redacted]	Normal†	Section B.3.5.1.3
Reduce dose 2-weekly cost	[redacted]	Normal†	
Administration cost per dose	£0.00	Normal†	
SoC treatment cost			
Monthly treatment cost	£63.71	Normal†	Section B.3.5.1.3
Monthly administration cost	£0.00	Normal†	
Resource use costs			
GP appointment	£28.00	Normal†	Section B.3.5.2
Blood tests	£2.96	Normal†	
Nephrologist visits	£196.88	Normal†	
Hospital haemodialysis	£187.86	Normal†	
Satellite haemodialysis	£163.51	Normal†	
Home haemodialysis	£218.76	Normal†	
Haemodialysis transport	£12.94	Normal†	
Peritoneal dialysis	£82.83	Normal†	
Transplantation pre-assessment	£414.76	Normal†	
Transplantation procedure cost	£17,838.14	Normal†	
Transplantation post-transplant assessment	£290.94	Normal†	
Tacrolimus	£42.92	Normal†	
Hospitalisation	£775.55	Normal†	
End of life costs			
Hospital care – 30 days to death	£3,222.10	Normal†	Section B.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

B.3.9.2 Assumptions

The main assumptions of the economic model alongside supporting justifications are presented in Table 41.

Table 41: Key assumptions of the analysis

Model input and cross reference	Source / assumption	Justification
Time horizon (B.3.2.3.1)	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 (137).
Perspective (B.3.2.3.2)	The perspective is that of the NHS in England and Wales, and PSS.	Preference specified in NICE reference case (137).
Patient population (B.3.2.2)	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 (B.3.2.4.2)	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 (108), which is assumed to represent optimised supportive care. KDIGO 2021 describes optimised supportive care as: blood pressure management; maximally tolerated dose of ACEi/ARB; lifestyle modification; and addressing cardiovascular risk (3).
Comparators (B.3.2.4.2)	The decision problem is assumed to be addressed by a comparison to optimised supportive care only.	The KDIGO 2021 guideline recommends “that patients who remain at high risk of progressive CKD despite maximal supportive care be considered for a 6-month course of glucocorticoid therapy” (Recommendation 2.3.11) (3). As such, there is some overlap in the expected 2022 MHRA licensed population for TRF-budesonide, and those who may be considered for a 6-month course of glucocorticoid therapy in practice. Concomitant glucocorticoid therapy was not permitted in NefIgArd Nef-301, and no head-to-head trial evidence exists for TRF-budesonide versus a 6-month course of currently available glucocorticoid treatment.
Inclusion of SGLT2is within SoC (B.3.2.4.2)	SGLT2is are included as part of the SoC for all patients within the model, but do not	Assumption is based on expert clinical feedback who anticipated that SGLT2is would form part of standard treatment for

Model input and cross reference	Source / assumption	Justification
	have any impact on efficacy versus that seen in the placebo arm of the NefIgArd Nef-301 trial.	all patients defined as part of this decision problem. SGLT2is have been shown to have an insignificant impact on eGFR decline in IgAN patients (120). 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.
Exclusion of glucocorticoids from SoC (B.3.2.4.2)	Glucocorticoids were not included as part of the SoC for patients within the model.	Assumption is based on expert clinical feedback who confirmed that glucocorticoids are not widely used in clinical practice for IgAN patients due to their poor risk-benefit profile demonstrated in the STOP-IgAN and TESTING studies.
Data from outside of Part A of the NefIgArd Nef-301 study (B.3.4 & B.3.5)	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 (B.3.2.4.1.1)	Only patients in CKD stages 1-3b at the time of retreatment are assumed to be eligible to receive retreatment with TRF-budesonide. Furthermore, it is assumed only a proportion of eligible patients will receive retreatment.	Data from the NefIgArd-OLE study which includes patients that are potentially eligible for retreatment with TRF-budesonide is not currently available. Therefore, the retreatment eligibility criteria aligns with Part A of the NefIgArd eligibility criteria (eGFR ≥35 mL/min/1.73m^2). Since patients that discontinue TRF-budesonide are unlikely to be retreated with TRF-budesonide, the model assumes patients that remained on treatment by month 8 would receive another round of treatment if they still remained in CKD 1 to CKD3b health states.
Retreatment efficacy (B.3.2.4.1.1)	It is assumed that TRF-budesonide's treatment effect does not diminish with retreatment cycles.	While the MHRA licence wording states retreatment may be considered at the discretion of the treating physician, there is no available safety or efficacy data regarding subsequent treatment courses of TRF-budesonide. As such, it was

Model input and cross reference	Source / assumption	Justification
		assumed the safety and efficacy data for retreatment with TRF-budesonide was equivalent to the safety and efficacy data for the initial treatment of TRF-budesonide. This strategy is in line with treatment guidelines from KDIGO 2021 (3) in which similar treatment patterns are advised for those who relapse. For example, patients with membranous nephropathy may be retreated with rituximab, or frequently relapsing patients with minimal change disease may be retreated with glucocorticoids.
Adverse events (B.3.4.4)	Only TESAEs that occur in more than one patient are included in the model.	Only TEAEs that would likely incur costs from the model's perspective are included. TESAEs were restricted to AEs that occurred in more than one patient to avoid the inclusion of anomaly adverse events and to ensure a manageable list to model.
Transitions between CKD health states (B.3.3)	Patients can only transition to CKD health states that neighbour the patients current CKD state.	Reflecting the observed patient movements in Part A of the NeflgArd 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 assumption was also validated by clinical experts.
Transitions to CKD 5 (B.3.3.2)	Risk of progression to CKD 5 is only possible from CKD 4 health state.	Assumption validated by clinical experts.

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 even

B.3.10 Base-case results

B.3.10.1 Base-case incremental cost-effectiveness analysis results

Table 42: 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]	16.060	[redacted]	-	-	-	-	-
SoC	[redacted]	15.958	[redacted]	[redacted]	0.102	[redacted]	£18,643	£18,643

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

Table 43: 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]	£509	£4,257

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.

Disaggregated results of the base-case incremental cost-effectiveness analysis are presented in Appendix J.

B.3.11 Exploring uncertainty

B.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, 10,000 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 variance-covariance matrix used to vary the transition probabilities in the PSA is specific to patients with primary IgAN with UPCR ≥1.5 g/g. However, it is noted that there was only one patient with CKD 1 at the start of the trial from which the transitions were calculated. Therefore, in the PSA the transition probability from CKD 1 to CKD 2 was amended to ensure illogical transitions (i.e. transition values below 0% and above 100%) were set to 0% and 100%, respectively. The result of this was a large spread of outcomes across iterations due to the high levels of uncertainty associated with the CKD 1 to CKD 2 transition.

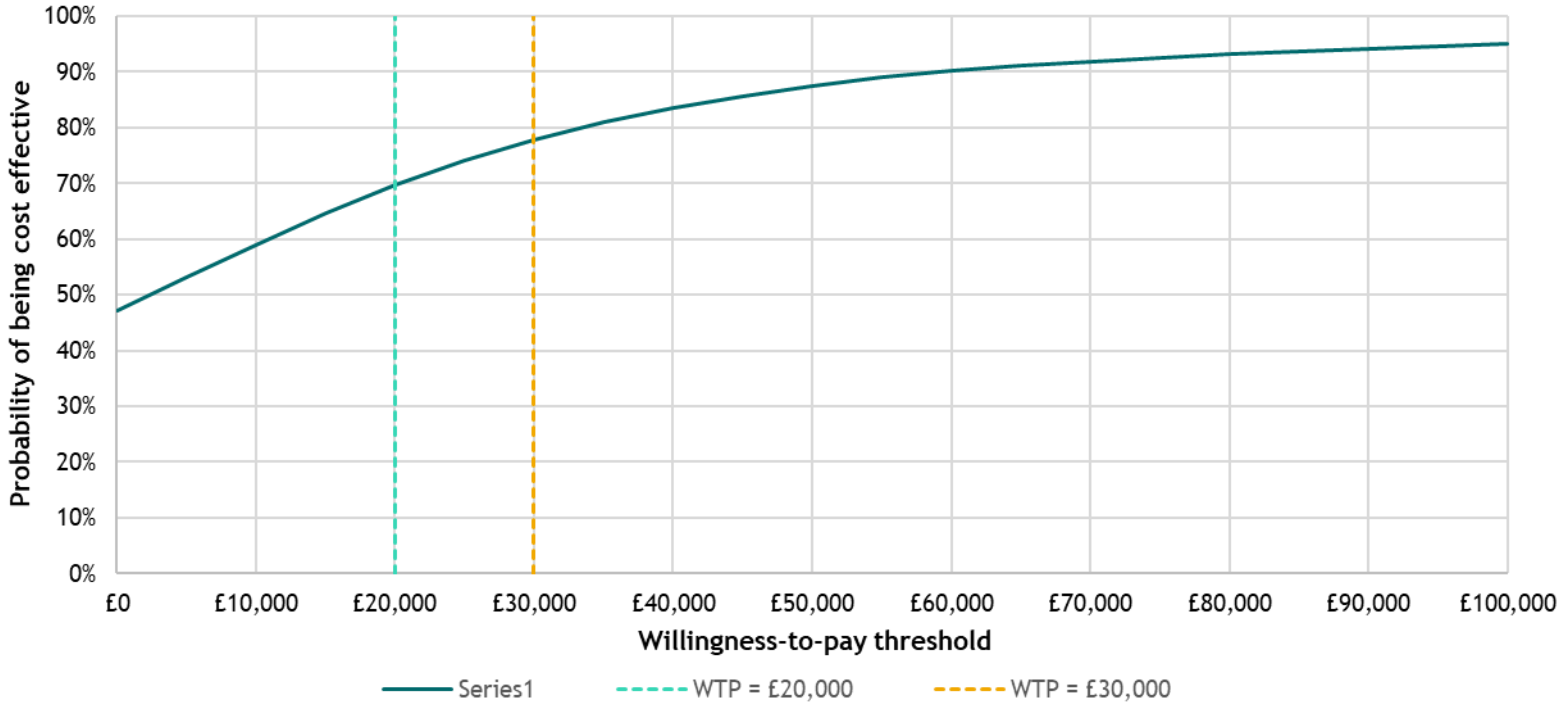
The PSA results are presented in Table 44. Cost-effectiveness acceptability curves are presented in Figure 24.

Table 44: 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]	16.569	[redacted]	-	-	-	-	-
SoC	[redacted]	16.166	[redacted]	[redacted]	0.403	[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.

Figure 22: Cost-effectiveness acceptability curve



Disaggregated mean results of the probabilistic incremental cost-effectiveness analysis are presented in Appendix J.

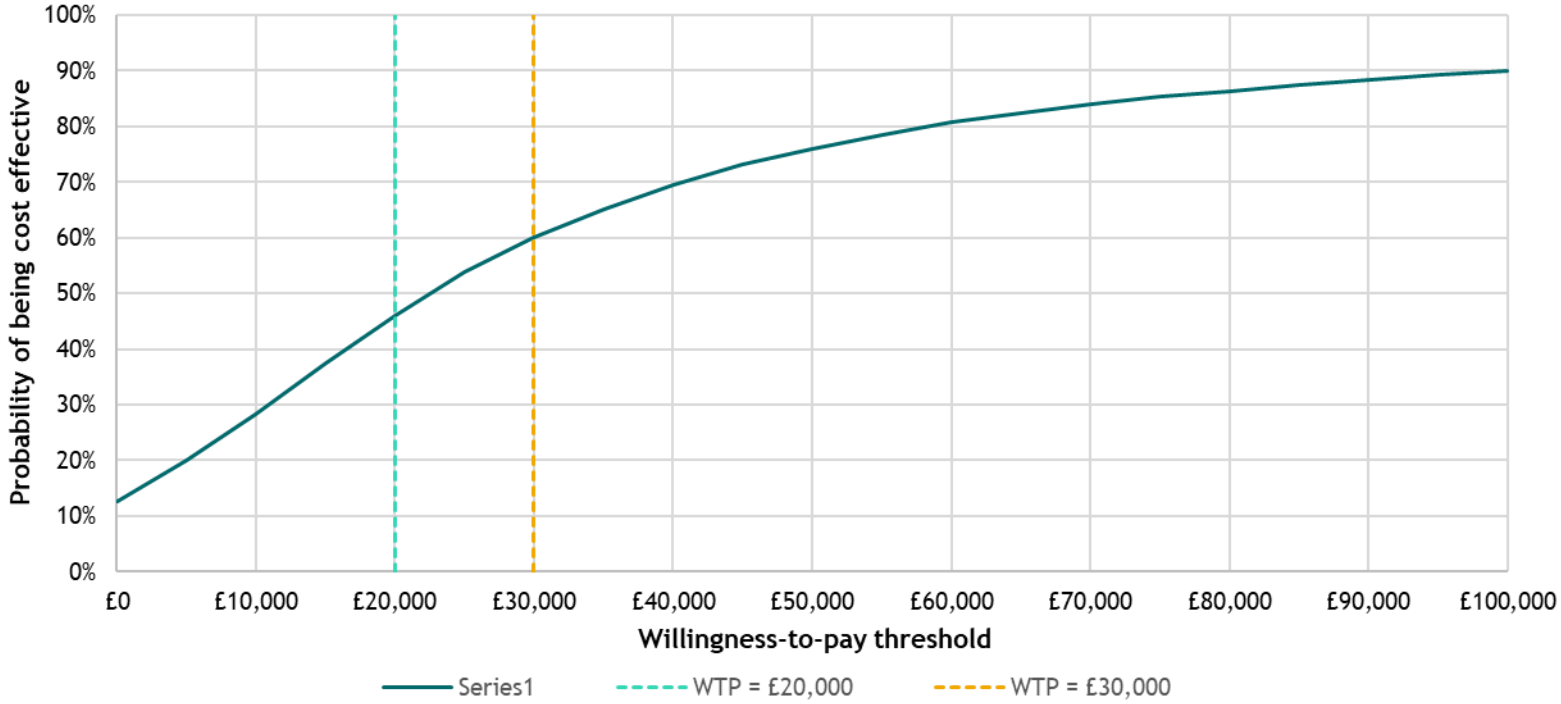
The transition between CKD 1 to CKD 2 in the TRF-budesonide arm is informed by data from [redacted] in Part A of the NeflgArd Nef-301 study. Therefore, when this transition is varied in the PSA, it often takes extreme values of either 0% or 100% which has a significant impact on the ICER produced in the PSA. Therefore, a PSA that excluded this transition was also run. The results of this PSA are presented in Table 45 and the cost-effectiveness acceptability cure is presented in Figure 23.

Table 45: Probabilistic incremental cost-effectiveness results excluding the CKD 1 to CKD 2 transition uncertainty

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
TRF-budesonide	[redacted]	16.127	[redacted]	-	-	-	-	-
SoC	[redacted]	15.988	[redacted]	[redacted]	0.139	[redacted]	£24,361	£24,361

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

Figure 23: Cost-effectiveness acceptability curve when the CKD 1 to CKD 2 transition in the TRF-budesonide arm is excluded



B.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.

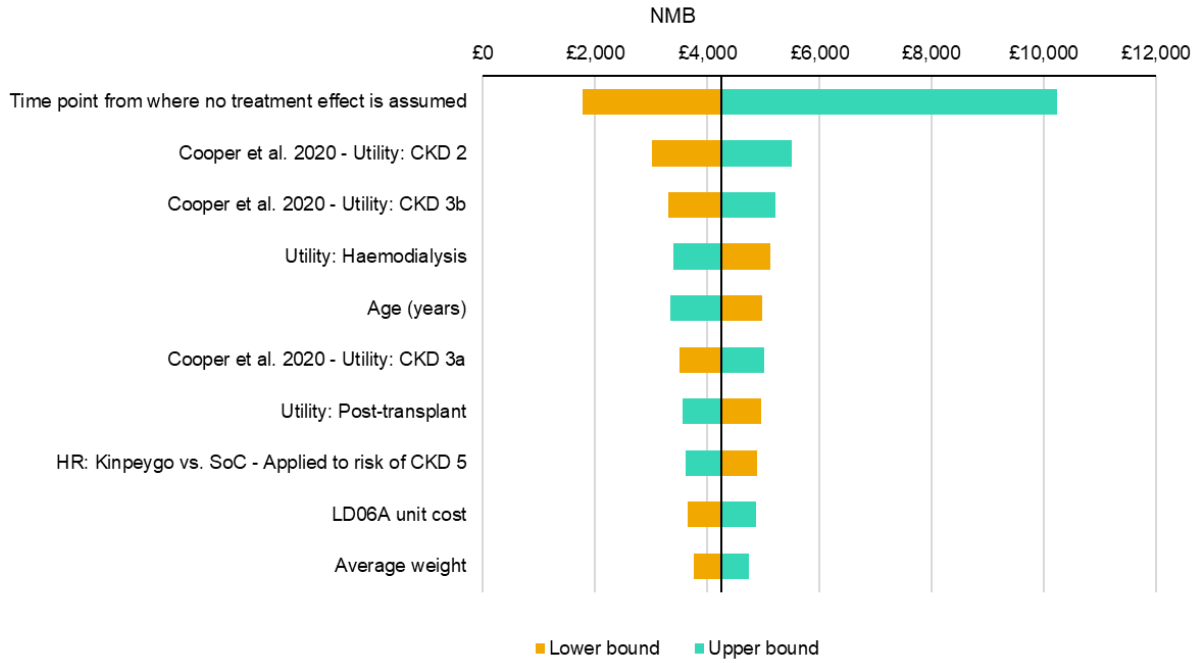
A list of the included variables is presented in Table 46. A tornado diagram showing the top ten parameters that have the greatest impact on the NMB (at a willingness to pay threshold of £30,000/QALY) is presented in Figure 24.

Table 46: DSA inputs used

Variable	Low NMB estimate	High NMB estimate	Change in NMB
Time point from where no treatment effect is assumed	[redacted]	[redacted]	£8,454
Cooper et al. 2020 - Utility: CKD 2	[redacted]	[redacted]	£2,492
Cooper et al. 2020 - Utility: CKD 3b	[redacted]	[redacted]	£1,903
Utility: Haemodialysis	[redacted]	[redacted]	£1,719
Age (years)	[redacted]	[redacted]	£1,636
Cooper et al. 2020 - Utility: CKD 3a	[redacted]	[redacted]	£1,512
Utility: Post-transplant	[redacted]	[redacted]	£1,391
HR: Kinpeygo vs. SoC - Applied to risk of CKD 5	[redacted]	[redacted]	£1,274
LD06A unit cost	[redacted]	[redacted]	£1,220
Average weight	[redacted]	[redacted]	£978

Abbreviations: CKD, chronic kidney disease; DSA, deterministic sensitivity analysis; NMB, net monetary benefit.

Figure 24: Tornado diagram



Abbreviations: CKD, chronic kidney disease; HR, hazard ratio: SoC, standard of care; NMB, net monetary benefit.

B.3.11.3 Scenario analyses

A summary of the scenario analyses conducted is presented in Table 47.

Table 47: Scenario analyses

Variable	Base case	Scenario analysis	Justification
Time horizon	56 years	10 years	To explore the impact of alternative time horizons on the model results
		20 years	
		30 years	
		40 years	
		50 years	
Distribution of patients across CKD states at baseline	Part A NefIgArd Nef-301 trial subgroup data for UPCR ≥1.5 g/g	UK RaDaR data	To assess the impact of using real world data has compared to clinical trial data has when informing baseline distribution across CKD stages.
		UK RaDaR data - apportioned to exclude CKD 4	
Parametric extrapolations to estimate time to CKD 5	Gamma	Exponential	To explore the uncertainty associated with parametric survival model fitted to extrapolate the risk of CKD 5 data
		Generalised gamma	
		Gompertz	
		Log-logistic	
		Log-normal	
		Weibull	

Variable	Base case	Scenario analysis	Justification
Risk of ESRD	UK RaDaR data - all patients	UK RaDaR data – ACEi and ARB patients	To explore uncertainty in the method for estimation of risk of CKD 5 in the SoC arm
		Leicester General Hospital data with HR applied	
SoC acquisition costs	£63.71	£0	To assess the impact of SoC costs associated with improved life expectancy
Time point from where no treatment effect is assumed	1 year	1.5 year	To explore uncertainty in the timepoint at which TRF-budesonide no longer has a treatment effect
		2 years	
		2.5 years	
		5 years	
Mortality source	UK RaDaR data	Greene et al. 2019 (164)	To assess the impact of using different sources of mortality rates
		Hastings et al. 2018 (17)	
CKD stage utility source	Cooper et al. 2020 (138)	Gorodetskaya et al. 2005 (165)	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
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
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 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
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	
Societal costs	Excluded	Included	To determine the impact societal costs have on the model results

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

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

B.3.11.3.1: Time horizon scenarios

Table 48: Scenario analysis results - Time horizon decreased from 56 years to 10 years

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
TRF-budesonide	[redacted]	8.27	[redacted]	-	-	-	-	-
SoC	[redacted]	8.22	[redacted]	[redacted]	0.04	[redacted]	£36,627	£36,627

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

Table 49: Scenario analysis results - Time horizon decreased from 56 years to 20 years

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
TRF-budesonide	[redacted]	13.15	[redacted]	-	-	-	-	-
SoC	[redacted]	13.07	[redacted]	[redacted]	0.09	[redacted]	£16,995	£16,995

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

Table 50: Scenario analysis results - Time horizon decreased from 56 years to 30 years

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
TRF-budesonide	[redacted]	15.44	[redacted]	-	-	-	-	-
SoC	[redacted]	15.34	[redacted]	[redacted]	0.10	[redacted]	£18,189	£18,189

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

Table 51: Scenario analysis results - Time horizon decreased from 56 years to 40 years

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
TRF-budesonide	[redacted]	16.03	[redacted]	-	-	-	-	-
SoC	[redacted]	15.93	[redacted]	[redacted]	0.10	[redacted]	£18,617	£18,617

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

Table 52: Scenario analysis results - Time horizon decreased from 56 years to 50 years

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
TRF-budesonide	[redacted]	16.06	[redacted]	-	-	-	-	-
SoC	[redacted]	15.96	[redacted]	[redacted]	0.10	[redacted]	£18,643	£18,643

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

B.3.11.3.2: Baseline distribution across CKD states at baseline scenario

Table 53: Scenario analysis results – UK RaDaR data (ACEi & ARB patients) to inform the baseline distribution across CKD states

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
TRF-budesonide	[redacted]	15.84	[redacted]	-	-	-	-	-
SoC	[redacted]	15.81	[redacted]	[redacted]	0.02	[redacted]	Dominant	Dominant

Abbreviations: ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; CKD, chronic kidney disease; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years; SoC, standard of care; TRF, targeted-release formulation; UK RaDaR; United Kingdom National Registry of Rare Kidney Diseases.

Table 54: Scenario analysis results – UK RaDaR data apportioned to exclude CKD 4 to inform the baseline distribution across CKD states

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
TRF-budesonide	[redacted]	16.04	[redacted]	-	-	-	-	-
SoC	[redacted]	15.94	[redacted]	[redacted]	0.10	[redacted]	£15,257	£15,257

Abbreviations: CKD, chronic kidney disease; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years; SoC, standard of care; TRF, targeted-release formulation; UK RaDaR; United Kingdom National Registry of Rare Kidney Diseases.

B.3.11.3.3: Parametric extrapolations to estimate time to CKD 5 scenarios

Table 55: Scenario analysis results – Exponential extrapolation

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
TRF-budesonide	[redacted]	16.12	[redacted]	-	-	-	-	-
SoC	[redacted]	16.02	[redacted]	[redacted]	0.10	[redacted]	£14,777	£14,777

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

Table 56: Scenario analysis results – Generalised gamma extrapolation

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
TRF-budesonide	[redacted]	16.08	[redacted]	-	-	-	-	-
SoC	[redacted]	15.97	[redacted]	[redacted]	0.10	[redacted]	£17,527	£17,527

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

Table 57: Scenario analysis results – Gompertz extrapolation

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
TRF-budesonide	[redacted]	15.87	[redacted]	-	-	-	-	-
SoC	[redacted]	15.75	[redacted]	[redacted]	0.12	[redacted]	£34,791	£34,791

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

Table 58: Scenario analysis results – Log-logistic extrapolation

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
TRF-budesonide	[redacted]	15.80	[redacted]	-	-	-	-	-
SoC	[redacted]	15.68	[redacted]	[redacted]	0.12	[redacted]	£41,287	£41,287

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

Table 59: Scenario analysis results – Log-normal extrapolation

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
TRF-budesonide	[redacted]	15.78	[redacted]	-	-	-	-	-
SoC	[redacted]	15.66	[redacted]	[redacted]	0.12	[redacted]	£43,661	£43,661

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: Scenario analysis results – Weibull extrapolation

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
TRF-budesonide	[redacted]	16.03	[redacted]	-	-	-	-	-
SoC	[redacted]	15.93	[redacted]	[redacted]	0.10	[redacted]	£21,011	£21,011

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

B.3.11.3.4: Risk of ESRD scenarios

Table 61: Scenario analysis results – Risk informed by UK RaDaR data (ACEi and ARB patients)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
TRF-budesonide	[redacted]	16.17	[redacted]	-	-	-	-	-
SoC	[redacted]	16.06	[redacted]	[redacted]	0.11	[redacted]	£18,839	£18,839

Abbreviations: ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years; SoC, standard of care; TRF, targeted-release formulation; UK RaDaR; United Kingdom National Registry of Rare Kidney Diseases.

Table 62: Scenario analysis results – Leicester General Hospital data with HR applied

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
TRF-budesonide	[redacted]	16.17	[redacted]	-	-	-	-	-
SoC	[redacted]	16.06	[redacted]	£[redacted]	0.11	[redacted]	£20,898	£20,898

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

B.3.11.3.5: SoC acquisition cost

Table 63: Scenario analysis results – £0 SoC acquisition cost

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
TRF-budesonide	[redacted]	16.06	[redacted]					
SoC	[redacted]	15.96	[redacted]	[redacted]	0.10	[redacted]	£16,100	£16,100

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

B.3.11.3.6: Time point from where no treatment effect is assumed

Table 64: Scenario analysis results – 1.5 years

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
TRF-budesonide	[redacted]	16.12	[redacted]	-	-	-	-	-
SoC	[redacted]	15.96	[redacted]	[redacted]	0.17	[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 65: Scenario analysis results – 2 years

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
TRF-budesonide	[redacted]	16.20	[redacted]	-	-	-	-	-
SoC	[redacted]	15.96	[redacted]	[redacted]	0.24	[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 66: Scenario analysis results – 2.5 years

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
TRF-budesonide	[redacted]	16.20	[redacted]	-	-	-	-	-
SoC	[redacted]	15.96	[redacted]	[redacted]	0.24	[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 67: Scenario analysis results – 5 years

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
TRF-budesonide	[redacted]	16.28	[redacted]	-	-	-	-	-
SoC	[redacted]	15.96	[redacted]	[redacted]	0.32	[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 68: Scenario analysis results – Treatment effect continues over entire time horizon

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
TRF-budesonide	[redacted]	18.15	[redacted]	-	-	-	-	-
SoC	[redacted]	15.96	[redacted]	[redacted]	2.19	[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.

B.3.11.3.7: Mortality source scenario

Table 69: Scenario analysis results – Greene et al. 2019 (164)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
TRF-budesonide	[redacted]	14.87	[redacted]	-	-	-	-	-
SoC	[redacted]	14.74	[redacted]	[redacted]	0.13	[redacted]	£29,553	£29,553

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

Table 70: Scenario analysis results – Hastings et al. 2018 (17)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
TRF-budesonide	[redacted]	14.87	[redacted]	-	-	-	-	-
SoC	[redacted]	14.78	[redacted]	[redacted]	0.09	[redacted]	£21,169	£21,169

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

B.3.11.3.8: CKD stage utility source scenario

Table 71: Scenario analysis results – Gorodetskaya et al. 2005 (165)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
TRF-budesonide	[redacted]	16.06	[redacted]	-	-	-	-	-
SoC	[redacted]	15.96	[redacted]	[redacted]	0.10	[redacted]	£15,730	£15,730

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

B.3.11.3.9: Age-adjusted utilities scenario

Table 72: Scenario analysis results – age-adjusted utilities excluded

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
TRF-budesonide	[redacted]	16.06	[redacted]	-	-	-	-	-
SoC	[redacted]	15.96	[redacted]	[redacted]	0.10	[redacted]	£18,126	£18,126

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

B.3.11.3.10: Treatment stopping approach scenario

Table 73: Scenario analysis results – TTD curve from the NeflgArd Nef-301 Part A CSR (107)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
TRF-budesonide	[redacted]	16.06	[redacted]	-	-	-	-	-
SoC	[redacted]	15.96	[redacted]	[redacted]	0.10	[redacted]	£18,711	£18,711

Abbreviations: CSR, clinical study report ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years; SoC, standard of care; TRF, targeted-release formulation; TTD, time to treatment discontinuation.

B.3.11.3.11: TRF-budesonide dose reduction scenario

Table 74: Scenario analysis results – Dose reduction excluded

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
TRF-budesonide	[redacted]	16.06	[redacted]	-	-	-	-	-
SoC	[redacted]	15.96	[redacted]	[redacted]	0.10	[redacted]	£15,011	£15,011

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

B.3.11.3.12: TRF-budesonide tapering period scenario

Table 75 presents the monthly treatment costs for TRF-budesonide for a tapered dose model cycle.

Table 75: TRF-budesonide cost per cycle, tapered dose

Treatment	Dose per admin	Tapered dose frequency	Tapered dose frequency per cycle (days)†	Total dose per cycle	Packs per cycle†	Admin cost per dose	Treatment cost per cycle
TRF-budesonide	4 mg	2 weeks	14.00	56.00	0.12	£0	£293.99

Abbreviations: TRF, targeted-release formulation.
† Equal to the model cycle length divided by the reduced dose frequency (7 days * 2 weeks).
‡ Packs per cycle calculated as total dose per cycle divided by table size (4 mg) divided by the pack size (120).
Figures presented in the table are rounded to two significant figures.

Table 76: Scenario analysis results – Tapering included

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
TRF-budesonide	[redacted]	16.06	[redacted]	-	-	-	-	-
SoC	[redacted]	15.96	[redacted]	[redacted]	0.10	[redacted]	£19,184	£19,184

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

B.3.11.3.13: TRF-budesonide retreatment scenarios

Table 77: Scenario analysis results – 1 rounds of treatment

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
TRF-budesonide	[redacted]	16.01	[redacted]	-	-	-	-	-
SoC	[redacted]	15.96	[redacted]	[redacted]	0.05	[redacted]	£36,372	£36,372

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

Table 78: Scenario analysis results – 3 rounds of treatment

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
TRF-budesonide	[redacted]	16.09	[redacted]	-	-	-	-	-
SoC	[redacted]	15.96	[redacted]	[redacted]	0.13	[redacted]	£12,047	£12,047

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

Table 79: Scenario analysis results – 4 rounds of treatment

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
TRF-budesonide	[redacted]	15.24	[redacted]	-	-	-	-	-
SoC	[redacted]	15.96	[redacted]	[redacted]	0.16	[redacted]	£11,703	£11,703

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

Table 80: Scenario analysis results – 5 rounds of treatment

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
TRF-budesonide	[redacted]	16.15	[redacted]	-	-	-	-	-
SoC	[redacted]	15.96	[redacted]	[redacted]	0.19	[redacted]	£12,653	£12,653

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

Table 81: Scenario analysis results – 6 rounds of treatment

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
TRF-budesonide	[redacted]	16.16	[redacted]	-	-	-	-	-
SoC	[redacted]	15.96	[redacted]	[redacted]	0.20	[redacted]	£13,054	£13,054

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

B.3.11.3.14: Societal cost scenarios

Table 82: Scenario analysis results – Societal costs included

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
TRF-budesonide	[redacted]	16.06	[redacted]	-	-	-	-	-
SoC	[redacted]	15.96	[redacted]	[redacted]	0.10	[redacted]	£14,453	£14,453

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

B.3.12 Subgroup analysis

No subgroup analyses were performed.

B.3.13 Benefits not captured in the QALY calculation

B.3.14 Validation

B.3.14.1 Validation of cost-effectiveness analysis

B.3.14.1.1 Internal validation

The model was subjected to an internal validation process in line with The Professional Society for Health Economics and Outcomes (ISPOR) best practices guidance. The validation consisted of an adapted form of the TECH-VER internal validity checklist (166, 167).

B.3.14.1.2 External validation

Health economic experts were consulted to assist in the validation of the economic model (2).

B.3.15 Interpretation and conclusions of economic evidence

The economic SLR (described in further detail in Appendix G) did not identify any UK cost-effectiveness analyses for IgAN and it was therefore necessary to develop a *de novo* economic model for this submission. The economic analysis estimates the cost-effectiveness of TRF-budesonide versus SoC for the treatment of people with IgAN at risk of rapid disease progression with a UPCR ≥1.5 g/g.

B.3.15.1 Relevance of the patient population

TRF-budesonide is indicated for adults with primary IgAN at risk of rapid disease progression with a UPCR of ≥1.5 g/g (1). The economic analysis utilises data from Part A of the NefIgArd Nef-301 study, the primary phase 3 study for TRF-budesonide in this indication (108), specifically the subgroup of patients with a baseline UPCR ≥1.5 g/g, in line with the TRF-budesonide licence and decision problem outlined in the earlier sections. Patients in both treatment arms of NefIgArd Nef-301 were maintained on optimised and stable RAS blockade but the trial did not include

patients on SGLT2 inhibitors. However, findings from the DAPA-CKD (120) study report that dapagliflozin did not have a statistically significant impact on eGFR over 36 months compared with placebo in patients with IgAN, therefore suggesting that data from the NefIgArd Nef-301 Part A study is relevant to the model's patient population.

B.3.15.2 Generalisability to clinical practice in England

Expert opinion indicated that the SoC arm included in the model is reflective of clinical practice in England (data on file (2)). The experts confirmed the placebo arm of NefIgArd Nef-301 Part A is assumed to be a good proxy for SoC in reflecting optimised supportive care. They also confirmed that they would expect SGLT2 inhibitors to be a component of SoC in clinical practice (data on file (2)). The assumption that glucocorticoids would not be a component of SoC for patients with IgAN in clinical practice was also validated by clinical experts (data on file (2)).

Some uncertainty regarding the retreatment of patients with TRF-budesonide in clinical practice may exist. The MHRA license wording indicates that retreatment may be considered at the discretion of the treating physician (1); however, there is no currently available data regarding the safety and efficacy of treatment with subsequent courses of TRF-budesonide. Therefore, variation across centres is anticipated regarding the number of treatment rounds with TRF-budesonide. To address the uncertainty regarding the number of retreatment cycles required and the safety and efficacy of subsequent treatment courses of TRF-budesonide, assumptions have been made. Despite this limitation, the model functionality allows for this uncertainty to be explored.

B.3.15.3 Strengths and limitations

The economic analysis utilises a Markov model cohort structure that was validated by experts and deemed representative of patients with IgAN. The analysis also incorporates clinical efficacy and safety data from the Part A of the NefIgArd Nef-301 trial, a multinational, randomised, double-blind, placebo-controlled, multicentre phase 3 clinical trial (NCT03643965), presenting the key evidence for TRF-budesonide in this indication. The model also includes real-world evidence from patients with IgAN and a UPCR ≥1.5 g/g obtained from UK RaDaR (36).

The main limitation of the model concerns the retreatment of patients with TRF-budesonide. Since the NefIgArd Part A study did not include retreatment of TRF-budesonide, the lack of available data meant assumptions regarding the safety and efficacy of retreatment were made which increase the level of uncertainty regarding retreatment. Similarly, the rarity of IgAN and the lack of published cost-effectiveness studies in IgAN made it challenging to identify suitable additional 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. 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.

B.3.15.4 Conclusions

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 people with IgAN at risk of rapid disease progression with a UPCR ≥1.5 g/g from the perspective of the UK NHS and PSS. This conclusion was consistent across the PSA and 85% of the scenario analyses.

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Appendices

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

Appendix D: Identification, selection and synthesis of clinical evidence

Appendix E: Subgroup analyses

Appendix F: Adverse reactions

Appendix G: Published cost-effectiveness studies

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

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

Appendix J: Clinical outcomes and disaggregated results from the model

Appendix K: Price details of treatments included in the submission

Appendix L: Checklist of confidential information

Appendix M: Results for the NeflgArd Nef-301 Part A trial Full Analysis Set

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Targeted-release budesonide for treating primary IgA nephropathy [ID1434]

Summary of Information for Patients (SIP)

April 2023

File name	Version	Contains confidential information	Date
ID1434_TRF-budesonide for IgAN_SIP_100523	3.0	No	10 May 2023

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

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

Targeted-release formulation (TRF)-budesonide (Kinpeygo®)

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

The population considered in the appraisal is adults with primary immunoglobulin A nephropathy (IgAN) at risk of rapid disease progression with a urine protein to creatinine ratio (UPCR), a measurement that can be used to assess kidney function, of ≥1.5 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.

The Committee for Medicinal Products for Human Use granted conditional marketing authorisation for TRF-budesonide in the treatment of IgAN on 19 May 2022 (1). Marketing authorisation for this indication was granted by the European Commission on the 15 July 2022 (2). The Summary of Product Characteristics can be found here https://mhraproducts4853.blob.core.windows.net/docs/5786115e5bd3d69956ba1c04b8c28ee84414fbf9 Marketing authorisation for this indication was granted by the Medicines and Healthcare Products Regulatory Agency on 01 February 2023 (3). The approved indication is: TRF-budesonide is indicated for the treatment of primary IgAN in adults at risk of rapid disease progression with a UPCR ≥1.5 g/g.

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.
IgAN is a rare, progressive, chronic disease that occurs when IgA antibodies, proteins that normally help the body fight infection, deposit in the kidney (4-6). The build-up of IgA antibodies in the kidneys causes inflammation and scarring, which can lead to a loss of kidney function and kidney failure (4-6). The mean age at diagnosis in the UK has been reported to be 41 (15) years and the majority of patients progress to end-stage renal disease (ESRD) within 10–15 years from diagnosis (7). People with IgAN who have an elevated UPCR are at risk of rapid disease progression; >50% of people with UPCR >1.76 g/g progress to ESRD within 5 years from diagnosis (7). The treatment options for people who have progressed to ESRD are limited to either a kidney transplant or chronic dialysis, which substantially increase disease burden (Section B.1.3.1.7 to B.1.3.1.9) (4, 8-11). In England, it is estimated that 1,824 people with IgAN are at risk of rapid disease progression, have UPCR ≥1.5 g/g, and are at CKD 1–3b stage (Section B.1.3.1.2 of the NICE submission). People with IgAN experience a broad range of symptoms, including blood and/or protein in the urine, loin pain, high blood pressure (12-14), and tiredness and fatigue which can cause physical limitations and restrict daily activities (11, 14-17). People with IgAN face an average 10-year reduction in life expectancy (18, 19) and have a high risk of certain other conditions, such as cardiovascular disease (20).

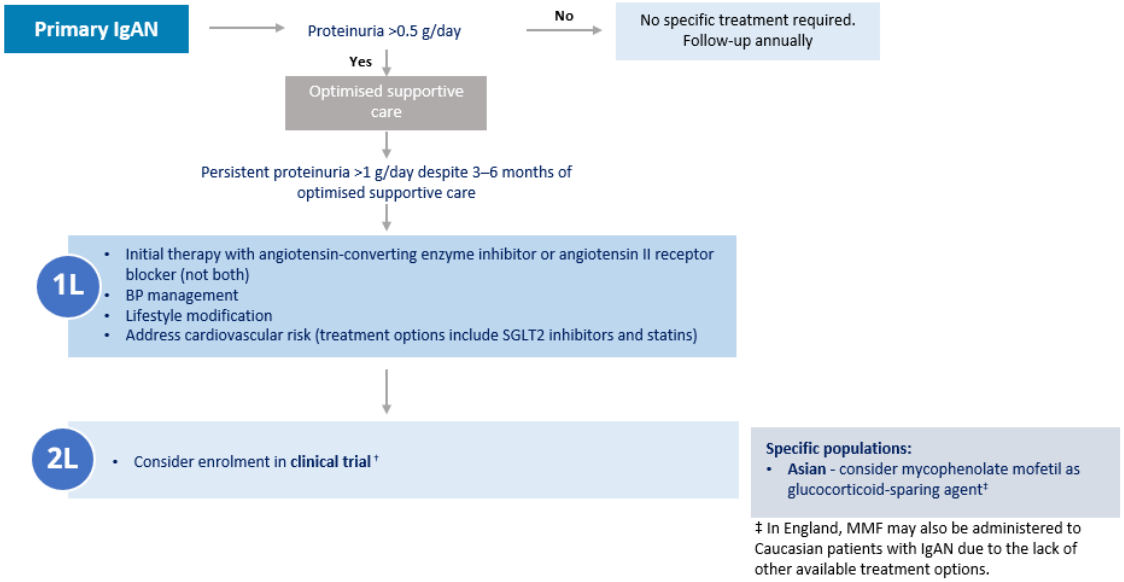
2b) Diagnosis of the condition (in relation to the medicine being evaluated)

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?
As many people with IgAN do not have symptoms in the early stages, a substantial proportion of people experience delayed diagnosis (median time from first clinical sign to diagnosis: 5.0 months; interquartile range: 0.9–29.3) (21). 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 kidney biopsy to detect the build-up of IgA protein (4, 9, 13, 22, 23). There are no additional diagnostic tests required for 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: o 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. o are there any drug–drug interactions and/or contraindications that commonly cause challenges for patient populations? If so, please explain what these are.
Overview of current clinical practice There are currently no therapies licensed specifically for the treatment of IgAN. In clinical practice in England, the treatment of IgAN is focused on optimised supportive care, which includes lifestyle modification, blood pressure management, maximum-tolerated treatment with renin-angiotensin system (RAS) inhibitors, and treatment with sodium-glucose cotransporter-2 (SGLT2) inhibitors to provide cardiovascular protection (Figure 1) (9, 24). For people with IgAN who remain at high risk of progressive chronic kidney disease (CKD) despite maximal supportive care, guidelines and clinical experts recommend participation in a clinical trial, if possible (9, 24). If a clinical trial is not accessible, systemic corticosteroid therapy is cautiously recommended due to an uncertain benefit-to-risk ratio and associated significant toxicity (9, 25-27). Mycophenolate mofetil (MMF) may be administered to people with IgAN in England as a glucocorticoid-sparing agent due to the lack of other available treatment options, despite clinical evidence showing benefit in only in Asian populations (2). However, in clinical practice in England, the use of immunosuppressive agents (corticosteroids and MMF) is avoided due to associated serious adverse events (24). 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 (4, 8-11, 28).

Figure 1: Current treatment pathway for IgAN in England

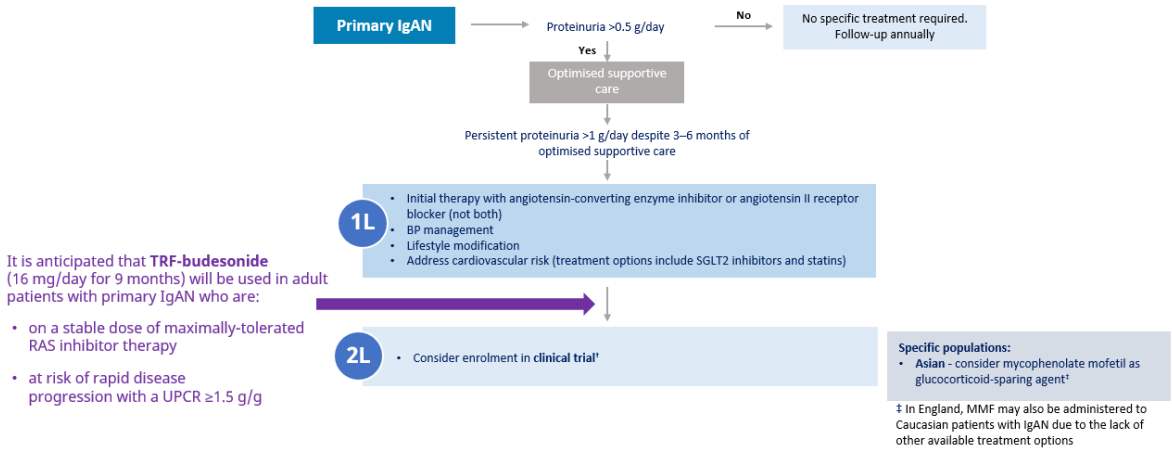


Abbreviations: BP, blood pressure; eGFR, estimated glomerular filtration rate; IgAN, Immunoglobulin A nephropathy; MMF, mycophenolate mofetil; SGLT2, sodium-glucose cotransporter-2.
† Based on the KDIGO 2021 guidelines (9), high risk of progression in IgAN is currently defined as proteinuria >0.75–1 g/d despite ≥90 days of optimised supportive care. Although CSs are included in the KDIGO 2021 treatment pathway (9), UK clinical experts indicated that the use of CSs in people with IgAN is avoided due to associated serious adverse events (AEs) and may only be considered in patients with nephrotic syndrome (24). CSs have therefore not been included in the treatment pathway diagram. Source: KDIGO, 2021 (9) and Britannia Pharmaceuticals TRF-budesonide UK advisory board report 2023 (24).

TRF-budesonide for the treatment of IgAN

If approved, TRF-budesonide can provide a novel treatment option in UK clinical practice for people with IgAN at risk of rapid disease progression with a UPCR ≥1.5 g/g (Figure 2).

Figure 2: Anticipated place in treatment pathway for TRF-budesonide



Abbreviations: BP, blood pressure; eGFR, estimated glomerular filtration rate; IgAN, Immunoglobulin A nephropathy; MMF, mycophenolate mofetil; RAS, renin-angiotensin system; SGLT2, sodium-glucose cotransporter-2; UPCR, urine protein to creatinine ratio.
† Although CSs are included in the KDIGO 2021 treatment pathway (9), UK clinical experts indicated that the use of CSs in people with IgAN is avoided due to associated serious adverse events (AEs) and may only be considered in patients with nephrotic syndrome (24). CSs have therefore not been included in the treatment pathway diagram. Note:Based on the KDIGO 2021 guidelines (9), high risk of progression in IgAN is currently defined as proteinuria >0.75–1 g/d despite ≥90 days of optimised supportive care. Source: KDIGO, 2021 (9) and Britannia Pharmaceuticals TRF-budesonide UK advisory board report 2023 (24).

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.

Few studies reporting the experience of patients living with IgAN have been identified in the literature. A retrospective social media listening study by Tyagi et al. 2019 (15) 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 (15). 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 (15).

A systematic review of the 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 (16). In one study of the priorities for outcomes in CKD (nominal group technique) 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 (29). 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 (29). In studies of the HRQoL of people with CKD, late-stage kidney disease has been reported to be associated with worse health-related quality of life (HRQoL) scores and perceived health scores compared with early-stage disease and healthy controls (30-34).

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?

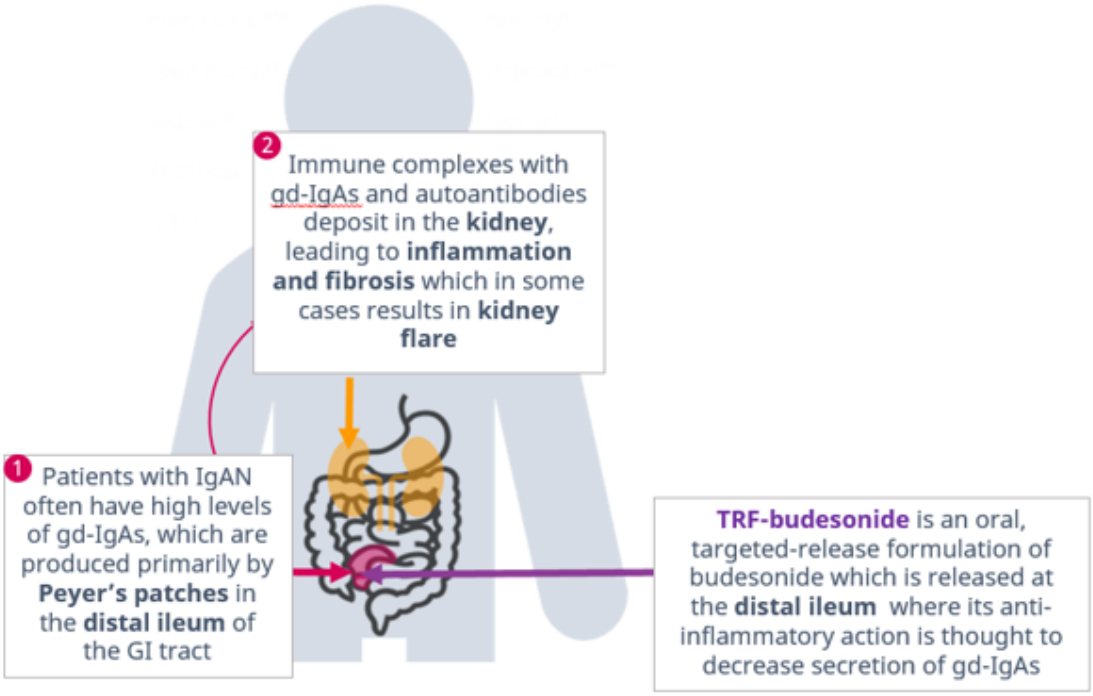
Please outline as clearly as possible important details that you consider relevant to patients relating to the mechanism of action and how the medicine interacts with the body

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.

TRF-budesonide is the first and only approved treatment specifically designed for people with IgAN. It has been formulated to release the active component, budesonide, in a segment of the small bowel called the distal ileum (37). Here, TRF-budesonide is expected to have an anti-inflammatory effect at a primary site of IgA antibody production called the Peyer's patches (37) (Figure 3). By reducing the levels of 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 (3, 37), providing a disease-modifying effect.

Figure 3: 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 (4); Del Vecchio et al. 2021 (37); Fellström et al. 2017 (38).

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.**
No, TRF-budesonide is not intended to be used in combination with other medicines except those used as part of standard of care for people with IgAN. Current standard of care includes lifestyle modification, blood pressure management, and maximum-tolerated RAS blockade (9, 24). In clinical practice in England, patients with IgAN are also treated with SLGT2 inhibitors as part of standard of care to provide cardiovascular protection (24). Although not evaluated, clinical experts have indicated that the safety and efficacy of TRF-budesonide should not be impacted by the combination with SGLT2 inhibitors (24).

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?
The recommended dose of TRF-budesonide is 16 mg (four 4 mg capsules) taken orally once daily in the morning, at least one hour before a meal, for 9 months (3). 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 (3).

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.
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) (39). The trial consisted of two parts; data from Part A are presented in this document. Part A of the NefIgArd NEF-301 study assessed the efficacy and safety of TRF-budesonide. Adults with primary IgAN were randomised 1:1 to receive either oral TRF-budesonide 16 mg/day (n=97) or placebo (n=102) for 9 months in addition to standard of care including optimised RAS inhibition therapy. The 9-month treatment period was followed by a 3 month follow-up period during which no study drug was administered. Part B of the NefIgArd NEF-301 study involved a further 12-month observational follow-up period of the patients included in Part A during which no study drug was administered. Study blinding remained in place during Part B to assess the effect of treatment on estimated glomerular filtration rate (eGFR) as a measure of kidney function. The study completed in February 2023 and preliminary positive findings have been published in a press release for the full trial population (40); full data analyses are expected to complete in Q3/4 2023. The NefIgArd-OLE open-label extension study is an ongoing phase 3b, multicentre, open-label, single-arm extension trial to evaluate the efficacy and safety of TRF-budesonide 16 mg/day treatment in people with IgAN who have completed the phase 3 NefIgArd trial. All participants will receive TRF-budesonide 16 mg/day for 9 months (including those who received NefIgArd and were previously treatment naïve to TRF-budesonide), as well a stable dose of RAS inhibitor therapy. Trial completion is due in May 2024.

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.

In the NefIgArd Nef-301 trial, TRF-budesonide significantly reduced proteinuria and slowed the decline in eGFR in people with primary IgAN who were already receiving optimised and stable RAS blockade (39). Changes in proteinuria (UPCR) and eGFR provide an indication of kidney function and disease progression in patients with kidney disease (9, 18, 41-48). Therefore, the improvements observed in people treated with TRF-budesonide in NefIgArd NEF-301 provide support for a disease-modifying treatment effect which may improve kidney function outcomes in people with IgAN.

After 9 months of treatment, TRF-budesonide 16 mg/day provided statistically significant and clinically-relevant improvements in the primary efficacy endpoint. A 27% reduction in UPCR was observed after 9 months of treatment with TRF-budesonide 16 mg/day compared with placebo in the full trial population (95% CI: 13, 39; p=0.0003). In addition, treatment with TRF-budesonide 16 mg/day maintained kidney function during the 9 months of treatment (0% eGFR decrease from baseline at 9 months; –0.17 mL/min/1.73 m^2 decrease), whereas participants receiving placebo experienced a 7% deterioration in eGFR (–4.04 mL/min/1.73 m^2 decrease versus baseline; p=0.0014). These treatment effects were maintained during 3 months of untreated follow-up.

The results presented for the full trial population were consistent with those obtained in the licensed population (people at risk of rapid disease progression with UPCR ≥1.5 g/g), in whom the efficacy benefits of TRF-budesonide 16 mg/day were more pronounced.

Preliminary data analyses from Part B of NefIgArd Nef-301 demonstrate that the UPCR reductions observed during Part A were durable during the 15-month follow-up period off treatment (40). In addition, a highly statistically significant benefit in eGFR was observed for TRF-budesonide compared with placebo (p<0.0001) over the 2-year study period (9-months of treatment with TRF-budesonide or placebo and 15-months of follow-up off) (40).

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

No improvements in HRQoL, assessed using the short-form 36 (SF-36) tool, were observed in either the TRF-budesonide or placebo groups of in NefIgArd NEF-301 following the 9-month treatment period, when compared with baseline. However, it should be noted that the SF-36 is a generic HRQoL measure without any domains specific to kidney disease.

The humanistic burden of IgAN is typically observed in late-stage kidney disease (30-34); the physical and mental health burden of IgAN increases with disease progression,

particularly when dialysis becomes necessary (16). 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 HRQoL decline associated with ESRD 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.

Like all medicines, TRF-budesonide is associated with side effects and adverse events; however, these are considered manageable, mild to moderate in severity, and in line with the known safety profile of an oral budesonide product.

In the NefIgArd Nef-301 trial (39), the 9-month treatment regimen of TRF-budesonide was well tolerated. In total, 86.6% of participants in the TRF-budesonide 16 mg/day group and 73.0% of participants in the placebo group in the full trial population reported treatment-emergent adverse events (TEAEs). The majority of TEAEs were of mild or moderate severity and reversible.

The most commonly reported TEAEs with a >5% greater incidence were swelling, high blood pressure, headache, muscle spasms, nausea, increased weight, cushingoid, skin irritation, vomiting, and increased white blood cell count. No severe infections were reported during treatment and there was no increased incidence of infections with TRF-budesonide 16 mg/day (26.4%) versus placebo (41.2%). This is notable as severe infections occur frequently during treatment with the use of systemic corticosteroids which can be used to treat people with IgAN (4, 9, 25-27).

There were no deaths during the trial.

The results presented for the full trial population were consistent with those obtained in the licensed population (people at risk of rapid disease progression with UPCR ≥1.5 g/g).

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

Mechanism of action

TRF-budesonide has been specifically designed to reduce inflammation within the small intestine where the majority of IgA antibodies are produced, leading to the development of IgAN (4, 37, 49). 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 (3, 37), providing a disease-modifying effect.

Effectiveness and Safety

The clinical benefits of TRF-budesonide versus placebo have been demonstrated in Part A of the NefIgArd Nef-301 trial (39, 50, 51). In the trial, 9 months of treatment with TRF-budesonide 16 mg/day, in addition to optimised and stable RAS blockade, resulted in clinically-important improvements in UPCR and stabilisation of eGFR (i.e. a delay in disease progression) compared with optimised supportive care alone (39).

Treatment with TRF-budesonide 16 mg/day was also well tolerated, with an acceptable safety profile in line with that expected for an oral budesonide product. Of note, no severe infections – which occur frequently during treatment with the use of systemic corticosteroids (4, 9, 25-27) – were reported during treatment with TRF-budesonide, and there was no increase in overall infections compared with placebo (39).

These results support the potential clinical benefit in delaying the progression of CKD associated with the use of TRF-budesonide in this population. They also suggest that TRF-budesonide has the potential to improve the treatment landscape for people for which no therapies are currently approved.

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

TRF-budesonide was generally well tolerated. Adverse events reported in Part A of the NefIgArd Nef-301 trial (39) were generally considered to be manageable and in line with the known safety profile of an oral budesonide product. The most commonly reported TEAEs (occurring in >5% of patients) reported in Part A of the NefIgArd Nef-301 trial were swelling, high blood pressure, headache, muscle spasms, nausea, increased weight, cushingoid, skin irritation, vomiting, and increased white blood cell count (39).

The efficacy and safety of TRF-budesonide were only studied for a total of 12 months in Part A of the NefIgArd Nef-301 trial. Full analyses of the Part B of the NefIgArd Nef-301 trial, investigating the treatment benefit of TRF-budesonide beyond 12 months, are pending (40).

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.

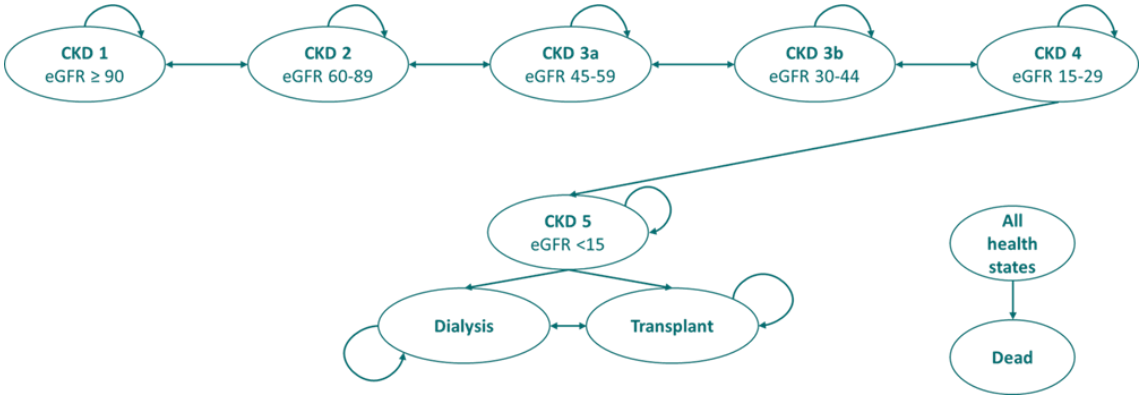
In completing your input to the NICE appraisal process for the medicine, you may wish to reflect on:

- 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 is used to determine the cost-effectiveness of TRF-budesonide compared with standard of care for the treatment of people with IgAN at rapid risk of disease progression with a UPCR ≥1.5 g/g. The model simulates IgAN by modelling 'health states', which are mutually exclusive states which patients occupy and can move between over time. Figure 4 presents the health states modelled

Figure 4: Modelled health states



- The health states used are:
  - CKD 1
  - CKD 2
  - CKD 3
  - CKD 4
  - CKD 5
  - Dialysis
  - Transplant
  - Death
- Though eGFR was a secondary endpoint in NefIgArd Nef-301 Part A study and UPCR was the primary endpoint, the published cost-effectiveness precedent in CKD has linked CKD health states to patient utility, health resource use, and transition probability data. Furthermore, there is no such precedent for UPCR-defined states in CKD, and as noted, no identified published CEM precedent is specific to IgAN. Therefore, defining health states by eGFR was deemed most appropriate to the economic evaluation
- The probability of a patient moving between these health states depends on their response to treatment. Patients will experience different quality of life depending on which health state they are in

Modelling how much a treatment extends life

- Treatment with TRF-budesonide extends life by delaying disease progression, in particular, delaying the expected time taken to reach the CKD 5 health state. The model uses eGFR outcomes reported in Part A of the NefIgArd Nef-301 trial as well as outcomes data sourced from other published studies

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 on. 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)
- No EQ-5D HRQoL data were collected in the NefIgArd Nef-301 trial which could be incorporated in the model. Therefore, the model relies on EQ-5D values from the literature to inform patient utility assumptions

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, the MHRA licence states retreatment may be considered at the discretion of the treating physician (3). 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
- With the exception of potential differences in TEAEs, the management of patients with IgAN at risk of rapid disease progression and UPCR ≥1.5 g/g is expected to be similar regardless of the treatment received

Uncertainty

- Uncertainty exists in the modelling of the cost-effectiveness of TRF-budesonide, as the rare nature of IgAN means that the only available phase 3 data comes from the NefIgArd Nef-301 trial in a limited number of patients. The small sample size is a major source of uncertainty, particularly given the heterogeneity within the patient population, including different treatment histories
- Data from published cost-effectiveness precedent in CKD were used to inform 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 data and no identified published CEM precedent in IgAN, this was considered the best available approach to the economic evaluation
- The MHRA license wording indicates that retreatment may be considered at the discretion of the treating physician (3). However, the safety and efficacy of treatment with subsequent courses of TRF-budesonide have not been established. As such,

assumptions regarding the efficacy of retreatment have been made in the model which increase the level of uncertainty regarding retreatment

Cost effectiveness results

- The results of this cost-effectiveness analysis indicate that TRF-budesonide is associated with an increase in life years, a gain in QALYs, and greater costs[1] than standard of care for the treatment of people with IgAN at risk of rapid disease progression with a UPCR ≥1.5 g/g from the perspective of the UK National Health Service (NHS) and Personal Social Services (PSS)
  - This conclusion was consistent across the sensitivity and scenario analyses that were performed on the model
- For full details on the modelled benefit in overall survival, QALYs gained, and the incremental cost-effectiveness ratio, see the company NICE Submission Document B Section B.3.10

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)

TRF-budesonide is the first and only approved treatment specifically designed for people with IgAN. It has been formulated to release the active component, budesonide, in a segment of the small bowel called the distal ileum (37). Here, TRF-budesonide is expected to have an anti-inflammatory effect at a primary site of IgA antibody production called the Peyer's patches (37). By reducing the levels of immune complexes circulating in the blood, it is anticipated that TRF-budesonide will have a disease-modifying effect, preventing the downstream effects of their deposition in the kidneys, such as kidney inflammation, damage, and loss of function (3, 37).

TRF-budesonide has the potential to improve the treatment landscape for people with IgAN, for whom no therapies are currently approved.

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

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

[1] The model decision-making results and incremental cost-effectiveness ratios (ICERs) considered by the committee may be different to the results described here.

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.

Further information on IgAN:

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

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

- Biopsy: a medical procedure that involves taking a small sample of body tissue 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 measurement of how well the kidneys filter blood which is used as a key indicator kidney function
- Immunoglobulin A (IgA): an antibody that plays 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) blockade/inhibitor therapy: 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

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:

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

[ID1434]

Clarification questions

April 2023

File name	Version	Contains confidential information	Date
ID1434 TRF-budesonide responses to EAG questions_050623_ACIC redacted	v1.0	No	05 June 2023

Notes for company

Highlighting in the template

Square brackets and grey highlighting are used in this template to indicate text that should be replaced with your own text or deleted. These are set up as form fields, so to replace the prompt text in [grey highlighting] with your own text, click anywhere within the highlighted text and type. Your text will overwrite the highlighted section.

To delete grey highlighted text, click anywhere within the text and press DELETE.

Section A: Clarification on effectiveness data

Literature searches

A 1. Priority question: Please confirm whether any additional searches, other than those reported in Appendix D section D.1, were conducted to retrieve information regarding adverse events (AEs) for targeted-release formulation (TRF)-budesonide and, if so, provide full details including date, resource names and search strategies used.

No additional specific search was conducted to identify studies reporting adverse events (AEs). AEs were included as outcomes of interest in the search for clinical evidence reported in company submission (CS) appendix D section D1.

A 2. There appears to be a disparity in the numbers of hits reported for the Medline search for clinical effectiveness between the PRISMA flowchart reported in Section D.1.5 (n=6,499) and the strategies listed in Section D.1.3 (n=499). Please confirm if this was a typographical error and that the PRISMA chart should have read 499.

This was a typographical error and should read n=499.

A 3. Sections D.1.4 and G.1.1.2 report a number of supplementary searches, please see the table below for a full list of resources.

a) Please provide full details, including the search strategies or search terms used, date searched, and hits retrieved per resource.

Please see Table 1, which provides details of the handsearching methods and results.

Table 1: Handsearching methodology and results (for all component SLRs)

Source	Date searched	Search details	Search terms	No. hits	No. downloaded	Comments
Conferences						
ASN	14/11/2022	2022 - https://www.asn-online.org/education/kidneyweek/archives/KW22Abstracts.pdf	Nephropathy	835	2	Conference indexed in Embase (Kidney week 2021-2020)
			IgAN	593	0	
			Immunoglobulin	86	0	
		2021 - https://www.asn-online.org/education/kidneyweek/archives/KW21Abstracts.pdf	NA	NA	NA	
		2020 - https://www.asn-online.org/education/kidneyweek/archives/KW20Abstracts.pdf	NA	NA	NA	
ERA	NA	NA	NA	NA	NA	Conference indexed in Embase (ERA-EDTA Congress) 2022-2019)
IIGANN	14/11/2022	2022 – no conference	NA	NA	NA	
		2021 – https://www.karger.com/Article/Abstract/519532	Nephropathy	393	0	
			IgAN	698	0	
			Immunoglobulin	39	0	
		2020 – no conference	NA	NA	NA	
		2019 – no conference	NA	NA	NA	
National Kidney Foundation	14/11/2022	2022 - https://cme.kidney.org/spa/courses/resource/2022-spring-clinical-meetings/event/home/posters	*The index only contained title/author information; searched sequentially through full poster abstracts*	NA	0	

Source	Date searched	Search details	Search terms	No. hits	No. downloaded	Comments
			(excluding case reports)			
		2021 - https://cme.kidney.org/spa/courses/resource/spring-clinical-meetings-21/event/home/posters	*The index only contained title/author information; searched sequentially through full poster abstracts (excluding case reports)*	NA	0	
		2020 - https://cme.kidney.org/spa/courses/resource/2020-spring-clinical-meetings/event/home/posters	*The index only contained title/author information; searched sequentially through full poster abstracts (excluding case reports)*	NA	0	
World Congress of Nephrology	14/11/2022	2022 - https://www.kireports.org/issue/S2468-0249(22)X0004-1	NA	NA	NA	Conferences indexed in Embase (2022 and 2019)
		2021 - https://www.kireports.org/issue/S2468-0249(21)X0004-6	*Searched sequentially through titles*	832	0	
		2020 – no conference	NA	NA	NA	
		2019 - https://www.kireports.org/issue/S2468-0249(19)X0002-9	NA	NA	NA	
HTA agencies						
NICE	14/11/2022	https://www.nice.org.uk/	IgAN	0	0	Technology appraisal guidance;
			Nephropathy	10	1	
			CKD	168	11	

Source	Date searched	Search details	Search terms	No. hits	No. downloaded	Comments
			ESKD	2	0	under development
			Kidney disease	51	0	
			Immunoglobulin	64	0	
SMC	14/11/2022	https://www.scottishmedicines.org.uk	IgAN	0	0	
			Nephropathy	3	0	
			CKD	14	14	
			ESKD	0	0	
			Kidney disease	51	0	
			Immunoglobulin	8	0	
CADTH including pCODR	14/11/2022	https://www.cadth.ca/	IgAN	0	0	
			Nephropathy	58	0	
			CKD	67	1	
			ESKD	10	0	
			Kidney disease	390	0	
			Immunoglobulin	174	0	
PBAC	14/11/2022	https://www.pbs.gov.au/pbs/home	IgAN	0	0	
			Nephropathy	2	0	
			CKD	63	2	
			ESKD	0	0	
			Kidney disease	84	0	
			Immunoglobulin	22	0	
AEMPS	14/11/2022	https://www.aemps.gob.es/	IgAN	30	0	
			Nephropathy	7	0	
			Enfermedad de los riñones (kidney disease)	7	0	
AIFA	14/11/2022	https://www.aifa.gov.it/	IgAN	1	0	
			Nephropathy	41	0	
			CKD	62	0	
			ESKD	1	0	
			Kidney disease	7	0	
HAS	14/11/2022	https://www.has-sante.fr/	IgAN	0	0	
			Nephropathy	22	0	
			CKD	49	1	
			ESKD	4	0	

Source	Date searched	Search details	Search terms	No. hits	No. downloaded	Comments
			Kidney disease	96	0	
IQWIG	14/11/2022	https://www.iqwig.de/	IgAN	1	0	
			Nephropathy	53	0	
			CKD	74	2	
			ESRD	27	0	
FDA	14/11/2022	https://www.fda.gov/	IgAN	0	0	
			Nephropathy	33	1	
			CKD	0	0	
			ESRD	2	0	
EMA	14/11/2022	https://www.ema.europa.eu/en	IgAN	38	0	
			IgA Nephropathy	207	0	
			CKD	281	0	
			ESRD	330	0	
FinCCHTA	14/11/2022	https://oys.fi/fincchta/	IgAN	0	0	
			Nephropathy	0	0	
			CKD	0	0	
			ESRD	0	0	
DEFACTUM	14/11/2022	http://www.defactum.net	IgAN	0	0	
			Nephropathy	0	0	
			CKD	0	0	
			ESRD	0	0	
NIPH	14/11/2022	http://www.fhi.no	IgAN	0	0	
			Nephropathy	5	0	
			CKD	2	0	
			ESRD	1	0	
SBU	14/11/2022	https://www.sbu.se/en/	IgAN	0	0	
			Nephropathy	0	0	
			CKD	0	0	
			ESRD	0	0	
TLV	14/11/2022	https://www.tlv.se	IgAN	0	0	
			Nephropathy	0	0	
			CKD	2	0	
			ESRD	0	0	
Trial Registers						
	23/1/2023	https://clinicaltrials.gov	IgA nephropathy	158	158	

Source	Date searched	Search details	Search terms	No. hits	No. downloaded	Comments
US NIH registry & results database						
WHO ICTRP registry	2/2/2022	http://apps.who.int/trialsearch/	IgA nephropathy	230	230	
Other sources						
EuroQoL website	14/11/2022	https://euroqol.org/	IgAN	0	0	
			Nephropathy	0	0	
			CKD	1	0	
ScHARRHUD database	14/11/2022	https://www.scharrhud.org/	IgAN	0	0	
			Nephropathy	2	0	
			CKD	4	0	
			ESRD	1	0	
RePEc website (EconPapers)	14/11/2022	https://econpapers.repec.org/	IgAN	118	0	
			CKD	394	2	
			ESRD	155	0	
INAHTA	14/11/2022	https://database.inahta.org/	IgAN	0	0	
			Nephropathy	18	0	
			CKD	19	0	
			ESKD	0	0	
			ESRD	12	0	
NIHR	14/11/2022	https://www.nihr.ac.uk/	IgAN	0	0	
			Nephropathy	1	0	
			CKD	1	0	
			ESRD	0	0	
ENCEPP	14/11/2022	https://www.encepp.eu/	IgAN	0	0	
			Nephropathy	0	0	
			CKD	0	0	
			ESRD	0	0	

Abbreviations: AEMPS, Agencia Española de Medicamentos y Productos Sanitarios; AIFA, Agenzia Italiana del Farmaco; ASN, American Society of Nephrology; CADTH, Canadian Agency for Drugs and Technologies in Health; EMA, European Medicines Agency; ENCEPP, European Network of Centres for Pharmacoepidemiology and Pharmacovigilance; ERA, European Renal Association; FDA, Food and drug Administration; FinCCHTA, Finnish Coordinating Centre for Heath Technology Assessment; HAS, Haute Autorité de Santé; HTA, health technology assessment; IIGANN, International Symposium on IgA Nephropathy; INAHTA, International Network of Agencies for Health Technology Assessment; IQWIG, Institute for Quality and Efficiency in Health Care; NA, not applicable; NICE, National Institute for Health and Care Excellence; NIHR, National Institutes of Health Research; NIPH, Norwegian Institute of Public Health; PBAC, Pharmaceutical Benefits Advisory Committee; pCODR, pan-Canadian Oncology Drugs Review; SBU, Swedish Agency for Health Technology Assessment and Assessment of Social Services; SMC, Scottish Medicines Consortium; TLV, Dental and Pharmaceutical Benefits Agency; WHO, World Health Organisation.

b) Please confirm that these additional searches with the exception of economic specific resources were conducted as a single set of searches and used to inform all sections of the submission (clinical and economic). Please also confirm that the economics-specific searches were used to inform all economics sections including cost effectiveness studies (Appendix G), health-related quality-of-life studies (Appendix H) and cost and healthcare resource identification, measurement and valuation (Appendix I).

Resource	Clinical Effectiveness SLR	Economics SLR
Conference proceedings	ASN	ASN
	ERA	ERA
	IIGANN	IIGANN
	National Kidney Foundation	National Kidney Foundation
	ISN WCN	ISN WCN
HTA Global bodies	NICE	NICE
	SMC	SMC
	CADTH	CADTH
	pCODR	pCODR
	PBS	PBS
	AEMPS	AEMPS
	AIFA	AIFA
	HAS	HAS
	IQWIG	IQWIG
	ICER	ICER
	FDA	FDA
	EMA	EMA
	FinCCHTA	FinCCHTA
	DEFACTUM	DEFACTUM
	NIPH	NIPH
	SBU	SBU
	TLV	TLV
Trial Registries	Clinicaltrials.gov	Clinicaltrials.gov
	WHO ICTRP	WHO ICTRP
Health Economics Resources		EuroQoL
		ScHARRHUD
		CEA Registry
		RePEc
		INAHTA
		NIHR
		ENCEPP

The supplementary searches undertaken were conducted to cover both the clinical and economic sections of the submission, and the specific economic resources were searched to inform all economic sections of the submission i.e. cost-effectiveness, health related quality of life and cost and health care resource identification, measurement and valuation.

Decision problem

A 4. Priority question: The comparison in the National Institute for Health and Care Excellence (NICE) scope is framed as budesonide as intervention versus established clinical management without targeted-release budesonide as comparator, described as standard of care (SoC) in the decision problem. In addition, in section B.2.9 of the company submission (CS), the company states that *"Part A of the NeflgArd Nef-301 study … provides sufficient comparative evidence vs SoC"*. However, the trial evaluates budesonide plus standard of care versus standard of care, which is very different comparison. It is difficult to envisage how effects for budesonide versus SoC can be inferred from the trial comparison.

a) Please clarify whether the decision problem should be re-expressed as budesonide plus SoC versus SoC.

b) If the decision problem is not re-expressed and the comparison is between budesonide and SoC then:

i. please explain the rationale for including SoC alongside budesonide in the trial.

ii. please explain how effects for *budesonide versus SoC*, as requested by the NICE scope and as defined in the decision problem, can be yielded from the *budesonide plus SoC versus SoC* data in the trial.

The current standard of care (SoC) for immunoglobulin A nephropathy (IgAN) in the United Kingdom (UK) is focused on optimised supportive care, which includes lifestyle modification, blood pressure management, maximum-tolerated renin-angiotensin system (RAS) blockade (angiotensin-converting enzyme inhibitors [ACEi] or angiotensin receptor blockers [ARB]), and addressing cardiovascular risk (1, 2).

Targeted-release formulation (TRF)-budesonide is intended to be used in addition to SoC, as outlined above, in patients with IgAN in line with its marketing authorisation, which specifies that its use is intended for patients on a stable dose of maximally-tolerated RAS inhibitor therapy (3).

In the NefIgArd Nef-301 study, TRF-budesonide was administered in addition to SoC in order to align with current clinical practice and the proposed positioning/indication of TRF-budesonide. A stable dose of RAS blockade was defined as being within 25% of the dose at trial randomisation, and patients remained on their regimen of RAS inhibitors for the whole duration of the study (details of concomitant medications were collated at each study visit). Of note, patients who could not tolerate RAS blockade therapy were considered in the study. It was recommended that patients achieve a target systolic blood pressure <125 mmHg and target diastolic blood pressure <75 mmHg, in accordance with the 2012 KDIGO guideline; the use of additional antihypertensive therapy was permitted as needed. Patients were informed at screening of potentially beneficial lifestyle choices including weight normalisation, smoking cessation, physical activity, and diet (low salt and low protein).

As such, the decision problem should be re-expressed as TRF-budesonide in addition to SoC versus SoC, where SoC is defined as: lifestyle modification, blood pressure management, maximum-tolerated RAS blockade and addressing cardiovascular risk.

A 5. Priority question: The SoC provided to both arms in the trial is unclear. Although it is clear that maximally-tolerated renin-angiotensin system inhibitor (RAS inhibitor) therapy is used in both arms, it is unclear which other aspects of SoC are provided (if any). Since the trial was a double blinded randomised controlled trial (RCT), the dosages and type of any SoC treatment (including RAS inhibitor therapy) should theoretically be similar in both the intervention and comparator arms (where the only difference between arms was the use of budesonide or placebo). However, the small sample size of 78 in the presented evidence makes it probable that there

could be chance differences in the SoC treatments across arms, leading to a possible reduction in internal validity. It is therefore important to know the precise SoC treatments used in each arm, so that an assessment can be made about potential threats to internal validity. The lack of clarity on SoC also influences the assessment of external validity, as without a clear idea of the SoC used in the trial it is not possible to gauge the representativeness of trial results to the target population (who will tend to have a particular SoC). In addition, the fact that the 78 people in the presented evidence (restricted to those with urine protein to creatinine ratio (UPCR) ≥ 1.5 g/g) were based on post-hoc sub-grouping increases the possibility of threats to internal and external validity.

a) **Please provide details of the SoC provided to each arm of the trial, in terms of the numbers receiving angiotensin receptor blockers (ARBs), the numbers receiving angiotensin converting enzyme (ACE) inhibitors, the mean doses of these, the numbers receiving specific Sodium-glucose cotransporter-2 inhibitors (SGLT2i), corticosteroids or any other drugs, the numbers receiving lifestyle modification, and the number receiving blood pressure management.**

b) **Please provide data on the typical SoC used in the United Kingdom (UK) target population (proportions that would receive each of the types of treatment listed in part a).**

a) In NefIgArd Nef-301, the SoC provided to both treatment arms consisted of 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, lifestyle modification (weight normalisation; smoking cessation; physical activity; and diet [low salt and low protein]), blood pressure management, and addressing cardiovascular risk. Systemic immunosuppressive drugs (including corticosteroids), except when used as rescue medications, were prohibited during the study. Of note, patients who could not tolerate RAS blockade therapy were considered in the study, in line with anticipated clinical practice.

Details of the concomitant medications received by >10% of total patients by anatomical therapeutic chemical class and the numbers receiving lifestyle modification for patients with a baseline urine protein to creatinine ratio (UPCR) ≥1.5 g/g in Part A of the NefIgArd Nef-301 are provided in Table 2. Other than ARBs and ACEIs, the overall most common classes of concomitant medications were the following:

- Hydroxy-3-methyl-glutaryl-coenzyme A reductase inhibitors ([redacted] of patients in the TRF-budesonide 16 mg/day group and [redacted] of patients in the placebo group);
- Dihydropyridine derivatives ([redacted] of patients in the TRF-budesonide 16 mg/day group and [redacted] of patients in the placebo group); and
- Preparations inhibiting uric acid production ([redacted] of patients in the TRF-budesonide 16 mg/day group and [redacted] of patients in the placebo group).

There were no clinically relevant differences in concomitant medication use across treatment groups. Overall, the concomitant medications were as expected, considering the comorbidities present in patients with IgAN.

Table 2: Concomitant medications (>10% of total patients) by ATC class – NefIgArd Nef-301 Part A baseline UPCR ≥1.5 g/g

ATC Class	TRF-budesonide 16 mg/day (N=[redacted]) n (%)	Placebo (N=[redacted]) n (%)
Patients who took any concomitant medications	[redacted]	[redacted]
ACE inhibitors, plain†	[redacted]	[redacted]
ARBs, plain†	[redacted]	[redacted]
HMG CoA reductase inhibitors	[redacted]	[redacted]
Dihydropyridine derivatives	[redacted]	[redacted]
Preparations inhibiting uric acid production	[redacted]	[redacted]
Vitamin D and analogues	[redacted]	[redacted]
Beta blocking agents, selective	[redacted]	[redacted]

ATC Class	TRF-budesonide 16 mg/day (N=[redacted]) n (%)	Placebo (N=[redacted]) n (%)
Proton pump inhibitors	[redacted]	[redacted]
Glucocorticoids	[redacted]	[redacted]
Sulphonamides, plain	[redacted]	[redacted]
Other antihistamines for systemic use	[redacted]	[redacted]
Alpha-adrenoreceptor antagonists	[redacted]	[redacted]
Other lipid modifying agents	[redacted]	[redacted]
Imidazoline receptor agonists	[redacted]	[redacted]
Thiazides, plain	[redacted]	[redacted]
Corticosteroids‡	[redacted]	[redacted]
Lifestyle choices according to protocol recommended to the patient	[redacted]	[redacted]

Concomitant medications were defined as medications that were taken on or after the first dose day of study treatment. Medication reported terms were coded using the WHO Drug Dictionary (Version March 2019G B3).
† These ATC classes were defined based on whether they were taken during treatment. These ATC classes are not inclusive of all RAS inhibitor therapy.
‡ Corticosteroids have been included in the table as per request in question 5a.
Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II type I receptor blocker; ATC, Anatomical Therapeutic Chemical; HMG CoA, 3-hydroxy-3-methyl-glutaryl-coenzyme A; WHO, World Health Organization.
Source: Calliditas Therapeutics AB. Data on file. Additional data from NefIgArd for baseline UPCR ≥1.5 g/g subgroup. 2022 (4). Calliditas Therapeutics AB. Data on file. Concomitant medications for patients with baseline UPCR ≥1.5 g/g. Table ir036. 2023 (5)

b) Clinicians have indicated that IgAN patients, including those with a UPCR ≥1.5 g/g, would receive optimised supportive care, i.e. lifestyle modification, blood pressure management, maximum-tolerated RAS blockade, and treatment for cardiovascular risk (1, 2). Data relating to the proportion of patients receiving different treatments as part of SoC in the UK are not currently available.

A 6. Priority question: The decision problem states for the population that patients *"are on a stable dose of maximally-tolerated RAS inhibitor therapy"*, but the CS does not specify or justify this criterion.

a) **Please verify that the patients not on maximally-tolerated RAS inhibitor therapy should not be considered in this appraisal.**

    i. **If so, please justify this**

b) **If they are included, then please provide:**

    i. **An estimate with evidence of the proportion of patients in UK clinical practice that would not be on a stable dose of maximally-tolerated RAS inhibitor therapy and who would be eligible for budesonide**

    ii. **The precise clinical criteria by which these patients would be identified in UK clinical practice**

    iii. **The nature of SoC for these patients**

    iv. **An estimate of the effectiveness of budesonide plus SoC versus SoC, where SoC is as expressed in answer to part iii.**

Current treatment of IgAN in the UK is focused on optimised supportive care, which includes lifestyle modification, blood pressure management, and maximum-tolerated RAS blockade (ACEi or ARB), and addressing cardiovascular risk (1, 2).

The licensed indication for TRF-budesonide is for adult patients with primary IgAN who are receiving a stable dose of maximally-tolerated RAS inhibitor therapy and are at risk of rapid disease progression with a UPCR ≥1.5 g/g (3). In accordance, in order to be eligible for randomisation in NefIgArd Nef-301 (6) – the pivotal Phase 3 trial in support of TRF-budesonide in the treatment of primary IgAN and primary source of evidence in the CS – patients were required to be receiving a stable dose of RAS inhibitor therapy (ACEIs and/or ARBs) at the maximum allowed dose or maximum tolerated dose, according to the 2012 KDIGO guideline, for at least 3 months prior to randomisation. A stable dose was defined as being within 25% of the dose at randomisation. Patients were to continue receiving their regimen of RAS inhibitors for the whole duration of the study (Part A and Part B) and study details of any concomitant medications received were collated at each study visit.

Of note, patients who could not tolerate RAS blockade therapy were considered in the NefIgArd Nef-301 study. In the Safety Analysis Set (SAS), there were 4 patients randomised to TRF-budesonide and 2 patients randomised to placebo who were not receiving RAS inhibitor therapy (ACEIs and/or ARBs) at baseline. In the TRF-budesonide group, one patient was receiving a combination product that included perindopril (an ACEI), and 1 patient was allergic to RAS blockade. The reason was not documented for the remaining 2 patients. In the placebo group, 1 patient was receiving a combination product that included telmisartan (an ARB), and 1 patient could not tolerate RAS therapy.

As TRF-budesonide is intended to be administered in addition to SoC for patients with primary IgAN with a UPCR ≥1.5 g/g, which includes maximum-tolerated RAS blockade, in line with its marketing authorisation (3), patients not receiving maximally-tolerated RAS inhibitor therapy should not be considered in this appraisal. However, patients who cannot tolerate RAS blockade therapy can be considered for treatment with TRF-budesonide, in line with anticipated use in clinical practice.

A 7. Priority question: The care pathway in Figure 8 states that mycophenolate mofetil (MMF) might be considered for Asian patients, but also Caucasian patients *"…due to the lack of other available treatment options."*. However, the company have excluded it as a comparator due to *"…lack of clinical evidence showing benefit of MMF in Caucasians…"*, citing a reference to an advisory board meeting.

a) Please clarify whether MMF would be given to some Asian and some Caucasian patients and, if so, according to precisely which criteria in patients with immunoglobulin A (IgA) nephropathy.

b) Please clarify if patients fulfilling these criteria would be eligible for budesonide. If not then please clarify that these patients should be excluded from the decision problem.

c) If patients who might be eligible for MMF are not excluded, then please include MMF as a comparator or, if MMF would be part of SoC, then as

part of a comparator for the subgroup of patients eligible for MMF. Please then conduct a systematic literature review (SLR) to estimate the effectiveness of budesonide plus SoC versus MMF plus SoC, where SoC resembles that in the NeflgArd Nef-301 study (as in answer to A5a) for the subgroup of patients eligible for MMF. This could be achieved by an indirect treatment comparison (ITC), ideally one which is anchored.

The KDIGO guidelines recommend the use of mycophenolate mofetil (MMF) in Chinese patients with primary IgAN who remain at high risk for progression after maximal supportive care as a glucocorticoid-sparing agent, only if a clinical trial is not accessible and the risk/benefit profile is considered to be acceptable (1). The KDIGO guidelines note that there is insufficient evidence to support the use of MMF in non-Chinese patients with primary IgAN (1). In the randomised controlled trials (RCT) of MMF in non-Chinese patients with IgAN, there was no evidence for efficacy of MMF (7).

UK clinical experts confirmed that in UK clinical practice (2), due to the lack of other available treatments and the high disease burden particularly in patients with severe disease, MMF could be used for the treatment of IgAN in both Asian and Caucasian patients as a last resort, steroid-sparing treatment, despite the lack of clinical evidence, only if a clinical trial is not accessible and the risk/benefit profile may be considered acceptable. However, the clinical experts reiterated that MMF is rarely used in UK clinical practice (2).

TRF-budesonide has an established efficacy and acceptable risk to benefit profile and would provide a treatment-option for patients with primary IgAN.

A 8. Priority question: Table 1 states that the Kidney Disease Improving Global Outcomes (KDIGO) guidelines recommend corticosteroids, which are in the NICE scope, and immunosuppressants, although only *"…if a clinical trial is not accessible and the risk/benefit profile is considered to be acceptable…"*. However, the company have excluded these as comparators due to clinical experts stating that they are used *"…sparingly/only in severe patients with*

kidney disease (i.e. patients with nephrotic syndrome or rapidly progressive glomerulonephritis)".

a) **Please provide the precise clinical criteria for the use of corticosteroids and immunosuppressants in patients with IgA nephropathy (IgAN).**

b) **Please clarify if patients fulfilling these criteria would be eligible for budesonide. If not, then please clarify that these patients should be excluded from the decision problem.**

c) **If such patients are eligible for budesonide, then please include corticosteroids and immunosuppressants as comparators, or if they would be part of SoC, then as part of a comparator for the subgroup of patients who would receive either of these two types of therapy. Please then conduct an SLR estimate of the effectiveness of budesonide plus SoC vs. corticosteroids or immunosuppressants plus SoC, where SoC resembles that in the NefIgArd Nef-301 study (as in answer to A5a) for the subgroup of patients eligible for either of these two types of therapy. This could be achieved by an ITC, ideally one which is anchored.**

The KDIGO criteria for the use of corticosteroids and immunosuppressants in patients with IgAN are as follows (1):

- Immunosuppressive drugs should be considered only in patients with IgAN who remain at high risk of progressive chronic kidney disease (CKD; defined as proteinuria >0.75–1 g/d despite ≥90 days of optimised supportive care) despite maximal supportive care
    - In all patients in whom immunosuppression is being considered, a detailed discussion of the risks and benefits of each drug should be undertaken with the patient recognising that adverse treatment effects are more likely in patients with an estimated glomerular filtration rate (eGFR) <50 mL/min/1.73 m^2

- Patients who remain at high risk of progressive CKD despite maximal supportive care should be considered for a 6-month course of glucocorticoid therapy. The important risk of treatment-emergent toxicity must be discussed with patients, particularly those who have an eGFR <50 mL/min/1.73 m^2
    - The clinical benefit of glucocorticoids in IgAN is not established and treatment should be given with extreme caution or avoided entirely in certain situations (e.g. eGFR <30 mL/min/1.73 m^2, diabetes, obesity)

In line with the KDIGO guidelines, in clinical practice, clinicians refrain from using corticosteroids and immunosuppressants due to their adverse event profile. Corticosteroids and immunosuppressants may only be used in patients with severe kidney disease (i.e. patients with nephrotic syndrome or rapidly progressive glomerulonephritis), in whom the poor risk-benefit profile is considered to be justifiable and only when a clinical trial is not available (2).

Data from the STOP-IgAN (8, 9) and TESTING (10) studies showed that immunosuppressive therapy and corticosteroids were associated with significantly higher rates of adverse events, particularly infection events, compared with SoC in patients with IgAN. In addition, in STOP-IgAN, which investigated the impact of treatment with corticosteroids in a large European IgAN cohort (32 nephrology centres in Germany), there was no significant difference in the annual decline in eGFR between the immunosuppressive therapy and placebo treatment groups over the 3-year study phase (8). Information specifically relating to the efficacy of immunosuppressants or corticosteroids in patients with primary IgAN with nephrotic syndrome or rapidly progressive glomerulonephritis has not been identified.

Patients fulfilling the KDIGO criteria for immunosuppressants or corticosteroids would be eligible for TRF-budesonide. However, given the caution surrounding use of immunosuppressants and corticosteroids, their limited use in clinical practice, and the lack of evidence available for their use patients with severe disease or patients specifically with a UPCR ≥1.5 g/g, immunosuppressants and corticosteroids were not considered to be relevant comparators for TRF-budesonide in the CS.

A 9. Priority question: Despite corticosteroids being excluded as comparators effectively because of an unacceptable risk/benefit profile, the intervention budesonide is itself listed under the heading of 'corticosteroids' in the British National Formulary (BNF).

a) Please explain how budesonide can be included when other corticosteroids are not.

b) Are there other corticosteroids, like budesonide, that could have been included as comparators? If so, then please include in all analyses.

TRF-budesonide is an oral, modified-release capsule formulation of budesonide that provides a two-step release by combining a delayed capsule disintegration with a sustained/prolonged release of the active substance, budesonide, in the ileum (6). By directing release of budesonide to the ileum where it is expected to exert an anti-inflammatory effect at a primary site of galactose-deficient immunoglobulin A (gd-IgA) production, the Peyer's patches (11), the targeted release profile of TRF-budesonide is considered to drive the disease-modifying effect observed in the clinical trial while also enabling TRF-budesonide to be well tolerated.

As a result of its targeted-release formulation, the systemic exposure of budesonide following administration of TRF-budesonide is limited, thus reducing the risk of immunosuppressive activity and serious side effects associated with systemic corticosteroids. This was verified in the NefIgArd Nef-301 study; the majority of adverse events (AEs) reported by patients who received TRF-budesonide 16 mg/day (in addition to optimised SoC) were mild to moderate ([redacted] in the TRF-budesonide 16 mg/day group and [redacted] in the placebo group experienced a severe treatment-emergent AE [TEAE]) and were in-line with the known safety profile of an oral budesonide product. Importantly, no severe infections – which occur frequently during treatment with the use of systemic corticosteroids (1, 8, 10, 12, 13) – were reported during treatment with TRF-budesonide, and there was no increase in overall infections compared with placebo ([redacted] patients in the TRF-budesonide group vs [redacted] patients in the placebo group experienced an infection). In contrast, in STOP-IgAN, which investigated the impact of treatment with corticosteroids in a

large European IgAN cohort (32 nephrology centres in Germany), the addition of immunosuppressive therapy to optimised supportive care in patients with IgAN was associated with a greater number of infection events vs supportive care alone (174 vs 111; p=0.07), of which 25% were considered by the investigators to be related to the study treatment (8).

No other therapies with a similar release profile or similar risk-benefit profile to TRF-budesonide exist to our knowledge.

Systematic review

A 10. There is no confirmation that the eligibility criteria (protocol) were formulated before any data collection had been carried out. There is also no record of the number of amendments (if any) made to the protocol after the searches had been commenced. If the protocol is not developed pre-hoc, or subject to significant changes after initiation of the search, there is a high risk of bias. Please confirm the status of the reported protocol in terms of when it was produced, and how many amendments were made after searches had commenced.

The protocol (eligibility criteria) was developed prior to commencement of searches and was registered with PROSPERO: CRD42022382841.

The following protocol amendments were made:

- 01/12/2022: inclusion/exclusion criteria altered to include all randomised interventions of interest (i.e. not limited to budesonide) and not limit inclusion by comparator. Criteria was also adapted to highlight studies of primary interest; studies assessing ACEIs/ARBs as standard care (patients were previously receiving ACEIs/ARBs prior to study commencement). This was not a stipulation for inclusion/exclusion but forms the basis of focus for the clinical SLR report since this is reflective of current clinical practice

- 3/02/2023: searches of HTA bodies were altered to change PBAC (Pharmaceutical Benefits Advisory Committee) to PBS (Pharmaceutical Benefits Scheme)

A 11. The company states that, “The final list of included studies for extraction was agreed with Britannia Pharmaceuticals Ltd.” (Appendix D.1.5). It is unclear whether this statement reflects an additional criterion for selection that supersedes the pre-hoc criteria for inclusion outlined in the protocol of the review. Please describe how the company influenced the ‘final list of included studies’, and whether this contravened the protocol.

The vendor conducting the SLRs provided the full list of included studies to the Company (Britannia Pharmaceuticals Ltd.) for review prior to data extraction to ensure all relevant studies were captured in accordance with the predefined eligibility criteria. There were no additional criteria for selection and Britannia Pharmaceuticals Ltd. did not influence the selection of studies.

A 12. There appear to be two tools used for quality appraisal of included studies: ‘the 8-domain tool recommended by NICE’ (p10 of Appendix D), and the ‘7-criteria checklist’ (p22 of Appendix D).

a) Please provide clarification on the quality evaluation tools used in the SLR

b) If more than one tool was used, please justify this.

The NICE risk of bias tool checklist was used for quality appraisal of clinical studies (14):

- NICE. Single technology appraisal and highly specialised technologies evaluation: User guide for company evidence submission template. Process

and methods [PMG24] Published: 08 January 2015 Last updated: 10 February 2022

The full 8-domain quality assessment of the TRF-budesonide studies identified during the SLR results are listed in Table 3.

Table 3. Quality assessment of the TRF-budesonide clinical trials identified in the SLR

Study	NEFIGAN (15)	NefigArd (16)	Roy Chaudhary 2022 (17)
Publication type	FP	FP	CA
1. Was randomisation adequate?	✓	✓	~
2. Was allocation adequately concealed?	✓	~	~
3. Were baseline characteristics similar between groups?	✓	✓	✓
4. Was the trial blinded?	✓	✓	×
5. Were there unexpected imbalances in dropouts between groups? If so, were they explained and adjusted for?	✓	×	×
6. Were any outcomes measured but not reported?	×	×	×
7. Was an ITT analysis used? If so, was this appropriate?	×	×	~
8. Did the authors of the study declare their conflicts of interest?	✓	✓	✓

Clinical effectiveness evidence

A 13. Priority question: The CS refers to four relevant budesonide trials in Table 4 of the CS (a: NeflgArd Nef-301, b: NeflgArd-OLE, c: Nefigan Nef-202, and d: NCT00767221) but only data from NeflgArd Nef-301 have been included in the CS. NeflgArd-OLE is still ongoing, and so its non-inclusion is understandable (but please see question A18). Likewise, NCT00767221 is a single arm study using a low dose of budesonide, and so its non-inclusion is also probably appropriate. However, the rationale for the non-inclusion of Nefigan Nef-202 is more difficult to explain.

a) Please explain fully why this double-blind RCT was not included.

b) Please include Nefigan Nef-202 (Fellstrom, 2017) in the analysis of clinical efficacy if appropriate

a) Nefigan Nef-202 (NCT01738035) was a Phase 2b, double-blind 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 (15). The results of Nefigan Nef-202 were in line with those of the Phase 3 NefIgArd Nef-301 study.

As such, the more robust and up to date data from NefIgArd Nef-301 were used to inform the company submission and relevant economic model, and data from Nefigan Nef-202 were not reported in Document B or used to inform the economic model. However, the Nefigan Nef-202 clinical study report (18) and relevant publication However, the Nefigan Nef-202 clinical study report (18) and relevant publication (15) are included in the CS reference pack.

b) The efficacy and safety results from the TRF-budesonide 16 mg/day group in the Nefigan Nef-202 Phase 2 trial (15, 18) were consistent with those from the NefIgArd Nef-301 Part A Phase 3 trial (6). The primary endpoint of mean change from baseline in UPCR over the 9-month treatment phase was met in a prespecified interim analysis triggered when 90 patients completed 9 months' treatment. At 9 months, geometric least squares (LS) mean UPCR was reduced from baseline by 27.3% (LS mean: 0.727; 95% confidence interval [CI]: 0.585, 0.903) in the 48 patients who received TRF-budesonide 16 mg/day. Geometric LS mean UPCR increased by approximately 3% (LS mean: 1.027; 95% CI: 0.842, 1.253) in the placebo group, and the difference between TRF-budesonide 16 mg/day and placebo-treated patients was statistically significant (p=0.0092). Analysis of the reduction in UPCR at 9 months versus baseline showed that TRF-budesonide had a consistent effect on the relative change in UPCR, irrespective of baseline UPCR levels. At 12 months from baseline (3 months untreated follow-up), geometric LS mean UPCR was reduced from baseline by 32% (LS mean: 0.680; 95% CI: 0.568, 0.815) in patients treated with TRF-budesonide 16 mg/day and increase by 0.5% (LS mean: 1.005; 95% CI: 0.857, 1.178) in placebo-treated patients. The difference between TRF-budesonide 16 mg/day and placebo-treated patients at 12 months was

statistically significant (p=0.0005), indicating that the treatment effect of TRF-budesonide 16 mg/day was sustained throughout follow-up.

The change in urine albumin to creatinine ratio (UACR) from baseline at 9 months was consistent with the change in UPCR, with a significant difference between the 16 mg/day TRF-budesonide group versus placebo. The geometric LS mean UACR at 9 months compared with baseline was 0.715 (95% CI: 0.573, 0.892) in the TRF-budesonide 16 mg/day group and 1.057 (95% CI: 0.865, 1.291) in the placebo group (p=0.0053). Similarly, at 12 months, the geometric LS mean UACR compared with baseline was 0.624 (95% CI: 0.508, 0.768) in the TRF-budesonide 16 mg/day group and 1.003 (95% CI: 0.838, 1.202) in the placebo group (p=0.0004).

Estimated GFR levels remained stable in the TRF-budesonide 16 mg/day group after 9 months' treatment and were sustained throughout the 3 months' untreated follow-up but decreased in the placebo-treated group at 9 and 12 months. The geometric LS mean eGFR at 9 months compared with baseline was 1.006 (95% CI: 0.946, 1.070) in the TRF-budesonide 16 mg/day arm and 0.902 (95% CI: 0.850, 0.956) in the placebo arm. At 12 months, the geometric LS mean eGFR compared with baseline was 0.993 (95% CI: 0.921, 1.069) and 0.892 (95%CI: 0.823. 0.954) in the TRF-budesonide 16 mg/day and placebo arms, respectively. Comparisons for TRF-budesonide 16 mg/day with placebo showed statistical significance at both 9 (difference: 1.12, 95% CI 1.034. 1.205; p=0.0026) and 12 months (difference: 1.11; 1.013, 1.225; p=0.0134).

In total, 133 (88.7%) patients in Nefigan Nef-202 experienced TEAEs. There was no dose relationship for the frequencies of patients with at least 1 TEAE and the total incidence of TEAEs was similar across treatment groups. There were higher frequencies for TEAEs considered drug-related in both TRF-budesonide groups compared with placebo (TRF-budesonide 16 mg/day: 11 [22.4%]; TRF-budesonide 8 mg/day: 9 [17.6]; placebo: 2 [4.0]). The incidence of TEAEs leading to withdrawal was greater for the TRF-budesonide 16 mg/day group (11 [22.4]) compared with the TRF-budesonide 8 mg/day (5 [9.8]) and placebo (2 [4.0]) groups. Serious AEs were reported at low numbers (2–14%) across treatment groups with no clear dose relationship and there were no deaths.

A 14. Priority question: Another seemingly relevant budesonide study was identified by the literature review in Appendix D (Roy-Chaudhary, 2022). However, this study is not mentioned in Table 4 of the CS as part of the clinical effectiveness evidence, and no data from this study are included in the CS.

a) Please provide a rationale for this omission.

b) Please include Roy-Chaudhary (2022) in the analysis of clinical efficacy if appropriate.

As Roy-Chaudhary (2022) (17) is published only as an abstract, limited information was reported about the study methodology and outcomes. Quality assessment of the study using the NICE risk of bias tool checklist revealed some methodological concerns and potential bias (Table 4). Of note, the trial results suggest a ~10.6 mL/min/1.73 m^2 increase in eGFR from baseline following the 9-month treatment with TRF-budesonide, an improvement that is unlikely to be clinically possible and thus also pointing to methodological and bias concerns. In addition, the study included a solely Indian patient population, which may not be comparable (and thus not relevant) to the target primary IgAN population in the UK.

As such, due to the limited information provided in the abstract, the patient population, and questions pertaining to the methodological concerns and potential bias, Roy-Chaudhary (2022) was not included in the CS.

Table 4: Quality assessment of Roy Chaudhary 2022

Study	Roy Chaudhary 2022 (17)
1. Was randomisation adequate?	~
2. Was allocation adequately concealed?	~
3. Were baseline characteristics similar between groups?	✓
4. Was the trial blinded?	×
5. Were there unexpected imbalances in dropouts between groups? If so, were they explained and adjusted for?	×
6. Were any outcomes measured but not reported?	×
7. Was an ITT analysis used? If so, was this appropriate?	~
8. Did the authors of the study declare their conflicts of interest?	✓

A 15. NCT00767221 (Smerud et al. 2011) was identified as a potentially relevant trial in Table 4 of the CS, but this was not generated by the literature review (it is not in the included studies list in Appendix D of the CS).

a) Please explain why and how this study was sourced.

b) Why was this single arm study included in Table 4 of the CS if it is not relevant?

NCT00767221 (Smerud et al. 2011 (19)) was an early pilot study (open-label, single arm) that investigated TRF-budesonide 8 mg/day in IgAN patients. Although it was identified by the SLR, it was not included in the final list of studies as it is a single-arm study (the SLR only considered RCTs for inclusion). NCT00767221 was included in Table 4 of the CS to provide complete information relating to the clinical trial profile of TRF-budesonide.

In the NCT00767221 pilot study (19), TRF-budesonide 8 mg/day treatment (treatment was given for 6 months, followed by a 3-month follow-up period) had a significant effect on urine albumin excretion, accompanied by a reduction of serum creatinine and (6%; interquartile range: -0.12 to -0.02; p=0.003), and an increase of

eGFR (assessed by Modification of Diet in Renal Disease, ~8% increase [interquartile range: 0.02-0.16, p=0.003]).

A 16. Priority question: Only 73 out of 306 randomised participants were included in the data presented in the CS. This is partly because the sample was appropriately restricted to those people who had a UPCR of ≥1.5 g/g, in line with the decision problem. However, the sample was also restricted to those who had received the full 9 months of treatment. The restriction to participants who had completed treatment impairs internal validity (as it makes the risk of attrition bias very serious through likely loss of the worse responders). This certainly suggests that the company's risk of bias assessment as 'low' requires revision. In addition, this restriction limits external validity (because in the real world many patients do not complete treatment).

a) Please provide the numbers (per arm) of patients with a UPCR of ≥1.5 g/g who were excluded from the dataset of 73 participants, due to not having completed treatment (or other protocol deviations).

b) For all outcomes, please present analyses for all participants who had a UPCR of ≥1.5 g/g, *including those who did not receive the full 9 months of treatment, or those who had any other protocol deviations*.

The results presented in the CS are for a subgroup of patients from the pre-planned NefIgArd Part A analysis set who had a baseline UPCR of ≥1.5 g/g. The pre-planned NefIgArd Part A analysis, with a data cut-off (DCO) date of 05 October 2020, was scheduled to occur once the first 201 patients randomised to NefIgArd Nef-301 had had the opportunity to complete their 9-month visit. The dataset extracted from the database, and cleaned for analysis, included all safety data from all patients dosed by the DCO date (05 October 2020) and all efficacy data up to and including the 12-month visit from all patients randomised at the DCO date. The sample was not restricted to patients who had received the full 9 months of treatment.

A 17. The detailed data in part A of NeflgArd Nef-301 are limited to short-term (9 months) effects. Part B of NeflgArd Nef-301 contains longer-term effects that would greatly enhance the committee's ability to evaluate budesonide, but these are not yet fully published. A brief summary of longer-term results from part B is made in section B.2.11 of the CS, and a reference is made to a webpage (https://www.calliditas.se/en/calliditas-announces-primary-endpoint-successfully-met-in-phase-3-nefigard-trial-evaluating-nefecon-in-iga-nephropathy/) which provides further information. However, these data are seriously limited in scope, only providing details for estimated glomerular filtration rate (eGFR). Where possible, please provide more detailed data from the part B study, particularly for health-related quality of life (HRQoL) and UPCR/ urine albumin to creatinine ratio (UACR).

Although Part B of NeflgArd Nef-301 completed in February 2023, data analyses are expected to be completed in Q3/4 2023. No data, other than those published within the webpage (https://www.calliditas.se/en/calliditas-announces-primary-endpoint-successfully-met-in-phase-3-nefigard-trial-evaluating-nefecon-in-iga-nephropathy/), is currently available from Part B.

As UPCR and eGFR are considered to be suitable markers of long-term clinical benefit, it is assumed that the treatment effects in Part A of NeflgArd Nef-301 will not only translate into improvements in later clinical endpoints but will also translate into a statistically significant and clinically meaningful improvement for the Part B primary endpoint. This has been verified in the preliminary results of Part B of NeflgArd Nef-301 (20), with a statistically significant ($p<0.0001$) benefit over placebo in eGFR observed over the 2-year period (9-months of treatment with TRF-budesonide or placebo and 15-months of follow-up off drug).

A 18. Priority question: It is important to know if the characteristics of participants in the trial match the characteristics of the UK target population. It is also important to know how any differences in characteristics may affect

outcome, so that an evaluation of the representativeness of trial results to the target population can be made. Therefore:

a) **Please provide relevant characteristics of the UK target population, such as mean age, gender ratios, baseline levels of proteinuria and eGFR, and the mean dose of RAS inhibitor.**

b) **Please conduct sub-group analyses of the trial study sample (*including those who did not complete 9 months of treatment*) for the characteristics listed above.**

a) The baseline characteristics of patients with UPCR ≥1.5 g/g at baseline in the NefIgArd Nef-301 Part A trial, the pivotal study in support of TRF-budesonide in this indication, are presented in Table 6 of the CS. The demographic and disease characteristics of the trial population broadly reflect the characteristics of the UK target population, as confirmed by UK clinical expert opinion (2).

In the UPCR ≥1.5 g/g subpopulation of the NefIgArd Nef-301 Part A trial, the proportion of men ([redacted]%) and women ([redacted]%) was consistent with that expected for a predominately White ([redacted]%) IgAN patient population (21, 22), with half ([redacted]%) of all patients aged <45 years. Median UPCR at baseline was [redacted] g/g; [redacted]% of patients had baseline proteinuria of ≥2 g/day, and kidney function was mildly-to-moderately impaired overall (median eGFR: [redacted] mL/min/1.73 m^2). In addition, most patients ([redacted]%) had micro-haematuria at baseline, detected by dipstick. The majority of patients ([redacted]%) were receiving ≥80% of the maximum allowable dose of RAS blockade; [redacted]% of patients were receiving 50–80% of the maximum allowable dose of RAS blockade and 23.6% were receiving <[redacted]% of the maximum allowable dose of RAS blockade at baseline (4). Data on the mean dose of RAS inhibitor received by patients in the NefIgArd Nef-301 trial are not currently available; the company has actioned the collation of the relevant information, which will be submitted separate to this response document.

The NefIgArd Nef-301 Part A population broadly matches the IgAN population included in the UK RaDaR study, the largest cohort UK study of IgAN patients (n=2,439) plus proteinuria >0.5 g/d or eGFR <60 mL/min per 1.73 m^2 at any time in

the history of their disease (23). The male population within the RaDaR study was larger than the female population (71% vs 29%), with the majority of patients being White (77%). For the full population (proteinuria >0.5 g/d or eGFR <60 mL/min per 1.73 m^2 at any time in the history of their disease) included in the RaDaR study, the median age at diagnosis was 41 years (31, 52); the median UPCR at diagnosis was 1.51 g/g (0.66, 3.09) with 7% of patients having nephrotic range proteinuria (>2.64 g/g); the median eGFR at diagnosis was 48 mL/min/1.73 m^2 (32, 75) (23).

b) Subgroup analyses of the heterogeneity of treatment effect was performed for UPCR and eGFR at 9 months for the full analysis set (FAS), patients with baseline UPCR ≥1.5 g/g, and across pre-defined subgroups (based on age, gender, region, baseline proteinuria, baseline eGFR and RAS inhibitor dose). The treatment effect of TRF-budesonide on UPCR was consistent between patients with baseline UPCR ≥1.5 g/g, the FAS, and across pre-defined subgroups. No differential treatment effect was observed on eGFR (chronic kidney disease epidemiology collaboration equation [CKD-EPI]) at 9 months, with the exception of gender, for which there was an apparent difference in the eGFR treatment effect between males and females (p=[redacted]).

No statistical analyses were performed on baseline characteristics (in the FAS population or in the subpopulation with UPCR ≥1.5 g/g at baseline

A 19. The company effectively dismisses the non-significant SF-36v2 findings, on the basis that SF-36v2 is not a disease-specific tool. However, SF-36v2 was the outcome chosen *pre-hoc* by the company. Please explain why SF-36v2, and not a disease-specific tool, was measured in the trial if this was not deemed appropriate.

The impact of IgAN on patient quality of life (QoL) has been reported to increase with disease progression, particularly when dialysis becomes necessary (24). A wide range of health-related quality of life (HRQoL) instruments, including short-form 36 (SF-36), have been used in assessments of the QoL of people with kidney disease (25) and IgAN (24). However, QoL has not been included as a primary outcome in

clinical trials in IgAN (8, 10, 26) and, to our knowledge, there is no precedent for the use of a particular disease-specific assessment tool.

QoL assessment using the SF-36 was included as a secondary outcome in the NefIgArd NEF-301 trial, and its use aimed to assess the impact of TRF-budesonide treatment on QoL and safety.

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 HRQoL decline associated with end-stage renal disease (ESRD) and dialysis in patients with primary IgAN and a baseline UPCR ≥1.5 g/g. Since Part A of NefIgArd Nef-301 only assessed 12 months of data, it was not expected that a substantial proportion of patients would reach ESRD or require dialysis; therefore, the lack of difference in QoL between treatment arms is not surprising. In addition, the lack of significance in the SF-36 results demonstrates minimal impact of adverse events associated with TRF-budesonide on patients' QoL and further supports its good safety profile. TRF-budesonide is a well-tolerated treatment associated with mild or moderate TEAEs and no severe infections – which occur frequently during treatment with the use of systemic corticosteroids (8, 10, 27).

A 20. In the description of the clinical efficacy results, the company claims 'clinical relevance' for the results of the outcomes UPCR, UACR and eGFR. However, no evidence is provided to back up this claim. Please provide evidence of the literature-based 'minimum important differences' (or similar) in these outcomes to justify the statement that results were clinically relevant.

Reducing proteinuria (assessed by measuring proteinuria over 24 hours, UPCR, and/or 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 (1, 2, 23, 28, 29). 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 (23, 28-32). For example, an analysis of patient level data from two

UK registries including patients with IgAN (Leicester General Hospital, LGH) 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% (31). Additional examples are presented in further detail in Section B2.3.2 of the CS.

A percentage decline in proteinuria or albuminuria of >30% has been shown to be predictive of protection from progression to kidney failure (33), endorsed by the 2021 KDIGO guidelines (1) and the workshop sponsored by the National Kidney Foundation in collaboration with the FDA and EMA (29, 34). After 9 months of treatment in Part A of the NefIgArd NEF-301 trial, a statistically significant [redacted]% reduction in UPCR was reported for patients treated with TRF-budesonide 16 mg/day and [redacted]% reduction in UACR, compared with placebo (95% CI: [redacted]; p=[redacted] and 95% CI: [redacted]; p=[redacted], respectively), demonstrating a clinically-relevant benefit. After 3 months of observational follow-up, UPCR was [redacted]% lower with TRF-budesonide 16 mg/day compared with placebo (95% CI: [redacted]; p=[redacted]) and UACR was [redacted]% lower compared with placebo (p=[redacted]), also demonstrating a clinically-relevant benefit. The reduction in UPCR compared with placebo observed following treatment with TRF-budesonide may translate to a delay in the progression of CKD, as a reduction in proteinuria has been consistently associated with corresponding beneficial effects on progression to ESRD and mortality in patients with IgAN (28-32).

In addition, reductions in eGFR are considered by regulatory authorities and clinical experts in England to be an acceptable surrogate outcome measure for kidney failure in clinical trials (1, 2, 29, 35). It is suggested that, based on eGFR and age at diagnosis, almost all patients are at risk of progression to kidney failure within their expected lifetime unless a rate of eGFR loss ≤1 mL/min/1.73 m^2/year can be maintained (23). The findings of Part A of the NefIgArd Nef-301 trial indicate a [redacted] mL/min/1.73 m^2 absolute change in eGFR from baseline following the 9-month treatment with TRF-budesonide (vs [redacted] mL/min/1.73 m^2 in the placebo arm), further indicating a reduction in the risk of progression to kidney failure.

A 21. The company states that the arms of the trial were comparable at baseline. However, there were noticeable differences in age, with the placebo group tending to be younger. In addition, more people in the placebo group had severely elevated baseline proteinemia. Time from diagnosis to inclusion was also longer in the placebo group. Finally, usage of ACE inhibitors (ACE inhibitor) and ARBs differed between groups. Whilst these differences do not all imply an advantage to budesonide (for example, the direction of effect of differences in RAS inhibitor drugs is unclear, and the budesonide group may have been disadvantaged by their older age), the budesonide group may have been advantaged by better baseline proteinemia, and a shorter time to inclusion. Overall, then, it is possible that baseline differences may have influenced the effects in the trial. In the light of this, please justify the statement that the arms of the trial were comparable.

Clinical expert opinion indicated that the baseline characteristics of patients with IgAN with UPCR ≥1.5 g/g at baseline in NefIgArd Nef-301 are reflective of a typical UK IgAN population (2). In general, there were minimal differences between treatment arms in the baseline characteristics and those reported are likely a result of random variation that can take place in small sample sizes. Feedback from the experts suggested that the differences in age and time from diagnosis observed between the two groups are unlikely to have influenced the effects in the trial.

In addition, although there were some small imbalances in the percentages of patients on ACEIs or ARBs between treatment groups, overall RAS inhibition was similar, with the majority of patients receiving at least 50% of the maximum allowed dose ([redacted]% in the TRF-budesonide group vs [redacted]% in the placebo group) (4). In addition, the blood pressure control was similar between the two groups further indicating that any differences in the usage of RAS inhibitors is unlikely to have influenced the effects in the trial.

A 22. The clinical evidence does not include the outcome of ‘disease progression’. Please justify why this outcome has been omitted, or provide data for this outcome.

Assessing the efficacy of treatments for IgAN is complicated by the long-term nature of disease progression in the majority of patients (28, 30). The evaluation of treatment efficacy therefore relies on the use of surrogate endpoints (1, 28, 29). In NefIgArd Nef-301, data for proteinuria (UPCR and UACR) as well as eGFR were collated as surrogate endpoints for disease progression (6, 36).

Reductions in proteinuria (assessed by measuring proteinuria over 24 hours, UPCR, and/or UACR) are accepted as a surrogate endpoint for improved outcomes in IgAN by KDIGO, the European Medicines Agency, and clinical experts in England (1, 2, 28, 29). 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 (28), and are discussed in further detail in Section B2.3.2 of the CS.

Similarly, reductions in eGFR from baseline over a 2- to 3-year period is considered by regulatory authorities and clinical experts in England to be an acceptable surrogate outcome measure for kidney failure in clinical trials (1, 2, 29, 35), also discussed in further detail in Section B2.3.2 of the CS. A further meta-analysis of 13 IgAN clinical trials found a treatment effect on 1-year eGFR slope to be a major, independent predictor of treatment effect on long-term clinical outcomes in IgAN, supporting its use as a surrogate endpoint (37). The study reported that a sustained effect on eGFR slope provided a clear indication of a disease-modifying treatment effect (37).

The NefIgArd Nef-301 Part A study has shown that 9 months of treatment with TRF-budesonide, in addition to optimised and stable RAS blockade, was well tolerated and resulted in clinically-important improvements in UPCR, UACR, and eGFR, compared with optimised supportive care alone (for the full data, please refer to Section 2.6.1 of the CS). As changes in proteinuria (UPCR and UACR) and eGFR can be used as surrogate endpoints for progression to ESRD and mortality in patients with CKD (1, 28-32, 38-41), the improvements observed to date in patients treated with TRF-budesonide provide support for a disease-modifying treatment effect which may delay progression to ESRD in patients with IgAN. In addition,

preliminary data analyses from Part B of NefIgArd Nef-301 demonstrate a statistically significant benefit in eGFR for TRF-budesonide compared with placebo ($p<0.0001$) over the 2-year study period (20). Supportive analyses of the 2-year eGFR slope also demonstrated a statistically significant and clinically meaningful treatment benefit (20).

A 23. One inclusion criterion for the trial was receiving a stable dose of RAS inhibitor therapy (ACE inhibitor and/or ARB) at the maximum allowed dose or the maximum tolerated dose for 3 months prior to randomisation. However, in Table 6 of the CS, it appears that not all relevant participants in the trial were on RAS inhibitor therapy (only 70/78 were reported as being on 'either ACE inhibitor or ARB'). Please clarify this.

In the NefIgArd Nef-301 study, TRF-budesonide was administered in addition to SoC in order to align with current clinical practice and the proposed positioning/indication of TRF-budesonide (1-3). Of note, patients who could not tolerate RAS blockade therapy were considered in the study, in line with anticipated use in clinical practice.

In the SAS, which included patients with UPCR ≥1.5 g/g at baseline, there were 4 patients randomised to TRF-budesonide 16 mg/day and two patients randomised to placebo who were not on RAS inhibitor therapy (ACEIs and/or ARBs) at baseline. In the TRF-budesonide 16 mg/day arm, 1 patient was on a combination product that included perindopril (an ACEI), and 1 patient was allergic to ACEIs and ARBs. The reason was not documented for the remaining 2 patients. In the placebo group, 1 patient was on a combination product that included telmisartan (an ARB), and 1 patient could not tolerate RAS therapy.

With regard to the NefIgArd Nef-301 Part A study population with UPCR ≥1.5 g/g at baseline, a total of 3 of 73 patients (1 patient in the TRF-budesonide 16 mg/day arm and 2 patients in the placebo arm) were reported to not be receiving either ACEi or ARB at baseline. No summary of the reasons for this is available specifically for patients with a baseline UPCR ≥1.5 g/g.

A 24. People with an eGFR of <35 mL/min/1.73 m^2 were excluded from the trial. An eGFR of 30-44 mL/min/1.73 m^2 is generally regarded as 'moderate kidney function', and although a value of 15-29 mL/min/1.73 m^2 indicates severe kidney damage, the patient might not necessarily be at a stage where participation in a trial would be contraindicated. If a patient group is excluded from the evidence, this makes it difficult to extend any recommendations to that excluded group.

a) Please explain the rationale for this exclusion criterion.

b) What is the proportion of people with IgAN (and an UPCR of ≥1.5 g/g) that will have an eGFR of <35 mL/min/1.73 m^2 at the point where treatment with budesonide is considered?

c) Please suggest the treatment pathway that will be available to those with an eGFR of <35 mL/min/1.73 m^2.

a) The KDIGO 2021 guidelines indicate that severe loss of kidney function (to an eGFR <20–30 mL/min per 1.73 m^2), referred to as a 'point of no return', may be accompanied by such extensive and irreversible kidney injury (primarily interstitial fibrosis and tubular atrophy, and/or bilateral renal atrophy) that any therapeutic strategy being tested cannot reasonably be expected to alter the natural history of progressive deterioration in kidney function (therapeutic futility) (1). The presumption is that such patients should be excluded from clinical trials since they are expected to be "non-responders," and therefore may dilute any treatment effect and adversely affect the power of the study (1). Furthermore, these subjects with reduced kidney function may be at higher risk of adverse effects of the therapies being tested (1). Of note, the KDIGO 2021 guidelines highlight that there is no clear definition for this 'point of no return' and recommend maximal supportive care among patients with an eGFR of <30 mL/min/1.73 m^2, directed at avoidance of non-kidney complications such as coronary artery disease, stroke, and congestive heart failure (1).

As such, patients with an eGFR of <35 mL/min/1.73 m^2 were not considered for inclusion in the NefIgArd Nef-301 trial to prevent diluting any treatment effect and adversely affecting the power of the study.

b) The findings of the UK RaDaR study, the largest IgAN retrospective cohort study (which enrolled patients with a biopsy-proven diagnosis of IgAN, plus proteinuria >0.5 g/day or eGFR <60 mL/min/1.73 m^2) suggest that ~21.4% of patients have an eGFR ≤30 mL/min/1.73 m^2 (CKD stages 4 and 5 at diagnosis) (23). In a subgroup analysis of patients with a UPCR of ≥1.5 g/g within the RaDaR cohort, [redacted]% ([redacted]) of patients had an eGFR ≤30 mL/min/1.73 m^2 (CKD stages 4 and 5 at diagnosis) (42).

c) In line with current treatment guidelines, patients with IgAN with an eGFR of ≤30 mL/min/1.73 m^2 should be offered maximal supportive care. Patients who remain at high risk of progressive CKD despite maximal supportive care should be offered the opportunity to participate in a clinical trial (1).

Indirect treatment comparison (ITC)

A 25. Priority question: The company argue that an ITC versus SGLT2is is unnecessary because "the DAPA-CKD study (120) suggest [ed] that dapagliflozin treatment in patients with IgAN (N=270) did not have a statistically significant impact on eGFR over 36 months compared with placebo". However, this is despite there being a numerical advantage to dapagliflozin in least mean squared eGFR, and a significant benefit in terms of the composite endpoint of sustained >50% decline in eGFR. Also, no other outcomes from this trial were presented and no systematic review to obtain evidence relating to SGLT2i effectiveness was conducted.

a) Please provide the precise clinical criteria for the use of SGLT2i in patients with IgAN.

b) **Please clarify if patients fulfilling these criteria would be eligible for budesonide. If not, then please clarify that these patients should be excluded from the decision problem.**

c) **If patients who might be eligible for an SGLT2i are not excluded, then please perform a SLR to collect all relevant evidence on the effectiveness of any SGLT2is that might be used in UK clinical practice, either as a comparator or, if part of SoC, then to facilitate a comparison between budesonide plus SoC and SGLT2i plus SoC, where SoC resembles that in the NeflgArd Nef-301 study (as in answer to A5a) for the subgroup of patients eligible for and SGLT2i.**

d) **Please perform an ITC of budesonide versus any SGLT2i or, if part of SoC, then an ITC of budesonide plus SoC vs. any appropriate SGLT2i plus SoC for the subgroup of patients eligible for an SGLT2i. Ideally the ITC should be one which is anchored.**

a), b)There is as yet no clinical guidance for the use of sodium-glucose cotransporter-2 inhibitor (SGLT2is) specific to patients with IgAN by NICE. However, dapagliflozin has received NICE approval for the treatment of CKD (TA775) (43) and is also anticipated to be used as part of SoC for the management of cardiovascular risk in patients with IgAN, as indicated by clinical expert opinion (2). As such, dapagliflozin is not considered to be a comparator for TRF-budesonide; it is anticipated that it will be administered in combination with TRF-budesonide as part of SoC.

c) The clinical SLR conducted for the CS included SGLT2i as a randomised intervention of interest, due to it being part of SoC for IgAN.

d) The findings of the DAPA-CKD study suggest that dapagliflozin treatment in patients with IgAN (N=270) did not have a statistically significant impact on eGFR over 36 months compared with placebo (26). The least mean squares eGFR slopes from baseline to end of treatment in the dapagliflozin and placebo groups were -3.5 (standard error [SE], 0.5) and -4.7 (SE, 0.5) mL/min/1.73 m^2 per year, respectively, resulting in an insignificant between-group difference of 1.2 mL/min/1.73 m^2 per year

(95% CI: -0.12, 2.51 mL/min/1.73 m^2 per year). Based on this, it can be inferred that the efficacy of SoC is not impacted by the inclusion of SGLT2 inhibitors in this population (26).

It is also noted that in clinical practice, TRF-budesonide would be administered in addition to a SoC regimen that may include an SGLT2i, i.e. dapagliflozin (2). As such, any potential benefits that may be observed from the addition of dapagliflozin to SoC, are anticipated to be additive to the TRF-budesonide treatment effect, especially since there is no crossover between their mechanisms of action (as indicated by clinical expert opinion (2)).

Adverse events

A 26. Priority question: Please provide a comprehensive list of all adverse events identified throughout the study along with the corresponding number of patients who had each one.

A comprehensive list of all adverse events identified in patients with a baseline UPCR ≥1.5 g/g in Part A of NefIgArd Nef-301 study is presented in Table 27 in Appendix 1. Equivalent data for the FAS are reported in the clinical study report (CSR) provided as part of the CS reference pack (6).

Section B: Clarification on cost-effectiveness data

Please note that after considering the EAG's clarification question B11 we have identified an error in the model that impacts the base case results. We would like to thank the EAG for bringing this to our attention. Full details are provided in our response to B11.

Correcting this error results in an increase to the base case deterministic incremental cost-effectiveness ratio (ICER) from £18,643 to £21,872. Given the impact this correction has, we have provided the scenarios requested by the EAG throughout section B of this document using this updated version of the model. Hence, the base case ICER referred to throughout is £21,872.

Model, population, and comparators

B 1. Priority question: The model allows patients in chronic kidney disease (CKD) 1-4 to transition to improved neighbouring health states (except for movements from CKD 5). On page 89, the CS states that "*to account for the bias of small changes in eGFR readings around threshold values, transitions to better health states (observed in the trial) were also incorporated*". Please explain if the assumption around patient transitioning to better health states was only incorporated to avoid bias around threshold values as indicated in the previous sentence or would this assumption reflect reality in clinical practice. In case of the later, please provide supporting evidence showing that patients between CKD1-4 health states can improve.

As noted in Document B, the assumption that patients in CKD 1-4 health states could transition to improved neighbouring health states was to account for the bias of small changes in eGFR readings around the threshold values. However, to validate this assumption, the model schematic, which displays these transitions to improved health states, was presented to clinical experts at an advisory board. None of the

clinical experts disagreed with this assumption. Furthermore, an assumption that patients could transition to improved health states was also included in the economic model used in TA775 (dapagliflozin for treating chronic kidney disease) (43), which was deemed acceptable for decision making purposes by the ERG and NICE committee.

B 2. Priority question: The NICE scope defines the treatment to be relevant for people with primary IgAN, whereas the decision problem and cost effectiveness analysis is limited to adult patients with primary IgAN who are on a stable dose of maximally-tolerated RAS inhibitor therapy focussing on the NefIgArd Nef-301 trial population (see question A6). In accordance with question A6, if some patients who would be eligible for budesonide would not be on a stable dose of maximally-tolerated RAS inhibitor therapy then please include a comparison with what would be SoC for these patients and update the cost effectiveness (CE) section (inputs and results) accordingly.

Please refer to our response to clarification question A6 which explains why patients not receiving maximally-tolerated RAS inhibitor therapy should not be considered in this appraisal. We have therefore made no changes to the cost-effectiveness model.

B 3. Priority question: As per NICE scope the comparator should be SoC, including ACE inhibitors and ARBs at the maximum tolerated licensed doses, diuretics and dietary and lifestyle modification, with or without 1) glucocorticoids and 2) SGLT2s.

a) The CS states that SoC can also include MMF as this treatment might be considered for Asian and Caucasian. However, the company have excluded MMF as a comparator (see question A7). As also indicated in question A7, if MMF would be part of SoC, then an ITC may be required. Please update the CE section (inputs and results) accordingly.

b) **The CS states that corticosteroids may still be recommended for patients at high risk of progression despite the toxicity concerns and the uncertain health benefits. However, the model does not account for corticosteroids in the SoC (see question A8). As explained in question A8, if IgA patients eligible for corticosteroids and immunosuppressants are also eligible for budesonide, then please include corticosteroids and immunosuppressants as part of SoC in the cost-effectiveness analysis. Please update the CE section (inputs and results) accordingly.**

c) **As indicated in the CS, SGLT2 inhibitors were also expected by clinical experts to be included as a component of SoC based on UK clinical practice. However, the model only accounts for the cost of such treatments, while the SoC data from the NefIgArd Nef-301 trial was not adjusted to account for the inclusion of SGLT2is. The justification was based on the DAPA-CKD study showing that patients with IgAN (N=270) did not present a statistically significant impact on eGFR over 36 months compared with placebo following treatment with dapagliflozin. However, the DAPA-CKD study showed that dapagliflozin patients presented an improvement in least mean squared eGFR, and a significant benefit in terms of the composite endpoint of sustained >50% decline in eGFR (see question A25). As per question A25, if patients eligible for an SGLT2is are not excluded, which seems to be the case considering SGLT2is costs are already considered in the cost calculations of SoC, then please conduct an ITC to appropriately incorporate treatment effectiveness of SGLT2is and update cost-effectiveness analyses accordingly.**

Please refer to our response to clarification question A7 which explains why patients receiving MMF should not be considered in this appraisal.

Please refer to our response to clarification question A8, which explains why patients receiving immunosuppressants or corticosteroids should not be considered in this appraisal.

Clinical experts confirmed that SGLT2is are considered a component of SoC for patients with primary IgAN at risk of rapid disease progression with a UPCR ≥1.5 g/g. Therefore, patients receiving SGLT2is as part of their SoC are eligible for treatment with TRF-budesonide in the model. In the cost-effectiveness model (CEM), SoC data from the NefIgArd Nef-301 trial was not adjusted to account for the inclusion of SGLT2 inhibitors. This was based on the findings of the DAPA-CKD study (26) which reported that dapagliflozin treatment in patients with IgAN (N=270) did not have a statistically significant impact on eGFR over 36 months, compared with placebo. Furthermore, the DAPA-CKD study showed that dapagliflozin patients presented an improvement in least mean squares eGFR, this improvement was statistically insignificant (26). However, the DAPA-CKD study did demonstrate a significant benefit in terms of the composite primary endpoint defined as a sustained >50% decline in eGFR, onset of end-stage kidney disease, kidney transplantation, or eGFR <15 mL/min per 1.73m^2, compared to placebo (26). However, the model health states were defined by eGFR values and the insignificant change in eGFR over 36 months compared with placebo was considered more relevant than the significant change in the composite primary endpoint compared with placebo.

B 4. The MHRA license states the TRF-budesonide dose may be reduced to 4 mg once daily for an additional 2 weeks following the end of the 9-month treatment course and the 2-week reduced therapy course. The electronic model includes functionality to include treatment tapering in the calculations, but this option is excluded from the base case analysis and only explored in scenario analysis. Please report the percentage of patients in the trial that used the tapering option. Furthermore, please indicate how many patients are expected to use this option in clinical practice (%).

[redacted] in Part A of the NefIgArd Nef-301 study received a tapered dose of 4 mg TRF-budesonide 2-weeks after discontinuing treatment.

Clinical experts at the Britannia advisory board recommended not to include the optional dose tapering (4 mg once daily for an additional 2 weeks) described in the

TRF-budesonide licence in the model base case as it may not be expected to form standard practice for most patients. The model therefore excludes treatment tapering in the base case and instead explores it in a scenario analysis.

Transition Probabilities

B 5. Priority question: Patients that discontinued the TRF-budesonide treatment before 9 months were assumed to incur the same transition probabilities (between CKD1-4 health states) as those remaining in full treatment (presented in Table 20 of the CS). Please provide further details on the number of patients that discontinued treatment and the reason behind treatment discontinuation. Please re-estimate the transition probabilities in Table 20 using the trial data while accounting for patients discontinuing treatment. Please run a scenario analysis using this new set of transition probabilities.

Table 5 presents the reasons for treatment discontinuation for patients with a baseline urine protein to creatinine ratio (UPCR) >1.5 g/g in Part A of the NefIgArd Nef-301 trial, derived from the CSR (44).

Table 5: Reasons for treatment discontinuation for patients with a baseline urine protein to creatinine ratio (UPCR) >1.5 g/g in Part A of the NefIgArd Nef-301

Reason for discontinuation	TRF-budesonide 16 mg (N=35) n (%)	Placebo (N=38) n (%)
Adverse event	[redacted]	[redacted]
Informed consent withdrawn	[redacted]	[redacted]
Pregnancy	[redacted]	[redacted]
Other reason	[redacted]	[redacted]

Abbreviations: UPCR, urine protein creatinine ratio.

The transition probabilities to inform patient movement between the CKD1–4 health states were directly informed from the observed NefIgArd Nef-301 trial data. Specifically, the FAS was used, which included all patients who had received at least one dose of the study drug and who had the opportunity to receive the full 9-month

treatment regimen. Therefore, because the trial data captured the period over which patients could have received treatment (9 months), the patient outcomes, and resulting transition probabilities, inherently capture the impact of treatment discontinuation. In essence, the observed outcomes reflect a mixture of patients who continue the full course of treatment and patients who discontinue treatment early (see response to question A16 for additional information).

Given the trial follow-up covers the treatment duration of TRF-budesonide, as demonstrated by the complete time to discontinuation Kaplan-Meier (KM) in Figure 21 of Document B, incorporating the impact of treatment discontinuation separately was not necessary.

B 6. Priority question: Transition probabilities from CKD4 to CKD5 are informed from the UK RaDaR database. The probabilities were estimated using the digitised patient-level data based on Figure 17 of the CS. The CS further states that Figure 17 presents the Kaplan-Meier (KM) curves for the probability of progressing to end-stage renal disease (ESRD) or mortality over time (page 93 of the CS).

a) **Please clarify if Figure 17 is based on patients transitioning from CKD4 to CKD5 or from patients in all stages to CKD5.**

b) **Please clarify what is t=0 for patients in Figure 17. Would this be time of CKD diagnosis at any stage or time of CKD4 diagnosis or something else?**

c) **The label of the x axis in Figure 17 states that the data show the patient probability from diagnosis to ESRD or death. However, these curves have been used to inform transition probabilities from CKD4 to CKD5, with CKD5 being assumed to be equivalent to ESRD. Please explain how the two different events (ESRD or death) were distinguished while using data from Figure 17 in the CS (or if any other approach was used, please explain). If there are additional data used for the estimation of these transition probabilities apart from those in Figure 17, please provide this**

further evidence. If the events in Figure 17 (ESRD or death) are not distinguishable in the calculations, please discuss the limitations and potential implications of using this data to estimate transitions from CKD4 to CKD5 in the model.

d) **To fit the observed data different parametric models were estimated. The CS states that the gamma model is used in the base case since it provides the best fit according to both AIC and BIC statistics. As per NICE DSU guidance on parametric modeling, the AIC and BIC values are not the only criteria used for appropriate model selection. Please report if external validity was considered in the model selection process. Please comment on the clinical plausibility of the alternative parametric models.**

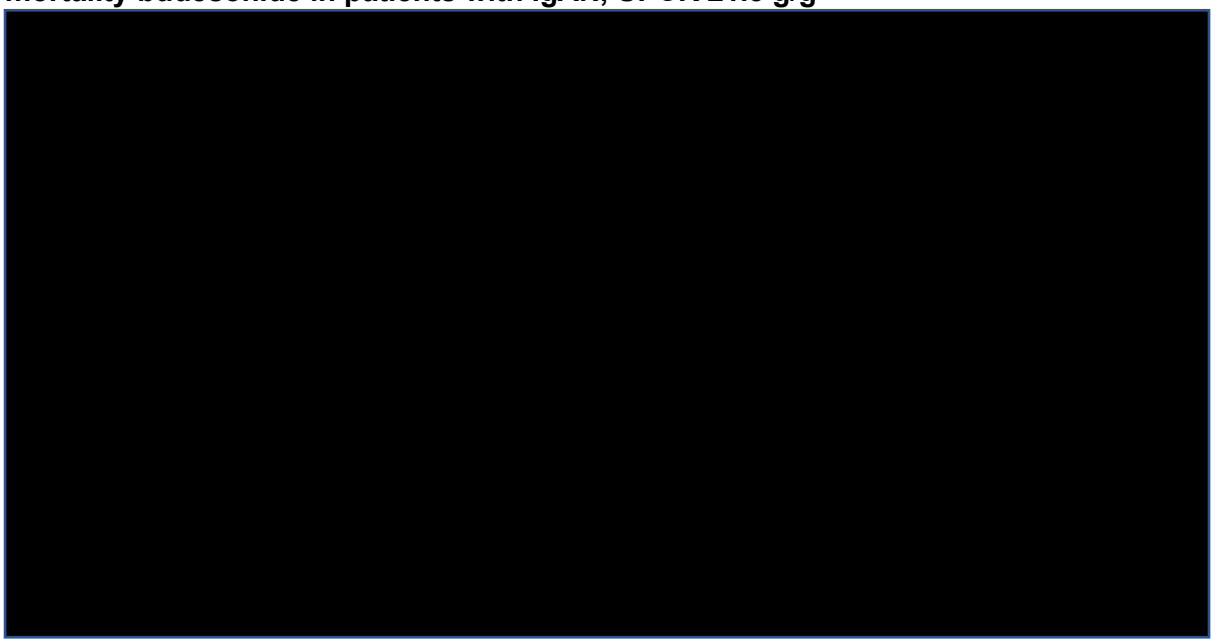
The UK RaDaR database was used to assess the time to ESRD or death from different CKD stages. As expected, this showed that the probability of ESRD or death increased with the higher CKD stages. In the model, real world data from UK RaDaR was used to inform the transition from CKD 4 to CKD 5.

It is confirmed that the KM curve in Figure 17 of the CS illustrates progression of CKD 4 patients only to ESRD or death.

In Figure 17, t=0 represents time from CKD 4 diagnosis.

The events in Figure 17 include both ESRD and death and no distinction was made between these events. UK RaDaR data that assesses the time to ESRD from CKD in patients with IgAN and UPCR ≥1.5 g/g has since been attained, as presented in Figure 1.

Figure 1: UK RaDaR KM curve estimating time from CKD 4 diagnosis to ESRD or mortality budesonide in patients with IgAN, UPCR ≥1.5 g/g



Abbreviations: CKD, chronic kidney disease; ESRD, end stage renal disease; PCR, protein creatinine ratio.

However, in this analysis, patients that died were censored if they did not reach ESRD before their time of death. Due to this censoring, the number of ESRD events are inflated as they are based on a smaller sample of patients. As it seemed less clinically plausible that the risk of ESRD was greater than the risk of ESRD or mortality, UK RaDaR data that considered either ESRD or mortality as an event was used in the model base case.

A scenario analysis that explored the impact of using UK RaDaR data on the time to ESRD to inform the risk of transitioning to CKD 5 was explored. The KM curve, which shows time from CKD 4 to ESRD was digitalised using Engauge Digitizer 12.1 software (44). The R packages “MASS” and “splines” (45) were used on the digitised data to generate pseudo patient level data (PLD). As data were only available for up to 5 years, parametric survival modelling was performed to extrapolate beyond the observed period, using the R packages “survival” and “flexsurv” (45). The Akaike information criterion (AIC) and Bayesian information criterion (BIC) rankings presented in Table 6 demonstrated that exponential was the best fit parametric model. The results of this scenario analysis are presented in Table 7.

Table 6: AIC and BIC statistics for time to CKD 5 models

Model	AIC	AIC rank	BIC	BIC rank
Exponential	82.63	1	83.89	1
Generalised gamma	85.88	6	89.66	6
Gompertz	83.94	2	86.46	2
Log-logistic	85.62	5	88.14	5
Log-normal	87.86	7	90.38	7
Weibull	84.01	3	86.52	3
Gamma	84.13	4	86.65	4

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

Table 7: Scenario analysis results

Scenario analysis	Base case ICER	ICER	Difference
Risk of ESRD: UK RADAR data - All patients (ESRD only) (exponential parametric distribution)	£21,872	£26,143	£4,271

Abbreviations: ACEi, Angiotensin-converting enzyme inhibitors; ARBs, Angiotensin receptor blockers; CKD, chronic kidney disease; SoC, standard of care.

In the base case submitted model, the choice of parametric model to inform the CKD 4 to CKD 5 transition was further validated by experts at the advisory board using visual inspection(2). On visual inspection of the extrapolated curves, the log-logistic and log-normal models do not provide a good fit to the tail of the KM and appear to overestimate time to ESRD. Additionally, the Gompertz model results in a curve that plateaus, suggesting that a proportion of patients (~5%) do not transition to ESRD. This was not considered to be clinically plausible given the progressive nature of the disease. Therefore, the statistical fit was used to determine the best fitting model out of those that were considered to be clinically and visually plausible.

B 7. Transitioning from CKD4 to CKD5 in the TRF-budesonide arm is informed by applying a hazard ratio (HR) to the risk of CKD5 in the SoC arm.

a) Please clarify if there were no trial data in either arm that could be used in to inform these transitions in the TRF-budesonide or SoC arms.

b) In the probabilistic sensitivity analysis (PSA), please modify the model to use the standard error as implied by the combination of the standard errors of slope, intercept and 1-year treatment effects, rather than using a standard error that is 10% of the mean.

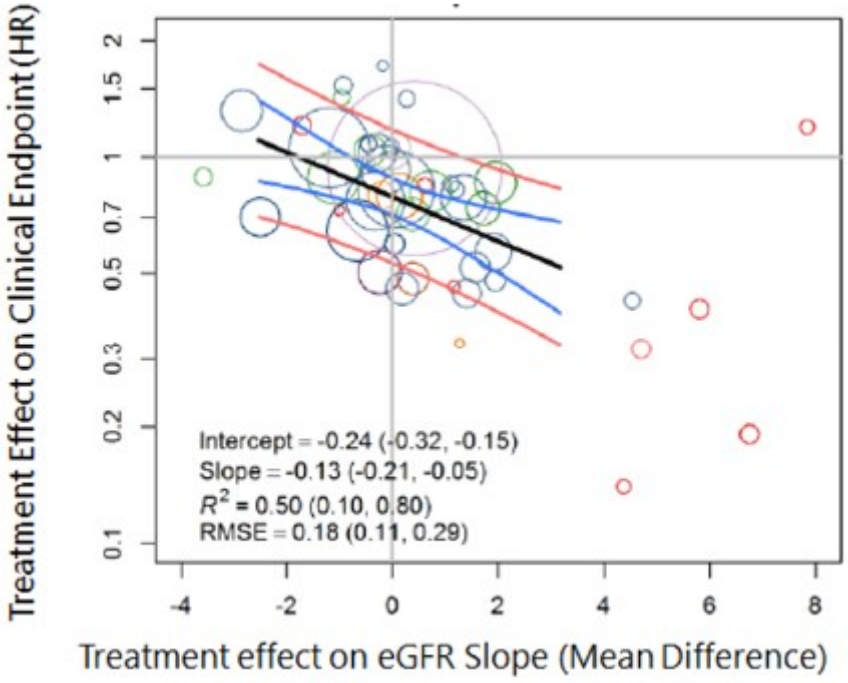
c) Two scenario analyses were done, where other sources of data (UK RaDaR data – ACE inhibitor and ARB patients and Leicester General Hospital data with HR applied) were used to inform the transition to CKD5. However, no information was provided in the CS about these data and the curve fitting procedure. Please explain why these two scenarios are considered relevant, and please provide detailed information, in line with the way the base case was presented in the CS.

The model transition probabilities for 0–12 months were calculated using baseline and 9-month data. Since the inclusion criteria for Part A of the NefIgArd Nef-301 trial did not allow patients with CKD 4 to enter the trial, there were insufficient data available from the trial to inform the transitions from CKD 4 to CKD 5.

As described in the CS, the hazard ratio of [redacted] was calculated using an intercept and slope coefficient identified from a published meta-analysis (46), and the treatment effect on 1-year eGFR total slope in the sub-population of patients with baseline UPCR ≥1.5 g/g of [redacted] mL/min/1.73 m^2 per year that was observed in Part A of the NefIgArd Nef-301 trial.

Within the submitted model, this hazard ratio was hard coded and therefore, in the PSA, the standard error applied to the hazard ratio was assumed to be 10% of the mean ([redacted]). The model has been updated so that the hazard ratio is calculated within the model using the intercept, slope, and 1-year treatment effect as inputs; the PSA now varies these coefficients rather than the hazard ratio itself. This is done within their corresponding upper and lower values, as presented in Figure 2.

Figure 2: Relationship between treatment effect on 1-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 (46). The meta-analysis of 47 trials in chronic kidney disease (Inker et al. 2019 supplement eFigure5) relating treatment effects on 1-year eGFR total slope to long-term clinical outcomes in IgAN was used to predict the HR associated with the treatment effect on 1-year eGFR total slope for TRF-budesonide 16 mg versus placebo in Nef-301.

Table 8 and Table 9 present the updated PSA results for this analysis.

Table 8: Base-case probabilistic incremental cost-effectiveness results (including CKD 1 to CKD 2 transition)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
TRF-budesonide	[redacted]	16.596	[redacted]					
SoC	[redacted]	16.181	[redacted]	[redacted]	0.414	[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 9: Base-case probabilistic incremental cost-effectiveness results (excluding CKD 1 to CKD 2 transition)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
TRF-budesonide	[redacted]	16.205	[redacted]					
SoC	[redacted]	16.053	[redacted]	[redacted]	0.153	[redacted]	£20,177	£20,177

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

A scenario analysis was run which explored using UK RaDaR data from patients with IgAN, UPCR ≥1.5 g/g, and on ACEI and/or ARBs at baseline to inform the risk of transitioning to CKD 5. This patient population was considered relevant because the use of ACEI and/or ARBs is reflective of the current UK SoC for IgAN patients. As shown in Table 10, the sample size decreases when the UK RaDaR database is restricted to only include patients with IgAN, UPCR ≥1.5 g/g, and ACEIs and ARBs at baseline. However, as discussed in our response to clarification question A6, although patients not receiving maximally-tolerated RAS inhibitor therapy should not be considered in this appraisal, for some patients 'maximally-tolerated' RAS inhibitor therapy would be no use of ACEI and/or ARBs as they may not be able to tolerate RAS inhibitors, in line with anticipated clinical practice. Therefore, UK RaDaR data for patients with IgAN and UPCR ≥1.5 g/g was used to inform the transition between CKD 4 and CKD 5 in the model base case.

Table 10: Number of patients with CKD 4 at risk of CKD 5 over time (UK RaDaR)

UK RaDaR patient population	Years from diagnosis of CKD 4 to ESRD or mortality			
	0	2	4	6
Patients with IgAN and UPCR ≥1.5 g/g	[redacted]	[redacted]	[redacted]	[redacted]
Patients with IgAN, UPCR ≥1.5 g/g, and on ACEi and/or ARBs at baseline	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CKD, chronic kidney disease; ESRD, end stage renal disease; IgAN, Immunoglobulin A Nephropathy; UPCR, Urine Protein Creatinine Ratio

The KM curve, presented in Figure 3, estimates the probability of patients with IgAN, UPCR ≥1.5 g/g, and on ACEI and/or ARBs at baseline progressing to ESRD or mortality over time, and was digitalised using Engauge Digitizer 12.1 software (44). The R packages (45) "MASS" and "splines" used the digitised data to generate pseudo PLD. As data were only available for up to 5 years, parametric survival modelling was performed to extrapolate beyond the observed period, using the R packages "survival" and "flexsurv" (45).

Figure 3: UK RaDaR KM curve estimating time from CKD 4 diagnosis to ESRD or mortality budesonide in patients with IgAN, UPCR ≥1.5 g/g, and on ACEi and/or ARBs at baseline

Abbreviations: ACEi, Angiotensin-converting enzyme inhibitors; ARBs, Angiotensin receptor blockers; CKD, chronic kidney disease; ESRD, end stage renal disease; IgAN, Immunoglobulin A Nephropathy; UPCR, Urine Protein Creatinine Ratio

Figure 4 presents the extrapolated and digitalised KM data with the standard parametric models fitted.

Figure 4: Digitised UK RaDaR – ACEi and ARB KM data and fitted parametric extrapolations to estimate time to CKD 5

Abbreviations: ACEi, Angiotensin-converting enzyme inhibitors; ARBs, Angiotensin receptor blockers; CKD, chronic kidney disease; SoC, standard of care

As presented in Table 11, both the AIC and BIC criterion rank exponential as the parametric model that provides the best statistical fit to the observed data. When comparing the exponential model to the KM, this also appears to provide a good visual fit.

Table 11: AIC and BIC statistics for time to CKD 5 models

Model	AIC	AIC rank	BIC	BIC rank
Exponential	81.74	1	83.00	1
Generalised gamma	84.20	5	87.97	6
Gompertz	82.21	2	84.73	2
Log-logistic	84.84	6	87.36	5
Log-normal	86.98	7	89.49	7
Weibull	82.72	3	85.23	3
Gamma	82.97	4	85.48	4

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

The results of the scenario analysis using UK RaDaR data from patients with IgAN, UPCR ≥1.5 g/g, and on ACEi and/or ARBs at baseline, with an exponential parametric model applied, are presented in Table 12.

Table 12: Scenario analysis results

Scenario analysis	Base case ICER	ICER	Difference
Risk of ESRD: UK RADAR data - ACEi and ARB patients (exponential parametric distribution)	£21,872	£25,921	£4,049

Abbreviations: ACEi, Angiotensin-converting enzyme inhibitors; ARBs, Angiotensin receptor blockers; CKD, chronic kidney disease; SoC, standard of care

The second scenario analysis that informed the risk of CKD 5 was run using a published KM curve derived from real-world registry data from patients at Leicester General Hospital (LGH) in the UK between 1992 to 2020. The KM curve was obtained from a report presenting the median time to the clinical outcome (the earliest of the doubling of serum creatinine from baseline, eGFR < 15 mL/min/1.73m^2 or ESRD) for an untreated reference group. LGH registry patients were included in the modelling only if they would have been eligible for the NefIgArd Nef-301 study and matched a NefIgArd Nef-301 patient, which required a baseline eGFR (CKD-EPI) between 35 and 90 mL/min/1.73m^2 inclusive and either proteinuria ≥1 g per day or UPCR ≥0.8 g/g. The patient population was then further refined to only consider

patients with UPCR ≥1.5 g/g in the analysis. For each NefIgArd Nef-301 patient, a maximum of five LGH registry patients were selected where both UPCR was within 25% and eGFR was within 5 mL/min/1.73 m^2 of the baseline values for that Nef-301 patient (5:1 matching). Where LGH registry patients were identified as a match more than once at different timepoints, the timepoint at which the match was closest to the baseline values for that NefIgArd Nef-301 patient was used based on the following distance formula:

$$\text{distance} = \frac{(\ln[\text{UPCR}_{301}] - \ln[\text{UPCR}_{\text{LR}}])^2}{\text{SD}(\ln[\text{UPCR}_{301}])^2} + \frac{(\ln[\text{eGFR}_{301}] - \ln[\text{eGFR}_{\text{LR}}])^2}{\text{SD}(\ln[\text{eGFR}_{301}])^2}$$

A total of 804 patients were recruited into the LGH registry; of which, 236 would have been eligible for the NefIgArd Nef-301 study and had further follow-up data available. In the analysis based on 5:1 matching in the sub-population with baseline UPCR ≥ 1.5 g/g, a total of 294 matched records were derived from these patients and used in the analysis to estimate the untreated reference group median time to clinical outcome. Of the 294 LGH matched patient records included in the analysis, 114 had an event (confirmed doubling of serum creatinine, confirmed eGFR <15 mL/min/1.73m^2 or ESRD), with a median follow-up of 3.66 years in censored patients and a maximum follow-up of 13.96 years. The red line in Figure 5 represents the KM curve estimating the time to CKD 5 for the SoC arm.

Figure 5: Time to clinical outcome/CKD 5 estimated from digitised LGH registry data and extrapolated over a lifetime horizon

Abbreviations: CKD, chronic kidney disease; LGH, Leicester General Hospital
Source: Calliditas Therapeutics AB. NEF-301 CSR. Data on file. 2021 (6).

The KM in Figure 5 is based on patients with CKD 1 – 4; however, the model structure only allows patients to transition to CKD 5 from CKD 4. To make the KM representative of CKD 4 patients, a hazard ratio (HR) was applied. The HR was derived by digitalising the KM curves from Hastings et al (47) (in the supplementary table), which presented the time to death from biopsy by CKD stages. The probability of death in the final time point was used to calculate the instant hazard rate for patients with CKD 4 and all patients (CKD 1-5). The exponential of the instant hazard rate multiplied by the model time horizon was taken away from 1 to determine the probability of death per cycle. The probability of death in CKD 4 was divided by the probability of death for all patients to derive a HR of 3.12. A potentially large assumption of this approach is that the increased risk of death for patients in CKD 4 is assumed equal to the increased risk of transitioning to CKD 5. Due to this assumption, the LGH registry was not considered appropriate for the model base case.

The KM data in Figure 5 was digitalised using Engauge Digitizer 12.1 software (44). Pseudo patient level data was generated from the digitised data using the R packages “MASS” and “splines” (45). Figure 6 presents the parametric survival

models that were fitted to these data using the R packages “survival” and “flexsurv” (45).

Figure 6: Digitised Figure 5 KM data and fitted survival models - Time to CKD 5 – SoC

Abbreviations: CKD, chronic kidney disease; KM, Kaplan Meier; SoC, standard of care

As presented in Table **13**, both the average of the AIC and BIC criterion rank exponential as the parametric model that provides the best statistical fit to the observed data.

Table 13: AIC and BIC statistics for time to CKD 5 models

Model	AIC	AIC rank	BIC	BIC rank
Exponential	805.56	1	812.93	2
Generalised gamma	807.17	5	810.86	1
Gompertz	805.98	2	813.35	3
Log-logistic	806.93	4	817.98	7
Log-normal	808.74	7	816.11	6
Weibull	807.67	6	815.04	5
Gamma	806.49	3	813.85	4

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

Following the long-term extrapolation of the LGH data, the HR derived from Hastings et al. 2018 was applied in order to ensure the curve was representative of the risk of CKD 4 patients progressing to CKD 5.

The results of the scenario analysis using LGH data with an applied HR and an exponential parametric model applied are presented in Table 14.

Table 14: Scenario analysis results

Scenario analysis	Base case ICER	ICER	Difference
Risk of ESRD: Leicester General Hospital data with HR applied (exponential parametric distribution)	£21,872	£27,429	£5,557

Abbreviations: ESRD, end stage renal disease; ICER, incremental cost-effectiveness ratio; HR, hazard ratio

The additional assumptions required to make the LGH data better reflect the risk of transitioning to CKD 5 for patients with CKD 4 adds more uncertainty into the model, therefore, due to this added uncertainty it was only considered as a scenario analysis and not as the base case.

B 8. The studies of Greene et al. 2019 and Hastings et al. 2018 were used in the scenario analyses to assess the impact of using alternative mortality rates in the calculations (Table 47 of the CS). Nonetheless, these studies were not presented or discussed in the CS. Please explain why these two sources were considered appropriate to inform mortality rates and how do they compare to the respective UK RaDaR data. Were these studies identified through an SLR?

Hastings et al. 2019 (47) was used to inform the risk of mortality from CKD stages 1-5 and dialysis in a scenario analysis. The paper was identified in the list of references from a US SLR that analysed published evidence on IgAN which was identified by the SLR. Hastings et al. was considered an appropriate alternative source of mortality as it reports life expectancy estimates for patients with IgAN in the form of OS KM plots, split by CKD stage. The study aimed to examine outcomes of progression to ESRD and age at death in 251 adult patients with IgAN from the south-eastern US, diagnosed between 1976 and 2005. The National Death Index

was used to establish the date of death. The OS KM curves for each CKD stage were digitised to calculate the probability of death per monthly cycle and converted to standardised mortality ratios (SMRs) to be applied to background mortality in the CEM.

Table 15 presents the Hastings et al. SMR weights used in the CEM for each of the CKD stages and dialysis health states.

Table 15: Hastings et al. 2019 (47) standard mortality ratios

Health state	SMR
CKD 1	1.00
CKD 2	2.38
CKD 3a	3.23
CKD 3b	3.23
CKD 4	7.42
CKD 5	7.24
Dialysis	7.24

Abbreviations: CKD, chronic kidney disease; SMR, standardised mortality ratio

However, a limitation of the SMRs in the Hastings et al. study (47) is that results are not specific to IgAN patients with a UPCR ≥1.5 g/g, and the results are based on data from US patients who were diagnosed between 1976 and 2005. In addition, the SMRs based on the UK RaDaR data are lower than the SMRs reported in Hastings et al. This is in line with discussions held with clinical experts who have highlighted that the mortality from CKD is liable to be greater in the US than the UK. As such, UK RaDaR data was used to inform the model base case.

Data from Greene et al. 2019 (48) were used to inform the risk of mortality in a separate scenario analysis. Since this study is not specific to IgAN patients, it was not identified in the SLR but was identified in a targeted literature review. Greene et al estimate the annual rate of death per CKD stage by assuming a linear relationship between the mortality hazard rate and a patients' underlying eGFR level, with higher death rates occurring at lower eGFR levels:

$$death\ rate = 0.03375 + (-0.000253 * eGFR)$$

The CEM estimates the annual risk of death for each CKD stage by inputting the mid-point eGFR for each CKD health state into the equation above. The annual rates of death are then converted to monthly probabilities to align with the model cycle length. The monthly probabilities of death available in the CEM, taken from the Greene et al. 2019 study, are presented in Table 16.

Table 16: Greene et al. 2019 (48) monthly probability of death

Health state	Average eGFR	Death rate	Death probability per cycle
CKD 1	95	0.009715	0.000813
CKD 2	74.5	0.014902	0.001250
CKD 3a	52	0.020594	0.001733
CKD 3b	37	0.024389	0.002055
CKD 4	22	0.028184	0.002380
CKD 5	12	0.030714	0.002596
Dialysis	12	0.030714	0.002596

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

Despite not being specific to patients with IgAN, the health states in the model are based on eGFR and therefore the death rates estimated by Greene et al. 2019 may be considered an appropriate mortality source to explore in the scenario analysis. However, the authors did not provide detail regarding the methods used to obtain the equation above, other than to state that the rate of death was assumed to be exponentially distributed over six-month intervals. Therefore, applying death rates estimated by Greene et al. 2019 adds additional uncertainty to the model. This uncertainty was validated with clinical input.

The use of an average eGFR for each CKD health state may also over or underestimate the risk of death in each CKD health state. Further to this, upper and lower bounds for CKD stage 1 and CKD 5 had to be defined to use the equation, with an upper bound of 100 mL/min/1.73m2 for CKD 1 and a lower bound of 5mL/min/1.73m2 for CKD 5 assumed in the CEM, in absence of data. Therefore, with these limitations to the data and methods, this data is only explored in a scenario analysis.

B 9. Data from the UK RaDaR database were used to inform the mortality rates from CKD stages 1–5 and dialysis by fitting cox-regression models. Please provide further details on this data (e.g. number of death cases per health state).

Table 17 presents the 10-year survival probability and the frequency count by CKD stage.

Table 17: 10-year survival probability

Health state	Frequency count	10-Year survival
CKD Stage 1	[redacted]	[redacted]
CKD Stage 2	[redacted]	[redacted]
CKD Stage 3a	[redacted]	[redacted]
CKD Stage 3b	[redacted]	[redacted]
CKD Stage 4	[redacted]	[redacted]
CKD Stage 5	[redacted]	[redacted]
Renal Replacement	[redacted]	[redacted]

Abbreviations: CKD, chronic kidney disease.

The 10-year survival probability values were converted into a probability of mortality by taking away each value from 1. These values were then used to estimate an instant hazard rate and probability of mortality per model cycle for each health state. The probability of mortality per cycle per health state was divided by the referent (probability of mortality for CKD 1) to calculate the standardized mortality ratios.

B 10. The transitions from CKD 5 to dialysis and transplantation were sourced directly from the DAPA-CKD Data as reported in TA775. The estimated monthly probability of patients in CKD 5 to dialysis is 4.5%. This results in a probability of still being in CKD 5 without dialysis after 1 year of >50%. Please clarify if experts have been consulted to consider the face validity of this transition probability for the current population, and please provide a justification for using this estimate.

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, as the model health states are based on eGFR values, data from the DAPA-CKD trial was considered appropriate to inform this transition. Although the face validity of this transition probability was not assessed in the Advisory Board, the same transition is applied to both the TRF-budesonide and SoC arm of the model. Additionally, previous engagements with clinicians have indicated that, as CKD 5 is distinct from ESRD and does not always require renal replacement therapies (i.e. dialysis), patients with CKD 5 can experience long durations without requiring such therapies.

Nonetheless, an additional scenario analysis was included in the model which demonstrated that increasing the transition probability such that the majority of patients with CKD 5 will receive dialysis after 1 year causes the ICER to decrease (Table 18). Therefore, the transition probability in DAPA-CKD is considered a conservative and appropriate data source given the lack of alternative data sources.

Table 18: Scenario analysis results

Scenario analysis	Base case ICER	ICER	Difference
Monthly transition probability from CKD 5 to dialysis - 6%	£21,872	£20,899	-£973

Abbreviations: CKD, chronic kidney disease; ICER, incremental cost-effectiveness ratio.

B 11. Priority question: The company acknowledges throughout the CS that there is a lot of uncertainty regarding the retreatment of patients with TRF-budesonide in clinical practice. The base-case analysis accounts for 2 rounds of treatment, and the scenario analyses explores the impact of using no retreatment option or a higher number of retreatment rounds. However, the number of patients allowed for retreatment and the interval time between retreatments can also be varied in the model.

a) The proportion of patients allowed to receive retreatment in the model (currently set at 88%) and the interval time between two rounds of treatment (currently set at 14.75) have been informed from the NeflgArd Nef-301 trial data. However, as stated in the CS, the retreatment option is at the discretion of the treating physician, implying high

uncertainty. Please explain how realistic the currently used values are for these two parameters based on expectations from clinical practice and if there has been any validity exercise performed for these two parameters.

b) **Please specify what alternative values could be used to inform the proportion of patients that is allowed to receive retreatment in the model and the interval time between the first and second treatment rounds. Please run different scenarios by changing these two parameters to the alternative (potentially realistic) specified values.**

c) **In the electronic model, when lowering the proportion of patients allowed to receive retreatment (current value 88%), the incremental cost-effectiveness ratio (ICER) lowers substantially. On the other hand, the ICER is relative insensitive to changes in the % of patients receiving retreatment when the treatment effect for retreatment is not taken into consideration. Considering that a higher number of retreated patients would be expected to lead to more health gains it may be counterintuitive to see that the ICER decreases with a lower number of retreated patients, especially when seeing that the ICER is relatively insensitive to this parameter once the treatment effect is disregarded and when considering the treatment benefit of the first treatment round lasts for 1 year. Please provide an explanation for these results.**

At the Britannia advisory board, clinical experts were uncertain about the specific time between retreatment rounds; as such, the time between the completion of 9 months of treatment in Part A of the NefIgArd Nef-301 trial and the start of the NefIgArd-OLE study (14.75 months) was considered appropriate given the lack of available evidence. Clinicians also stated that 14.75 months would be the initial minimum time between treatment cycles since this aligns with the open label extension trial (NefIgArd-OLE study). Therefore, scenario analyses that increase the time between retreatment by 6 months were added to the model. The results of these scenarios are presented in Table 19.

Table 19: Scenario analysis results

Scenario analysis	Base case ICER	ICER	Difference
Time between retreatment cycles - 20.75 months	£21,872	£18,221	-£3,651
Time between retreatment cycles - 26.75 months		£15,361	-£6,511
Time between retreatment cycles - 32.75 months		£13,294	-£8,578

Abbreviations: ICER, incremental cost-effectiveness ratio.

Clinical experts also stated that not all patients would require retreatment but were unable to provide an estimate of a feasible proportion. Therefore, given the lack of evidence to inform this, an assumption was made that only patients who completed the full 9 months of treatment in Part A of the NefIgArd Nef-301 trial would be eligible for retreatment; this was [redacted]. Consistent with the eligibility criteria for Part A of the NefIgArd Nef-301 (eGFR ≥35 mL/min/1.73m^2), only patients in CKD stages 1 to 3b at the time of retreatment are assumed to be eligible to receive retreatment with TRF-budesonide; therefore, this [redacted] was applied to the proportion of patients meeting this criterion, resulting in roughly [redacted] of patients receiving the second round of treatment. Scenario analyses that explore the impact of varying the proportion of patients eligible for retreatment has on the model outcomes were explored. Since patients that discontinued treatment would not be retreated with TRF-budesonide, [redacted] was considered the maximum proportion of patients eligible for retreatment. The results of the scenario analyses are presented in Table 20.

Table 20: Scenario analysis results

Scenario analysis	Base case ICER	ICER	Difference
Patients eligible for retreatment - 25%	£21,872	£26,993	£5,121
Patients eligible for retreatment - 50%		£23,755	£1,883

Abbreviations: ICER, incremental cost-effectiveness ratio.

Thank you for highlighting the discrepancies between the model results and expectations. On further investigation errors have been identified and corrected in the model calculations. A summary of the identified errors, and subsequent fixes, are explored in more detail below:

1. Column AW in the “PFlow – Kinpeygo” worksheet

a. The formulae were incorrectly resetting the transition probabilities back to the transition probabilities used at the start of the model time horizon with each new retreatment round. As such, the risk of transitioning to CKD 5 in the TRF-budesonide arm was being underestimated.

b. A correction has been made to the formulae to ensure the risk of progressing to CKD 5 is taken directly from the estimated probability of transition calculated on the “Risk_of_CKD5” worksheet (‘Risk_of_CKD5 ‘!X97:X3749).

2. Risk_of_CKD5 S97:S3749

    a. Treatment effect on CKD 4 to CKD 5 transitions for those receiving a retreatment was incorrectly being applied to all patients in the model instead of only the proportion who were identified as being eligible for retreatment (i.e. [redacted]).

    b. A weighted average probability of transitioning to CKD 5 is now used in the model (‘Risk_of_CKD5 ‘!X97:X3749) depending on the proportion of patients who are retreated, and those who are not retreated.

3. Risk_of_CKD5 R97:R3749

    a. TRF-budesonide treatment effect calculations were incorrectly implemented in the formula. This resulted in risk of transition to CKD 5 for patients receiving four or more Kinpeygo treatment rounds being higher than in the SOC arm.

    b. The offending calculations were changed accordingly:

        i. Old calculations: R96-(O97*R94)

        ii. New calculations: R96*(1-$O97)^$R$94

Where R96 represents % in CKD 4 in the previous model cycle. O97 is the SOC probability of transitioning to CKD 5. R94 represents the HR applied to the SOC arm to reflect the treatment benefit of TRF-budesonide.

After correcting for these discrepancies in calculations, the base case ICER has subsequently been updated. A summary of the changes can be found in Table **21**.

Table 21: Scenario analysis results

Scenario analysis	Old model version	New model version	Difference
Base case ICER	£18,643	£21,872	£3,229

Abbreviations: ICER, incremental cost-effectiveness ratio

As these changes have impacted the base case results in the model, this new base case has been reflected in the scenarios throughout this document.

B 12. Priority question: In the base case analysis, the transition probabilities for patients in the retreatment round are assumed to follow the 0–12 month TRF-budesonide transition probabilities in the initial 12 months of treatment, so assuming the same treatment benefit for the retreated patients. Please confirm this is correct. As in absence of data, there seems to be a lot of uncertainty around this assumption, please explore the impact of alternative scenarios that allow for a reduced benefit of TRF-budesonide for the retreated patients. If possible, please make the required model changes to allow for (at least) an additional parameter that accounts for a lower treatment effect in the TRF-budesonide retreated patient population.

It is confirmed that the model base case applied the 0–12-month TRF-budesonide transition probabilities in retreatment cycles as it is assumed the treatment effect will be the same when patients are retreated with TRF-budesonide.

As requested, the model has subsequently been updated with an additional parameter (Controls!K87), which allows the user to include a reduced treatment effect in the TRF-budesonide arm for retreatment cycles. The use of this parameter

weights the transition probabilities applied to the TRF-budesonide arm during retreatment by assuming the % selected by the user have transition probabilities equivalent to the TRF-budesonide arm of the NefIgArd Nef-301 trial, whilst the complement of the % selected by the user is assumed to use transition probabilities equivalent to the placebo arm of the NefIgArd Nef-301 trial.

Adverse Events

B 13. Priority question: In the CS it is stated that the adverse events included in the model comprised of all treatment-emergent AEs (TEAEs) occurring in ≥4% of patients in either treatment arm and of all treatment-emergent severe adverse events (TESAEs) occurring in ≥1 patient in either treatment group. However, Table 23 also presents TEAEs occurring in <4% of patients in either treatment arm. Moreover, Table 41 of the CS presenting the key assumptions of the analysis, indicates that only TESAEs that occur in more than one patient are included in the model.

a) **Please clarify if indeed all treatment-related AEs occurring in ≥4% of patients in either treatment arm is also included in the model and if a different cut-off value has been used instead of 4% (e.g. occurring in ≥1 patient in either treatment group). In case of an error, please edit the text in the CS accordingly.**

b) **Please confirm if the full analysis set (FAS) data have been used to define the cut-off value for TEAEs (4%), while safety analysis set (SAS) data are used to define AE incidence in the model. If this is correct, please justify why was this approach is taken instead of using one set of data to define the cut-off value and the same set to define AE incidence used in the model. Please comment accordingly on the approach taken for TESAEs and discuss potential implications and impact on the results.**

c) **Costs related to the TESAEs pulmonary embolism and renal impairment have been included in the model, whereas loss in quality of life related**

to these two TEAEs is assumed to be zero. Please explain this approach, explain if another alternative value for quality-of-life deterioration could be used for these two TESAEs and, in that case, run a scenario analysis using alternative disutility values for these two TEAEs. As these two TESAEs can also entail long-term deterioration in quality of life, please also reconsider and comment on the duration the loss in quality of life should be applied.

The list of TEAEs to include in the model was defined as all TEAEs occurring in ≥4% of patients in either treatment arm of Part A of the FAS in the NefIgArd Nef-301 trial. 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. Our use of the FAS to apply the ≥4% criterion to, rather than the SAS, explains why Table 23 presents TEAEs occurring in <4% of patients in either treatment arm. Limiting the TEAEs to all TEAEs occurring in ≥4% of patients in either treatment arm of Part A 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.

The list of TESAEs included in the model was defined as all TESAEs occurring in ≥1 patient in either treatment group of the SAS. Data from the Part A SAS also informed the rates of TESAEs.

The initial targeted literature review did not yield disutility values or length of duration for pulmonary embolism or renal impairment. Further targeted literature reviews have since been conducted which yielded disutility values, as presented in Table 22. The targeted literature review also identified a disutility duration for pulmonary embolism of 1 month however a specific disutility duration was not identified renal impairment. Therefore, the scenario analysis assumes a disutility duration of 1 month for renal impairment.

Table 23 presents the results of these scenario analyses.

Table 22: Treatment-emergent severe adverse event disutility and duration

TESAE	Disutility	Duration
Pulmonary embolism	0.018 (49)	1 month (49)
Renal impairment	0.0603 (50)	1 month

Abbreviations: TESAE, treatment emergent severe adverse event.

Table 23: Scenario analysis results

Scenario analysis	Base case ICER	ICER	Difference
Pulmonary disutility of 0.018 and duration of 1 month	£21,872	£21,929	£57
Renal impairment disutility of 0.0603 and duration of 1 month		£22,064	£192

Abbreviations: ICER, incremental cost-effectiveness ratio.

Quality of life

B 14. Priority question: In the CS it is stated although short form-36 (SF-36) data were collected in NeflgArd Nef-301 and could be used to inform CKD1 to CKD4 health states in the model, those have not been used. As per question A19, the company seems to be dismissing the non-significant SF-36v2 outcomes. Please run a scenario analysis using the SF-36 trial data.

Although SF-36 data were collected in Part A of the NeflgArd Nef-301, these data were not used to generate utility values given the perceived limitations. Generating these is not possible within the timelines to respond to the EAG's clarification questions.

Patients with IgAN do not experience substantial changes in QoL until they reach ESRD, where dialysis or a transplant is required. Patients in Part A of NeflgArd 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 quality of life estimates in the CKD 1–4 health states. Although the follow-up period in Part B of NeflgArd Nef-301 will be 2 years, it is not expected that a substantial proportion of patients will reach ESRD within this timeframe. Therefore, for consistency, using one source to inform the utility values in the CKD 1–5 health states was deemed most appropriate.

As the SF-36 data appeared to demonstrate minimal differences 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 tested. The scenarios assume that the health states are associated with the same utility value as CKD 1 (0.85) (51). Table 24 presents the results of these scenario analyses.

Table 24: Scenario analysis results

Scenario analysis	Base case ICER	ICER	Difference
The same utility value for CKD 1 – 4 health states	£21,872	£19,979	-£1,893
The same utility value for CKD 1 – 3b health states		£19,964	-£1,908

Abbreviations: CKD, chronic kidney disease; ICER, incremental cost-effectiveness ratio.

B 15. Cooper et al. 2020 is used to source quality of life inputs for the different health states. For CKD4 the CS states that data from the US based on Cooper et al. 2020 are used as no UK values are available. However, the values presented in the Cooper et al. 2020 table 4 (and consequently in this CS) are the same values as the values in table 3 of the Jesky et al. 2016 study, which is a UK study. Please clarify if this is an error in the Cooper et al. 2020 study or if indeed another source from the US has been used in the CS for CKD 4 quality of life input.

As stated in the CS, no UK-specific EQ-5D studies were identified in the economic SLR for patients with IgAN. Cooper et al. 2020 (51) was identified as a source of QoL inputs from the reference list included in TA775 (43). Jesky et al. 2016 (52), referenced within the Cooper et al. 2020 publication, is a UK study exploring the relationship between pre-dialysis CKD and HRQoL outcomes using the Euroqol EQ-5D-3L. Table 4 in Cooper et al. references Jesky et al. 2016 (52) for the CKD 4 utility value; however, it does appear this is incorrectly labelled as a USA study. Since the utility value for CKD 4 listed in Cooper et al. does in fact appear to be a UK-specific value; it can be confirmed that no alternative sources were used to inform the utilities associated with CKD 1–5 health states in the model base case.

B 16. Priority question: Cooper et al. 2020 is used to source quality of life inputs for the different health states and was identified through cross-checking of the references listed in recent CKD submissions to NICE. Given that the utility values for CKD1 to CKD 5 in Cooper are essentially based on the study by Jesky et al. 2016, which was not specific to IgAN, it appears that the company considers the population of patients with CKD an appropriate proxy in absence of utility values specific to IgAN patients. Thus, please clarify if an additional systematic literature search was performed to identify newer UK-specific EQ-5D studies for patients with CKD given such studies for patients with IgAN were not identified. Please justify the selection of Cooper et al. 2020 compared to other (and maybe more recent) identified studies.

No additional SLR searches were undertaken to identify EQ-5D data for CKD. Cooper et al. 2020 (51) was identified from additional searching of more recent CKD HTA submissions rather than conducting a full broad review of CKD studies. The Jesky et al. 2016 (52) study was also identified as a reference used in the NICE TA775 CKD submission documents.

Costs and resource use

B 17. The CS states that because TRF-budesonide is self-administered orally, the cost of TRF-budesonide administration is assumed to be zero in the cost effectiveness model. However, oral treatments may still subject to dispensing fees. Please comment on whether treatment dispensing fees are relevant for the model computations.

An additional scenario analysis has been included in the model which considers the impact a monthly dispensing fee of £10.60 has on the model outcomes. The dispensing fee was assumed to be equal to the cost of 12 minutes of a Band 6 Pharmacist time. The hourly rate of a hospital-based Band 6 Pharmacist (£53) was

obtained from the PSSRU unit costs 2022 (53). The dispensing fee was applied to both the TRF-budesonide and SoC arms. Table 25 presents the results of the model base case and the scenario analysis.

Table 25: Scenario analysis results

Scenario analysis	Base case ICER	ICER	Difference
Including a monthly dispensing fee of £10.60	£21,872	£22,277	£405

Abbreviations: ICER, incremental cost-effectiveness ratio

B 18. The company states that while relative dose intensity (RDI) was recorded in the NeflgArd Nef-301 study, this was not taken into account in the model as it is anticipated that any dose reductions or treatment breaks will have no consequence for treatment acquisition costs. Please comment on the RDI data from the trial and run a scenario analysis including RDI in model computations as per the trial data.

The CSR indicates that the compliance rate in the FAS of Part A of the NeflgArd Nef-301 trial was [redacted] in patients receiving TRF-budesonide. This was calculated as 100 x total number of actual capsules taken / total number of expected capsules.

While RDI was not considered in the submitted model base case, a scenario analysis that explores this has been included. When RDI is included in the model, the compliance rate of [redacted] is only applied to the full dose per cycle and reduced per cycle. It is not applied to the tapered dose per cycle since the CSR states that the tapering period was not included in the compliance calculations. Table 26 presents the results of the model base case and the scenario analysis that explores including RDI.

Table 26: Scenario analysis results

Scenario analysis	Base case ICER	ICER	Difference
Include relative dose intensity	£21,872	£17,887	-£3,985

Abbreviations: ICER, incremental cost-effectiveness ratio.

B 19. Priority question: To inform treatment costs for the TRF-budesonide arm, the number of patients that continue treatment each month prior to 9 months was informed by the time to treatment discontinuation (TTD) data from the NeflgArd Nef-301 study.

a) Please reproduce Figure 21 (TTD data) with numbers at risk included in the plot.

b) While the model assumes the same treatment benefit for patients discontinuing treatment as those who those remaining in full treatment (see question B5), TTD data are used to inform TRF-Budesonide treatment costs. That means that treatment costs are lower for some part of patients, indicating an inconsistency between the modelled treatment effects and costs. Please comment on this inconsistency and provide results from a scenario in which costs are set equal to full TRF-Budesonide treatment costs for all patients.

A KM curve of time to discontinuation of study treatment for the Part A FAS, along with numbers at risk, is presented in Figure 7.

Figure 7: Digitised KM curve of time to discontinuation of study treatment – TRF-budesonide

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

As discussed in the response to clarification question B5, the transition probabilities were informed by the FAS, which utilised data observed in Part A of the NefIgArd Nef-301 trial, and, therefore, the outcomes reflect patients who remained on treatment as well as those that prematurely discontinued treatment. As such, there is no need to separate out discontinued patients and apply different transition probabilities to these patients.

To ensure patients that prematurely discontinued treatment did not incur the cost of TRF-budesonide, treatment costs were only applied to patients receiving treatment each month.

Although the transition probabilities considered a mixture of patients who remained on treatment for the full duration and those who prematurely discontinued, it was necessary to separate out the discontinuing patients for costing purposes to ensure that the treatment costs of TRF-budesonide are not overestimated. Because the time to discontinuation data and the transition probabilities used in the model are directly derived from the same trial population, we do not agree that there is an inconsistency between the modelled treatment effects and costs.

Probabilistic sensitivity analysis

B 20. In the CS it is explained (page 130) that the PSA outcomes are very much influenced by the transition probability between CKD 1 and CKD 2 in the TRF-budesonide arm. Thus, the CS shows the results of a PSA that excluded this transition. Please explain the precise changes that were made in the model to facilitate this analysis, and please add a control to the model so that this adjusted PSA can easily be selected.

As the transition between CKD 1 to CKD 2 in the TRF-budesonide arm is informed by data from [redacted] in Part A of the NefIgArd Nef-301 study, when this transition is varied in the PSA, it often takes extreme values of either 0% or 100% which has a significant impact on the ICER produced in the PSA. This transition can be excluded from the PSA by setting cell Y338' on the sheet 'Parameters' to No. When set to 'No'

the progressed disease log-odds for CKD 1 in cell N117 on the sheet ‘Transitions’ remain at its base case value of [redacted] in each PSA simulation. When cell Y338 on the sheet ‘Parameters’ is set to ‘Yes’, the log-odd value is varied in each PSA simulation based on the variance-covariance matrix.

As requested, a dropdown has been added to the ‘PSA’ worksheet (cell J14) that automates the changes outlined above to easily facilitate the running of the PSA for these two scenarios.

Section C: Textual clarification and additional points

C 1. The title of Figure 17 states to present time to diagnosis of ESRD or mortality. However, the x-axis label is "years from disease diagnosis to ESRD or mortality". Please clarify which one is correct and edit accordingly.

The x-axis of Figure 17 in the CS represents the number of years from when a patient is diagnosed with CKD 4 to when they are diagnosed with ESRD or die.

C 2. In Table 69 of the CS, the reference 164 is incomplete.

Reference 164 should read: Greene T, Ying J, Vonesh EF, Tighiouart H, Levey AS, Coresh J, et al. Performance of GFR Slope as a Surrogate End Point for Kidney Disease Progression in Clinical Trials: A Statistical Simulation. Journal of the American Society of Nephrology : JASN. 2019;30(9):1756-69.

C 3. In the electronic model, on sheet ‘Transitions’, please confirm that in cell K122 the heading should read ‘Monthly rate’ and in cell M122 ‘Per cycle probability’ (or something similar)

It is agreed that cells M122 and X122 on the sheet ‘Transitions’ should read ‘Monthly probability of transitioning’. Cell K122 and V122 on sheet ‘Transitions’ should read ‘Per cycle probability’. The labelling has subsequently been updated in the new version of the model.

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Appendix 1. Adverse events of TRF-budesonide

Table 27: Treatment-Emergent Adverse Events by System Organ Class and Preferred Term Safety Analysis Set (Baseline UPCR ≥1.5 g/g) NeflgArd Nef-301

System organ class Preferred term	TRF-budesonide 16 mg	Placebo	Total
Any treatment-emergent adverse events			
Oedema peripheral†			
Hypertension†			
Abdominal pain†			
Abdominal discomfort†			
Alopecia†			
Cushingoid†			
Dermatitis†			
Mood swings†			
Anaemia†			
Face oedema†			
Hirsutism†			
Hypersensitivity†			
Infections and infestations			
Nasopharyngitis			
Upper respiratory tract infection			
Urinary tract infection			
Corona virus infection			
Influenza			
Cellulitis			
Cytomegalovirus infection			
Dermatophytosis of nail			
Folliculitis			
Gastroenteritis viral			
Herpes zoster			
Lower respiratory tract infection			
Otitis media acute			
Pharyngitis			
Pharyngotonsillitis			
Pyoderma			
Respiratory tract infection			
Tooth abscess			
Tooth infection			

System organ class Preferred term	TRF-budesonide 16 mg	Placebo	Total
Viral infection			
Viral upper respiratory tract infection			
Wound infection			
Gastrointestinal disorders			
Nausea			
Diarrhoea			
Abdominal pain upper			
Abdominal pain			
Vomiting			
Abdominal discomfort			
Abdominal distension			
Dental caries			
Dyspepsia			
Abdominal pain lower			
Abdominal tenderness			
Eructation			
Faeces discoloured			
Flatulence			
Gastritis			
Gastritis haemorrhagic			
Gastrooesophageal reflux disease			
Haemorrhoids			
Inguinal hernia			
Pancreatitis necrotising			
Steatorrhoea			
Toothache			
General disorders and administration site conditions			
Oedema peripheral			
Pyrexia			
Fatigue			
Asthenia			
Chest pain			
Face oedema			
Influenza like illness			
Malaise			
Peripheral swelling			

System organ class Preferred term	TRF-budesonide 16 mg	Placebo	Total
Skin and subcutaneous tissue disorders			
Rash			
Alopecia			
Acne			
Eczema			
Hair growth abnormal			
Hirsutism			
Rash pruritic			
Cold sweat			
Dermatitis			
Erythema			
Exfoliative rash			
Hyperhidrosis			
Ingrowing nail			
Lipohypertrophy			
Nail growth abnormal			
Pruritus			
Rash generalised			
Rash papular			
Skin atrophy			
Skin striae			
Swelling face			
Nervous system disorders			
Headache			
Dizziness			
Dysgeusia			
Lethargy			
Dysarthria			
Hypoaesthesia			
Migraine			
Somnolence			
Transient ischaemic attack			
Musculoskeletal and connective tissue disorders			
Muscle spasms			
Back pain			
Arthralgia			

System organ class Preferred term	TRF-budesonide 16 mg	Placebo	Total
Bursitis			
Flank pain			
Intervertebral disc protrusion			
Limb discomfort			
Muscle tightness			
Muscular weakness			
Musculoskeletal chest pain			
Musculoskeletal discomfort			
Musculoskeletal pain			
Myalgia			
Myositis			
Neck pain			
Pain in extremity			
Tendonitis			
Investigations			
Weight increased			
Blood pressure increased			
White blood cell count increased			
Blood creatinine increased			
Blood lactate dehydrogenase increased			
Glycosylated haemoglobin increased			
Alanine aminotransferase increased			
Aspartate aminotransferase increased			
Blood creatine phosphokinase increased			
Blood glucose increased			
Gamma-glutamyl transferase increased			
Hepatic enzyme increased			
Neutrophil count increased			
Transaminases increased			
Urine output decreased			
Vascular disorders			
Hypertension			
Hypotension			
Accelerated hypertension			
Deep vein thrombosis			
Hot flush			

System organ class Preferred term	TRF-budesonide 16 mg	Placebo	Total
Injury, poisoning and procedural complications			
Ligament sprain			
Animal bite			
Contusion			
Dental restoration failure			
Face injury			
Fall			
Femur fracture			
Meniscus injury			
Procedural pain			
Skin laceration			
Soft tissue injury			
Renal and urinary disorders			
Renal impairment			
Renal pain			
Acute kidney injury			
Dysuria			
Haematuria			
Proteinuria			
Urinary bladder haemorrhage			
Respiratory, thoracic and mediastinal disorders			
Cough			
Dyspnoea			
Oropharyngeal pain			
Dry throat			
Epistaxis			
Hyperactive pharyngeal reflex			
Nasal septum deviation			
Snoring			
Metabolism and nutrition disorders			
Diabetes mellitus			
Gout			
Folate deficiency			
Glucose tolerance impaired			
Hyperphosphataemia			

System organ class Preferred term	TRF-budesonide 16 mg	Placebo	Total
Hypokalaemia			
Increased appetite			
Metabolic acidosis			
Psychiatric disorders			
Insomnia			
Mood swings			
Anxiety			
Sleep disorder			
Agitation			
Depressed mood			
Libido decreased			
Psychotic disorder			
Suicidal ideation			
Blood and lymphatic system disorders			
Lymphadenopathy			
Anaemia			
Bone marrow oedema			
Iron deficiency anaemia			
Leukocytosis			
Thrombocytosis			
Cardiac disorders			
Palpitations			
Cardiac failure congestive			
Tachycardia			
Endocrine disorders			
Cushingoid			
Cushing's syndrome			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Meningioma			
Pyogenic granuloma			
Skin papilloma			
Reproductive system and breast disorders			
Menorrhagia			
Vulvovaginal dryness			
Eye disorders			
Ocular discomfort			

System organ class Preferred term	TRF-budesonide 16 mg	Placebo	Total
Swelling of eyelid			
Immune system disorders			
Drug hypersensitivity			
Seasonal allergy			
Ear and labyrinth disorders			
Hypoacusis			
Pregnancy, puerperium and perinatal conditions			
Abortion spontaneous			

Abbreviations: AE, adverse event; TRF, targeted-release formulation.
† The first PT term is selected to represent the AE group: cushingoid/cushing's syndrome, alopecia/alopecia areata, hypersensitivity/drug hypersensitivity, anaemia/iron deficiency anaemia, dermatitis/hand dermatitis/perioral dermatitis/seborrheic dermatitis/eczema, mood swings/mood altered/irritability, abdominal pain/abdominal pain upper/abdominal pain lower, abdominal discomfort/abdominal tenderness/abdominal distension, oedema peripheral/peripheral swelling, face oedema/swelling face, hirsutism/hypertrichosis, hypertension/essential hypertension.
Source: Calliditas Therapeutics AB. Data on file. Additional data from NefIgArd for baseline UPCR ≥1.5 g/g subgroup. Table 14.3.1.2.1b.

NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Targeted-release budesonide for treating IgA nephropathy [ID1434]

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.

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 2021/22 shows the majority 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: - AstraZeneca: £53,760 - Novartis: £23,760

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?	We spoke to a range of people living with IgA nephropathy, both in a focus group, and in one-on-one interviews. We identified participants through our 'Kidney Voices' patient network.

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?	IgA Nephropathy (IgAN) is a common chronic kidney disease which mainly affects young adults. Prevalence of subclinical (asymptomatic and undiagnosed) IgAN may be as high as 16% of general population[1]. Around 30 per cent of IgAN patients will progress to kidney failure and will require a transplant or life on dialysis. There are currently no reliable tests available to predict which of these patients, known as progressors, will lose their kidney function. This uncertainty, particularly for young people, can have several significant impacts. It can impact the person's career – one patient reported to us how, once diagnosed, they could no longer move abroad to progress their career. This is particularly pertinent should a person's condition progress to a point where dialysis is required. "...needing to go to hospital for four-hour dialysis sessions, three times a week, so a machine can keep you alive..." We also heard how this uncertainty can also extend to the clarity of an accurate diagnosis, and to understanding whether children of those with IgAN will be more likely to develop the condition in the future. For those with IgA there is not always a simple linear 'line of progression' – it can be impossible to predict when kidney function may drop to a serious level. This is frequently described as 'crash landing'. The suddenness by which the kidneys can begin to fail for some patients can be extremely traumatic. "It flipped my world upside down." The effect of IgA nephropathy on loved ones, who frequently will fulfil certain elements of informal care, is also substantial. Appointments, regular trips for dialysis and associated travel can make the condition a part of a network of loved ones' lives. This associated impact is also emotional, as well as physical. Given many who are diagnosed with IgA are relatively young, patients reported that a lot of the burden could fall on parents.

	Despite this, there can be a lack of understanding of what IgA nephropathy is, and subsequently, what it means to have the condition. This can be isolating for the patient resulting in a sense of "dealing with it alone".

[1] https://ukkidney.org/rare-renal/clinician/iga-nephropathy#:~:text=Prevalence%20of%20subclinical%20(asymptomatic%20and,as%2016%25%20of%20general%20population.

Current treatment of the condition in the NHS

7. What do patients or carers think of current treatments and care available on the NHS?	When speaking to people with IgAN, we heard varied experiences of diagnosis and subsequent care. This varied experience can particularly relate to the lack of information given to patients by healthcare professionals about the condition, and its likely future impact, as well as some pre-existing 'management' for the condition, such as diet changes. Being told that there is essentially no treatment that can proactively slow down or prevent a decline in kidney function can take a big toll on the wellbeing of patients. Kidney disease is known to be associated with an increased risk of mental ill-health. In a survey of 1,000 adult kidney patients carried out by Kidney Research UK in January 2022, 67% reported symptoms of depression and 27% had considered self-harm or suicide. It has been identified to us that when being treated for kidney disease, the kidney can become the "focus of everything". "Sometimes (I) think they might be more interested in my kidney than me…" As such, holistic whole-person care, which considers the impact of treatments and the condition on mental health, as well as the physical burden, is important to kidney patients and their families.

8. Is there an unmet need for patients with this condition?	Currently, there are no specific disease-modifying therapies approved for the treatment of IgA nephropathy in England. This realisation alone can be difficult for patients to comprehend. "You presume there's a medication for everything…" Transplantation and dialysis are not sustainable treatment options. They are not permanent, and are extremely gruelling, for patients, loved ones and the health system. One patient described to us how starting dialysis was their "lowest point", with an expectation that they would at least begin to feel better, but they did not. A transplant is not a cure, lasting on average twenty years, and the fear of infection or rejection of the transplant has a significant impact upon patients' mental health. Support relating to education and wellbeing, not just for patients but also loved ones, was identified as crucial to improving patient outcomes for IgA patients

Advantages of the technology

9. What do patients or carers think are the advantages of the technology?	A treatment that could slow down progression of the condition for patients would be welcome. Patients thought that a potential benefit was the possibility of a new technology enabling a greater level of information and awareness about the condition. If a treatment could improve clarity, or reduce levels of uncertainty about the condition's progression, this would be welcomed by patients as a way of enabling a happier day-to-day life. Life on dialysis was described by some patients as "no life at all" – emphasising the incredible impact the condition's progression can have on the lives of those with IgA. Patients discussed how the technology, if effective, could provide some uplift to emotional wellbeing for reasons outlined. There are several advantages to delaying progression of kidney disease to the point of requiring dialysis or transplantation: ▪ Improved quality of life: Dialysis and transplantation are both intensive treatments that require significant time commitments and can have significant side effects. ▪ 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. ▪ 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?	Corticosteroids can have significant side effects and are not effective for all patients. No potential disadvantages specifically relating to the technology were identified by patients we spoke to. However, it is important potential side effects are seriously considered. "I don't want a treatment to be the cause of another diagnosis …" Support relating to education and wellbeing, not just for patients but also loved ones, was identified as crucial to improve patient outcomes for IgA patients. It is important that patient wellbeing is actively considered alongside any introduction of the technology.

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 and people in these cohorts progress faster to end stage renal failure*. The RaDaR study in the UK has shown that the most deprived group of patients with IGaN have a significantly faster progression to end-stage kidney disease (ESKD). They had a 26% higher risk of progressing to ESKD faster than the middle quintile, as determined by Cox regression analysis. This data will be presented at a scientific meeting later this year. * Kidney Health Inequalities in the UK: Reflecting on the past, reducing in the future. Kidney Research UK 2018

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 South East Asians. In this patient population, it 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?	

Key messages

14. In up to 5 bullet points, please summarise the key messages of your submission.	• IgA nephropathy is a severe condition, that can have significant impact on the quality of a patient's life. • The uncertainty surrounding disease progression leaves a significant burden, and the suddenness by which the kidneys can fail can be devastating. • Loved ones become a big part of the journey of experiencing IgA nephropathy, particularly given the youth of those often diagnosed. • There is a huge unmet treatment need for those with IgA nephropathy. There are currently no disease-modifying treatments available. When kidneys fail, options available, such as dialysis or transplantation, are gruelling, and not permanent treatment options. A new treatment, which could offer some slowing of disease progression, would be welcome by kidney patients, and would be seen as an 'emotional uplift'. • IGaN disproportionately affects those from deprived communities and ethnic minority groups, as does kidney disease as a whole. Given the treatment unmet need, there is a clear issue of health inequalities that decision makers should seek to address.

Thank you for your time.

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in collaboration with:

Erasmus School of Health Policy & Management

Maastricht University

Targeted-release budesonide for treating primary IgA nephropathy [ID1434]

Produced by Kleijnen Systematic Reviews (KSR) Ltd in collaboration with Erasmus University Rotterdam (EUR) and Maastricht University

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Rider on responsibility for report

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Contributions of authors

Robert Wolff acted as project lead and systematic reviewer on this assessment, critiqued the clinical effectiveness methods and evidence and contributed to the writing of the report. Mark Perry, Kevin McDermott, Mubarak Patel, Jiongyu Chen and Xiaoyu Tian acted as systematic reviewers, critiqued the clinical effectiveness methods and evidence and contributed to the writing of the report. Maria Clarke and Caro Noake critiqued the search methods in the submission and contributed to the writing of the report. Venetia Qendri, Eline Krijkamp, and Nigel Armstrong acted as health economists on this assessment, critiqued the company's economic evaluation and contributed to the writing of the report. Maiwenn Al acted as health economic project lead, critiqued the company's economic evaluation and contributed to the writing of the report.

Abbreviations

ACE	Angiotensin converting enzyme
ACEi	Angiotensin converting enzyme inhibitor
ACP	American College of Physicians
AE(s)	Adverse event(s)
AESI	Adverse events of special interest
AEMPS	Agencia Española de Medicamentos y Productos Sanitarios
AiC	Academic in confidence
AIC	Akaike information criterion
AIFA	Agenzia Italiana del Farmaco
AJKD	American Journal of Kidney Disease
ARB	Angiotensin receptor blocker
ASN	American Society of Nephrology
ATC	Anatomical Therapeutic Chemical
AUC	Area under the curve
BIC	Bayesian information criterion
BMI	Body-mass index
BNF	British National Formulary
CADTH	Canadian Agency for Drugs and Technologies in Health
CEA	Cost effectiveness analysis
CEAC	Cost effectiveness acceptability curve
CEM	Cost effectiveness model
CENTRAL	Cochrane Central Register of Controlled Trials
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CiC	Commercial in confidence
CKD	Chronic kidney disease
CKD-EPI	Chronic kidney disease epidemiology collaboration equation
CRD	Centre for Reviews and Dissemination
CS	Company submission
CSR	Clinical study report
DARE	Database of Abstracts of Reviews of Effects
DBP	Diastolic blood pressure
DCO	Data cut-off
DM	Diabetes mellitus
DSA	Deterministic sensitivity analysis
EAG	Evidence Assessment Group
EBM	Evidence-based medicine
EED	Economic Evaluation Database
eGFR	Estimated glomerular filtration rate
EMA	European Medicines Agency
eMIT	Electronic market information tool
ENCEPP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EQ-5D	European Quality of Life-5 Dimensions
EQ-5D-3L	European Quality of Life-5 Dimensions, 3 levels
ERA	European Renal Association
ESHPM	Erasmus School of Health Policy & Management
ESKD	End-stage kidney disease
ESRD	End-stage renal disease
EUR	Erasmus University Rotterdam
FAS	Full analysis set
FDA	Food and Drug Administration
FinCCHTA	Finnish Coordinating Centre for Heath Technology Assessment
gd-IgA1	Galactose-deficient immunoglobulin A

GI	Gastrointestinal
GP	General practitioner
HAS	Haute Autorité de Santé
HMG CoA	3-hydroxy-3-methyl-glutaryl-coenzyme A
HR	Hazard ratio
HRG	Health Resource Group
HRQoL	Health-related quality of life
HSUV	Health state utility value
HTA	Health technology assessment
ICER	Incremental cost-effectiveness ratio
ICER	Institute for Clinical and Economic Review
ICTRP	International Clinical Trials Registry Platform
IgA	Immunoglobulin A
IgAN	Immunoglobulin A nephropathy
IIGAN	International IgA Nephropathy Network
INAHTA	International Network of Agencies for Health Technology Assessment
Incr.	Incremental
IQR	Interquartile range
IQWiG	Institute for Quality and Efficiency in Health Care
ISN	International Society of Nephrology
ISPOR	Professional Society for Health Economics and Outcomes Research
ITC	Indirect treatment comparison
IV	Intravenous
KDIGO	Kidney Disease Improving Global Outcomes
KM	Kaplan-Meier
KSR	Kleijnen Systematic Reviews
LGH	Leicester General Hospital
LS	Least squares
LYG	Life years gained
Max	Maximum
MeSH	Medical subject headings
MHRA	Medicines and Healthcare Products Regulatory Agency
Min	Minimum
Min	Minute
MMF	Mycophenolate mofetil
MMRM	Mixed-Effects Model for Repeated Measures
MRU	Medical resource use
MTD	Maximum tolerated dose
N/A	Not applicable
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NIH	National Institutes of Health
NIHR	National Institute for Health and Care Research
NIPH	Norwegian Institute of Public Health
NL	The Netherlands
OD	Once daily
OLE	Open-label extension
ONS	Office for National Statistics
PAS	Patient access scheme
PBAC	Pharmaceutical Benefits Advisory Committee
PBS	Pharmaceutical Benefits Scheme
pCODR	Pan-Canadian Oncology Drugs Review
PLD	Patient level data
PRESS	Peer Review of Electronic Search Strategies
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses

PSA	Probabilistic sensitivity analysis
PSS	Personal Social Services
PSSRU	Personal Social Services Research Unit
PT	Preferred term
QALY	Quality-adjusted life year
QoL	Quality of life
R	Randomisation
RaDaR	UK National Registry of Rare Kidney Diseases
RAS	Renin-angiotensin system
RASi	Renin-angiotensin system inhibitor
RCT	Randomised controlled trial
RDI	Relative dose intensity
SAE	Serious adverse event
SAS	Safety analysis set
SBP	Systolic blood pressure
SBU	Swedish Agency for Health Technology Assessment and Assessment of Social Services
ScHARRHUD	School of Health and Related Research Health Utility Database
SD	Standard deviation
SE	Standard error
SF-36	Short-form 36
SF-36v2	Short Form 36 version 2
SGLT2	Sodium-glucose cotransporter-2
SGLT2i	Sodium-glucose cotransporter-2 inhibitors
SLR	Systematic literature review
SMC	Scottish Medicines Consortium
SoC	Standard of care
STA	Single technology appraisal
TA	Technology appraisal
TEAE	Treatment-emergent adverse event
TESAE	Treatment-emergent serious adverse event
TLV	Tandvårds- och läkemedelsförmånsverket (Dental and Pharmaceutical Benefits Agency)
TRF	Targeted-release formulation
TTD	Time to treatment discontinuation
tx	Treatment
UACR	Urine albumin to creatinine ratio
UK	United Kingdom
UKRR	United Kingdom Renal Registry
UPCR	Urine protein to creatinine ratio
USA	United States of America
UTI	Urinary tract infection
WCN	World Congress of Nephrology
WHO	World Health Organization
WTP	Willingness to pay

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1. EXECUTIVE SUMMARY

This summary provides a brief overview of the key issues identified by the Evidence Assessment Group (EAG) as being potentially important for decision making. If possible, 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 presents the key model outcomes, Section 1.3 discusses the decision problem, Section 1.4 issues relate to the clinical effectiveness, and Section 1.5 relates to the cost effectiveness. Other key issues are discussed in Section 1.6, while a summary is presented in Section 1.7.

Background information on the condition, technology and evidence and information on key issues as well as non-key issues are in the main EAG report; please see Sections 2 (decision problem), 3 (clinical effectiveness) and 4 (cost effectiveness) for more details.

All issues identified represent the EAG's view and are not the opinion of the National Institute for Health and Care Excellence (NICE).

1.1 Overview of the EAG's key issues

Table 1.1: Summary of key issues

ID1457	Summary of issue	Report Section
1	Reduced applicability of the trial evidence to those patients not on RASi therapy, given that only six patients (four on budesonide and two on placebo) were not receiving RASi therapy in the NefIgArd Nef-301 trial.	2.1
2	Each of the following drugs may be a relevant comparator for different subgroups of patients: corticosteroids, MMF and SGLT2is. ITCs may enable these potential comparators to be incorporated into the economic model.	2.3, 3.4
3	Follow up is restricted to 12 months for the CS data, despite longer term follow-up data being available.	2.4
4	One potentially relevant study is missing from the analysis.	3.2.1
5	Patients with an eGFR of <35 ml/min/1.73 m^2 were excluded from the trial, even though these may make up an important subgroup of patients who might benefit from budesonide.	3.2.1.1
6	The arms of the trial were not comparable at baseline, increasing the risk of selection bias.	2.3, 3.2.3
7	The outcome of disease progression is not included in the trial evidence.	2.4, 3.2.5.3
8	It is unclear if the trial results are applicable to the UK target population.	2.3, 3.2.5.6
9	Insufficient evidence regarding retreatment of patients.	4.2.6.2
10	Data source for estimating the transition from CKD 4 to CKD 5.	4.2.6.2

CS = company submission; CKD = chronic kidney disease; EAG = Evidence Assessment Group; eGFR = estimated glomerular filtration rate; ITC = indirect treatment comparison; MMF = mycophenolate mofetil; RASi = renin-angiotensin system inhibitors; SGLT2i = sodium-glucose cotransporter-2 inhibitor; UK = United Kingdom

1.2 Overview of key model outcomes

National Institute for Health and Care Excellence technology appraisals (TAs) 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:

- Increasing the number of patients in better health states (lower chronic kidney disease (CKD) stage), thus improving their health-related quality of life (HRQoL) and their life expectancy.

Overall, the technology is modelled to affect costs by:

- The costs of targeted-release formulation (TRF) budesonide, which are added to current care
- Increasing the number of patients in better health states (lower CKD stage), thus lowering the costs of management of CKD, the costs of dialysis and the costs of kidney transplantation.

The modelling assumptions that have the greatest effect on the ICER are:

- Whether retreatment of patients with TRF-budesonide is incorporated into the model
- Which data source is used to estimate the transition probability from CKD 4 to CKD 5
- Time point from where no treatment effect is assumed (base case is 1 year).

1.3 The decision problem: summary of the EAG's key issues

The decision problem addressed in the company submission (CS) is broadly in line with the final scope issued by NICE. However, there is a concern that extension of the therapy to those not on renin-angiotensin system (RAS) blockade would not be supported by the evidence (Table 1.2). There is also a possible additional need to evaluate the relative effect of budesonide and non-targeted corticosteroids, mycophenolate mofetil (MMF) and dapagliflozin (Table 1.3). There is also a key issue related to the short follow-up of outcomes (Table 1.4)

Table 1.2: Key issue 1: Applicability of the trial evidence to those patients not on RASi therapy

Report Section	**2.1**
Description of issue and why the EAG has identified it as important	In the response to the clarification letter, the company stated that *"patients who cannot tolerate RAS blockade therapy can be considered for treatment with TRF-budesonide, in line with anticipated use in clinical practice"*. This suggests a contra-diction to the licensed indication, but the EAG's main concern would be regarding the applicability of the trial evidence to those patients not on RASi therapy, given that only six patients (four on budesonide and two on placebo) were not receiving RASi therapy in the NefIgArd Nef-301 trial.
What alternative approach has the EAG suggested?	Any recommendations for budesonide should not be extended to people who are not on RASi therapy.
What is the expected effect on the cost effectiveness estimates?	None.
What additional evidence or analyses might help to resolve this key issue?	If it is wished to consider therapy to those not on RAS blockade therapy, then further data in this population need to be analysed.
EAG = Evidence Assessment Group; RAS = renin-angiotensin system; RASi = renin-angiotensin system inhibitors; TRF = targeted-release formulation	

Table 1.3: Key issue 2: Corticosteroids, MMF and SGLT2i may be relevant comparators for different subgroups of patients

Report Section	**2.3, and 3.4**
Description of issue and why the EAG has identified it as important	Corticosteroids are excluded as a comparator, but there may be a sub-group of patients eligible for budesonide for whom cortico-steroids might also be indicated. There may therefore be a need for the comparison of *budesonide + SoC versus cortico-steroids + SoC* in this sub-group. MMF is excluded because of lack of evidence of efficacy in Caucasian patients, but it is unclear if those eligible for MMF are excluded by the population in the decision problem. If there is a sub-group of participants who could be eligible for both treatments, then there may be a need for the comparison of budesonide + SoC versus MMF + SoC in this sub-group. Despite the CS stating that dapagliflozin has no benefits for people with IgAN, there is little evidence to support this claim. The DAPA-CKD study shows that dapagliflozin led to a statistically significant improvement in the primary outcome (HR for dapagliflozin versus placebo = 0.29 (95% CI, 0.12–0.73); P = 0.005). There was also a numerical improvement in eGFR. In response to clarification the company then argued that an SGLT2i should not be a comparator because it would be part of SoC. However, it appears not to have been part of SoC in the TRF-budesonide trial. Therefore, for at least a subgroup of people who are eligible for both budesonide and an SGLT2i, there may be a need for the comparison of budesonide + SoC possibly including an SGLT2i (depending on whether budesonide is added to or would replace an SGLT2i) versus an SGLT2i + SoC.
What alternative approach has the EAG suggested?	The comparison of *budesonide + SoC versus corticosteroids + SoC* could be yielded through two approaches: 1) a new direct comparison or 2) via an ITC (which would derive *budesonide + SoC versus corticosteroids + SoC* indirectly via the direct trial estimate of *budesonide + SoC versus SoC* and any direct estimates of *corticosteroids + SoC versus SoC* in the literature). The comparison of *budesonide + SoC versus MMF + SoC* could be yielded through two approaches: 1) a new direct comparison or 2) via an ITC (which would derive *budesonide + SoC versus MMF + SoC* indirectly via the direct trial estimate of *budesonide + SoC versus SoC* and any direct estimates of *MMF + SoC versus SoC* in the literature). A comparison of *budesonide + SoC versus an SGLT2i + SoC* could be yielded through two approaches: 1) a new direct comparison or 2) via an ITC (which would derive *budesonide + SoC versus dapagliflozin + SoC* indirectly via the direct trial estimate of *budesonide + SoC versus SoC* and any direct estimates of *dapagliflozin + SoC versus SoC* in the literature). If

Report Section	2.3, and 3.4
	budesonide would be added to the SGLT2i, then such an ITC would require a trial arm with the two treatments combined.
What is the expected effect on the cost effectiveness estimates?	The use of a more active comparator may reduce cost-effectiveness estimates
What additional evidence or analyses might help to resolve this key issue?	See alternative approaches suggested by the EAG above. All of these approaches would need to be informed by an appropriate SLR.
CI = confidence interval; CS = company submission; EAG = Evidence Assessment Group; eGFR = estimated glomerular filtration rate; HR = hazard ratio; IgAN = immunoglobulin A nephropathy; ITC = indirect treatment comparison; MMF = mycophenolate mofetil; SGLT2i = sodium-glucose cotransporter-2 inhibitors; SLR = systematic literature review; SoC = standard of care; TRF = targeted-release formulation	

Table 1.4: Key issue 3: Short-term follow-up

Report Section	2.4
Description of issue and why the EAG has identified it as important	Follow-up is restricted to 12 months. This makes it difficult to form realistic evaluations of long-term benefit and cost.
What alternative approach has the EAG suggested?	Data are available but they have yet to be published.
What is the expected effect on the cost effectiveness estimates?	Unknown.
What additional evidence or analyses might help to resolve this key issue?	Making the longer-term data available for analysis and including them in the submission.
EAG = Evidence Assessment Group	

1.4 The clinical effectiveness evidence: summary of the EAG's key issues

The EAG identified five major concerns with the evidence presented on the clinical effectiveness, namely the omission of two potentially relevant studies (Table 1.5), the exclusion of patients with an estimated glomerular filtration rate (eGFR) of <35 ml/min/1.73 m^2 (Table 1.6), potential selection bias (Table 1.7), the omission of an important outcome (Table 1.8), unclear applicability of trial evidence to the UK target population (Table 1.9).

Table 1.5: Key issue 4: Omission of relevant evidence

Report Section	3.2.1
Description of issue and why the EAG has identified it as important	One potentially relevant study (NEFIGAN Nef-202) is missing from the analysis.
What alternative approach has the EAG suggested?	The company should include the study.
What is the expected effect on the cost effectiveness estimates?	The new evidence may change the magnitude and precision of the clinical efficacy estimates, and therefore change cost effectiveness estimates. The direction of change is currently not known.

Report Section	3.2.1
What additional evidence or analyses might help to resolve this key issue?	Inclusion of the new study, with synthesis of the new and existing data.
EAG = Evidence Assessment Group	

Table 1.6: Key issue 5: Exclusion of potentially relevant subgroup

Report Section	3.2.1.1
Description of issue and why the EAG has identified it as important	Patients with an eGFR of <35 ml/min/1.73 m^2 were excluded from the trial, even though these may make up an important subgroup of patients who might benefit from budesonide.
What alternative approach has the EAG suggested?	Relevant data from other studies comprising people with an eGFR <35 ml/min/1.73 m^2 could be sought.
What is the expected effect on the cost effectiveness estimates?	Unknown.
What additional evidence or analyses might help to resolve this key issue?	Relevant data from other studies comprising people with an eGFR <35 ml/min/1.73 m^2 could be sought.
EAG = Evidence Assessment Group; eGFR = estimated glomerular filtration rate	

Table 1.7: Key issue 6: Possible selection bias

Report Section	2.3, and 3.2.3
Description of issue and why the EAG has identified it as important	The arms of the trial were not comparable at baseline, increasing the risk of selection bias. This arose from differences in SoC, as well as other differences evident in the baseline characteristics table.
What alternative approach has the EAG suggested?	The data could be re-analysed with adjustment for confounding.
What is the expected effect on the cost effectiveness estimates?	The baseline differences may have exerted effects both benefitting and harming the intervention group, so the expected effect on the cost effectiveness estimates is unclear.
What additional evidence or analyses might help to resolve this key issue?	The data could be re-analysed with adjustment for confounding.
EAG = Evidence Assessment Group; SoC = standard of care	

Table 1.8: Key issue 7: Disease progression not reported

Report Section	2.4, and 3.2.5.3
Description of issue and why the EAG has identified it as important	The outcome of disease progression is not included in the trial evidence.
What alternative approach has the EAG suggested?	These data should be included if they were collected. Alternatively, data on this outcome from other relevant literature could be used.
What is the expected effect on the cost effectiveness estimates?	Unclear.

Report Section	2.4, and 3.2.5.3
What additional evidence or analyses might help to resolve this key issue?	This data should be included if they were collected. Alternatively, data on this outcome from other relevant literature could be used.
EAG = Evidence Assessment Group	

Table 1.9: Key issue 8: Applicability of evidence

Report Section	2.3, and 3.2.5.6
Description of issue and why the EAG has identified it as important	It is unclear if the trial results are applicable to the UK target population. There is a need for more information on the UK target population characteristics, as well as subgroup analyses to evaluate outcome modifying characteristics.
What alternative approach has the EAG suggested?	The company should firstly assess for differences between the trial population and UK target population. For any characteristics that differ between populations, a subgroup analysis of the trial data, based on the strata of that characteristic, should be carried out to establish the magnitude of potential effect modification. This should yield an understanding of whether the trial results are applicable to the UK target population.
What is the expected effect on the cost effectiveness estimates?	Unclear
What additional evidence or analyses might help to resolve this key issue?	The company should firstly assess for differences between the trial population and UK target population. For any characteristics that differ between populations, a subgroup analysis of the trial data, based on the strata of that characteristic, should be carried out to establish the magnitude of potential effect modification. This should yield an understanding of whether the trial results are applicable to the UK target population.
EAG = Evidence Assessment Group; UK = United Kingdom	

1.5 The cost effectiveness evidence: summary of the EAG's key issues

A full summary of the cost effectiveness evidence review conclusions can be found in Section 6.4 of this report. The company's cost effectiveness results are presented in Section 5, the EAG's summary and detailed critique in Section 4, and the EAG's amendments to the company's model and results are presented in Section 6. The key issues in the cost effectiveness evidence are discussed in Tables 1.10 to 1.11.

Table 1.10: Key issue 9: Insufficient evidence regarding retreatment of patients

Report Section	4.2.6.2
Description of issue and why the EAG has identified it as important	The EAG does not agree with the company's assumption that all patients will be retreated with TRF-budesonide, with the same effectiveness as with the first treatment. There is currently no data to substantiate these assumptions.
What alternative approach has the EAG suggested?	The EAG has set the probability of retreatment to zero.
What is the expected effect on the cost effectiveness estimates?	Excluding retreatment changes the ICER to £33,276 from the company base case after clarification of £21,872.

Report Section	4.2.6.2
What additional evidence or analyses might help to resolve this key issue?	This issue might be (partially) resolved once the data from NefIgArd Nef-301 Part B and Nef-301 OLE become available.

EAG = Evidence Assessment Group; ICER = incremental cost-effectiveness ratio; OLE = open-label extension; TRF = targeted-release formulation

Table 1.11: Key issue 10: Data source for estimating the transition from CKD 4 to CKD 5

Report Section	4.2.6.2
Description of issue and why the EAG has identified it as important	The UK RaDaR data analysis, using all patients with IgAN and UPCR ≥1.5 g/g and with ESRD and death cases used to define the event outcome is likely overestimating the risk of ESRD as the company also incorporates the risk of death and thus, this data analysis is not considered appropriate for the base case analysis.
What alternative approach has the EAG suggested?	To inform the transition probability from CKD 4 to CKD 5, the EAG considers that data from patients at LGH in the UK between 1992 to 2020 more appropriate than the UK RaDaR data. Patients from the LGH registry were matched to NefIgArd Nef-301 patients, using baseline eGFR between 35 and 90 mL/min/1.73 m^2 and either proteinuria ≥1 g per day or UPCR ≥0.8 g/g. Patients were further selected for UPCR ≥1.5 g/g. The matching was done on a 5:1 ratio using a maximum of five LGH registry patients for each patient in the NefIgArd Nef-301 trial, leading to 294 matched records ready for analysis. The scenario using these data was limited by an assumption required to estimate the rate of movement from CKD 4 to CKD 5 based on the rate of movement from CKD 1-4 to CKD 5 to. Another option would be the UK RaDaR data limited though to those using ACEi and/or ARBs at baseline. This limitation leaves a group of patients more aligned with the NefIgArd Nef-301 patients in terms of RASi use. However, this approach suffers from the same issue of overestimating the risk of ESRD as the company's base case analysis.
What is the expected effect on the cost effectiveness estimates?	Changing the source that was used to estimate the transition probability from CKD 4 to CKD 5 changes the ICER to £27,429 from the company base case after clarification of £21,872.
What additional evidence or analyses might help to resolve this key issue?	The EAG considers UK RaDaR data with baseline ACEi and/or ARBs more aligned with the study population than when using all patients from UK RaDaR database. For that subgroup of patients, an analysis, correctly implemented, should be done with transition to ESRD as the sole event.

ACEi = angiotensin converting enzyme inhibitor; ARB = angiotensin receptor blocker; CKD = chronic kidney disease; EAG = Evidence Assessment Group; eGFR = estimated glomerular filtration rate; ESRD =

Report Section	4.2.6.2
end-stage renal disease; ICER = incremental cost-effectiveness ratio; IgAN = immunoglobulin A nephropathy; LGH = Leicester General Hospital; RaDaR = UK National Registry of Rare Kidney Diseases; UPCR = urine protein to creatinine ratio; UK = United Kingdom	

1.6 Other key issues

None.

1.7 Summary of the EAG's view

Compared to placebo + standard of care (SoC), the randomised trial evidence demonstrated that budesonide + SoC leads to significantly reduced UPCR and urine albumin to creatinine ratio (UACR), as well as a significant relative reduction in the rate of eGFR, immediately after 9 months treatment, and also following a 3-month post-treatment follow-up. However, there were no significant group differences in HRQoL. Budesonide was relatively well-tolerated, and there were no deaths in either group.

There were several problems with the evidence provided by the company. Not all relevant evidence was included and patients with an eGFR of 35 ml/min/1.73 m^2 were excluded. There were also risks of selection bias resulting from baseline inequivalence. In addition, the important patient-centred outcome of disease progression was not included, and follow-up was restricted to 1 year. Furthermore, the applicability of evidence to the UK target population was unclear. Although corticosteroids were excluded as a comparator by the company, there is a subgroup of patients who might be eligible for both drugs. A relevant comparison (in this subgroup) would therefore be budesonide + SoC versus corticosteroids + SoC. Similar arguments might be made for two other potential comparators: MMF and dapagliflozin.

Table 1.12 summarises the ICERs of both the company's and EAG's preferred base cases, as well as the impact of each EAG preferred assumption applied separately to the company base case.

Each of the changes increases the ICER, with the largest impact seen when the probability of retreatment is set to zero. The smallest impact has the incorporation of more drug classes into the SoC costs, and this change was mostly made for completeness' sake.

Combining all changes in the model lead to an EAG preferred base case incremental cost effectiveness result of £41,598 per QALY gained, which is higher than the company ICER of £21,872 per QALY gained (after clarification).

The probabilistic ICER, £49,821 per QALY gained, is substantially higher than the EAG deterministic base case. The EAG was unable to find a suitable explanation for this, so it is not clear if this is simply an artefact of the choices made regarding distributions and their parameters, or if it is caused by modelling errors. The probabilistic sensitivity analysis (PSA) shows that the probability that TRF-budesonide + SoC cost effective is at thresholds of £20,000 and £30,000 per QALY gained are 10.0% and 22.1%, respectively, using the EAG base case assumptions.

Several scenarios were explored, and most of these led to modest changes in the ICER. The most substantial change occurred when the time point from where no treatment effect is increased, in which scenario TRF-budesonide would be the dominant treatment. Using alternative options to estimate transition probabilities from CKD 4 to CKD 5 based on different parametric models to fit the available real-world data from LGH as well as data from different subpopulations of the UK RaDaR database

combined with different parametric models showed the ICER was sensitive to these assumptions varying from £30,371 to [redacted]. Various scenarios regarding percentage of patients being retreated, duration until retreatment starts, and the percentage of the original effectiveness obtained during retreatment were run, yielding ICERs ranging from £15,177 to £46,379.

Table 1.12: EAG base case and individual impact of EAG preferred assumptions13

Preferred assumption	TRF-budesonide + SoC		SoC		Incr. Costs (£)	Incr. QALYs	ICER (£/QALY)
	Costs (£)	QALYs	Costs (£)	QALYs			
Company base case (original)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£18,643
Company base case (after clarification)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£21,872**
EAG change on the source used to estimate transition probability from CKD 4 to CKD 5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£27,429
EAG change on retreatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£33,141
EAG change on disutility of TESAEs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£22,122
EAG change on cost of SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£22,009
EAG's preferred base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£41,598**

Based on the EAG preferred assumptions in the electronic model following the clarification question
CKD = chronic kidney disease; EAG = Evidence Assessment Group; ICER = incremental cost-effectiveness ratio; Incr. = incremental; QALY = quality-adjusted life year; SoC = standard of care; TESAEs = treatment-emergent serious adverse events; TRF = targeted-release formulation

2. CRITIQUE OF COMPANY'S DEFINITION OF DECISION PROBLEM

Table 2.1: Statement of the decision problem (as presented by the company)

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comment
Population	People with primary IgA nephropathy	Adult patients with primary IgAN who: • are on a stable dose of maximally tolerated RAS inhibitor therapy • are at risk of rapid disease progression with a UPCR ≥1.5 g/g	The population addressed in the company submission is in line with the licence of TRF-budesonide.	The restriction to people at risk of rapid disease progression and to people at maximally tolerated RASi therapy is according to the marketing authorisation and is therefore appropriate.
Intervention	Targeted-release budesonide	As per scope		Maximally tolerated RAS blockade is given alongside budesonide in the included evidence, as part of SoC treatment. It was not originally reported which other aspects of standard of care treatment (if any) are given alongside budesonide, but this information has been provided by the company in response to the request for clarification.
Comparator(s)	Established clinical management without targeted-release budesonide, including ACE inhibitors and ARBs at the maximum tolerated licensed doses, diuretics and dietary and	SoC: • Blood pressure management; maximally tolerated dose of ACEi/ARB; lifestyle	• The comparators selected are in line with SoC for patients with IgAN • The KDIGO guideline and UK clinical expert opinion indicated that SoC includes lifestyle modification, blood	In contrast to the NICE scope, (non-targeted) glucocorticoids/ corticosteroids are not included as part of standard care in the decision problem. However, it is likely that there is a subgroup of patients for whom budesonide is indicated, who are also eligible for corticosteroids. Therefore,

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comment
	lifestyle modification, with or without: • Glucocorticoids • SGLT2i	modification; and addressing cardiovascular risk • SGLT2i are given to patients with IgAN as part of SoC for cardiovascular protection	pressure management, and maximum-tolerated RAS blockade (ACEi or ARBs) • Dapagliflozin has received NICE approval for the treatment of CKD (TA775) and is also anticipated to be used as part of SoC in patients with IgAN, as indicated by clinical expert opinion • The KDIGO guidelines state that corticosteroids and immunosuppressants are only recommended if a clinical trial is not accessible and the risk/benefit profile is considered to be acceptable. UK clinical experts reported that in practice, corticosteroids are used sparingly/only in severe patients with kidney disease (i.e., patients with nephrotic syndrome or rapidly progressive glomerulonephritis) • MMF is recommended in Chinese patients only, where it can be used as a glucocorticoid-sparing agent.	for the efficacy of budesonide to be properly compared to the most relevant comparators, there is a need for the comparison of budesonide + SoC versus corticosteroids + SoC in this subgroup. Similar arguments apply to the comparators MMF and SGLT2i. For further information please see Section 2.3. The trial evidence comparator is placebo, with optimised RASi therapy as SoC treatment. Importantly, optimised RASi therapy is also given in the intervention arm as an adjunct to budesonide. Therefore, the comparison is effectively budesonide + SoC versus placebo + SoC, which is different to the NICE scope of budesonide versus SoC: having the same SoC component in both arms is highly unlikely to yield the outcomes that would be seen if only the comparator arm included SoC. This discrepancy between the trial evidence and the NICE scope/decision problem has been raised with the company and they have agreed to amend the decision problem comparison to budesonide + SoC versus SoC.

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comment
			In clinical practice in England, MMF may be administered to Caucasian as well as Asian patients with IgAN due to the lack of other available treatment options. Due to a lack of clinical evidence showing benefit of MMF in Caucasians, it is not considered a relevant comparator for TRF-budesonide • No UK/NICE guidelines for the management of IgAN have been published to date.	
Outcomes	The outcome measures to be considered include: • proteinuria (for example, change from baseline in UPCR) • disease progression (dialysis and/or transplant) • mortality • adverse effects of treatment • health-related quality of life	As per scope.		The decision problem is in line with the scope. However, in the clinical evidence the outcome of 'disease progression' is not covered.
Economic analysis	The reference case stipulates that the cost effectiveness of	As per scope.		N/A

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comment
	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 PSS perspective. The availability of any commercial arrangements for the intervention, comparator and subsequent treatment technologies will be taken into account.			
Subgroups to be considered				
Special considerations including issues related to equity or equality				
Based on Table 1 in CS[1]				

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comment
ACE = angiotensin converting enzyme; ACEi = angiotensin converting enzyme inhibitor; ARB = angiotensin receptor blockers; CKD = chronic kidney disease; CS = company submission; EAG = Evidence Assessment Group; IgA = immunoglobulin A; IgAN = immunoglobulin A nephropathy; KDIGO = Kidney Disease Improving Global Outcomes; MMF = mycophenolate mofetil; N/A = not applicable; NHS = National Health Service; NICE = National Institute for Health and Care Excellence; PSS = Personal Social Services; RAS = renin-angiotensin system; RASi = renin-angiotensin system inhibitors; SGLT2i = sodium-glucose cotransporter-2 inhibitors; SoC = standard of care; TA = technology appraisal; TRF = targeted-release formulation; UK = United Kingdom; UPCR = urine protein to creatinine ratio				

2.1 Population

The National Institute for Health and Care Excellence (NICE) scope defines the population as people with primary immunoglobulin A (IgA) nephropathy (IgAN). The decision problem in the company submission (CS) describes a narrower population, namely adult patients with primary IgAN who 1) are at risk of rapid disease progression with a urine protein to creatinine ratio (UPCR) ≥1.5 g/g, and who 2) are on a stable dose of maximally tolerated renin-angiotensin system inhibitor (RASi) therapy.

EAG comment:

- The restriction to people at risk of rapid disease progression is reported as being due to the marketing authorisation and is therefore appropriate. However, the restriction to people at maximally tolerated RASi therapy was not fully justified in the CS.[1] Although RASi therapy is recommended as part of the standard of care by the Kidney Disease Improving Global Outcomes (KDIGO) guidelines, it is not clear why the population had to be limited to these people. The company were therefore asked to verify if patients not on maximally tolerated renin-angiotensin system (RAS) inhibitor therapy should also be considered with this appraisal. [2] The company responded by stating that, "*The licensed indication for TRF-budesonide is for adult patients with primary IgAN who are receiving a stable dose of maximally-tolerated RAS inhibitor therapy and are at risk of rapid disease progression with a UPCR ≥1.5 g/g. In accordance, in order to be eligible for randomisation in NefIgArd Nef-301 – the pivotal Phase 3 trial in support of TRF-budesonide in the treatment of primary IgAN and primary source of evidence in the CS – patients were required to be receiving a stable dose of RAS inhibitor therapy (ACEIs and/or ARBs) at the maximum allowed dose or maximum tolerated dose, according to the 2012 KDIGO guideline, for at least 3 months prior to randomisation. A stable dose was defined as being within 25% of the dose at randomisation"*.[3] This response, where the company confirmed that patients not receiving maximally tolerated RASi therapy should not be considered in this appraisal, clearly demonstrates that the restriction to people on maximal RAS therapy is justified by the licencing indication.
- In their response to clarification the company also stated that *"patients who cannot tolerate RAS blockade therapy can be considered for treatment with TRF-budesonide, in line with anticipated use in clinical practice*." [3] This initially suggests a contradiction to the licensed indication, but this is not the case as the company has pointed out that the licence stipulation of receiving a maximally-tolerated dose of RAS inhibitor therapy can include a maximally tolerated dose of zero. More importantly though, an additional concern of the Evidence Assessment Group (EAG) would be the low applicability of the presented evidence to those patients not on RASi therapy, given that only six patients (four on budesonide and two on placebo) did not receive RASi therapy in the NefIgArd Nef-301 trial. This is therefore a key issue.

2.2 Intervention

The NICE scope defines the intervention as targeted release budesonide. The decision problem accepts the same definition. In the clinical trials the main dosage is 16 mg per day for 9 months, which agrees with the marketing authorisation.

EAG comment:

- Maximally tolerated RAS blockade is given alongside budesonide in the included evidence, as part of standard of care (SoC). The CS[1] does not report the types and quantities of other aspects of SoC that were given alongside budesonide. Although the precise nature of the SoC was unclear, it was clear that SoC of some kind was being provided alongside budesonide. The EAG therefore

requested clarification that the intervention should be expressed as 'budesonide + SoC' as opposed to 'budesonide', to which the company agreed.[3] This issue is discussed further in Section 2.3.

- The intervention of budesonide is a corticosteroid. However, corticosteroids are not included as comparators in the decision problem because 'corticosteroids and immunosuppressants should only be used in special circumstances'. The company were asked to clarify this apparent contradiction[2]. In response, the company stated that, *"TRF-budesonide is an oral, modified-release capsule formulation of budesonide that provides a two-step release by combining a delayed capsule disintegration with a sustained/prolonged release of the active substance, budesonide, in the ileum. By directing release of budesonide to the ileum where it is expected to exert an anti-inflammatory effect at a primary site of galactose-deficient immunoglobulin A (gd-IgA) production, the Peyer's patches, the targeted release profile of TRF-budesonide is considered to drive the disease-modifying effect observed in the clinical trial while also enabling TRF-budesonide to be well tolerated. As a result of its targeted-release formulation, the systemic exposure of budesonide following administration of TRF-budesonide is limited, thus reducing the risk of immunosuppressive activity and serious side effects associated with systemic corticosteroids. This was verified in the NefIgArd Nef-301 study; the majority of adverse events (AEs) reported by patients who received TRF-budesonide 16 mg/day (in addition to optimised SoC) were mild to moderate [redacted] patients in the TRF-budesonide 16 mg/day group and [redacted] patient in the placebo group experienced a severe treatment-emergent AE [TEAE]) and were in-line with the known safety profile of an oral budesonide product. Importantly, no severe infections – which occur frequently during treatment with the use of systemic corticosteroids – were reported during treatment with TRF-budesonide, and there was no increase in overall infections compared with placebo (26.4% patients in the TRF-budesonide group vs 41.2% patients in the placebo group experienced an infection). In contrast, in STOP-IgAN, which investigated the impact of treatment with corticosteroids in a large European IgAN cohort (32 nephrology centres in Germany), the addition of immunosuppressive therapy to optimised supportive care in patients with IgAN was associated with a greater number of infection events vs supportive care alone (174 vs 111; p=0.07), of which 25% were considered by the investigators to be related to the study treatment. No other therapies with a similar release profile or similar risk-benefit profile to TRF-budesonide exist to our knowledge".*[3] This answer explains the apparent contradiction, and the EAG is satisfied that the use of targeted-release budesonide as the intervention does not contradict the company's concerns about the use of corticosteroids as comparators.

2.3 Comparators

The NICE scope states that the comparator should be SoC: that is, established clinical management without targeted-release budesonide, including angiotensin converting enzyme inhibitors (ACEi) and angiotensin receptor blockers (ARBs) at the maximum tolerated licensed doses (RASi), diuretics and dietary and lifestyle modification, with or without glucocorticoids or sodium-glucose cotransporter-2 inhibitors (SGLT2i).

The decision problem defines SoC as blood pressure management, maximally tolerated dose of ACEi/ARB (RASi), lifestyle modification and addressing cardiovascular risk. The CS[1] reports that SGLT2i (such as dapagliflozin) are also given to patients with IgAN as part of SoC for cardiovascular protection.

2.3.1 Corticosteroids and immunosuppressants

EAG comment:

- The decision problem definition of the comparator (SoC) is similar to the NICE scope, with the exception that glucocorticoids/corticosteroids are not included in the decision problem. This is justified in the CS by reference to the KDIGO guideline, which recommends that corticosteroids and immunosuppressants are only recommended if a clinical trial is not accessible and the risk/benefit profile is considered to be acceptable, in line with the KDIGO guidelines. However, this caveat implies that there is a particular subgroup of patients for whom corticosteroids/immunosuppressants (hereafter referred to as *corticosteroids* for brevity) *are* indicated, who are also eligible for budesonide. Because corticosteroids are a direct treatment for IgAN that could be used as an alternative to budesonide in this subgroup, corticosteroids could be regarded as a direct comparator rather than just a component of SoC. Therefore, for the efficacy of budesonide to be properly compared to the most relevant comparators, there is a need for the comparison of *budesonide + SoC versus corticosteroids + SoC* in this sub-group. This could be achieved through 1) a new direct comparison, or 2) via an indirect treatment comparison (ITC). The ITC could indirectly derive an estimate of the *budesonide + SoC versus corticosteroids + SoC* effect from both the direct trial estimate of *budesonide + SoC versus SoC* and any direct estimates of *corticosteroids + SoC versus SoC* in the literature.
- In line with the points above, the company were asked for clarification on the following points[2]:
    - the precise clinical criteria for the use of corticosteroids and immunosuppressants.
    - whether patients fulfilling these criteria would also be eligible for budesonide.
    - if such patients were eligible for budesonide, the company were asked to include corticosteroids and immunosuppressants as comparators.
    - the company were also asked to conduct a systematic literature review (SLR) estimate of the effectiveness of budesonide + SoC versus corticosteroids or immunosuppressants + SoC, where SoC resembles that in the NefIgArd Nef-301 study for the subgroup of patients eligible for either of these two types of therapy. The company were informed that this could be achieved by an ITC, ideally one which is anchored.
- In response,[1] the company stated that: *"The KDIGO criteria for the use of corticosteroids and immunosuppressants in patients with IgAN are as follows: Immunosuppressive drugs should be considered only in patients with IgAN who remain at high risk of progressive chronic kidney disease (CKD; defined as proteinuria >0.75–1 g/d despite ≥90 days of optimised supportive care) despite maximal supportive care . In all patients in whom immunosuppression is being considered, a detailed discussion of the risks and benefits of each drug should be undertaken with the patient recognising that adverse treatment effects are more likely in patients with an estimated glomerular filtration rate (eGFR) <50 mL/min/1.73 m^2. Patients who remain at high risk of progressive CKD despite maximal supportive care should be considered for a 6-month course of glucocorticoid therapy. The important risk of treatment-emergent toxicity must be discussed with patients, particularly those who have an eGFR <50 mL/min/1.73 m^2. The clinical benefit of glucocorticoids in IgAN is not established and treatment should be given with extreme caution or avoided entirely in certain situations (e.g. eGFR <30 mL/min/1.73 m^2, diabetes, obesity). In line with the KDIGO guidelines, in clinical practice, clinicians refrain from using corticosteroids and immunosuppressants due to their adverse event profile. Corticosteroids and immunosuppressants may only be used in patients with severe kidney disease (i.e. patients with nephrotic syndrome or rapidly progressive glomerulonephritis), in whom the poor risk-benefit profile is considered to be justifiable and only when a clinical trial is not available). Data from the STOP-IgAN[4, 5] and TESTING [6] studies showed that immunosuppressive therapy and corticosteroids were associated*

with significantly higher rates of adverse events, particularly infection events, compared with SoC in patients with IgAN. In addition, in STOP-IgAN, which investigated the impact of treatment with corticosteroids in a large European IgAN cohort (32 nephrology centres in Germany), there was no significant difference in the annual decline in eGFR between the immunosuppressive therapy and placebo treatment groups over the 3-year study phase. Information specifically relating to the efficacy of immunosuppressants or corticosteroids in patients with primary IgAN with nephrotic syndrome or rapidly progressive glomerulonephritis has not been identified. Patients fulfilling the KDIGO criteria for immunosuppressants or corticosteroids would be eligible for TRF-budesonide. However, given the caution surrounding use of immunosuppressants and corticosteroids, their limited use in clinical practice, and the lack of evidence available for their use patients with severe disease or patients specifically with a UPCR ≥1.5 g/g, immunosuppressants and corticosteroids were not considered to be relevant comparators for TRF-budesonide in the CS".[3] In this response, the company failed to respond to any of the EAG's questions directly, but instead repeated much of what had been written in the CS. The company are clearly stating that patients who currently would get immunosuppressants or corticosteroids could instead be given budesonide and so, unless that subgroup of patients are excluded from the population in the decision problem, they must be comparators, regardless of their limited use. Given the lack of a satisfactory response from the company in terms of ruling out this subgroup or providing a formal comparison, this remains a key issue.

2.3.2 Mycophenolate mofetil (MMF)

EAG comment:

- Mention is also made of mycophenolate mofetil (MMF) as an aspect of SoC by the company when discussing their decision problem, even though this is not directly specified as a component of SoC in the NICE scope. Mycophenolate mofetil is described by the company as excluded from SoC because of lack of evidence of efficacy in Caucasian patients, but it is unclear if those eligible for MMF are excluded by the population in the decision problem. The company have therefore been asked[2] to clarify the following:
  - whether MFF would be given to some Asian and some Caucasian patients and, if so, according to precisely which criteria in patients with IgA nephropathy.
  - if patients fulfilling these criteria would be eligible for budesonide. If not, whether these patients should be excluded from the decision problem.
  - if patients who might be eligible for MFF are not excluded, then the company were asked to include MMF as a comparator.
  - the company were also asked to conduct an SLR to estimate the effectiveness of budesonide + SoC versus MMF + SoC, where SoC resembles that in the NefIgArd Nef-301 study for the subgroup of patients eligible for MFF. The company were informed that this could be achieved by an ITC, ideally one which is anchored.
- The company responded but did not directly answer any of the EAG's questions. Reiterating what they had previously written in the CS,[1] the company stated that *"the KDIGO guidelines recommend the use of mycophenolate mofetil (MMF) in Chinese patients with primary IgAN who remain at high risk for progression after maximal supportive care as a glucocorticoid-sparing agent, only if a clinical trial is not accessible and the risk/benefit profile is considered to be acceptable. The KDIGO guidelines note that there is insufficient evidence to support the use of MMF in non-Chinese patients with primary IgAN. In the randomised controlled trials (RCT) of MMF in non-Chinese patients with IgAN, there was no evidence for efficacy of MMF. UK clinical experts confirmed that in UK clinical practice, due to the lack of other available treatments and the high disease burden*

particularly in patients with severe disease, MMF could be used for the treatment of IgAN in both Asian and Caucasian patients as a last resort, steroid-sparing treatment, despite the lack of clinical evidence, only if a clinical trial is not accessible and the risk/benefit profile may be considered acceptable. However, the clinical experts reiterated that MMF is rarely used in UK clinical practice. TRF-budesonide has an established efficacy and acceptable risk to benefit profile and would provide a treatment-option for patients with primary IgAN".[3] As with corticosteroids and immunosuppressants, the company is clearly stating that MMF would be a comparator to budesonide for at least the subgroup eligible for MMF. Given the company's failure to address the questions posed to them, this is a key issue, which is further discussed in Section 3.4.

2.3.3 SGLT2i such as dapagliflozin

EAG comment:

- The company did include SGLT2i as comparators in the decision problem in accordance with the scope, but effectively ruled them out by arguing that a formal comparison is unnecessary because: "*…the DAPA-CKD study [7] suggest [ed] that dapagliflozin treatment in patients with IgAN (N=270) did not have a statistically significant impact on eGFR change over 36 months compared with placebo*".[1] However, it should be noted that the dapagliflozin treatment led to a 26% reduction in estimated glomerular filtration rate (eGFR) decline compared to placebo for this outcome in the DAPA-CKD study, which could represent a type II error given the high variance. Furthermore, the study also showed that dapagliflozin had a statistically significant effect on the primary (composite) outcome comprising a first occurrence of any of the following: 1) sustained >50% decline in eGFR (confirmed by a second serum creatinine after at least 28 days); 2) onset of end-stage kidney disease (ESKD) (defined as maintenance dialysis for at least 28 days, kidney transplantation, or eGFR <15 ml/min per 1.73 m^2); or 3) death from a kidney disease–related or cardiovascular cause. The hazard ratio (HR) for dapagliflozin versus placebo for this composite outcome was 0.29 (95% (confidence interval (CI): 0.12 to 0.73).
  In response to the request for clarification, the company made another argument as to why SGLT2i should be excluded as a comparator, which is that they are part of SoC.[3] However, as shown in Table 2.2, no patients in the trial of budesonide + SoC versus SoC received an SGLT2i, which means that the effect of targeted-release formulation (TRF)-budesonide added to SGLT2i versus SGLT2i has not been presented. Also, as argued below, it cannot be assumed that the difference that budesonide makes is independent of the type of SoC to which it is added. The EAG would also point out that SGLT2i were included as comparators and therefore it is unclear whether TRF-budesonide would be added to or replace an SGLT2i. Therefore, for at least a subgroup of people who are eligible for both budesonide and an SGLT2i, there may be a need for the comparison of TRF-budesonide + SoC, possibly including an SGLT2i versus SoC including SGLT2i. This key issue is discussed further in Section 3.4.

2.3.4 Standard of care treatment (SoC)

EAG comment:

- In the trial evidence the comparator is placebo with optimised RASi therapy (an aspect of SoC). Importantly, optimised RASi therapy is also given in the intervention arm as an adjunct to budesonide. Therefore, the trial comparison is effectively budesonide + SoC versus placebo + SoC, which is different to the NICE scope comparison of budesonide versus SoC. Having the same SoC component in both arms is highly unlikely to yield the outcomes that would be seen if only the comparator arm included SoC. This discrepancy between the trial evidence and the NICE scope/decision problem required justification, and the company were asked to clarify whether the

decision problem should be re-expressed as budesonide + SoC versus SoC.[2] The company responded by stating that, *"the decision problem should be re-expressed as TRF-budesonide in addition to SoC versus SoC, where SoC is defined as: lifestyle modification, blood pressure management, maximum-tolerated RAS blockade and addressing cardiovascular risk"*.[3]
The EAG notes the change to the decision problem definition but suggests that the new decision problem still conflicts with the NICE scope. It is possible that the NICE scope was unrealistic, and that budesonide could not reasonably be given without SoC treatments; if so, the committee should ignore the conflict with the NICE scope. Otherwise, the committee might consider whether the company has framed the decision problem inappropriately.

- It was initially unclear which of the other SoC treatments are given in each arm alongside RASi therapy (such as blood pressure monitoring, lifestyle modification, or other drugs such as SGLT2i) or indeed whether these are given at all. Since the trial was a double-blinded randomised controlled trial (RCT), the types and amounts of SoC treatment (including RASi therapy) should theoretically be similar in both the intervention and comparator arms. However, the small sample size of 78 in the presented evidence made it probable that there could be chance differences in the SoC treatments in each arm, leading to a reduction in internal validity. The EAG therefore asked the company about the dosages and types of SoC treatments used in each arm, so that an assessment could be made about potential threats to internal validity.[2] In response, the company provided the table below (Table 2.2), and responded comprehensively as follows: *"In NefIgArd Nef-301, the SoC provided to both treatment arms consisted of 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, lifestyle modification (weight normalisation; smoking cessation; physical activity; and diet [low salt and low protein]), blood pressure management, and addressing cardiovascular risk. Systemic immunosuppressive drugs (including corticosteroids), except when used as rescue medications, were prohibited during the study. Of note, patients who could not tolerate RAS blockade therapy were considered in the study, in line with anticipated clinical practice. Details of the concomitant medications received by >10% of total patients by anatomical therapeutic chemical class and the numbers receiving lifestyle modification for patients with a baseline urine protein to creatinine ratio (UPCR) >1.5 g/g in Part A of the NefIgArd Nef-301 are provided in [the table below]. Other than ARBs and ACEIs, the overall most common classes of concomitant medications were the following:Hydroxy-3-methyl-glutaryl-coenzyme A reductase inhibitors ([redacted] of patients in the TRF-budesonide 16 mg/day group and [redacted] of patients in the placebo group);Dihydropyridine derivatives ([redacted] of patients in the TRF-budesonide 16 mg/day group and [redacted] of patients in the placebo group); and Preparations inhibiting uric acid production ([redacted] of patients in the TRF-budesonide 16 mg/day group and [redacted] of patients in the placebo group).There were no clinically relevant differences in concomitant medication use across treatment groups. Overall, the concomitant medications were as expected, considering the comorbidities present in patients with IgAN"*.[3] In response to this, the EAG note some important numerical differences between the trial arms in terms of concomitant medications. These are differences in:
    - Angiotensin converting enzyme (ACE) inhibitors (greater number in budesonide group)
    - ARBs (greater number in placebo group)
    - 3-hydroxy-3-methyl-glutaryl-coenzyme A (HMG CoA) reductase inhibitors (greater number in budesonide group)
    - Sulphonamides (greater number in budesonide group)
    - Corticosteroids (greater number in placebo group)

- The EAG acknowledge that these differences in concomitant medication are most likely to be random effects secondary to small samples. However, the EAG think that the magnitude of these differences is nevertheless sufficient to impair internal validity. This is therefore a key issue. Please also see Section 3.2.3 for further discussion of other baseline variables that could impair internal validity.
- The SoC used in the trial may also have potential effects on external validity, and it is important to gauge the applicability of the SoC in the trial with that used in the target population. The company were therefore asked to provide details of the SoC used in the United Kingdom (UK) target population. [2] The company responded by stating that *"clinicians have indicated that IgAN patients, including those with a UPCR ≥1.5 g/g, would receive optimised supportive care, i.e. lifestyle modification, blood pressure management, maximum-tolerated RAS blockade, and treatment for cardiovascular risk. Data relating to the proportion of patients receiving different treatments as part of SoC in the UK are not currently available"*.[3] The EAG accept the limitations of the currently available data but are concerned that it is unknown if the SoC used in UK clinical practice is relevant to that used in the trials. Potentially reduced external validity is therefore a key issue. See also Section 3.2.5.6 for further discussion on other sources of reduced external validity in the submission.

Table 2.2: Concomitant medications (>10% of total patients) by ATC class – NefIgArd Nef-301 Part A baseline UPCR ≥1.5 g/g

ATC Class	TRF-budesonide 16 mg/day (N=[redacted]), n (%)	Placebo (N=[redacted]), n (%)
Patients who took any concomitant medications	[redacted]	[redacted]
ACE inhibitors, plain†	[redacted]	[redacted]
ARBs, plain†	[redacted]	[redacted]
HMG CoA reductase inhibitors	[redacted]	[redacted]
Dihydropyridine derivatives	[redacted]	[redacted]
Preparations inhibiting uric acid production	[redacted]	[redacted]
Vitamin D and analogues	[redacted]	[redacted]
Beta blocking agents, selective	[redacted]	[redacted]
Proton pump inhibitors	[redacted]	[redacted]
Glucocorticoids	[redacted]	[redacted]
Sulphonamides, plain	[redacted]	[redacted]
Other antihistamines for systemic use	[redacted]	[redacted]
Alpha-adrenoreceptor antagonists	[redacted]	[redacted]
Other lipid modifying agents	[redacted]	[redacted]
Imidazoline receptor agonists	[redacted]	[redacted]
Thiazides, plain	[redacted]	[redacted]
Corticosteroids‡	[redacted]	[redacted]
Lifestyle choices according to protocol recommended to the patient	[redacted]	[redacted]

Based on Table 2 of the response to the request for clarification[3]

ATC Class	TRF-budesonide 16 mg/day (N=[redacted]), n (%)	Placebo (N=[redacted]), n (%)
Concomitant medications were defined as medications that were taken on or after the first dose day of study treatment. Medication reported terms were coded using the WHO Drug Dictionary (Version March 2019 G B3). † These ATC classes were defined based on whether they were taken during treatment. These ATC classes are not inclusive of all RAS inhibitor therapy. ‡ Corticosteroids have been included in the table as per request in question 5a. ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; ATC = Anatomical Therapeutic Chemical; HMG CoA = 3-hydroxy-3-methyl-glutaryl-coenzyme A; TRF = targeted-release formulation; UPCR = urine protein to creatinine ratio; WHO = World Health Organization		

2.4 Outcomes

The NICE scope lists the following outcome measures:

- proteinuria (for example, change from baseline in UPCR)
- disease progression (dialysis and/or transplant)
- mortality
- adverse effects of treatment
- HRQoL

EAG comment:

- The decision problem agrees with the NICE scope outcomes, but the trial evidence does not address 'disease progression', a highly patient-relevant outcome. This issue has been further discussed in Section 3.2.5.3.
- Because the longer-term data (part B of NefIgArd Nef-301) are not yet fully published, detailed outcomes in the CS are restricted to those at 9 months (part B of NefIgArd Nef-301). This makes it difficult to make meaningful decisions on the longer-term efficacy of budesonide.[1]
- A brief summary of longer-term results is made in Section B.2.11 of the CS,[1] and a reference is made to a web page[8] which provides further information. However, these data are seriously limited in scope, only providing details for eGFR. The company were asked to provide any more detailed data from the part B study.[2] The company replied by stating that *"no data, other than those published within the webpage is currently available from Part B"*. However, the company also stated that *"as UPCR and eGFR are considered to be suitable markers of long-term clinical benefit, it is assumed that the treatment effects in Part A of NefIgArd Nef-301 will not only translate into improvements in later clinical endpoints but will also translate into a statistically significant and clinically meaningful improvement for the Part B primary endpoint. This has been verified in the preliminary results of Part B of NefIgArd Nef-301 (20), with a statistically significant (p<0.0001) benefit over placebo in eGFR observed over the 2-year period (9-months of treatment with TRF-budesonide or placebo and 15-months of follow-up off drug)"*.[3]
  This information is not sufficient to convince the EAG that long-term benefits for UPCR can be assumed. Presentation of evidence supporting the capacity of early UPCR benefits to be markers for longer benefits would bolster the company's argument, but, in the absence of such data, this has been deemed a key issue.

2.5 Other relevant factors

The intended action of TRF-budesonide is the suppression of mucosal B-cells, located in the Peyer's patches in the ileum, and inhibition of their proliferation and differentiation into plasma cells that produce mucosal galactose-deficient immunoglobulin A (gd-IgA1) antibodies. Consequently, it is expected that the occurrence of gd-IgA1 antibodies and formation of immune complexes in the systemic

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

The Committee for Medicinal Products for Human Use (CHMP) recommended the granting of a conditional marketing authorisation for TRF-budesonide on 19 May 2022. Marketing authorisation was granted by the European Commission on the 15 July 2022. Marketing authorisation by the Medicines and Healthcare Products Regulatory Agency (MHRA) on 1 February 2023.

On 17 December 2021, the Food and Drug Administration (FDA) in the United States of America (USA) granted accelerated approval for budesonide delayed release capsules to reduce proteinuria (increased protein levels in the urine) in adults with primary IgA nephropathy at risk of rapid disease progression.

IgAN is more frequently diagnosed in males than females and in Caucasian and Asian populations compared with Black populations. While the epidemiology of IgAN will affect the demographics of patients eligible for treatment with TRF-budesonide, the use of TRF-budesonide is not expected to raise any equality issues.

3. CLINICAL EFFECTIVENESS

3.1 Critique of the methods of review(s)

3.1.1 Searches

The following paragraphs contain summaries and critiques of the searches related to clinical effectiveness presented in the CS.[1] The Canadian Agency for Drugs and Technologies in Health (CADTH) evidence-based checklist for the Peer Review of Electronic Search Strategies (PRESS), was used to inform this critique.[9, 10] The EAG has presented only the major limitations of each search strategy in the report.

A summary of the sources searched is provided in Table 3.1.

Table 3.1: Data sources for Appendix D: Identification, selection and synthesis of clinical evidence (as reported in CS)

Resource	Host/Source	Date ranges	Date searched
Electronic databases			
Embase	Ovid	1974-02/11/2022	03/11/22
MEDLINE, including: MEDLINE Epub Ahead of Print MEDLINE In-Process & Other Non-Indexed Citations MEDLINE Daily	Ovid	1946-02/11/2022	03/11/22
American College of Physicians (ACP) Journal Club	EBM Reviews (Ovid)	1991-10/2022	03/11/22
Cochrane Central Register of Controlled Trials (CENTRAL)	EBM Reviews (Ovid)	to 09/2022	03/11/22
Cochrane Database of Systematic Reviews	EBM Reviews (Ovid)	2005-02/11/2022	03/11/22
Cochrane Clinical Answers	EBM Reviews (Ovid)	to 10/2022	03/11/22
Cochrane Methodology Register	EBM Reviews (Ovid)	to 3rd Quarter 2012	03/11/22
Database of Abstracts of Reviews of Effects (DARE)	EBM Reviews (Ovid)	1991-to 1st Quarter 2015	03/11/22
HTA database	EBM Reviews (Ovid)	2001- 4th Quarter 2016	03/11/22
National Health Service Economic Evaluation Database (NHS EED)	EBM Reviews (Ovid)	1995- to 1st Quarter 2015	03/11/22
Conferences			
American Society of Nephrology (ASN)		2020, 2021, 2022	14/11/22
European Renal Association (ERA)			N/A: Conference indexed in Embase

Resource	Host/Source	Date ranges	Date searched
International IgA Nephropathy Network (IIGANN) International Symposium on IgA Nephropathy		2021 (no conference 2019, 2020, 2022)	14/11/22
National Kidney Foundation		2020, 2021, 2022	14/11/22
World Congress of Nephrology (WCN)		2019, 2021, 2022 (no conference 2020)	14/11/22
Trials registries			
USA NIH registry & results database	https://clinicaltrials.gov		23/01/2023
WHO ICTRP	http://apps.who.int/trialsearch/		02/02/2022
HTA global bodies			
National Institute for Health and Care Excellence (NICE)	Internet		14/11/2022
Scottish Medicines Consortium (SMC)	Internet		14/11/2022
Canadian Agency for Drugs and Technologies in Health (CADTH), including the pan-Canadian Oncology Drugs Review (pCODR)	Internet		14/11/2022
Pharmaceutical Benefits Scheme (PBS)	Internet		14/11/2022
Agencia Española de Medicamentos y Productos Sanitarios (AEMPS)	Internet		14/11/2022
Agenzia Italiana del Farmaco (AIFA)	Internet		14/11/2022
Haute Autorité de Santé (HAS)			14/11/2022
Institute for Quality and Efficiency in Health Care (IQWIG)	Internet		14/11/2022
Institute for Clinical and Economic Review (ICER)			Not reported
USA Food and Drug Administration (FDA)	Internet		14/11/2022
European Medicines Agency (EMA)	Internet		14/11/2022
Finnish Coordinating Centre for Heath Technology Assessment (FinCCHTA)	Internet		14/11/2022

Resource	Host/Source	Date ranges	Date searched
DEFACTUM Social & Health Services and Labour Market	Internet		14/11/2022
Norwegian Institute of Public Health (NIPH)	Internet		14/11/2022
Swedish Agency for Health Technology Assessment and Assessment of Social Services [Statens beredning för medicinsk och social utvärdering] (SBU)	Internet		14/11/2022
Dental and Pharmaceutical Benefits Agency (Tandvårds- och läkemedelsförmånsverket) (TLV)	Internet		14/11/2022

Based on Appendix D of the CS[11]
ACP = American College of Physicians; AEMPS = Agencia Española de Medicamentos y Productos Sanitarios; AIFA = Agenzia Italiana del Farmaco; ASN = American Society of Nephrology; CADTH = Canadian Agency for Drugs and Technologies in Health; CENTRAL = Cochrane Central Register of Controlled Trials; CS = company submission; DARE = Database of Abstracts of Reviews of Effects; EBM = evidence-based medicine; EED = Economic Evaluation Database; EMA = European Medicines Agency; ERA = European Renal Association; FDA = Food and Drug Administration; FinCCHTA = Finnish Coordinating Centre for Heath Technology Assessment; HAS = Haute Autorité de Santé; HTA = health technology assessment; ICER = Institute for Clinical and Economic Review; ICTRP = International Clinical Trials Registry Platform; IIGAN = International IgA Nephropathy Network; IQWiG = Institute for Quality and Efficiency in Health Care; ISN = International Society of Nephrology; N/A = not applicable; NHS = National Health Service; NICE = National Institute for Health and Care Excellence; NIH = National Institute of Health; NIPH = Norwegian Institute of Public Health; PBS = Pharmaceutical Benefits Scheme; pCODR = pan-Canadian Oncology Drugs Review; SMC = Scottish Medicines Consortium; TLV = Tandvårds- och läkemedelsförmånsverket (Dental and Pharmaceutical Benefits Agency); USA = United States of America; WCN = World Congress of Nephrology; WHO = World Health Organization

EAG comment:

- Searches were undertaken in November 2022 to identify relevant clinical evidence for the efficacy and safety of TRF-budesonide and relevant comparators for the treatment of primary IgA nephropathy. The CS, Appendix D and the Company's response to clarification provided sufficient details (including database host(s), date searched, and date ranges covered) for the EAG to appraise the literature searches.[1, 3, 11]
- A broad range of databases and grey literature including trials registers, conference proceedings and health technology assessment (HTA) websites were searched. Reference checking was conducted.
- Database searches were not restricted by publication date or language.
- Searches were well structured, transparent and reproducible, and a good range of subject indexing terms (Medical Subject Headings (MeSH)/EMTREE) and free text was used.
- The EAG noted a disparity in the number of hits reported for the MEDLINE search for clinical effectiveness between the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flowchart reported in Section D.1.5 (n=6,499) and the strategies listed in Section D.1.3 (n=499). The company confirmed that this was a typographical error and that the PRISMA chart should have read 499.
- The full details of the supplementary searches, search strategies, search terms, date searched and the results missing from the CS,[1, 11] were provided in the company's response to clarification.[3] The

company also confirmed that *"the supplementary searches undertaken were conducted to cover both the clinical and economic sections of the submission"*.

- Study design filters to identify RCTs were applied to the searches of Embase and MEDLINE.
- Separate searches to retrieve information regarding adverse events (AEs) for safety outcomes for TRF-budesonide were not conducted. In response to the request for clarification, the company reported that *"AEs were included as outcomes of interest in the search for clinical evidence reported in company submission (CS) appendix D section D1"*.[3] However these searches were limited to RCTs, guidance by the Centre for Reviews and Dissemination (CRD)[12] and Golder 2019[13] recommend that if searches have been limited by a study design filter, additional searches should be undertaken to ensure that AEs that are long-term, rare or unanticipated are not missed.

3.1.2 Inclusion criteria

An SLR, conducted in November 2022, was performed by the company to identify evidence of efficacy, safety and HRQoL outcomes for patients with primary IgAN and treated with TRF-budesonide or relevant established treatments.

The eligibility criteria used in the search strategy for RCTs and non-RCTs is presented in Table 3.2.

EAG comment:

- There is no confirmation in the CS that the eligibility criteria (protocol) were formulated before any data collection had been carried out. The company were asked to comment on this, and responded by confirming that *"the protocol (eligibility criteria) was developed prior to commencement of searches and was registered with PROSPERO: CRD42022382841"*.[3] The EAG is satisfied with this response.
- There is also no record in the CS of the number of amendments made to the protocol after the searches had been commenced. If the protocol is not adhered to closely without significant changes, there is a high risk of bias. The company provided details of two sets of protocol amendments made: *"01/12/2022: inclusion/exclusion criteria altered to include all randomised interventions of interest (i.e. not limited to budesonide) and not limit inclusion by comparator. Criteria was also adapted to highlight studies of primary interest; studies assessing ACEIs/ARBs as standard care (patients were previously receiving ACEIs/ARBs prior to study commencement). This was not a stipulation for inclusion/exclusion but forms the basis of focus for the clinical SLR report since this is reflective of current clinical practice" and "3/02/2023: searches of HTA bodies were altered to change PBAC (Pharmaceutical Benefits Advisory Committee) to PBS (Pharmaceutical Benefits Scheme)"*.[3] The EAG does not see either of these two sets of protocol amendments as potential risks of bias.

Table 3.2: Eligibility criteria used in the systematic review

Clinical effectiveness	Inclusion criteria	Exclusion criteria
Population	People with primary IgAN	No restriction
Intervention	TRF-budesonide ACEis ARBs Diuretics Dietary and lifestyle modifications SGLT2i	No restriction

Clinical effectiveness	Inclusion criteria	Exclusion criteria
	Glucocorticoids Cyclophosphamide	
Comparators	No restriction (priority studies were those assessing ACEis/ARBs as standard care)	No restriction
Outcomes	Efficacy: Change from baseline in UPCR Renal function as measured by eGFR Disease progression (incidence of dialysis and/or transplant post treatment) Mortality rate Survival rates Safety: Adverse effects of treatment (all SAE, AE, TEAE) Death/any AE leading to mortality† Onset of DM† Fracture† Osteonecrosis† Infections† Severe infections leading to hospitalisations‡ GI bleeding requiring hospitalisation‡ Cataract formation‡ Onset of glaucoma‡ Peripheral oedema Cushingoid Weight gain Hypertension HRQoL	No restriction
Subgroups	Patients at risk of rapid disease progression Patients with greater than 1.5 g/g UPCR	No restriction
Study design	RCTs Other prospective experimental studies Previously conducted SLRs/meta-analyses (to reference check)	Observational studies Qualitative studies Case studies
Follow-up times	No restriction	No restriction
Geography	No restriction	No restriction
Publication date	No restriction	No restriction
Language restrictions	No restriction	No restriction

Based on Table 1 of Appendix D of the CS[11]
† AE of primary interest
ACEi = angiotensin-converting enzyme inhibitor; AE = adverse event; ARB = angiotensin receptor blockers; CS = company submission; DM = diabetes mellitus; eGFR = estimated glomerular filtration rate; GI = gastrointestinal; HRQoL = health-related quality of life; IgAN = immunoglobulin A nephropathy; RCT = randomised controlled trial; SAE = serious adverse event; SGLT2i = sodium-glucose co-transporter-2 inhibitors; SLR = systematic literature review; TEAE = treatment emergent adverse event; TRF = targeted release formulation; UPCR = urine protein creatinine ratio

3.1.3 Critique of data extraction

Two reviewers, with a third party for disputes or consensus, were used for sifting and extraction. An appropriate PRISMA diagram outlined the inclusion and exclusion of studies.

EAG comment:

- The company states in the CS that *"the final list of included studies for extraction was agreed with Britannia Pharmaceuticals Ltd"*.[1] It is unclear whether this statement reflects an additional criterion for inclusion or exclusion by the company that is over and above the pre-hoc criteria for inclusion outlined in the protocol of the review. The company were therefore asked to comment on this.[2] The company stated that *"the vendor conducting the SLRs provided the full list of included studies to the Company (Britannia Pharmaceuticals Ltd.) for review prior to data extraction to ensure all relevant studies were captured in accordance with the predefined eligibility criteria. There were no additional criteria for selection and Britannia Pharmaceuticals Ltd. did not influence the selection of studies"*.[3] The EAG is satisfied with this response.

3.1.4 Quality assessment

There are two references to quality appraisal: 'the 8-domain tool recommended by NICE', and the '7-criteria checklist'.

EAG comment:

- It was initially unclear why the company referred to two different criteria. The company have been asked to clarify this.[2] The company's response[3] made it clear that the two criteria are very similar, except for minor differences in vocabulary and the fact that the 8-domain tool has an additional criterion relating to declarations of conflict of interest. The EAG is satisfied with this response.

3.1.5 Evidence synthesis

There were 51 individual publications included by the SLR. Of these, three papers concerned budesonide, and were therefore relevant to the critical appraisal for this submission: Barratt 2022,[14] Fellström 2017[15] and Roy-Chaudhary 2022[16]. These represent three separate trials. Barratt 2022[14] represents part A of NefIgArd, Fellström 2017[15] represents the NEFIGAN trial and Roy-Chaudhary 2022[16] represents an independent trial that is possibly unconnected from the company. No report is made of the evidence synthesis.

It should be noted that because a specific search for AEs was not undertaken by the company (see Section 3.1.1), the systematic review cannot be regarded as providing an overview of the full range of AEs relevant to budesonide.

3.2 Critique of trials of the technology of interest, their analysis and interpretation (and any standard meta-analyses of these)

3.2.1 Details of the included trials

As stated earlier, the SLR revealed three relevant trials.[14-16] Barratt 2023[14] represents part A of NefIgArd, Fellström 2017[15] represents the NEFIGAN trial and Roy-Chaudhary 2022[16] represents an independent trial that is possibly unconnected from the company.

Meanwhile, the CS reports the clinical evidence as three separate trials (Table 3.3).[1] These are 1) NefIgArd Nef-301 parts A and B, and NefIgArd-OLE (open-label extension), 2) NEFIGAN Nef-202 and 3) Phase 2a of NCT00767221.[17]

However, the SLR and CS (Table 3.2) do not contain the same three trials. Whilst NefIgArd and NEFIGAN are common to both, Roy-Chaudhary 2022[16] was yielded by the SLR, but was not included in the CS,[1] and Phase 2a of NCT00767221[17] was included in the CS but not yielded from the SLR.[1]

Furthermore, the clinical efficacy evidence only contains one of the studies in Table 3.3: part A of NefIgArd.

Table 3.3: Clinical effectiveness evidence

Study	NefIgArd Nef-301 (NCT03643965)				NefIgArd-OLE (NCT04541043)		NEFIGAN Nef-202 (NCT01738035)		Phase 2a (NCT00767221)	
	Part A		Part B							
Primary sources	CSR, Barratt 2023[14]				Study protocol[18]		Fellström 2017[15]		Smerud 2011[17]	
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		Open-label, uncontrolled proof-of-concept study	
	Part A evaluated the efficacy and safety of TRF-budesonide		Part B is evaluating TRF-budesonide for long-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		≥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		>18 years U-albumin >500 mg/day S-creatinine <200 µmol/l	
Intervention(s)	Optimised RASi therapy + TRF-budesonide 16 mg/day		No intervention		Optimised RASi therapy + TRF-budesonide 16 mg/day (all patients)		Optimised RASi therapy + TRF-budesonide 16 mg/day or TRF-budesonide 8 mg/day or placebo (1:1:1 randomisation stratified by baseline UPCR)		Optimised RASi therapy + TRF-budesonide 8 mg/day	
Comparator(s)	Optimised RASi therapy + placebo									
Status	Completed		Completed February 2023. Data analyses expected to complete Q3/4 2023.		Ongoing (end date: May 2024)		Completed		Completed	
Indicate if study supports application for marketing authorisation	Yes	*X*	Yes		Yes		Yes	*X*	Yes	
	No		No	X	No	X	No		No	X
	Yes	*X*	Yes		Yes		Yes		Yes	

Study	NefIgArd Nef-301 (NCT03643965)				NefIgArd-OLE (NCT04541043)		NEFIGAN Nef-202 (NCT01738035)		Phase 2a (NCT00767221)	
	Part A		Part B							
Indicate if study used in the economic model	No		No	X	No	X	No	X	No	X
Rationale if study not used in model	Not applicable		Study ongoing – data not available		Study ongoing – data not available		Phase 2 study		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 (analysis to be performed when the last patient randomised has complete Visit 17b)		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		Change in 24-h urine albumin excretion	
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		2-year eGFR slope Time to 30% reduction from baseline in eGFR Time to rescue medication Ratio of UPCR, UACR, and eGFR compared with baseline averaged over time points between 12 and 24 months, inclusive Proportion of patients without microhaematuria in at least two time points		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		Changes in serum creatinine, eGFR and serum concentrations of IgA and IgA antibodies against gliadin Safety endpoints	

Study	NefIgArd Nef-301 (NCT03643965)		NefIgArd-OLE (NCT04541043)	NEFIGAN Nef-202 (NCT01738035)	Phase 2a (NCT00767221)
	Part A	**Part B**			
	Safety variables	Proportion of patients receiving rescue treatment SF-36 at 9 and 24 months Exploratory analyses on blood and urine Safety variables			

Based on Table 4 of the CS[1]
Note: Outcomes marked in bold have been incorporated into the economic model.
AUC = Area Under Curve; CSR = clinical study report; eGFR = estimated glomerular filtration rate; IgA = immunoglobulin A; IgAN = immunoglobulin A nephropathy; OLE = open label extension; RASi = renin-angiotensin system inhibitors; RCT = randomised controlled trial; SF-36 = short-form 36; TEAE = treatment emergent adverse event; TRF = targeted-release formulation; UACR = urine albumin to creatinine ratio; UPCR = urine protein to creatinine ratio

EAG comment:

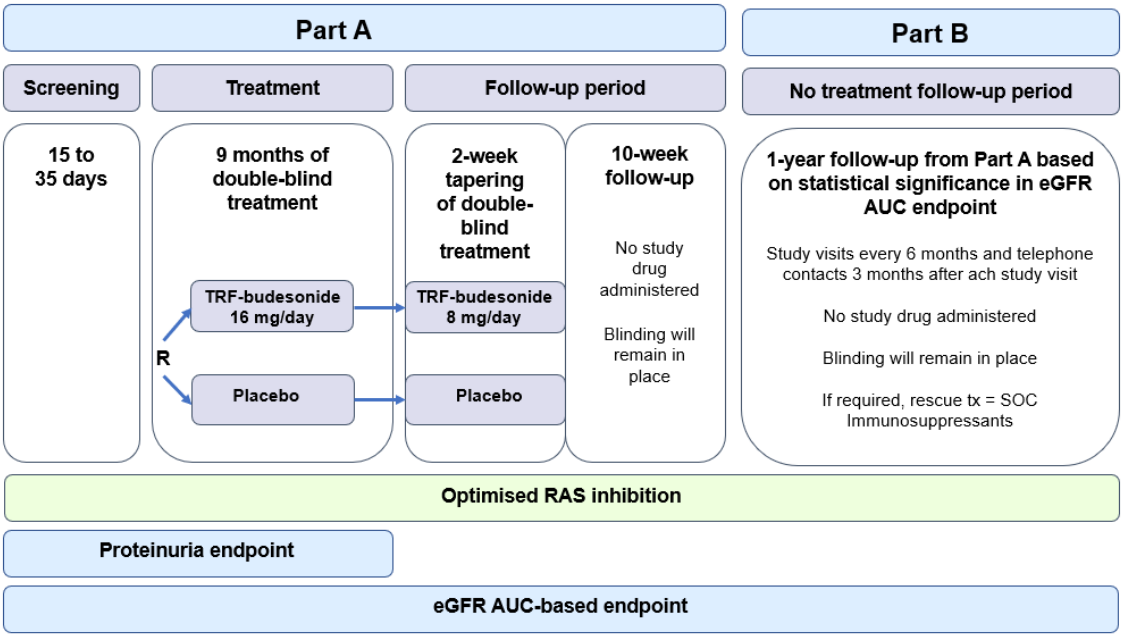
- Of the studies in the company's 'clinical efficacy evidence' table (Table 3.3) only the data of part A of NefIgArd is included in the reported clinical efficacy evidence in the CS.[1]
  - Part B of NefIgArd Nef-301 is awaiting completion of data analysis, and data collection in NefIgArd-OLE is still ongoing. Therefore, their non-inclusion as part of the clinical efficacy data is understandable.
  - NCT00767221[17] is a single arm study using an 8 mg dose of budesonide (rather than the 16 mg dose used in all other studies), and so its non-inclusion as part of the clinical efficacy data is also appropriate. It should also be pointed out, however, that Smerud 2011[17] was not found by the literature review. The company were asked where it was sourced, and why it was included in Table 3.3 if it had not been derived by the literature review. The company explained that the study had been derived from the literature review but not included as it was a single arm study. The EAG is satisfied with this response.
  - The rationale for the non-inclusion of NEFIGAN Nef-202[15] is more difficult to explain. The CS[1] states that it has not been included because it is a phase 2 study, but this does not change the fact that it is a double-blind RCT, and therefore potentially highly relevant. The company were asked why this study was not included, and to include it if appropriate.[2] The company responded by stating that *"the results of Nefigan Nef-202 were in line with those of the Phase 3 NefIgArd Nef-301 study. …As such, the more robust and up to date data from NefIgArd Nef-301 were used to inform the company submission and relevant economic model, and data from Nefigan Nef-202 were not reported in Document B or used to inform the economic model"*.[3] The company then provided a clear account of the results in NEFIGAN Nef-202, demonstrating similar results. However, for the UPCR and urine albumin to creatinine ratio (UACR) outcomes, the magnitudes of effect for budesonide in NEFIGAN Nef-202 were slightly lower than those from NefIgArd Nef-301, and so the omission of the NEFIGAN Nef-202 results from the CS may have led to a slight overestimation of the efficacy of budesonide.[1] The EAG would therefore like the NEFIGAN Nef-202 results to be incorporated into the final cost effectiveness analysis (CEA), in the form of a synthesis with the current data. This has been deemed a key issue.
- Another budesonide trial (Roy-Chaudhary 2022[16]) was identified by the systematic review. However, this was not mentioned in Table 3.3 as relevant evidence, and its data have not been included as part of the CS [1] evidence. The company were asked why this study was not included, and to include it if appropriate.[2] The company stated that *"as Roy-Chaudhary (2022) [16] is published only as an abstract, limited information was reported about the study methodology and outcomes. Quality assessment of the study using the NICE risk of bias tool checklist revealed some methodological concerns and potential bias (Table 4). Of note, the trial results suggest a ~10.6 mL/min/1.73 m^2 increase in eGFR from baseline following the 9-month treatment with TRF-budesonide, an improvement that is unlikely to be clinically possible and thus also pointing to methodological and bias concerns. In addition, the study included a solely Indian patient population, which may not be comparable (and thus not relevant) to the target primary IgAN population in the UK (…) As such, due to the limited information provided in the abstract, the patient population, and questions pertaining to the methodological concerns and potential bias, Roy-Chaudhary (2022) was not included in the CS"*.[3] The EAG agree that the company's rationale for exclusion was appropriate.

3.2.1.1. NefIgArd trial (part A)

NefIgArd Nef-301 is a multinational, randomised, double-blind, placebo-controlled, multicentre clinical trial (NCT03643965) with a two-part design (Figure 3.1). The aim was to evaluate the efficacy, safety, and tolerability of oral TRF-budesonide 16 mg/day compared with placebo in patients with primary IgAN treated with optimised RAS inhibition therapy. A placebo comparator was selected due to the lack of approved treatments for patients with IgAN at risk of progressing to end-stage renal disease (ESRD).

The methodology of NefIgArd Nef-301 Part A, which constitutes the key evidence supporting this submission, is provided in Table 3.4. The trial included adult patients with primary IgAN, but this submission focuses on the subgroup of adult patients with primary IgAN with a UPCR ≥1.5 g/g, in line with the licensed indication.

Figure 3.1: NefIgArd Nef-301 phase 3 trial design



Based on Figure 11 of the CS[1]

AUC = area under the curve; CS = company submission; eGFR = estimated glomerular filtration rate; R = randomisation; RAS = renin-angiotensin system; SoC = standard of care; TRF = targeted-release formulation; tx = treatment

Table 3.4: Summary of NefIgArd Nef-301 (NCT03643965) Part A methodology

Study	NefIgArd Nef-301 (NCT03643965) Part A
Study objective	The primary objective of Part A of NefIgArd Nef-301 was to assess the effect of TRF-budesonide 16 mg/day treatment on urine UPCR over 9 months compared with placebo.
Trial design	Multinational, randomised, double-blind, placebo-controlled, multicentre clinical trial.
Duration of study	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 5 October 2020; the Part A DCO was scheduled to occur once the first 201 randomised patients had had the opportunity to complete their 9-month visit.

Study	NefIgArd Nef-301 (NCT03643965) Part A
Method of randomisation	Patients were randomised 1:1, using an Interactive Response Technology system, to receive: • TRF-budesonide 16 mg (four 4 mg capsules administered orally OD) • Placebo (four matching capsules administered orally OD) 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).
Method of blinding (care provider, patient, and outcome assessor)	Double-blinded study, i.e., the patients, investigators, and site staff conducting study procedures, evaluating patients, entering study data, and/or evaluating study data were blinded to treatment assignment.
Eligibility criteria for participants	Key inclusion 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 Key exclusion criteria • 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 corticosteroids within the 3 months before randomisation or treated with any systemic corticosteroids within the 12 months before randomisation except for a maximum of three periods of 2 weeks with the equivalent of ≤0.5 mg/kg/day prednisolone for non-IgAN indications. • Treated with immunosuppressive medications within the 12 months before randomisation. • Taking potent inhibitors of cytochrome P450 3A4 • Pregnant, breastfeeding, or unwilling to use highly effective contraception (women of childbearing potential)

Study	NefIgArd Nef-301 (NCT03643965) Part A
	• 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
Settings and locations where the data were collected	NefIgArd Nef-301 is being conducted across 155 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, UK, USA.
Trial drugs (the interventions for each group with sufficient details to allow replication, including how and when they were administered) **Intervention(s) (n=[x]) and comparator(s) (n=[x])**	Study drugs: Patients were assigned to receive: TRF-budesonide 16 mg/day (four 4 mg capsules OD), or matching placebo (four matching capsules OD) administered orally for 9 months during the treatment period (Part A). After completing 9 months of study treatment, the daily dose of study drug was reduced from four capsules OD (TRF-budesonide 16 mg or placebo) to two capsules OD (TRF-budesonide 8 mg or placebo) for 2 weeks to prevent adrenal insufficiency (tapering period in Part A). 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.
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 in any 2-year period for non-IgAN indications, provided no treatment course was greater than 2 weeks and the corticosteroids dose did not exceed the equivalent of 0.5 mg/kg/day prednisolone. • Topical or inhalation products containing corticosteroids or immunosuppressants. Excluded medications: • Systemic immunosuppressive drugs (including corticosteroids), 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 - patients were also instructed to avoid grapefruit and grapefruit juice. • Patients were to avoid starting new medications and making changes to existing medications
Primary outcomes (including scoring methods and timings of assessments)	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, and 12 months to describe the time course of effect.
Other outcomes used in the economic	Ratio of eGFR at 3, 6, 9, and 12 months compared with baseline calculated using the CKD-EPI formula Ratio of UACR at 3, 6, 9, and 12 months compared with baseline

Study	NefIgArd Nef-301 (NCT03643965) Part A
model/specified in the scope	1-year eGFR slope Treatment-emergent adverse events assessed at all visits Adverse events of special interest assessed at all visits SF-36 quality of life assessment at 9 months
Pre-planned subgroups	The pre-defined subgroups for the Part A primary endpoint and eGFR at 9 months were: • Age (<45 years, or ≥45 and <65 years) • Gender (male or female) • Region (Europe or North America) • Baseline proteinuria (<2 g/24 hours or ≥2 g/24 hours) • Baseline eGFR (<60 ml/min/1.73 m^2 or ≥60 ml/min/1.73 m^2) • Dose of RAS inhibitor therapy (ACEis and/or ARBs) with patients split into three groups: <50%, ≥50% to <80% and ≥80% of the maximum allowed dose Subgroup analyses of eGFR according to weight (<85 kg or ≥85 kg) and baseline UPCR (<1.5 g/g or ≥1.5 g/g) were added post hoc.

Based on Table 5 of the CS[1]
† A stable dose was defined as doses within 25% of the dose at randomisation; patients on a stable dose of RAS inhibitor therapy (ACEis and/or ARBs) below the maximum allowed dose or MTD according to the 2012 KDIGO guideline were permitted if an attempt to reach the maximum allowed dose or MTD had been performed or if such attempt was deemed unsafe for the patient by the Investigator.
ACEi = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; CKD-EPI = Chronic Kidney Disease Epidemiology Collaboration equation; CS = company submission; DBP = diastolic blood pressure; DCO = data cut-off; DM = diabetes mellitus; eGFR = estimated glomerular filtration rate; GI = gastrointestinal; IgA = immunoglobulin A; IgAN = immunoglobulin A nephropathy; KDIGO = Kidney Disease Improving Global Outcomes; MTD = maximum tolerated dose; OD = once daily; SBP = systolic blood pressure; SF-36 = short-form 36; TRF = targeted-release formulation; UACR = urine albumin to creatinine ratio; UK = United Kingdom; UPCR = urine protein to creatinine ratio; USA = United States of America; UTI = urinary tract infection

EAG comment:

- One inclusion criterion was receiving a stable dose of RAS inhibitor therapy (ACEi and/or ARB) at the maximum allowed dose or maximum tolerated dose (MTD) according to the 2012 KDIGO guideline for 3 months prior to randomisation. However, in Table 3.4, it appears that not all participants were on RASi therapy (only 70/78 on either ACEi or ARB). The company were asked to clarify this apparent anomaly.[2] The company stated that *"patients who could not tolerate RAS blockade therapy were considered in the study, in line with anticipated use in clinical practice. In the SAS, which included patients with UPCR ≥1.5 g/g at baseline, there were 4 patients randomised to TRF-budesonide 16 mg/day and two patients randomised to placebo who were not on RAS inhibitor therapy (ACEIs and/or ARBs) at baseline. In the TRF-budesonide 16 mg/day arm, 1 patient was on a combination product that included perindopril (an ACEI), and 1 patient was allergic to ACEIs and ARBs. The reason was not documented for the remaining 2 patients. In the placebo group, 1 patient was on a combination product that included telmisartan (an ARB), and 1 patient could not tolerate RAS therapy. With regard to the NefIgArd Nef-301 Part A study population with UPCR ≥1.5 g/g at baseline, a total of 3 of 73 patients (1 patient in the TRF-budesonide 16 mg/day arm and 2 patients in the placebo arm) were reported to not be receiving either ACEi or ARB at baseline. No summary of the reasons for this is available specifically for patients with a baseline UPCR ≥1.5 g/g"*.[3] Whilst this might at first sight appear to be a deviation

from the study exclusion criterion, it should be remembered that the licence stipulation of patients being on a maximally-tolerated dose of RAS inhibitors can include a dose of zero if any dose at all is not tolerated.

- People with an eGFR of <35 ml/min/1.73 m^2 were excluded. An eGFR of 30-44 ml/min/1.73 m^2 is generally regarded as 'moderate kidney function', and although a value of 15-29 indicates severe kidney damage, the patient may not necessarily be at a stage where participation in a trial would be impossible. The rationale for the exclusion of the entire group of people with an eGFR of <35 ml/min/1.73 m^2 was therefore unclear. If a patient group is excluded from the evidence, this makes it difficult to extend any recommendations to that excluded group and so the unexplained exclusion of patients with an eGFR of <35 ml/min/1.73 m^2 required justification. The company were asked to explain this exclusion criterion, the proportion of patients who are likely to have an eGFR of <35 ml/min/1.73 m^2, and the treatment pathway available to those with an eGFR of <35 ml/min/1.73 m^2.[2] The company stated that *"the KDIGO 2021 guidelines indicate that severe loss of kidney function (to an eGFR <20–30 mL/min per 1.73 m2), referred to as a 'point of no return', may be accompanied by such extensive and irreversible kidney injury (primarily interstitial fibrosis and tubular atrophy, and/or bilateral renal atrophy) that any therapeutic strategy being tested cannot reasonably be expected to alter the natural history of progressive deterioration in kidney function (therapeutic futility). The presumption is that such patients should be excluded from clinical trials since they are expected to be "non-responders," and therefore may dilute any treatment effect and adversely affect the power of the study. Furthermore, these subjects with reduced kidney function may be at higher risk of adverse effects of the therapies being tested. Of note, the KDIGO 2021 guidelines highlight that there is no clear definition for this 'point of no return' and recommend maximal supportive care among patients with an eGFR of <30 mL/min/1.73 m2, directed at avoidance of non-kidney complications such as coronary artery disease, stroke, and congestive heart failure. As such, patients with an eGFR of <35 mL/min/1.73 m2 were not considered for inclusion in the NefIgArd Nef-301 trial to prevent diluting any treatment effect and adversely affecting the power of the study. The findings of the UK RaDaR study, the largest IgAN retrospective cohort study (which enrolled patients with a biopsy-proven diagnosis of IgAN, plus proteinuria >0.5 g/day or eGFR <60 mL/min/1.73 m2) suggest that ~21.4% of patients have an eGFR ≤30 mL/min/1.73 m2 (CKD stages 4 and 5 at diagnosis) (23). In a subgroup analysis of patients with a UPCR of >1.5 g/g within the RaDaR cohort,* [redacted] *of patients had an eGFR ≤30 mL/min/1.73 m2 (CKD stages 4 and 5 at diagnosis). In line with current treatment guidelines, patients with IgAN with an eGFR of ≤30 mL/min/1.73 m2 should be offered maximal supportive care. Patients who remain at high risk of progressive CKD despite maximal supportive care should be offered the opportunity to participate in a clinical trial".*[3] The EAG think that [redacted] of patients with an eGFR of ≤30 ml/min/1.73 m^2 in the population of people with UPCR >1.5 g/g is significant, given the lack of treatment options available for that group. It should be further noted that there will be even more people in the excluded group with eGFR of ≤35 ml/min/1.73 m^2. Although it is assumed by the company that this group will not respond to treatment, this is an untested assumption, and inclusion of this group in the trial, where clinically indicated, would allow an evidence-based recommendation to be made for this group. Finally, it appears somewhat incoherent for the company to suggest that a possible treatment option for this group is participation in a clinical trial when that same group was denied entry into the current clinical trial. This is therefore a key issue.

3.2.2 Statistical analysis of the included trials

3.2.2.1 Analysis sets

The following analysis sets were defined for the NefIgArd Nef-301 study Part A:

- The Part A full analysis set (FAS, n=197), which included all patients who had received at least one dose of study drug, provided an evaluation of efficacy and safety in a population of patients who had the opportunity to receive the full 9-month treatment regimen.
- The Part A safety analysis set (SAS, n=294), which included all randomised patients who had received at least one dose of study drug as of the data cut-off (DCO), was presented for completeness.
- The Part A per protocol set included all data from patients in the FAS for whom no protocol deviations occurred during the study period that were considered to have the potential to impact the efficacy evaluation. The Part A per protocol set was determined through blinded review prior to Part A database lock.

The evaluation of the efficacy of TRF-budesonide in patients with a baseline UPCR of ≥1.5 g/g was a subgroup analysis in the NefIgArd Nef-301 study. The TRF-budesonide indication is for the treatment of adult patients with primary IgAN at risk of rapid disease progression with a UPCR ≥1.5 g/g, the results for this patient population are presented in the main body of this submission.

In all efficacy analyses, any data impacted by rescue medication were excluded.

3.2.2.2 Statistical analysis

Based on the NefIgArd NEF-202 study (phase 2b, double-blind, RCT), 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 predefined 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%.

EAG comment:

- Labelling the trial as a 'superiority' trial does not automatically mean that the study results can only go in one direction, and that a one-tailed test is therefore justified. The term 'superiority trial' reflects the alternative *hypothesis* that the intervention is superior, but this is merely a conjecture, and does not mean that the intervention is definitely superior. Indeed, if it were certain that the intervention was definitely superior to the placebo, then randomly assigning people to the placebo group would be unethical, and an RCT should not have taken place. Given that the trial is ethical, there must therefore be some uncertainty about the trial result, and so it is still possible for results to go in either direction. This means that a 2-sided test is more appropriate, and the incorrect use of a 1-sided test will increase the risk of type I errors. However, the company has alleviated this risk by setting alpha to 0.025 (rather than the standard 0.05). The EAG therefore see no practical problems with this approach but point it out to the committee in case there is any discomfiture at the company's unconventional use of a one-tailed test.
  All statistical analyses were performed in SAS™. All efficacy endpoints, apart from eGFR 1-year slope, were log-transformed prior to analysis. Urine protein to creatinine ratio and UACR were

analysed using a mixed-effect model for repeated measures, including baseline, 3-, 6-, 9-, and 12-month data. Baseline UPCR was included as a covariate and was calculated as the geometric mean of the 2 pre-randomisation UPCR measurements and log-transformed prior to inclusion in the analysis model. The model also included terms for treatment group, visit, log(baseline)-by-visit, and visit-by-treatment group interaction. A common unstructured covariance structure was used to model the within-patient errors. The Kenward-Roger's degrees of freedom adjustment was used. Restricted maximum likelihood was used to obtain parameter estimates.

Estimated glomerular filtration rate analyses at 9 and 12 months were performed using robust regression with Huber weights and a cut-off value of 2 with sequentially multiply imputed missing data. The imputation model for eGFR included treatment, baseline eGFR, and the 3, 6, 9, and 12-month eGFR values.

3.2.2.3 Sample size and power calculation

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. 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.

3.2.2.4 Sensitivity analyses and other supportive analyses

No sensitivity analyses were performed for the sub population with a baseline UPCR ≥1.5 g/g, which is the focus of this submission.

3.2.2.5 Data management and 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 was documented in the electronic case report form. If a patient withdrew prematurely from the study, study staff were to make every effort to complete an Early Termination Visit if the patient discontinued prior to completion of Study Visit 11, or an End of Study Visit if the patient discontinued after completion of Study Visit 11 but prior to completion of Part B.

For continuous endpoints to be analysed using the Mixed-Effects Model for Repeated Measures (MMRM), no explicit imputation of missing data was needed, as the MMRM analysis was performed on observed cases and implicitly imputes missing data.

3.2.2.6 Participant flow in the relevant randomised controlled trials

In total, of patients with a baseline UPCR of ≥1.5 g/g, 35 treated with TRF-budesonide and 38 treated with placebo completed the 9-month treatment period and 3-month follow-up period. For further details, please refer to Appendix M.[11]

EAG comment:

- Only 73 participants were included in the data presented in the CS.[1] This is partly because the sample was appropriately restricted to those people who had a UPCR of ≥1.5 g/g, in line with the decision problem. In addition, the wording of the CS suggested that the sample were also restricted to those who had *completed* the full 9 months of treatment, which would make the risk of attrition bias very serious.[1] However, the company clarified that the sample was definitely not restricted to

patients who had *completed* the full nine months of treatment; instead, the reference to 9 months of treatment merely indicated that the patients were assigned to the 9-month treatment, but were not required to complete it. Therefore, the original EAG concerns about attrition bias are allayed.

3.2.3 Baseline characteristics in the included trials

The CS[1] states that characteristics were balanced between groups. Baseline characteristics are summarised in Table 3.5.

Table 3.5: Baseline characteristics of patients with UPCR ≥1.5 g/g at baseline in NefIgArd Nef-301 Part A

Characteristic	TRF-budesonide 16 mg (n=[redacted])	Placebo (n=[redacted])	Total (n=[redacted]
Median age (range), years	[redacted]	[redacted]	[redacted]
Age distribution, n (%)			
<45 years	[redacted]	[redacted]	[redacted]
≥45 and <65 years	[redacted]	[redacted]	[redacted]
≥65 years	[redacted]	[redacted]	[redacted]
Sex, n (%)			
Male	[redacted]	[redacted]	[redacted]
Female	[redacted]	[redacted]	[redacted]
Childbearing potential (female only), n (%)			
n[†]	[redacted]	[redacted]	[redacted]
Yes	[redacted]	[redacted]	[redacted]
No	[redacted]	[redacted]	[redacted]
Race, n (%)			
White	[redacted]	[redacted]	[redacted]
Asian	[redacted]	[redacted]	[redacted]
Black or African American	[redacted]	[redacted]	[redacted]
Other	[redacted]	[redacted]	[redacted]
Weight, kg			
Median (IQR)	[redacted]	[redacted]	[redacted]
Min, max	[redacted]	[redacted]	[redacted]
BMI, kg/m^2			
Median (IQR)	[redacted]	[redacted]	[redacted]
Min, max	[redacted]	[redacted]	[redacted]
SBP, mmHg			
Median (IQR)	[redacted]	[redacted]	[redacted]
Min, max	[redacted]	[redacted]	[redacted]

Characteristic	TRF-budesonide 16 mg (n=[redacted])	Placebo (n=[redacted])	Total (n=[redacted]
DBP, mmHg			
Median (IQR)	[redacted]	[redacted]	[redacted]
Min, max	[redacted]	[redacted]	[redacted]
Proteinuria (UPCR or UACR)			
UPCR (g/g), median (IQR)	[redacted]	[redacted]	[redacted]
UACR (g/g), median (IQR)	[redacted]	[redacted]	[redacted]
Proteinuria (quantities)			
Proteinuria, g/day, median (IQR)	[redacted]	[redacted]	[redacted]
<2 g/day	[redacted]	[redacted]	[redacted]
≥2 and ≤3.5 g/day	[redacted]	[redacted]	[redacted]
>3.5 g/day	[redacted]	[redacted]	[redacted]
eGFR (CKD-EPI), ml/min/1.73 m^2			
eGFR (CKD-EPI), ml/min/1.73 m^2, median (IQR)	[redacted]	[redacted]	[redacted]
Time from IgAN diagnosis to trial entry, years			
n†	[redacted]	[redacted]	[redacted]
Median (IQR)	[redacted]	[redacted]	[redacted]
Prior corticosteroids or immunosuppressive use			
Patients with prior corticosteroids or immunosuppressive use, n (%)	[redacted]	[redacted]	[redacted]
Use of any RAS inhibitor therapy, n (%)			
Patients on either ACEi or ARB	[redacted]	[redacted]	[redacted]
Patients on ACEi alone	[redacted]	[redacted]	[redacted]
Patients on ARB alone	[redacted]	[redacted]	[redacted]
Patients on both ACEi and ARB	[redacted]	[redacted]	[redacted]

Based on Table 6 of the CS[1]
† Number of participants recorded if different from the full sets for the subgroup.
Baseline was defined as the last measurement prior to the first dose of study drug. Baseline for SBP and DBP was defined as the arithmetic mean of all measurements prior to the first dose of study drug. Baseline proteinuria and eGFR, were calculated as the geometric mean of the two consecutive measurements prior to randomisation.

Characteristic	TRF-budesonide 16 mg (n=[redacted])	Placebo (n=[redacted])	Total (n=[redacted]
ACEi = angiotensin-converting enzyme inhibitor; ARB = angiotensin II type I receptor blocker; BMI = body-mass index; CKD-EPI = Chronic Kidney Disease Epidemiology Collaboration equation; CS = company submission; DBP = diastolic blood pressure; eGFR = estimated glomerular filtration rate; IgAN = immunoglobulin A nephropathy; IQR = interquartile range; Max = maximum; Min = minimum; RAS = renin-angiotensin system; SBP = systolic blood pressure; TRF = targeted-release formulation; UACR = urine albumin to creatinine ratio; UPCR = urine albumin to creatinine ratio			

EAG comment:

- Despite the claim of balanced groups, there were noticeable differences in age, with the placebo group tending to be younger. More in the placebo group had worse baseline proteinemia, although baseline eGFR values were similar. Time from diagnosis to inclusion was also longer in the placebo group. Usage of ACEi and ARBs between groups was different.
- Although the placebo group will have been favoured by younger age, they may have been disadvantaged by worse baseline proteinemia, and a longer time to inclusion. Overall, then, it is possible that baseline differences may have conferred a relative advantage to the budesonide group.
- The company were therefore asked to justify the statement that the arms of the trial were comparable.[2] The company stated that *"in general, there were minimal differences between treatment arms in the baseline characteristics and those reported are likely a result of random variation that can take place in small sample sizes. Feedback from the experts suggested that the differences in age and time from diagnosis observed between the two groups are unlikely to have influenced the effects in the trial…..In addition, although there were some small imbalances in the percentages of patients on ACEIs or ARBs between treatment groups, overall RAS inhibition was similar, with the majority of patients receiving at least 50% of the maximum allowed dose ([redacted] in the TRF-budesonide group vs [redacted] in the placebo group). In addition, the blood pressure control was similar between the two groups further indicating that any differences in the usage of RAS inhibitors is unlikely to have influenced the effects in the trial"*.[3] The EAG notes that although the company refers to expert opinion on the prognostic effects of age and time from diagnosis, the company does not refer to expert opinion on the possible effects of the differing baseline proteinemia. Although the EAG agrees that such baseline differences were probably random (secondary to a small sample size) this does not stop the difference in baseline proteinuria having some effect on outcome. Therefore, this is a key issue. Please see Section 2.3 for further discussion about threats to internal validity resulting from differences in SoC across arms.

3.2.4 Risk of bias in the included trials

A quality assessment of NefIgArd Nef-301 in accordance with the NICE-recommended checklist for the assessment of bias in RCTs was carried out by the company (Table 3.6). The risk of bias in the NefIgArd Nef-301 study was described as being low.

Table 3.6: Quality assessment results for NefIgArd Nef-301

Trial name	NefIgArd Nef-301
Was randomisation carried out appropriately?	Yes
Was the concealment of treatment allocation adequate?	Unclear
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes

Trial name	NefIgArd Nef-301
Were the care providers, participants and outcome assessors blind to treatment allocation?	Yes
Were there any unexpected imbalances in drop-outs 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
Based on Table 7 of the CS.[1] Adapted from Systematic reviews: CRD's guidance for undertaking reviews in health care (University of York Centre for Reviews and Dissemination). CRD = Centre for Reviews and Dissemination; CS = company submission	

EAG comment:

- The unclear allocation concealment creates a high risk of selection bias that was not acknowledged by the CS.[1] Therefore, the overall risk of bias of the trial should not be regarded as low.

3.2.5 Efficacy results in the included trials

3.2.5.1 Proteinuria

3.2.5.1.1 Change in UPCR from baseline

After 9 months of treatment, the ratio of UPCR compared with baseline was [redacted] for patients with a baseline UPCR ≥1.5 g/g treated with TRF-budesonide 16 mg/day and [redacted] for those who received placebo (Table 3.7). This equated to a [redacted]% reduction in UPCR for patients treated with TRF-budesonide 16 mg/day compared with placebo (95% CI: [redacted]; p = [redacted]).

A reduction of UPCR from baseline with TRF-budesonide 16 mg/day was seen at all timepoints, including during 3-months of untreated follow-up (Table 3.8). At the 12-month timepoint (after 3 months of observational follow-up following the 9-month treatment period), UPCR was [redacted]% lower with TRF-budesonide 16 mg/day compared with placebo (95% CI: [redacted]; p = [redacted]).

EAG comment:

- The company claims that the relative 35% reduction in UPCR is 'clinically relevant'. This claim is not made with reference to any evidence-based minimum important differences. The company was therefore asked to justify their statement that the effect is clinically relevant.[2] In response to the request for clarification, the company stated that *"a percentage decline in proteinuria or albuminuria of >30% has been shown to be predictive of protection from progression to kidney failure, endorsed by the 2021 KDIGO guidelines and the workshop sponsored by the National Kidney Foundation in collaboration with the FDA and EMA"*.[3] The EAG is satisfied that this response supports the claim of a clinically relevant change.

Table 3.7: Analysis of the UPCR (g/g) at 9 months compared with baseline in patients with a baseline UPCR ≥1.5 g/g in NefIgArd Nef-301 Part A

	TRF-budesonide 16 mg/day† n=[redacted]	Placebo† n=[redacted]
Ratio of geometric LS mean UPCR at 9 months compared with baseline (95% CI)	[redacted]	[redacted]
Corresponding % reduction (95% CI)	[redacted]	[redacted]
TRF-budesonide versus placebo		
Ratio of geometric LS mean UPCR at 9 months compared with baseline (95% CI)	[redacted]	
Corresponding % reduction (95% CI)	[redacted]	
P value	[redacted]	

Based on Table 8 of the CS[1]
† Treatment in addition to RAS inhibition.
CI = confidence interval; CS = company submission; LS = least squares; RAS = renin-angiotensin system; TRF = targeted-release formulation; UPCR = urine protein to creatinine ratio

Table 3.8: Analysis of UPCR (g/g) at 3, 6, 9, and 12 months using MMRM for patients with a baseline UPCR ≥1.5 g/g in NefIgArd Nef-301 Part A

Timescale	Ratio of geometric LS mean UPCR compared with baseline (95% CI)		Comparison of TRF-budesonide 16 mg/day† vs placebo†; ratio of geometric LS means (95% CI); p value	Corresponding % change‡
	TRF-budesonide (n=[redacted])	Placebo (n=[redacted])		
3 months	[redacted]	[redacted]	[redacted]	[redacted]
6 months	[redacted]	[redacted]	[redacted]	[redacted]
9 months	[redacted]	[redacted]	[redacted]	[redacted]
12 months	[redacted]	[redacted]	[redacted]	[redacted]

Based on Table 9 of the CS[1]
† Treatment in addition to RAS inhibition.
‡ Calculated as (1 – ratio) of LS means * 100.
CI = confidence interval; CS = company submission; LS = least squares; MMRM = mixed-effects model for repeated measures; RAS = renin-angiotensin system; TRF = targeted-release formulation; UPCR = urine protein to creatinine ratio

3.2.5.1.2 Change in UACR from baseline

Urine albumin to creatinine ratio, like UPCR, is a measure of proteinuria - a surrogate endpoint for improved outcomes in IgAN. Consistent with the primary endpoint, after 9 months of treatment, patients with a baseline UPCR ≥1.5 g/g treated with TRF-budesonide 16 mg per day showed a [redacted] reduction in UACR compared with placebo (95% CI: [redacted]; p = [redacted]; Table 3.9). After 3 months of observational follow-up, a [redacted]% reduction in UACR with TRF-budesonide 16 mg was observed at 1 year compared with placebo (p = [redacted]).

EAG comment:

- The company claims that the relative 31% reduction in UACR is 'clinically relevant'. This claim is not made with reference to any evidence-based minimum important differences. The company was therefore asked to justify their statement that the effect is clinically relevant.[2] The company stated that, "*A percentage decline in proteinuria or albuminuria of >30% has been shown to be predictive of protection from progression to kidney failure, endorsed by the 2021 KDIGO guidelines and the workshop sponsored by the National Kidney Foundation in collaboration with the FDA and EMA.*". [3] The EAG is satisfied that this response supports the claim of a clinically relevant change.

Table 3.9: Analysis of UACR (g/g) at 3, 6, 9, and 12 months compared with baseline using MMRM in patients with a baseline UPCR ≥1.5 g/g in NefIgArd Nef-301 Part A

Timescale	Ratio of geometric LS mean UACR at 9 months compared with baseline (95% CI)		Comparison of TRF-budesonide 16 mg/day† vs placebo†; ratio of geometric LS means (95% CI); p value	Corresponding % change‡
	TRF-budesonide (n=[redacted])	Placebo (n=[redacted])		
3 months	[redacted]	[redacted]	[redacted]	[redacted]
6 months	[redacted]	[redacted]	[redacted]	[redacted]
9 months	[redacted]	[redacted]	[redacted]	[redacted]
12 months	[redacted]	[redacted]	[redacted]	[redacted]

Based on Table 10 of the CS[1]
† Treatment in addition to RAS inhibition.
‡ Calculated as (1 – ratio) of LS means * 100.
CI = confidence interval; CS = company submission; LS = least squares; MMRM = mixed-effects model for repeated measures; TRF = targeted-release formulation; UACR = urine albumin to creatinine ratio; UPCR = urine protein to creatinine ratio

3.2.5.2 Kidney function (eGFR)

3.2.5.2.1 Ratio of eGFR compared with baseline

After 9 months of treatment, a benefit on eGFR was observed with TRF-budesonide 16 mg/day compared with placebo for patients with a baseline UPCR of ≥1.5 g/g (Table 3.10).

The eGFR treatment benefit for TRF-budesonide 16 mg/day versus placebo continued after 3 months of non-treated follow-up; the estimated difference in absolute change in eGFR from baseline for TRF-budesonide versus placebo was [redacted] ml/min/1.73 m^2 at the 12-month timepoint (Table 3.11).

EAG comment:

- The company claims that the group difference favouring budesonide the change from baseline in eGFR is 'clinically-relevant'. This claim is not made with reference to any evidence-based minimum important differences. The company was therefore asked to justify their statement that the effect is clinically relevant.[2] In response to the request for clarification, the company stated that *"a percentage decline in proteinuria or albuminuria of >30% has been shown to be predictive of protection from progression to kidney failure, endorsed by the 2021 KDIGO guidelines and the workshop sponsored by the National Kidney Foundation in collaboration with the FDA and EMA.*

....In addition, reductions in eGFR are considered by regulatory authorities and clinical experts in England to be an acceptable surrogate outcome measure for kidney failure in clinical trials. It is suggested that, based on eGFR and age at diagnosis, almost all patients are at risk of progression to kidney failure within their expected lifetime unless a rate of eGFR loss ≤1 mL/min/1.73 m2/year can be maintained. The findings of Part A of the NefIgArd Nef-301 trial indicate a [redacted] mL/min/1.73 m^2 absolute change in eGFR from baseline following the 9-month treatment with TRF-budesonide (vs [redacted] mL/min/1.73 m2 in the placebo arm), further indicating a reduction in the risk of progression to kidney failure".[3] The EAG is satisfied that this response supports the claim of a clinically relevant change.

Table 3.10: Analysis of the ratio of eGFR (ml/min/1.73 m^2) at 9 months in patients with a baseline UPCR ≥1.5 g/g in NefIgArd Nef-301 Part A

	TRF-budesonide 16 mg/day† n=[redacted]	Placebo† n=[redacted]
Ratio of geometric LS mean eGFR at 9 months compared with baseline (95% CI)	[redacted]	[redacted]
Corresponding % change (95% CI)	[redacted]	[redacted]
Estimated absolute change from baseline (ml/min/1.73 m^2)	[redacted]	[redacted]
TRF-budesonide vs placebo		
Ratio of geometric LS mean eGFR at 9 months compared with baseline (95% CI)	[redacted]	
p value	[redacted]	
Estimated difference in absolute change (ml/min/1.73 m^2)	[redacted]	

Based on Table 11 of the CS[1]
† Treatment in addition to RAS inhibition.
CI = confidence interval; CS = company submission; eGFR = estimated glomerular filtration rate; LS = least squares; RAS = renin-angiotensin system; TRF = targeted-release formulation; UPCR = urine protein to creatinine ratio

Table 3.11: Analysis of the ratio of eGFR (CKD-EPI) (ml/min/1.73 m^2) at 3, 6, 9, and 12 months compared with placebo using robust regression in patients with a baseline UPCR ≥1.5 g/g in NefIgArd Nef-301 Part A

Time-point	Comparison of TRF-budesonide 16 mg/day† versus placebo†		
	Ratio of geometric LS means (95% CI); p value	Corresponding % change‡	Difference in absolute change (ml/min/1.73 m^2)
3 months	[redacted]	[redacted]	[redacted]
6 months	[redacted]	[redacted]	[redacted]
9 months	[redacted]	[redacted]	[redacted]
12 months	[redacted]	[redacted]	[redacted]

Based on Table 12, CS.[1]
† Treatment in addition to RAS inhibition; ‡ Calculated as (1 – ratio) of LS means * 100.
CI = confidence interval; CKD-EPI = Chronic Kidney Disease Epidemiology Collaboration; CS = company submission; eGFR = estimated glomerular filtration rate; LS = least squares; RAS = renin-angiotensin system; TRF = targeted-release formulation; UPCR = urine protein to creatinine ratio

3.2.5.2.2 Decline in eGFR at 1-year eGFR (total slope)

The results of the supportive analysis of 1-year eGFR total slope for patients with baseline UPCR ≥1.5 g/g are presented in Table 3.12. Treatment with TRF-budesonide 16 mg/day provided an improvement in slope of [redacted] ml/min/1.73 m^2 per year compared with placebo (95% CI: [redacted]; P=[redacted]).

Table 3.12: Supportive analysis of 1-year eGFR (CKD-EPI) (ml/min/1.73 m^2 per year) total slope for the of patients with baseline UPCR ≥1.5 g/g

1-year eGFR slope	TRF-budesonide 16 mg/day† n=[redacted]	Placebo† n=[redacted]
LS mean	[redacted]	[redacted]
95% CI LS mean	[redacted]	[redacted]
TRF-budesonide versus placebo		
Difference in LS means versus placebo	[redacted]	
95% CI difference in LS means versus placebo	[redacted]	
p value versus placebo	[redacted]	

Based on Table 13 of the CS[1]
† Treatment in addition to RAS inhibition.
CI = confidence interval; CKD-EPI = Chronic Kidney Disease Epidemiology Collaboration; CS = company submission; eGFR = estimated glomerular filtration rate; LS = least squares; RAS = renin-angiotensin system; TRF = targeted-release formulation; UPCR = urine protein to creatinine ratio

3.2.5.3 Disease progression (dialysis and/or transplant)

No data were provided for this outcome.

EAG comment:

- It was unclear why this important and patient-related outcome was not reported, and so the company were asked to provide a rationale.[2] In response to the request for clarification, the company stated that *"assessing the efficacy of treatments for IgAN is complicated by the long-term nature of disease progression in the majority of patients. The evaluation of treatment efficacy therefore relies on the use of surrogate endpoints. In NefIgArd Nef-301, data for proteinuria (UPCR and UACR) as well as eGFR were collated as surrogate endpoints for disease progression. Reductions in proteinuria (assessed by measuring proteinuria over 24 hours, UPCR, and/or UACR) are accepted as a surrogate endpoint for improved outcomes in IgAN by KDIGO, the European Medicines Agency, and clinical experts in England. 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,[19] and are discussed in further detail in Section B2.3.2 of the CS. Similarly, reductions in eGFR from baseline over a 2- to 3-year period is considered by regulatory authorities and clinical experts in England to be an acceptable surrogate outcome measure for kidney failure in clinical trials, also discussed in further detail in Section B2.3.2 of the CS. A further meta-analysis of 13 IgAN clinical trials found a treatment effect on 1-year eGFR slope to be a major, independent predictor of treatment effect on long-term clinical outcomes in IgAN, supporting its use as a surrogate endpoint. The study reported that a sustained effect on eGFR slope provided a clear indication of a disease-modifying treatment effect. The NefIgArd Nef-301 Part A study has shown that 9 months of treatment with TRF-budesonide, in addition to optimised and stable RAS blockade, was well tolerated and resulted in clinically-important*

improvements in UPCR, UACR, and eGFR, compared with optimised supportive care alone (for the full data, please refer to Section 2.6.1 of the CS). As changes in proteinuria (UPCR and UACR) and eGFR can be used as surrogate endpoints for progression to ESRD and mortality in patients with CKD, the improvements observed to date in patients treated with TRF-budesonide provide support for a disease-modifying treatment effect which may delay progression to ESRD in patients with IgAN. In addition, preliminary data analyses from Part B of NefIgArd Nef-301 demonstrate a statistically significant benefit in eGFR for TRF-budesonide compared with placebo (p<0.0001) over the 2-year study period. Supportive analyses of the 2-year eGFR slope also demonstrated a statistically significant and clinically meaningful treatment benefit".[3] The EAG accept the points about surrogate endpoints, but still question why disease progression, a highly patient-relevant outcome that was named in the NICE scope, was not included. Although the follow-up was short, there may still have been some patients with disease progression that could have been captured. The company's assumption that these events would not have happened is difficult to justify. Therefore, this is a key issue.

3.2.5.4 Mortality

No deaths were reported in either arm (see AEs in Section 3.2.6).

3.2.5.5 Health-related quality of life

No improvements in HRQoL, assessed using the short-form 36 (SF-36) tool, were observed in either the TRF-budesonide or placebo groups following the 9-month treatment period, when compared with baseline (Table 3.13). The company stresses that the SF-36 is a generic HRQoL measure without any domains specific to kidney disease, as opposed to a tool specific to people with kidney disease, which may be more sensitive to potential changes in response to therapy. It is also implied that longer-term studies might indicate more decisive results.

EAG comment:

- 'Generic' HRQoL measures are designed to measure HRQoL and have been shown to be valid in this respect. Although they may not directly measure issues related to kidney health, they are designed to be sensitive to the effects of any disease process, regardless of the source, on overall quality of life (QoL).
- Despite the company's criticism of the Short-Form 36 version 2 (SF-36v2) as an appropriate tool, the company made a pre-hoc decision to use the SF-36v2 to measure HRQoL for this research study, rather than a disease-specific tool. The EAG wonder if the company would have dismissed the results of the SF-36v2 so readily had the results supported budesonide. The company's failure to accept the results of the outcome that had been chosen *pre-hoc* indicates possible bias. The company were asked why SF-36v2, and not a disease-specific tool, was measured if this was not deemed appropriate.[2] The company did not respond to the question in a way that fully justified the use of a tool that had been regarded as insensitive by the company pre-hoc, but instead stated that disease specific tools had not been used in the exact context before. The company also reiterated that QoL measures might not be able to pick up any changes at such an early follow-up. Given that QoL is the key outcome for establishing cost effectiveness, the EAG is concerned that no differences between arms were detected at the available follow-up. The technology needs to be judged on the available evidence, and although some QoL benefits may become apparent at a later follow-up, these cannot be assumed.
- The company's implication that longer-term follow up might be better at indicating QoL benefits is undoubtedly true. However, this reinforces the EAG's opinion that utilisation of short-term

outcomes as the only evidence in a single technology appraisal (STA) is inappropriate. See Section 2.4 for more discussion of this key issue.

Table 3.13: Analysis summary of SF-36v2 scores for the of patients with baseline UPCR ≥1.5 g/g

Subscale		TRF-budesonide 16 mg/day† (n=[redacted])	Placebo† (n=[redacted])
Bodily Pain	Baseline, mean (SD)	[redacted]	[redacted]
	Month 9, mean (SD)	[redacted]	[redacted]
	Change from baseline, mean (SD)	[redacted]	[redacted]
General Health	Baseline, mean (SD)	[redacted]	[redacted]
	Month 9, mean (SD)	[redacted]	[redacted]
	Change from baseline, mean (SD)	[redacted]	[redacted]
Mental Health Summary Measure	Baseline, mean (SD)	[redacted]	[redacted]
	Month 9, mean (SD)	[redacted]	[redacted]
	Change from baseline, mean (SD)	[redacted]	[redacted]
Mental Health Norm-Based Score	Baseline, mean (SD)	[redacted]	[redacted]
	Month 9, mean (SD)	[redacted]	[redacted]
	Change from baseline, mean (SD)	[redacted]	[redacted]
Physical Health Summary Measure	Baseline, mean (SD)	[redacted]	[redacted]
	Month 9, mean (SD)	[redacted]	[redacted]
	Change from baseline, mean (SD)	[redacted]	[redacted]
Physical Function	Baseline, mean (SD)	[redacted]	[redacted]
	Month 9, mean (SD)	[redacted]	[redacted]
	Change from baseline, mean (SD)	[redacted]	[redacted]
Role-Emotional	Baseline, mean (SD)	[redacted]	[redacted]
	Month 9, mean (SD)	[redacted]	[redacted]
	Change from baseline, mean (SD)	[redacted]	[redacted]
Role-Physical	Baseline, mean (SD)	[redacted]	[redacted]
	Month 9, mean (SD)	[redacted]	[redacted]

Subscale		TRF-budesonide 16 mg/day† (n=[redacted])	Placebo† (n=[redacted])
	Change from baseline, mean (SD)	[redacted]	[redacted]
Social Function	Baseline, mean (SD)	[redacted]	[redacted]
	Month 9, mean (SD)	[redacted]	[redacted]
	Change from baseline, mean (SD)	[redacted]	[redacted]
Vitality	Baseline, mean (SD)	[redacted]	[redacted]
	Month 9, mean (SD)	[redacted]	[redacted]
	Change from baseline, mean (SD)	[redacted]	[redacted]

Based on Table 14 of the CS[1]
† Treatment in addition to RAS inhibition.
CS = company submission; RAS = renin-angiotensin system; SD = standard deviation; SF-36v2 = Short-Form 36 version 2; UPCR = urine protein to creatinine ratio

3.2.5.6 Sub-grouping

No sub-grouping was carried out for the data presented in the CS.[1]

EAG comment:

- It is important to know if the characteristics of participants in the trial differ from the characteristics of the UK target population, and how any such differences may affect outcome. This is in order that an evaluation of the representativeness of trial results to the target population can be made. Therefore, the company were asked [2] to provide relevant characteristics of the UK target population, such as mean age, gender ratios, baseline levels of proteinuria and eGFR, and the mean dose of RASi. They were also asked to conduct sub-group analyses of the trial study sample (those with a UPCR ≥1.5 g/g) for the characteristics listed above.[2] In response to the request for clarification, the company stated that *"the demographic and disease characteristics of the trial population broadly reflect the characteristics of the UK target population, as confirmed by UK clinical expert opinion"*.[3] However, this statement is not supported by the evidence presented by the company from the UK National Registry of Rare Kidney Diseases (RaDaR) study, where there was a lack of detail in important variables. For example, although the proportion of white patients in the UK target population (77%) was reasonably close to that in the trial ([redacted]), no information of the proportions of other ethnicities were given. In addition, the male proportion in the UK population (71%) appeared larger than that in the trial ([redacted]). Finally, only a small number of variables are compared. Given the possibility, therefore, of some differences in ethnicity and other variables between target and trial populations, it is important to establish if any such variables have the capacity to alter outcomes. Unfortunately, the company did not perform a subgroup analysis as requested: restricted to the patient stratum in the trial relevant to the submission (those with UPCR >1.5g/g). Therefore, it remains unclear whether any potential differences between target and trial population could have led to different outcomes, which prohibits the exclusion of applicability issues. Whilst the company did use UPCR levels as a subgrouping strategy, it should be noted that this functioned as an independent stratification of the overall dataset (those with an unrestricted UPCR level), which is not the same as performing subgroup analyses relating to a range of relevant variables within the >1.5 g/g stratum itself. This is a key issue. Please see Section 2.3 for further discussion of applicability (relating to SoC).

3.2.6 Adverse events in the included trials

3.2.6.1 Overview of safety in NefIgArd Nef-301

Overall, the 9-month treatment regimen of TRF-budesonide was well tolerated. Of the patients with a baseline UPCR ≥1.5 g/g, [redacted] of [redacted] ([redacted]%) patients in the TRF-budesonide 16 mg/day group and [redacted] of [redacted]%) patients in the placebo group reported treatment-emergent adverse events (TEAEs), up until 14 days after the last dose of study treatment (Table 3.14). The TEAE incidence rates were slightly lower in the SAS with baseline UPCR ≥1.5 g/g; [redacted] of [redacted] ([redacted]%) patients in the TRF-budesonide 16 mg/day group and [redacted] of [redacted] ([redacted]%) patients in the placebo group reported AEs.

The majority of TEAEs were of mild or moderate severity and reversible (Table 3.14). [redacted] in the TRF-budesonide 16 mg group and [redacted] in the placebo group experienced an AE graded severe. The frequencies of TEAEs in patients with baseline UPCR ≥1.5 g/g considered likely to be study treatment-related by the Investigator were higher in the TRF-budesonide 16 mg/day group compared with the placebo group ([redacted] with TRF-budesonide 16 mg/day, [redacted] with placebo).

The most commonly reported TEAEs with a >5% greater incidence were peripheral oedema, hypertension, headache, muscle spasms, nausea, increased weight, cushingoid, dermatitis, vomiting and increased white blood cell count. Notably, no severe infections were reported during treatment with TRF-budesonide and there was no increased incidence of infections with TRF-budesonide 16 mg/day ([redacted]) versus placebo ([redacted]).

The AE profile of TRF-budesonide was consistent between patients with baseline UPCR ≥1.5 g/g and the full trial population (Table 3.14).

Table 3.14: Overview of AEs in NefIgArd Nef-301

Adverse events, n (%)	Baseline UPCR ≥1.5 g/g				Nef-301 full study population			
	FAS		SAS		FAS		SAS	
	TRF-budesonide 16 mg† n=[redacted]	Placebo† n=[redacted]	TRF-budesonide 16 mg† n=[redacted]	Placebo† n=[redacted]	TRF-budesonide 16 mg† n=97	Placebo† n=100	TRF-budesonide 16 mg† n=[redacted]	Placebo† n=[redacted]
Any TEAE	[redacted]	[redacted]	[redacted]	[redacted]	84 (86.6)	73 (73.0)	[redacted]	[redacted]
Maximum severity of TEAEs								
Mild	[redacted]	[redacted]	[redacted]	[redacted]	49 (50.5)	46 (46.0)	[redacted]	[redacted]
Moderate	[redacted]	[redacted]	[redacted]	[redacted]	31 (32.0)	26 (26.0)	[redacted]	[redacted]
Severe	[redacted]	[redacted]	[redacted]	[redacted]	4 (4.1)	1 (1.0)	[redacted]	[redacted]
Maximum severity of study treatment-related TEAEs								
Mild	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Moderate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Severe	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Any AESI	[redacted]	[redacted]	[redacted]	[redacted]	2 (2.1)	0 (0.0)	[redacted]	[redacted]
Any SAE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Any study treatment-related TEAE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Any study treatment-related TESAE	[redacted]	[redacted]	[redacted]	[redacted]	2 (2.1)	2 (2.0)	[redacted]	[redacted]
Any AE leading to death	[redacted]	[redacted]	[redacted]	[redacted]	0 (0.0)	0 (0.0)	[redacted]	[redacted]
Any TEAE leading to discontinuation of study treatment	[redacted]	[redacted]	[redacted]	[redacted]	9 (9.3)	1 (1.0)	[redacted]	[redacted]

Based on Table 14 of the CS[1]
† Treatment in addition to RAS inhibition.
TEAEs were defined as AEs that occurred for the first time after dosing with study treatment or existed before but worsened in severity or relationship to study treatment after dosing. Study treatment-related TEAEs were those assessed by the Investigator to have a reasonable possibility that the event may have been caused by the study

Adverse events, n (%)	Baseline UPCR ≥1.5 g/g				Nef-301 full study population			
	FAS		SAS		FAS		SAS	
	TRF-budesonide 16 mg† n=[redacted]	Placebo† n=[redacted]	TRF-budesonide 16 mg† n=[redacted]	Placebo† n=[redacted]	TRF-budesonide 16 mg† n=97	Placebo† n=100	TRF-budesonide 16 mg† n=[redacted]	Placebo† n=[redacted]
treatment. If the relationship was missing, then it was considered as study treatment-related. AEs that started >14 days after the last dose of study treatment were excluded from the summary. The last dose was defined as the last dose the patient received, including the tapering period, regardless of the duration of treatment. AE = adverse event; AESI = adverse event of special interest; CS = company submission; FAS = full analysis set; RAS = renin-angiotensin system; SAE = serious adverse event; SAS = safety analysis set; TEAE = treatment-emergent adverse event; TESAE = treatment-emergent serious adverse event; TRF = targeted-release formulation; UPCR = urine protein to creatinine ratio							

3.2.6.2 Serious AEs in patients with a baseline UPCR ≥1.5 g/g

Of the patients with a baseline UPCR ≥1.5 g/g, [redacted] patients reported [redacted] treatment-emergent serious AEs: [redacted] patients in the TRF-budesonide 16 mg/day group and [redacted] patients in the placebo group.

3.2.6.3 Discontinuations and deaths in patients with a baseline UPCR ≥1.5 g/g

In total, [redacted] in the TRF-budesonide 16 mg group with a baseline UPCR ≥1.5 g/g and [redacted] in the placebo group discontinued study treatment due to a TEAE (up until 14 days after the last dose of study treatment; Table 3.14). There were no deaths during the trial.

Adverse events of special interest (AESIs) identified prior to the trial included severe infection requiring hospitalisation, new onset of diabetes mellitus, confirmed fracture, new osteonecrosis, gastrointestinal bleeding that required hospitalisation, cataract formation and onset of glaucoma. During the 9-month treatment period (up until 14 days after the last dose of study treatment), [redacted] patients in the TRF-budesonide 16 mg group and [redacted] in the placebo group reported an AESI.

EAG comment:

- It is important to know the number of patients who suffered from each type of adverse event, even if data are minimal. Therefore, the company were asked to provide a thorough list of all AEs and the corresponding number of patients who suffered with each one. The company responded by providing a detailed list of all specific adverse events experienced by participants in the trial (Table 3.15). The EAG thinks that this table provides a more complete picture of the adverse event profile, which demonstrates that budesonide is reasonably well-tolerated.

Table 3.15: Specific AEs in NefIgArd Nef-301

System organ class Preferred term	TRF-budesonide 16 mg; [redacted]	Placebo [redacted]	Total [redacted]
Any treatment-emergent adverse events	[redacted]	[redacted]	[redacted]
Oedema peripheral†	[redacted]	[redacted]	[redacted]
Hypertension†	[redacted]	[redacted]	[redacted]
Abdominal pain†	[redacted]	[redacted]	[redacted]
Abdominal discomfort†	[redacted]	[redacted]	[redacted]
Alopecia†	[redacted]	[redacted]	[redacted]
Cushingoid†	[redacted]	[redacted]	[redacted]
Dermatitis†	[redacted]	[redacted]	[redacted]
Mood swings†	[redacted]	[redacted]	[redacted]
Anaemia†	[redacted]	[redacted]	[redacted]
Face oedema†	[redacted]	[redacted]	[redacted]
Hirsutism†	[redacted]	[redacted]	[redacted]
Hypersensitivity†	[redacted]	[redacted]	[redacted]
Infections and infestations	[redacted]	[redacted]	[redacted]
Nasopharyngitis	[redacted]	[redacted]	[redacted]
Upper respiratory tract infection	[redacted]	[redacted]	[redacted]
Urinary tract infection	[redacted]	[redacted]	[redacted]

System organ class Preferred term	TRF-budesonide 16 mg; [redacted]	Placebo[redacted]	Total[redacted]
Corona virus infection	[redacted]	[redacted]	[redacted]
Influenza	[redacted]	[redacted]	[redacted]
Cellulitis	[redacted]	[redacted]	[redacted]
Cytomegalovirus infection	[redacted]	[redacted]	[redacted]
Dermatophytosis of nail	[redacted]	[redacted]	[redacted]
Folliculitis	[redacted]	[redacted]	[redacted]
Gastroenteritis viral	[redacted]	[redacted]	[redacted]
Herpes zoster	[redacted]	[redacted]	[redacted]
Lower respiratory tract infection	[redacted]	[redacted]	[redacted]
Otitis media acute	[redacted]	[redacted]	[redacted]
Pharyngitis	[redacted]	[redacted]	[redacted]
Pharyngotonsillitis	[redacted]	[redacted]	[redacted]
Pyoderma	[redacted]	[redacted]	[redacted]
Respiratory tract infection	[redacted]	[redacted]	[redacted]
Tooth abscess	[redacted]	[redacted]	[redacted]
Tooth infection	[redacted]	[redacted]	[redacted]
Viral infection	[redacted]	[redacted]	[redacted]
Viral upper respiratory tract infection	[redacted]	[redacted]	[redacted]
Wound infection	[redacted]	[redacted]	[redacted]
Gastrointestinal disorders	[redacted]	[redacted]	[redacted]
Nausea	[redacted]	[redacted]	[redacted]
Diarrhoea	[redacted]	[redacted]	[redacted]
Abdominal pain upper	[redacted]	[redacted]	[redacted]
Abdominal pain	[redacted]	[redacted]	[redacted]
Vomiting	[redacted]	[redacted]	[redacted]
Abdominal discomfort	[redacted]	[redacted]	[redacted]
Abdominal distension	[redacted]	[redacted]	[redacted]
Dental caries	[redacted]	[redacted]	[redacted]
Dyspepsia	[redacted]	[redacted]	[redacted]
Abdominal pain lower	[redacted]	[redacted]	[redacted]
Abdominal tenderness	[redacted]	[redacted]	[redacted]
Eructation	[redacted]	[redacted]	[redacted]
Faeces discoloured	[redacted]	[redacted]	[redacted]
Flatulence	[redacted]	[redacted]	[redacted]
Gastritis	[redacted]	[redacted]	[redacted]
Gastritis haemorrhagic	[redacted]	[redacted]	[redacted]
Gastro-oesophageal reflux disease	[redacted]	[redacted]	[redacted]
Haemorrhoids	[redacted]	[redacted]	[redacted]

System organ class **Preferred term**	**TRF-budesonide 16 mg;** [redacted]	**Placebo** [redacted]	**Total** [redacted]
Inguinal hernia	[redacted]	[redacted]	[redacted]
Pancreatitis necrotising	[redacted]	[redacted]	[redacted]
Steatorrhoea	[redacted]	[redacted]	[redacted]
Toothache	[redacted]	[redacted]	[redacted]
General disorders and administration site conditions	[redacted]	[redacted]	[redacted]
Oedema peripheral	[redacted]	[redacted]	[redacted]
Pyrexia	[redacted]	[redacted]	[redacted]
Fatigue	[redacted]	[redacted]	[redacted]
Asthenia	[redacted]	[redacted]	[redacted]
Chest pain	[redacted]	[redacted]	[redacted]
Face oedema	[redacted]	[redacted]	[redacted]
Influenza like illness	[redacted]	[redacted]	[redacted]
Malaise	[redacted]	[redacted]	[redacted]
Peripheral swelling	[redacted]	[redacted]	[redacted]
Skin and subcutaneous tissue disorders	[redacted]	[redacted]	[redacted]
Rash	[redacted]	[redacted]	[redacted]
Alopecia	[redacted]	[redacted]	[redacted]
Acne	[redacted]	[redacted]	[redacted]
Eczema	[redacted]	[redacted]	[redacted]
Hair growth abnormal	[redacted]	[redacted]	[redacted]
Hirsutism	[redacted]	[redacted]	[redacted]
Rash pruritic	[redacted]	[redacted]	[redacted]
Cold sweat	[redacted]	[redacted]	[redacted]
Dermatitis	[redacted]	[redacted]	[redacted]
Erythema	[redacted]	[redacted]	[redacted]
Exfoliative rash	[redacted]	[redacted]	[redacted]
Hyperhidrosis	[redacted]	[redacted]	[redacted]
In growing nail	[redacted]	[redacted]	[redacted]
Lipohypertrophy	[redacted]	[redacted]	[redacted]
Nail growth abnormal	[redacted]	[redacted]	[redacted]
Pruritus	[redacted]	[redacted]	[redacted]
Rash generalised	[redacted]	[redacted]	[redacted]
Rash papular	[redacted]	[redacted]	[redacted]
Skin atrophy	[redacted]	[redacted]	[redacted]
Skin striae	[redacted]	[redacted]	[redacted]
Swelling face	[redacted]	[redacted]	[redacted]
Nervous system disorders	[redacted]	[redacted]	[redacted]
Headache	[redacted]	[redacted]	[redacted]

System organ class Preferred term	TRF-budesonide 16 mg; [redacted]	Placebo[redacted]	Total[redacted]
Dizziness	[redacted]	[redacted]	[redacted]
Dysgeusia	[redacted]	[redacted]	[redacted]
Lethargy	[redacted]	[redacted]	[redacted]
Dysarthria	[redacted]	[redacted]	[redacted]
Hypoaesthesia	[redacted]	[redacted]	[redacted]
Migraine	[redacted]	[redacted]	[redacted]
Somnolence	[redacted]	[redacted]	[redacted]
Transient ischaemic attack	[redacted]	[redacted]	[redacted]
Musculoskeletal and connective tissue disorders	[redacted]	[redacted]	[redacted]
Muscle spasms	[redacted]	[redacted]	[redacted]
Back pain	[redacted]	[redacted]	[redacted]
Arthralgia	[redacted]	[redacted]	[redacted]
Bursitis	[redacted]	[redacted]	[redacted]
Flank pain	[redacted]	[redacted]	[redacted]
Intervertebral disc protrusion	[redacted]	[redacted]	[redacted]
Limb discomfort	[redacted]	[redacted]	[redacted]
Muscle tightness	[redacted]	[redacted]	[redacted]
Muscular weakness	[redacted]	[redacted]	[redacted]
Musculoskeletal chest pain	[redacted]	[redacted]	[redacted]
Musculoskeletal discomfort	[redacted]	[redacted]	[redacted]
Musculoskeletal pain	[redacted]	[redacted]	[redacted]
Myalgia	[redacted]	[redacted]	[redacted]
Myositis	[redacted]	[redacted]	[redacted]
Neck pain	[redacted]	[redacted]	[redacted]
Pain in extremity	[redacted]	[redacted]	[redacted]
Tendonitis	[redacted]	[redacted]	[redacted]
Investigations	[redacted]	[redacted]	[redacted]
Weight increased	[redacted]	[redacted]	[redacted]
Blood pressure increased	[redacted]	[redacted]	[redacted]
White blood cell count increased	[redacted]	[redacted]	[redacted]
Blood creatinine increased	[redacted]	[redacted]	[redacted]
Blood lactate dehydrogenase increased	[redacted]	[redacted]	[redacted]
Glycosylated haemoglobin increased	[redacted]	[redacted]	[redacted]
Alanine aminotransferase increased	[redacted]	[redacted]	[redacted]
Aspartate aminotransferase increased	[redacted]	[redacted]	[redacted]
Blood creatine phosphokinase increased	[redacted]	[redacted]	[redacted]
Blood glucose increased	[redacted]	[redacted]	[redacted]
Gamma-glutamyl transferase increased	[redacted]	[redacted]	[redacted]

System organ class Preferred term	TRF-budesonide 16 mg; [redacted]	Placebo[redacted]	Total[redacted]
Hepatic enzyme increased	[redacted]	[redacted]	[redacted]
Neutrophil count increased	[redacted]	[redacted]	[redacted]
Transaminases increased	[redacted]	[redacted]	[redacted]
Urine output decreased	[redacted]	[redacted]	[redacted]
Vascular disorders	[redacted]	[redacted]	[redacted]
Hypertension	[redacted]	[redacted]	[redacted]
Hypotension	[redacted]	[redacted]	[redacted]
Accelerated hypertension	[redacted]	[redacted]	[redacted]
Deep vein thrombosis	[redacted]	[redacted]	[redacted]
Hot flush	[redacted]	[redacted]	[redacted]
Injury, poisoning and procedural complications	[redacted]	[redacted]	[redacted]
Ligament sprain	[redacted]	[redacted]	[redacted]
Animal bite	[redacted]	[redacted]	[redacted]
Contusion	[redacted]	[redacted]	[redacted]
Dental restoration failure	[redacted]	[redacted]	[redacted]
Face injury	[redacted]	[redacted]	[redacted]
Fall	[redacted]	[redacted]	[redacted]
Femur fracture	[redacted]	[redacted]	[redacted]
Meniscus injury	[redacted]	[redacted]	[redacted]
Procedural pain	[redacted]	[redacted]	[redacted]
Skin laceration	[redacted]	[redacted]	[redacted]
Soft tissue injury	[redacted]	[redacted]	[redacted]
Renal and urinary disorders	[redacted]	[redacted]	[redacted]
Renal impairment	[redacted]	[redacted]	[redacted]
Renal pain	[redacted]	[redacted]	[redacted]
Acute kidney injury	[redacted]	[redacted]	[redacted]
Dysuria	[redacted]	[redacted]	[redacted]
Haematuria	[redacted]	[redacted]	[redacted]
Proteinuria	[redacted]	[redacted]	[redacted]
Urinary bladder haemorrhage	[redacted]	[redacted]	[redacted]
Respiratory, thoracic and mediastinal disorders	[redacted]	[redacted]	[redacted]
Cough	[redacted]	[redacted]	[redacted]
Dyspnoea	[redacted]	[redacted]	[redacted]
Oropharyngeal pain	[redacted]	[redacted]	[redacted]
Dry throat	[redacted]	[redacted]	[redacted]
Epistaxis	[redacted]	[redacted]	[redacted]
Hyperactive pharyngeal reflex	[redacted]	[redacted]	[redacted]

System organ class Preferred term	TRF-budesonide 16 mg; [redacted]	Placebo[redacted]	Total[redacted]
Nasal septum deviation	[redacted]	[redacted]	[redacted]
Snoring	[redacted]	[redacted]	[redacted]
Metabolism and nutrition disorders	[redacted]	[redacted]	[redacted]
Diabetes mellitus	[redacted]	[redacted]	[redacted]
Gout	[redacted]	[redacted]	[redacted]
Folate deficiency	[redacted]	[redacted]	[redacted]
Glucose tolerance impaired	[redacted]	[redacted]	[redacted]
Hyperphosphataemia	[redacted]	[redacted]	[redacted]
Hypokalaemia	[redacted]	[redacted]	[redacted]
Increased appetite	[redacted]	[redacted]	[redacted]
Metabolic acidosis	[redacted]	[redacted]	[redacted]
Psychiatric disorders	[redacted]	[redacted]	[redacted]
Insomnia	[redacted]	[redacted]	[redacted]
Mood swings	[redacted]	[redacted]	[redacted]
Anxiety	[redacted]	[redacted]	[redacted]
Sleep disorder	[redacted]	[redacted]	[redacted]
Agitation	[redacted]	[redacted]	[redacted]
Depressed mood	[redacted]	[redacted]	[redacted]
Libido decreased	[redacted]	[redacted]	[redacted]
Psychotic disorder	[redacted]	[redacted]	[redacted]
Suicidal ideation	[redacted]	[redacted]	[redacted]
Blood and lymphatic system disorders	[redacted]	[redacted]	[redacted]
Lymphadenopathy	[redacted]	[redacted]	[redacted]
Anaemia	[redacted]	[redacted]	[redacted]
Bone marrow oedema	[redacted]	[redacted]	[redacted]
Iron deficiency anaemia	[redacted]	[redacted]	[redacted]
Leukocytosis	[redacted]	[redacted]	[redacted]
Thrombocytosis	[redacted]	[redacted]	[redacted]
Cardiac disorders	[redacted]	[redacted]	[redacted]
Palpitations	[redacted]	[redacted]	[redacted]
Cardiac failure congestive	[redacted]	[redacted]	[redacted]
Tachycardia	[redacted]	[redacted]	[redacted]
Endocrine disorders	[redacted]	[redacted]	[redacted]
Cushingoid	[redacted]	[redacted]	[redacted]
Cushing's syndrome	[redacted]	[redacted]	[redacted]
Neoplasms benign, malignant and unspecified (including cysts and polyps)	[redacted]	[redacted]	[redacted]
Meningioma	[redacted]	[redacted]	[redacted]
Pyogenic granuloma	[redacted]	[redacted]	[redacted]

System organ class Preferred term	TRF-budesonide 16 mg; [redacted]	Placebo[redacted]	Total[redacted]
Skin papilloma	[redacted]	[redacted]	[redacted]
Reproductive system and breast disorders	[redacted]	[redacted]	[redacted]
Menorrhagia	[redacted]	[redacted]	[redacted]
Vulvovaginal dryness	[redacted]	[redacted]	[redacted]
Eye disorders	[redacted]	[redacted]	[redacted]
Ocular discomfort	[redacted]	[redacted]	[redacted]
Swelling of eyelid	[redacted]	[redacted]	[redacted]
Immune system disorders	[redacted]	[redacted]	[redacted]
Drug hypersensitivity	[redacted]	[redacted]	[redacted]
Seasonal allergy	[redacted]	[redacted]	[redacted]
Ear and labyrinth disorders	[redacted]	[redacted]	[redacted]
Hypoacusis	[redacted]	[redacted]	[redacted]
Pregnancy, puerperium and perinatal conditions	[redacted]	[redacted]	[redacted]
Abortion spontaneous	[redacted]	[redacted]	[redacted]

Based on Table 27 of the response to the request for clarification[3]
† The first PT term is selected to represent the AE group: cushingoid/Cushing's syndrome, alopecia/alopecia areata, hypersensitivity/drug hypersensitivity, anaemia/iron deficiency anaemia, dermatitis/hand dermatitis/perioral dermatitis/seborrheic dermatitis/eczema, mood swings/mood altered/irritability, abdominal pain/abdominal pain upper/abdominal pain lower, abdominal discomfort/abdominal tenderness/abdominal distension, oedema peripheral/peripheral swelling, face oedema/swelling face, hirsutism/hypertrichosis, hypertension/essential hypertension.
AE = adverse event; PT = preferred term; TRF = targeted-release formulation

3.2.7 Ongoing studies

The NefIgArd-OLE open-label extension (OLE) study is an ongoing phase 3b, multicentre, open-label, single-arm extension trial to evaluate the efficacy and safety of TRF-budesonide 16 mg/day treatment in patients with IgAN who have completed the phase 3 NefIgArd Nef-301 trial. Trial completion is due in May 2024.

3.3 Critique of trials identified and included in the indirect comparison and/or multiple treatment comparison

The company states that the findings of the DAPA-CKD study suggest that dapagliflozin treatment in patients with IgAN (N=270) does not have a statistically significant impact on eGFR over 36 months compared with placebo.[7] The least mean squares eGFR slopes from baseline to end of treatment in the dapagliflozin and placebo groups were -3.5 (standard error [SE], 0.5) and -4.7 (SE, 0.5) ml/min/1.73 m^2 per year, respectively, resulting in an insignificant between-group difference of 1.2 ml/min/1.73 m^2 per year (95% CI: -0.12, 2.51 ml/min/1.73 m^2 per year). Based on this, the company inferred that the efficacy of SoC is not impacted by the inclusion of sodium-glucose cotransporter-2 inhibitors (SGLT2i) in this population, and therefore conducting an ITC of TRF-budesonide versus SoC including dapagliflozin was not deemed relevant.

Immunosuppressive agents were not considered by the company to be relevant comparators for TRF-budesonide, and an ITC was not considered to be relevant to this submission. This was based on clinical

expert opinion indicating that in England, the use of immunosuppressive agents (corticosteroids and MMF) is not advised due to their uncertain benefit-to-risk ratio.

3.4 Critique of the indirect comparison and/or multiple treatment comparison

No ITC was carried out by the company. As already mentioned in Section 2.3, this included no comparison with an SGLT2i.

EAG comment:

- As mentioned above, the company have argued that an SGLT2i would form part of SoC to which budesonide would be added. However, as shown in Table 2.2, dapagliflozin was not part of the SoC in the trial. Therefore, there is no direct evidence of the effect of budesonide + SoC (including SGLT2i) versus SoC (including an SGLT2i).
- Most importantly, the evidence for dapagliflozin does *not* demonstrate no effect – the primary outcome of the trial was a composite endpoint including sustained ≥50% decline in eGFR, which yielded a significant benefit for the intervention (HR for dapagliflozin versus placebo = 0.29 [95% CI, 0.12 to 0.73]; P = 0.005).
- Therefore, in order to estimate budesonide + SoC including an SGLT2i versus SoC including an SGLT2i indirectly, then direct evidence for budesonide + SoC versus SoC from the NefIgArd Nef-301 trial could probably not be used, if indeed budesonide would be added to an SGLT2i. Of course, if budesonide replaced an SGLT2i then the trial could be used together with a trial of an SGLT2i + SoC versus SoC if SoC was as in the NefIgArd Nef-301 trial.
- The DAPA-CKD study[7] could potentially be used as direct evidence for dapagliflozin + SoC versus SoC, given that the another publication of the trial states that *"our trial adds to the literature by examining the effect of an SGLT2 inhibitor, added to background therapy including an ACE inhibitor or ARB, in participants with chronic kidney disease, with or without type 2 diabetes".*[20] However, the population in the Wheeler study[7] is not restricted to those with a UPCR of ≥1.5 g/g, and so any ITC might be compromised by clinical heterogeneity. Thus, other evidence might be required.
- The company were therefore asked to provide an SLR to collect all relevant evidence on the effectiveness of SGLT2i, and to perform an ITC if possible.[2] However, the company failed to answer this question, merely reiterating what had been stated in the CS[1] as follows *"There is as yet no clinical guidance for the use of sodium-glucose cotransporter-2 inhibitor (SGLT2is) specific to patients with IgAN by NICE. However, dapagliflozin has received NICE approval for the treatment of CKD (TA775) (43) and is also anticipated to be used as part of SoC for the management of cardiovascular risk in patients with IgAN, as indicated by clinical expert opinion. As such, dapagliflozin is not considered to be a comparator for TRF-budesonide; it is anticipated that it will be administered in combination with TRF-budesonide as part of SoC. The clinical SLR conducted for the CS included SGLT2i as a randomised intervention of interest, due to it being part of SoC for IgAN. The findings of the DAPA-CKD study suggest that dapagliflozin treatment in patients with IgAN (N=270) did not have a statistically significant impact on eGFR over 36 months compared with placebo. The least mean squares eGFR slopes from baseline to end of treatment in the dapagliflozin and placebo groups were -3.5 (standard error [SE], 0.5) and -4.7 (SE, 0.5) mL/min/1.73 m2 per year, respectively, resulting in an insignificant between-group difference of 1.2 mL/min/1.73 m2 per year (95% CI: -0.12, 2.51 mL/min/1.73 m2 per year). Based on this, it can be inferred that the efficacy of SoC is not impacted by the inclusion of SGLT2 inhibitors in this population. It is also noted that in clinical practice, TRF-budesonide would be administered in addition to a SoC regimen that may include an SGLT2i, i.e. dapagliflozin. As such, any potential*

benefits that may be observed from the addition of dapagliflozin to SoC, are anticipated to be additive to the TRF-budesonide treatment effect, especially since there is no crossover between their mechanisms of action (as indicated by clinical expert opinion)".[3]

- Given that SGLT2i are comparators in the scope and the decision problem, evidence should have been presented, based on a full SLR and assessment of feasibility of an ITC, of a comparison between budesonide + SoC possibly including an SGLT2i versus SoC including an SGLT2i. The lack of this evidence constitutes a key issue, notwithstanding the lack of ability to use the NefIgArd Nef-301 trial as part of this evidence should budesonide be added to, rather than a substitute for, an SGLT2i.
- Similarly (as suggested in Section 2.3) if it were wished to estimate budesonide + SoC versus corticosteroids + SoC indirectly, then the direct evidence for budesonide + SoC versus SoC could be used, along with any direct evidence for corticosteroids + SoC versus SoC.
- Likewise (as suggested in Section 2.3) if it were wished to estimate budesonide + SoC versus MMF + SoC indirectly, then the direct evidence for budesonide + SoC versus SoC could be used, along with any direct evidence for MMF + SoC versus SoC.

3.5 Additional work on clinical effectiveness undertaken by the EAG

None undertaken.

3.6 Conclusions of the clinical effectiveness section.

The CS[1, 11] and response to clarification[3] provided sufficient details for the EAG to appraise the literature searches conducted to identify relevant clinical evidence for the efficacy and safety of TRF-budesonide and relevant comparators for the treatment of primary IgA nephropathy. Searches conducted in November 2022 were transparent and reproducible, and appropriate strategies were used. A broad range of databases, trials registers and grey literature sources (including conference proceedings and websites of HTA organisations) were searched. Overall, the EAG has no major concerns about the literature searches conducted, however separate adverse events searches may have retrieved additional studies.

Compared to placebo + SoC, the randomised trial evidence demonstrated that budesonide + SoC leads to significantly reduced UPCR and UACR immediately after 9 months treatment, and also following a 3-month post-treatment follow-up. A significant relative reduction in the rate of eGFR decline was also seen in the budesonide + SoC group compared to the SoC group at 9 and 12 months. However, there were no significant group differences in HRQoL. Budesonide was relatively well-tolerated, with a low level of severe TEAEs (5.7%), and (albeit with a risk of type II errors) no significant differences in the risk of severe, moderate or mild TEAEs between groups. There were no deaths in either group.

There were several problems with the evidence provided by the company. Not all relevant evidence was included[15] and patients with an eGFR of 35 ml/min/1.73 m^2 were excluded. There were also risks of selection bias resulting from baseline inequivalence. In addition, the important patient-centred outcome of disease progression was not included, and follow-up was restricted to one year. Furthermore, the applicability of evidence to the UK target population was unclear.

Although corticosteroids were excluded as a comparator by the company, there is a subgroup of patients who might be eligible for both drugs. A relevant comparison (in this subgroup) would therefore be budesonide + SoC versus corticosteroids + SoC. This could be derived from another trial, or indirectly via an ITC (using budesonide + SoC versus SoC and corticosteroids +SoC versus SoC as the direct evidence). Similar approaches might be used for two other potential comparators: MMF and dapagliflozin.

Despite these caveats, the trial results do suggest an overall benefit for budesonide + SoC against SoC. These results cannot be extrapolated to indicate a benefit for budesonide alone against SoC, which was

the original decision problem. The company have since revised their decision problem to fit the trial methodology. However, the mismatch between decision problem and the NICE scope remains, which requires discussion.

4. COST EFFECTIVENESS

4.1 EAG comment on company's review of cost effectiveness evidence

This section pertains mainly to the review of CEA studies. However, the search section (4.1.1) also contains summaries and critiques of other searches related to cost effectiveness presented in the company submission. Therefore, the following section includes searches for the CEA review, measurement and evaluation of health effects as well as for cost and healthcare resource identification, measurement and valuation.

4.1.1 Searches performed for cost effectiveness section

The following paragraphs contain summaries and critiques of all searches related to cost effectiveness presented in the CS.[1, 11] The CADTH evidence-based checklist for PRESS was used to inform this critique.[9, 10] The EAG has presented only the major limitations of each search strategy in the report.

The company provided separate searches for economic evaluations costs and resource utilisation outcomes, and HRQoL and heath state utility value (HSUV) outcomes associated with patients with primary IgAN (see Appendix G, H and I of the CS).[11] These sections were also informed by searches of additional sources previously reported in Appendix D along with other economic specific resources. Searches were performed in November 2022.

A summary of the sources searched is provided in Table 4.1.

Table 4.1: Published cost effectiveness studies (as reported in CS)

Resource	Host/Source	Date ranges	Date searched
Electronic databases			
Embase	Ovid	1974-08/11/2022	09/11/22
MEDLINE, including: MEDLINE Epub Ahead of Print MEDLINE In-Process & Other Non-Indexed Citations MEDLINE Daily	Ovid	1946-08/11/2022	09/11/22
American College of Physicians (ACP) Journal Club	EBM Reviews (Ovid)	1991-10/2022	09/11/22
Cochrane Database of Systematic Reviews	EBM Reviews (Ovid)	2005-02/11/2022	09/11/22
Cochrane Clinical Answers	EBM Reviews (Ovid)	up to 10/2022	09/11/22
Cochrane Methodology Register	EBM Reviews (Ovid)	up to 3rd Quarter 2012	09/11/22
Database of Abstracts of Reviews of Effects (DARE)	EBM Reviews (Ovid)	1991-to be confirmed	09/11/22
HTA database	EBM Reviews (Ovid)	2001- 4th Quarter 2016	09/11/22
National Health Service Economic Evaluation Database (NHS EED)	EBM Reviews (Ovid)	1995-to be confirmed	09/11/22

Resource	Host/Source	Date ranges	Date searched
Econlit	Ovid	1886 – 27/10/2022	09/11/22
Conferences			
American Society of Nephrology (ASN)		2020, 2021, 2022	14/11/22
European Renal Association (ERA)			NA
International IgA Nephropathy Network (IIGANN) International Symposium on IgA Nephropathy		2021 (no conference 2019, 2020, 2022)	14/11/22
National Kidney Foundation		2020, 2021, 2022	14/11/22
World Congress of Nephrology (WCN)		2019, 2021, 2022. (no conference 2020)	14/11/22
Trials registries			
USA NIH registry & results database	https://clinicaltrials.gov		23/1/2023
WHO ICTRP	http://apps.who.int/trialsearch/		2/2/2022
HTA global bodies			
National Institute for Health and Care Excellence (NICE)	Internet		14/11/2022
Scottish Medicines Consortium (SMC)	Internet		14/11/2022
Canadian Agency for Drugs and Technologies in Health (CADTH), including the pan-Canadian Oncology Drugs Review (pCODR)	Internet		14/11/2022
Pharmaceutical Benefits Scheme (PBS)	Internet		14/11/2022
Agencia Española de Medicamentos y Productos Sanitarios (AEMPS)	Internet		14/11/2022
Agenzia Italiana del Farmaco (AIFA)	Internet		14/11/2022
Haute Autorité de Santé (HAS)	Internet		14/11/2022
Institute for Quality and Efficiency in Health Care (IQWIG)	Internet		14/11/2022
Institute for Clinical and Economic Review (ICER)			Not reported

Resource	Host/Source	Date ranges	Date searched
US Food and Drug Administration (FDA)	Internet		14/11/2022
European Medicines Agency (EMA)	Internet		14/11/2022
Finnish Coordinating Centre for Heath Technology Assessment (FinCCHTA)	Internet		14/11/2022
DEFACTUM Social & Health Services and Labour Market	Internet		14/11/2022
Norwegian Institute of Public Health (NIPH)	Internet		14/11/2022
Swedish Agency for Health Technology Assessment and Assessment of Social Services [Statens beredning för medicinsk och social utvärdering] (SBU)	Internet		14/11/2022
Dental and Pharmaceutical Benefits Agency [Tandvårds- och läkemedelsförmånsverket] (TLV)	Internet		14/11/2022
Additional sources			
EuroQoL	Internet		14/11/2022
University of Sheffield's ScHARRHUD database			
CEA Registry			
RePEc website (EconPapers):			
International Network of Agencies for Health Technology Assessment (INAHTA)			
National Institute for Health Research (NIHR)			
European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCEPP)			

Based on Appendix G of the CS[11]

ACP = American College of Physicians; AEMPS = Agencia Española de Medicamentos y Productos Sanitarios; AIFA = Agenzia Italiana del Farmaco; ASN = American Society of Nephrology; CADTH = Canadian Agency for Drugs and Technologies in Health; CEA = cost effectiveness analysis; CS = company submission; DARE = Database of Abstracts of Reviews of Effects; EBM = evidence-based medicine; EED = Economic Evaluation Database; EMA = European Medicines Agency; ENCEPP = European Network of Centres for Pharmacoepidemiology and Pharmacovigilance; ERA = European Renal Association; FDA = Food and Drug Administration; FinCCHTA = Finnish Coordinating Centre for Heath Technology Assessment; HAS = Haute Autorité de Santé; HTA = health technology assessment; ICER = Institute for Clinical and Economic Review; ICTRP = International Clinical Trials Registry Platform; IIGAN = International IgA Nephropathy Network; INAHTA = International Network of Agencies for Health Technology Assessment; IQWiG = Institute for Quality and Efficiency in Health Care; ISN = International Society of Nephrology;

Resource	Host/Source	Date ranges	Date searched
NHS = National Health Service; NICE = National Institute for Health and Care Excellence; NIH = National Institutes of Health; NIHR = National Institute for Health and Care Research; NIPH = Norwegian Institute of Public Health; PBS = Pharmaceutical Benefits Scheme; pCODR = pan-Canadian Oncology Drugs Review; QoL = quality of life; SBU = Swedish Agency for Health Technology Assessment and Assessment of Social Services; ScHARRHUD = School of Health and Related Research Health Utility Database; SMC = Scottish Medicines Consortium; TLV = Tandvårds- och läkemedelsförmånsverket (Dental and Pharmaceutical Benefits Agency); USA = United States of America; WCN = World Congress of Nephrology; WHO = World Health Organization			

EAG comment:

- Searches were undertaken in November 2022 to identify relevant economic evaluation outcomes for patients with primary IgAN and treated with targeted release budesonide (in comparison to established management). The CS, Appendix G and the Company's response to clarification provided sufficient details (including database host(s), date searched, and date ranges covered) for the EAG to appraise the literature searches.[1, 3, 11]
- Searches were well structured, transparent and reproducible, and a good range of subject indexing terms (MeSH/EMTREE) and free text was used.
- A broad range of databases and grey literature sources including trials registers, conference proceedings, HTA websites, and specialist economics resources were searched. The reference lists of eligible studies were also screened to identify any further relevant publications not identified by the searches.
- At clarification the company confirmed that *"the supplementary searches undertaken were conducted to cover both the clinical and economic sections of the submission, and the specific economic resources were searched to inform all economic sections of the submission i.e. cost-effectiveness, health related quality of life and cost and health care resource identification, measurement and valuation"*.[3]. These additional searches are reported in the table above (Table 4.1); the following tables and comments will focus only on those searches unique to identifying information on HRQoL and resource use.

Table 4.2: Health-related quality of life studies (as reported in CS)

Resource	Host/Source	Date ranges	Date searched
Electronic databases			
Embase	Ovid	1974-14/11/2022	15/11/22
MEDLINE, including: MEDLINE Epub Ahead of Print MEDLINE In-Process & Other Non-Indexed Citations MEDLINE Daily	Ovid	1946-14/11/2022	15/11/22
American College of Physicians (ACP) Journal Club	EBM Reviews (Ovid)	1991-10/2022	15/11/22
Cochrane Database of Systematic Reviews	EBM Reviews (Ovid)	2005-09/11/2022	15/11/22
Cochrane Clinical Answers	EBM Reviews (Ovid)	up to 10/2022	15/11/22

Resource	Host/Source	Date ranges	Date searched
Cochrane Methodology Register	EBM Reviews (Ovid)	up to 3rd quarter 2012	15/11/22
Database of Abstracts of Reviews of Effects (DARE)	EBM Reviews (Ovid)	Up to 1st quarter 2016	15/11/22
HTA database	EBM Reviews (Ovid)	Up to 4th quarter 2016	15/11/22
National Health Service Economic Evaluation Database (NHS EED)	EBM Reviews (Ovid)	Up to 1st quarter 2016	15/11/22

Based on Appendix H of the CS[11]
ACP = American College of Physicians; CS = company submission; DARE = Database of Abstracts of Reviews of Effects; EBM = evidence-based medicine; EED = Economic Evaluation Database; HTA = health technology assessment; NHS = National Health Service

EAG comment:

- Searches were undertaken in November 2022 to identify HRQoL and HSUV outcomes associated with patients with primary IgAN. The CS, Appendix H and the company's response to clarification provided sufficient details (including database host(s), date searched, and date ranges covered) for the EAG to appraise the literature searches.[1, 3, 11]
- A broad range of databases and grey literature sources including trials registers, conference proceedings, HTA websites, and specialist economics resources were searched.
- Searches were well structured, transparent and reproducible, and a good range of subject indexing terms (MeSH/EMTREE) and free text was used.

Table 4.3: Cost and healthcare resource identification, measurement and valuation (as reported in CS)

Resource	Host/Source	Date ranges	Date searched
Electronic databases			
Embase	Ovid	1974-08/11/2022	09/11/22
MEDLINE, including: MEDLINE Epub Ahead of Print MEDLINE In-Process & Other Non-Indexed Citations MEDLINE Daily	Ovid	1946-08/11/2022	09/11/22
American College of Physicians (ACP) Journal Club	EBM Reviews (Ovid)	1991-10/2022	09/11/22
Cochrane Database of Systematic Reviews	EBM Reviews (Ovid)	2005-02/11/2022	09/11/22
Cochrane Clinical Answers	EBM Reviews (Ovid)	up to 10/2022	09/11/22
Cochrane Methodology Register	EBM Reviews (Ovid)	up to 3rd quarter 2012	09/11/22

Resource	Host/Source	Date ranges	Date searched
Database of Abstracts of Reviews of Effects (DARE)	EBM Reviews (Ovid)	Up to 1st quarter 2016	09/11/22
HTA database	EBM Reviews (Ovid)	Up to 4th quarter 2016	09/11/22
National Health Service Economic Evaluation Database (NHS EED)	EBM Reviews (Ovid)	Up to 1st quarter 2016	09/11/22
Based on Appendix I of the CS[11] ACP = American College of Physicians; CS = company submission; DARE = Database of Abstracts of Reviews of Effects; EBM = evidence-based medicine; EED = Economic Evaluation Database; HTA = health technology assessment; NHS = National Health Service			

EAG comment:

- Searches were undertaken in November 2022 to identify costs and resource utilisation outcomes associated with patients with primary IgAN. The CS, Appendix I and the company's response to clarification provided sufficient details (including database host(s), date searched, and date ranges covered) for the EAG to appraise the literature searches.[1, 3, 11]
- A broad range of databases and grey literature sources including trials registers, conference proceedings, HTA websites, and specialist economics resources were searched.
- Searches were well structured, transparent and reproducible, and a good range of subject indexing terms (MeSH/EMTREE) and free text was used.

4.1.2 Inclusion/exclusion criteria

The in- and exclusion criteria used by the company are presented in Appendices G, H, and I, Tables 6, 10, and 14. The EAG considers the in- and exclusion criteria suitable to capture all relevant evidence.

4.1.3 Findings of the cost-effectiveness review

The PRISMA flow diagrams for the cost effectiveness studies can be found in Figure 2 of Appendix G, for the quality of life studies in Figure 3 of Appendix H, and for the cost/resource use in Figure 4 of Appendix I. A total of two cost effectiveness studies, six quality-of-life studies and nine cost/resource use studies were included. The two included cost effectiveness studies were not suitable to assess the cost effectiveness for a treatment for IgAN in the UK. None of the QoL studies used the European Quality of Life-5 Dimensions (EQ-5D) for measuring QoL, and none of the included cost/resource use studies provided data relevant for the UK setting.

Thus, the company searched for HTA submissions that could be relevant, and this resulted in seven selected previous NICE Technology Appraisals (TAs) in chronic kidney disease (CKD) that could inform the model structure, functionality, assumptions and data sources. A summary list is provided in Table 16 of the company submission.

4.1.4 Conclusions of the cost effectiveness review

The CS[1, 11] and response to clarification[3] provided sufficient details for the EAG to appraise the literature searches conducted to identify economic, HRQoL and cost data of TRF-budesonide for the treatment of primary IgA nephropathy. Searches were transparent and reproducible, and appropriate strategies were used. A broad range of databases and grey literature sources were searched. Overall, the EAG has no major concerns about the literature searches conducted.

As no models were identified that fully addressed the decision problem, the company build a de novo model. Aspects of the model structure used in NICE TA 775 were utilised in the model structure.[6]

4.2 Summary and critique of company's submitted economic evaluation by the EAG

4.2.1 NICE reference case checklist

Table 4.4: 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.	As per the reference case.
Perspective on costs	NHS and PSS.	As per the reference case.
Type of economic evaluation	Cost utility analysis with full incremental analysis.	As per the reference case.
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared.	As per the reference case.
Synthesis of evidence on health effects	Based on systematic review.	As per the reference case.
Measuring and valuing health effects	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of HRQoL in adults.	Health effects expressed in QALYs. HRQoL values from the literature for CKD stages using the EQ-5D-3L. No specific values for patients with IgAN were identified.
Source of data for measurement of health-related quality of life	Reported directly by patients and/or carers.	As per the reference case.
Source of preference data for valuation of changes in health-related quality of life	Representative sample of the UK population.	Representative sample of UK population. Utility scores were sourced from Cooper 2020[21] using UK values from Jesky 2016[22] and Lee 2005.[23]
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit.	No equity issues have been identified.
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.	As per the reference case.
Discounting	The same annual rate for both costs and health effects (currently 3.5%).	As per the reference case.

CKD = chronic kidney disease; IgAN = Immunoglobulin A nephropathy; EQ-5D = EuroQoL-5 Dimensions; EQ-5D-3L = EuroQoL-5 Dimensions, 3 levels; EAG = Evidence Assessment Group; HRQoL = health related

Element of health technology assessment	Reference case	EAG comment on company's submission
quality of life; NHS = National Health Service; NICE = National Institute for Health and Care Excellence; PSS = Personal Social Services; QALY = quality-adjusted life year; UK = United Kingdom		

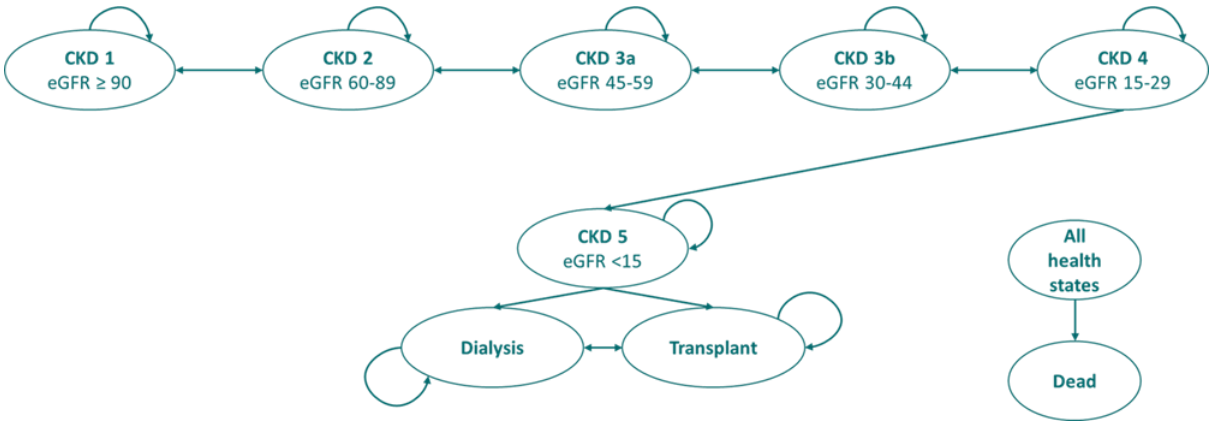
4.2.2 Model structure

4.2.2.1 Health states/events and transitions

The company developed a Markov model in Microsoft Excel® to assess the CE of TRF-budesonide for the treatment of primary IgAN in adults at risk of rapid disease progression with a UPCR ≥1.5 g/g.

The model consists of eight mutually exclusive health states and an absorbing mortality state as shown in Figure 4.1: the eight mutually exclusive health states are six core health states defined by the level of CKD disease (i.e., CKD 1, CKD 2, CKD 3a, CKD 3b, CKD 4, and CKD 5), and the health states of renal transplant and dialysis. Chronic kidney disease health states were populated using the baseline distribution of CKD states in the NefIgArd Nef-301 Part A study.

Figure 4.1: Model structure



Based on Figure 15 of the CS[1]
CKD = chronic kidney disease; CS = company submission; eGFR = estimated glomerular filtration rate

The CKD health states included in the model were defined using eGFR levels, despite the fact eGFR was a secondary endpoint in the NefIgArd Nef-301 study with the primary endpoint being UPCR levels. According to the CS, this is justified as there was no previously published CEA identified specific to IgAN patients, whilst the previously published cost effectiveness analyses in patients with CKD only used eGFR levels to define CKD stages.

Patients in the model can move between CKD states through neighbouring states at each cycle, except for patients in CKD 5, dialysis and transplant health states, who cannot return to an improved CKD health state. Transitions between dialysis and transplant health states are also only allowed between those two health states to account for patients experiencing transplant rejection and recurrent disease. Patients can move to the health state of death from every other health state, with the risk of death being informed from the UK RaDaR, a real-world evidence database.

Costs and utilities are applied to each health state to calculate total costs and quality-adjusted life year (QALYs) per model cycle, which was set at one month. A half-cycle correction is implemented in the model. The input values of the model and their underlying assumptions are further elaborated in the remaining part of Section 4 of the EAG report.

EAG comment:

The main concern of the EAG regarding the model structure considers the validity of the assumption that allowed patients in CKD 1-4 health states to transition to improved neighbouring health states (question B1 in the clarification letter).[3] Nonetheless, the company in their response clarified that this assumption was validated with clinical experts and further aligned with the model structure used in the previous TA775 NICE submission.[24]

4.2.3 Population

Consistent with the NICE scope, the population considered in the CS (Table 1 in CS[1]) was people with primary IgA nephropathy. The MHRA licensed indication of TRF-budesonide is for the treatment of primary IgAN in adults at risk of rapid disease progression with a UPCR ≥1.5 g/g. The phase 3 trial evidence for TRF-budesonide in this submission considers evidence from Part A of the NefIgArd Nef-301 study which included adult patients with primary IgAN with a UPCR ≥0.8 g/g or proteinuria ≥1 g/day. The patient population in the CS focused on the subgroup of patients who had a UPCR ≥1.5 g/g to align with the licensed indication and NICE scope (N=73). In total, 35 patients treated with TRF-budesonide and 38 patients treated with placebo completed the 9-month treatment period while having a baseline UPCR of ≥1.5 g/g. Data from these patients formed the FAS dataset and were used in the current submission. It is noteworthy that the decision problem and CEA as defined by the company in Table 1 of the CS [1]further restricts TRF-budesonide treatment to adult patients with IgAN who are on a stable dose of maximally tolerated RASi therapy (questions A6 and B2 in the clarification letter.[3])

The key baseline patient characteristics in the economic model were derived from the NefIgArd Nef-301 Part A study and are listed in Table 4.5 below.

Table 4.5: Key baseline patient characteristics used in the economic model

Parameter	Mean (%)	DSA* (Low; high values)	Source
Age	[redacted]	[redacted]	NefIgArd Part A data from NefIgArd Nef-301 for baseline UPCR ≥1.5 g/g subgroup 2022 [25]
Proportion female	[redacted]	[redacted]	
Average weight	[redacted]	[redacted]	

Based on Table 17 of the CS[1]
*Low and high values for age were sourced directly from the NefIgArd Part A study. In the absence of data, low, high values were calculated as ±10% of mean value.
CS = company submission; DSA = deterministic sensitivity analysis; UPCR = urine protein to creatinine ratio

EAG comment:

a) The main concerns of the EAG relate to the target population for the TRF-budesonide treatment as defined by the company in Table 1 of the CS. The company stated that according to the MHRA license of budesonide, the target population is limited to adult patients with primary IgAN who are on a stable dose of maximally tolerated RAS inhibitor therapy (ACEi or ARB) (see Section 2.1). In response to clarification questions A6 and B2, the company clarified that the NefIgArd Nef-301 trial '*required patients to be receiving a stable dose of RAS inhibitor therapy (ACEIs and/or ARBs) at the maximum allowed dose or maximum tolerated dose, according to the 2012 KDIGO guideline, for at least 3 months prior to randomisation'* and that patients would continue receiving this treatment during the trial duration. Moreover, in the SAS data of the NefIgArd Nef-301 trial, four

patients in the TRF-budesonide arm and two patients in the placebo arm were not receiving RAS inhibitor therapy at baseline because of tolerability issues with this therapy. The company in their response to question A6 stated that TRF-budesonide treatment is intended to be complementing SoC, which includes maximum tolerated RAS blockade, while patients not receiving maximally tolerated RAS inhibitor therapy should not be considered in this appraisal.[3] However, the company further in the response noted that patients who cannot tolerate RAS blockade therapy can still be eligible for TRF-budesonide, in line with anticipated use in clinical practice (see response in clarification question A6[3]). The EAG considers these statements to be subject to confusion (see EAG comment in Section 2.1).

b) Regarding the restriction of the patient population on the RASi therapy, the EAG also noticed that to inform the transition probability of patients from CKD 4 to CKD 5 in the SoC arm, the company presented data from the UK RaDaR database using different subgroups of patients (for EAG comment on the appropriate methods to inform this transition probabilities see EAG comment in Section 4.2.6). As part of this analysis, the company presented survival data for i) all patients in the UK RaDaR database who had IgAN and UPCR ≥1.5 g/g, consisting of [redacted] patients (Figure 17 of the CS[1]) ii) patients in the UK RaDaR database with IgAN who had a UPCR ≥1.5 g/g and were on ACEi and/or ARBs at baseline, consisting of [redacted] patients (Table 10 and Figure 3 of the clarification letter.[3] These numbers indicate that according to the UK RaDaR database, about 41% of patients with IgAN and UPCR ≥1.5 g/g will be using ACEi and/or ARBs at baseline. However, as mentioned above, in the NefIgArd Nef-301 trial only six patients in the SAS dataset ([redacted]) were not using RASi therapy at baseline, which raises concerns to the EAG about the representativeness of the trial population, especially if patients who cannot tolerate RAS blockade therapy are still eligible to receive TRF-budesonide treatment.
   In addition, the EAG would have liked to see the same patient characteristics as reported in Table 4.5 for the [redacted] and [redacted] selected patients from the UK RaDaR database, respectively.

4.2.4 Interventions and comparators

The intervention considered in the model was TRF-budesonide in combination with SoC. TRF-budesonide is self-administered as four 4 mg tablets once daily (OD) for 9 months which is consistent with the anticipated licenced indication. Before discontinuing TRF-budesonide treatment, patients would switch to 8 mg OD for 2 weeks. According to the MHRA license, TRF-budesonide may be reduced to 4 mg OD for 2 more weeks following the 9-month treatment period and the 2-week treatment discontinuation period, with the decision being at the discretion of the treating physician. This option is defined as treatment tapering throughout the CS and while it is excluded from the base case analysis, its impact on the cost effectiveness outcomes is explored in scenario analyses provided by the company.

According to the CS, at the discretion of the treating physician there is also the option of retreating patients with TRF-budesonide. In the base case analysis, the company assumed a second treatment round for patients in CKD stages 1 to 3b following 14.75 months from the completion of the original 9-month treatment round. The 14.75 months was informed using the time between completion of the TRF-budesonide treatment in Part A of the NefIgArd Nef-301 trial (9 months) and the start of the NefIgArd-OLE study, which was initiated at approximately 24 months following the NefIgArd Nef-301 Part A baseline visit. To account for treatment discontinuation during the first round of treatment, the company base case assumed that [redacted] of TRF-budesonide patients would undergo retreatment, based on the number of patients that completed the full treatment course in Part A of the NefIgArd Nef-301 study. When adjusted for the proportion of patients in CKD stages 1 to 3b at the time of retreatment, the percentage of patients receiving a second treatment round is [redacted] (see response to clarification question B11a.[3]).

The modelled comparator treatment is SoC without TRF-budesonide. To inform SoC in the CEA, the placebo arm of NefIgArd Nef-301 trial was used, in which SoC was defined as optimised and stable RAS blockade therapy. As per NICE scope, SoC should include ACE inhibitors and ARBs at the maximum tolerated licensed doses, diuretics and dietary and lifestyle modification, with or without 1) glucocorticoids and 2) SGLT2i. However, in the CS, glucocorticoids were not defined to be part of the SoC based on clinical experts' input stating that they would not use glucocorticoids in clinical practice to treat people with IgAN and a UPCR ≥1.5 g/g due to the low treatment benefits and safety profile of such treatments. Sodium-glucose cotransporter-2 inhibitors, on the other hand, were expected by clinical experts to be part of the SoC arm following clinical practice in the UK. Nonetheless, the NefIgArd Nef-301 trial did not include patients on SGLT2i because, at the time of recruitment, SGLT2i were not deemed to be part of SoC. Based on these, the economic analysis provided by the company only considered the costs of SGLT2i within the SoC arm and disregarded any treatment benefit derived from their use in their calculations. The company noted in the submission that this approach is justifiable considering the evidence in the DAPA-CKD study, in which dapagliflozin treatment in patients with IgAN (N=270) did not present a statistically significant improvement on eGFR over 36 months compared with placebo.[7] Regarding the list of comparators, the CS further stated that MMF treatment may also be used for Asian and Caucasian patients, even though this is not directly specified as a component of SoC in the NICE scope. However, MMF was also not included as a relevant comparator or part of the SoC in the CEA.

EAG comment: The EAG considers the composition of the SoC as defined in the CEA not to be aligned with the decision problem, as set out earlier in Section 2.3. The SoC in the CEA does not appropriately reflect the current treatment options for adult patients with primary IgAN at risk of rapid disease progression with a UPCR ≥1.5 g/g in the UK. For this reason, in the clarification phase the company was requested to incorporate the potential impact of 1) MMF, 2) glucocorticoids and 3) SGLT2i in the CEA as part of the SoC or as a separate comparator if appropriate using ITC methods in the absence of trial data (see questions A7, A8, A25, B3 of the clarification letter).[3] Especially for the SGLT2i, the EAG noted that, although dapagliflozin did not have a statistically significant impact on eGFR over 36 months compared with placebo, it has shown a numerical advantage in least mean squared eGFR, and a significant benefit in terms of the composite endpoint of sustained >50% decline in eGFR based on the DAPA-CKD study. For this reason, the company was requested to obtain more evidence relating to SGLT2i effectiveness using a systematic review and appropriate ITC methods and to incorporate the SGLT2i' effectiveness in the CEA (question A25 and B3 in the clarification letter).[3]

The company responded that 1) in UK clinical practice, MMF is rarely used and is only applied as a last-resort treatment option of IgAN in both Asian and Caucasian patients, conditional on an acceptable risk/benefit profile and if a clinical trial is not accessible, only reiterating what was already mentioned in the CS without appropriately addressing the question (response A7 in the clarification letter). Moreover, the company stated in clarification response B3 that "*patients receiving MMF should not be considered in this appraisal*" and referred to clarification response A6 on the reasoning. However, the EAG considers the response to clarification question A6 unclear as explained in Section 2.3; 2) immunosuppressants and corticosteroids were not considered to be relevant comparators for TRF-budesonide, because these would only be used in patients with severe kidney disease (i.e., patients with nephrotic syndrome or rapidly progressive glomerulonephritis), for whom the poor risk-benefit profile of these treatments would be justifiable in the absence of a clinical trial. Furthermore, the company stated that evidence on the efficacy of immunosuppressants or corticosteroids in patients with primary IgAN with nephrotic syndrome or rapidly progressive glomerulonephritis has not been

identified and similar to the response for the MMF patients, reported that *"patients receiving immunosuppressants or corticosteroids should not be considered in this appraisal"* (response B3 in the clarification letter). The EAG considers that the company provided an unsatisfactory response also in this question while the company's response was primarily repeating what had been written in the original CS (see also EAG comment in Section 2.3); 3) dapagliflozin is acknowledged to be administered in combination with TRF-budesonide as part of SoC and reiterated the argument included in the original CS that the DAPA-CKD study did not show a statistically significant impact on eGFR over 36 months following treatment with dapagliflozin compared with placebo in patients with IgAN (N=270). Furthermore, the company commented that because TRF-budesonide would be administered simultaneously to dapagliflozin as part of the SoC, any potential benefits derived from dapagliflozin would only be additive to the TRF-budesonide treatment effect, considering their different mechanisms of action (responses A25 and B3 in the clarification letter).[3] The EAG considers that the company also failed to appropriately answer this question as explained in Section 3.4 with the response only reproducing what was already written in the CS.[1]

4.2.5 Perspective, time horizon and discounting

The economic analyses were conducted from the perspective of the National Health Service (NHS) and Personal Social Services (PSS) perspective, in line with the NICE reference case. The model has a time horizon of 56 years that is considered appropriate as a lifetime horizon, in line with the NICE reference case, given that the average age of patients at the start of treatment is [redacted] years. Costs and QALYs were discounted at 3.5% as per the NICE reference case. The model cycle length is 1 month (30.4375 days), and a half-cycle correction is applied.

4.2.6 Transition probabilities, treatment effectiveness and extrapolation

The main sources of evidence on treatment effectiveness used for the intervention and comparator arms are Part A of the NefIgArd Nef-301 trial and the UK RaDaR database.

4.2.6.1 Transition matrices between CKD 1 - CKD 4 health states

Transition probabilities between CKD 1 and CKD 4 health states were estimated by comparing the eGFR values at baseline and after 9 months of treatment which were then mapped to reflect patients in different CKD health states (see Figure 4.1 for cut-off points for eGFR per health state). Logistic regressions were fitted to patient level data from PART A of the NefIgArd Nef-301 trial and were used to estimate the log odds of transitioning to a better or worse CKD health state, evaluated by treatment arm and baseline CKD stage. The log odds ratios were converted to 9-month transition probabilities and thereafter to monthly probabilities to align with the model cycle length. Table 4.6 below shows the monthly transition probabilities for CKD 1 to CKD 4 health states. As there were no patients in the NefIgArd Nef-301 trial with CKD 4 at baseline, transitions in CKD 4 were assumed equal to transitions in CKD 3b. The CS stated that patients discontinuing treatment were assumed to incur the TRF-budesonide transition probabilities as patients completing the 9-month treatment.

Table 4.6: CKD 1 – CKD 4 monthly transition probabilities (0–12 months)

Treatment Arm/ Baseline CKD stage	CKD stage at 9 months					
	CKD 1	CKD 2	CKD 3a	CKD 3b	CKD 4	Total
TRF-budesonide						
CKD 1	[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]
SoC						
CKD 1	[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]

Based on Table 20 of the CS[1]
CS = company submission; CKD = chronic kidney disease; SoC = standard of care; TRF = targeted-release formulation

Although the transitions presented in Table 4.6 above were calculated based on a 9-month follow-up period, these transitions were assumed to be applicable for a 1-year period. This was justified based on the eGFR levels in the TRF-budesonide and placebo arms seen in the 3-month of off-treatment observational follow-up period. The 3-month observational follow-up analysis showed that the treatment effect of TRF-budesonide compared to placebo observed in the 9-month treatment period was maintained during this observational period (see Figure 16 of the CS).[1]

Regarding the transition probabilities for subsequent years, there were no data available from Part A of the NefIgArd Nef-301 trial beyond 12 months. Therefore, these transitions in both the TRF-budesonide and SoC arms were set equal to the transition probabilities observed in the NefIgArd Nef-301 SoC arm during the 9-month follow up period, as presented in Table 4.6 above. According to the company, this is in line with the NefIgArd Nef-301 Part B where the change in eGFR of the TRF-budesonide arm from month 12 to month 24 was not significantly different to that of the placebo arm for the full trial population.

4.2.6.2 Transitions probabilities from CKD 4 to CKD 5 health states

Since CKD 4 patients were not eligible to participate in the NefIgArd Nef-301 trial, the transition probability from CKD 4 to CKD 5 in the SoC arm was informed using real-world evidence from patients with IgAN and UPCR ≥1.5 g/g from the UK RaDaR database. As shown in Figure 4.2, Kaplan-Meier (KM) curves estimating the probability of progressing from CKD 4 to ESRD or mortality for a follow-up period of 4 years from the UK RaDaR database were digitised to obtain pseudo patient level data (PLD), which were then used to fit different parametric survival models. End-stage renal disease was assumed to be equivalent to CKD 5 in this process. The gamma model was selected for the base case analysis, based on Akaike information criterion (AIC) and Bayesian information criterion (BIC) statistics and clinical plausibility (see response to clarification question B6), while the impact of using alternative parametric models was explored in the scenario analyses.[3]

Figure 4.2: UK RaDaR KM curve estimating time from CKD 4 diagnosis to ESRD or mortality in patients with IgAN.

Based on Figure 17 of the CS[1]
CS = company submission; CKD = chronic kidney disease; ESRD = end-stage renal disease; IgAN = immunoglobulin A nephropathy; KM = Kaplan Meier; RaDaR = National Registry of Rare Kidney Diseases; UK = United Kingdom; UPCR = urine protein to creatinine ratio

In the TRF-budesonide arm, the transition probability from CKD 4 to CKD 5 was estimated by applying a HR of [redacted] to the respective risk in the SoC arm. The HR ratio was estimated using an intercept and a slope coefficient from a published meta-analysis of 47 studies which used the treatment effects on eGFR slope from baseline and from 3-month follow-up to predict benefits on clinical end points (HR).[26] The observed treatment effect on the 1-year eGFR total slope in the sub-population of patients from the NefIgArd Nef-301 trial with baseline UPCR ≥1.5 g/g of [redacted] ml/min/1.73 m^2 per year (95% CI: [redacted], [redacted]) predicted a HR of [redacted] for the clinical outcome.[1]

The duration of the treatment effect in the base case analysis was assumed to be one year, similar to the treatment effect estimated for CKD 1 to CKD 4 health states. Thus, the transition probability from CKD 4 to CKD 5 beyond 12 months in the TRF-budesonide arm was also assumed to be equal to the respective in the SoC arm.

EAG comment:

a) The main concerns of the EAG relate to the transition probabilities from CKD 4 to CKD 5 that in the base case of the company were estimated using survival data for patients with IgAN and UPCR ≥1.5 g/g from the UK RaDaR database. As discussed in the clarification question B6, these probabilities were estimated using the digitised patient level data from Figure 4.2 presented above. However, Figure 4.2 shows the survival probability from diagnosis of CKD 4 to ESRD or death, with the event cases between ESRD or death being indistinct and hence the estimated transition probabilities for patients from CKD 4 to CKD 5 not being appropriately defined. In addition, due to the separate modelling of mortality from CKD 4, too many patients will leave the CKD 4 state

each month due to a form of double counting. Thus, the EAG requested the company to explain if and how the two different events (ESRD or death) were distinguished from the available UK RaDaR data (see clarification question B6).[3] The company confirmed in their response that the events between ESRD and death cases from Figure 4.2 could not be separated. To address this limitation, the company provided in the clarification phase additional survival data from the UK RaDaR database assessing the time from CKD 4 diagnosis to ESRD in patients with IgAN and UPCR ≥1.5 g/g as shown in Figure 4.3 below. The company noted that in this survival data, patients who died were censored if they did not reach ESRD before their time of death. The company explained that because of this censoring, the number of ESRD events were likely inflated due to the smaller sample of patients, as it seemed less clinically plausible that the risk of ESRD in Figure 4.3 to be greater than the risk of ESRD or death in Figure 4.2. Therefore, the company considered the UK RaDaR data that used the combination of ESRD or death to measure event outcomes to be more appropriate for the base case analysis. Nonetheless, a scenario analysis was conducted in the clarification phase using the updated UK RaDaR data with only ESRD as event outcome (Figure 4.3) and an exponential model for long-term extrapolations (best fit based on AIC and BIC values). The ICER in this scenario increased from £21,872 per QALY gained (new company's base case following the clarification phase) to £26,143 per QALY gained. However, it is presently unclear to the EAG why the number of patients at risk at t=0 in Figure 4.3 ([redacted]) is different than the same number in Figure 4.2 ([redacted]) above, as the additional analysis only entails a change in the recording of the death events. Based on this and additional reasons that are explained below, the EAG considers it very likely that this analysis has been implemented incorrectly.

Figure 4.3: UK RaDaR KM curve estimating time from CKD 4 diagnosis to ESRD in patients with IgAN

Based on Figure 1 of the clarification response[3]
CKD = chronic kidney disease; ESRD = end-stage renal disease; IgAN = Immunoglobulin A nephropathy; KM = Kaplan Meier; RaDaR = National Registry of Rare Kidney Diseases; UK = United Kingdom; UPCR = urine protein to creatinine ratio

b) In addition to the scenario presented above (using UK RaDaR data to assesses the time from CKD 4 diagnosis to ESRD in patients with IgAN and UPCR ≥1.5 g/g), the company conducted two additional scenario analyses in the original submission to inform the risk of transitioning from CKD 4 to CKD 5 health states. The EAG requested further details on these two scenarios in the clarification phase (question B7).[3] The first scenario considered a subpopulation of the UK RaDaR data focussing on patients with IgAN, UPCR ≥1.5 g/g and being on ACEi and/or ARBs at baseline. According to this scenario, of the total number of [redacted] patients that were originally identified in the UK RaDaR database to have IgAN and UPCR ≥1.5 g/g presented in Figure 4.2 above, [redacted] patients would be on ACEi and/or ARBs at baseline (Table 10 and Figure 3 in the clarification letter). The EAG noticed that Figure 3 in the clarification letter presenting the survival data for this scenario analysis is the same as Figure 1 in the clarification letter (shown in Figure 4.3 above) which was used to inform the risk from CKD 4 diagnosis to ESRD in patients with IgAN and UPCR ≥1.5 g/g. The EAG thinks this is an error which may have further led to an implementation error in the electronic model for the scenario analysis presented above. Figure 4.4 below presents the survival data included in the electronic model for the different subgroups of patients from the UK RaDaR database. The survival curves for the subpopulation using ACEi and/or ARBs at baseline and focusing only on ESRD event outcomes almost overlap. Also, although the estimated parametric model fits in the electronic model for all distributions are close to each other for these two scenarios, the covariances matrices are quite different for many distributions, with some of them having non-permitted values (i.e., one variance is negative, and one covariance implies a correlation >1, both in analysis for all patients, with only ESRD as event). These issues in combination with the comment around the number of patients at risk at t=0 discussed above, strengthen the EAG concerns around erroneous implementation for the scenario analysis focusing on ESRD event outcomes, which the EAG is unable to resolve. Note that in the scenario presented by the company in which the risk of CKD 4 to CKD 5 was informed from patients with ACEi and/or ARBs at baseline, the ICER increased from £21,872 per QALY gained (new company's base case following the clarification phase) to £25,921 per QALY gained (using the exponential distribution).

Figure 4.4: KM curves estimating time from CKD 4 diagnosis to ESRD in patients with IgAN based on the survival data in the electronic model

Based on survival data included in the electronic model[3]

ACEi = angiotensin converting enzyme inhibitors; ARB = angiotensin receptor blockers; CKD = chronic kidney disease; ESRD = end-stage renal disease; IgAN = immunoglobulin A nephropathy; KM = Kaplan-

Meier; RaDaR = National Registry of Rare Kidney Diseases; UK = United Kingdom; UPCR = urine protein to creatinine ratio

c) The second scenario informing the risk from CKD 4 to CKD 5 in the original submission used data from a real-world registry from patients at Leicester General Hospital (LGH) in the UK between 1992 to 2020. As revealed in the response to clarification, patients from the LGH registry were matched to NefIgArd Nef-301 patients, using baseline eGFR between 35 and 90 ml/min/1.73 m^2 and either proteinuria ≥1 g per day or UPCR ≥0.8 g/g. Patients were further selected for UPCR ≥1.5 g/g.[3] The matching was done on a 5:1 ratio using a maximum of five LGH registry patients for each patient in the NefIgArd Nef-301 trial, leading to 294 matched records. Of the 294 LGH matched patient records included in the analysis, 114 had an event which was defined as the earliest of confirmed doubling of serum creatinine, confirmed eGFR <15 ml/min/1.73 m^2 or ESRD. The KM curve estimating the time from CKD 1-4 diagnosis to ESRD is shown in Figure 4.4 above. To obtain the risk of transitioning from CKD 4 (as opposed to CKD 1-4) to CKD 5, the company assumed that the increased risk of death for patients in CKD 4 versus CKD 1-4 is equal to the increased risk of transitioning to CKD 5. To make this adjustment, an HR of [redacted] was used which was estimated using the probability of death for patients with CKD 4 versus all patients in CKD 1-4 from Hastings 2018.[27] Due to this adjustment, the company considered these data inappropriate for the base case analysis. The KM data from the LGH registry following the adjustment is also presented in Figure 4.4 above. The ICER using the LGH data increased from £21,872 per QALY gained (new company's base case following the clarification phase) to £27,429 per QALY gained (using the exponential distribution).

d) Following the evidence presented above, the EAG considers the LGH data more appropriate for the base case analysis. The UK RaDaR data using all patients with IgAN and UPCR ≥1.5 g/g and ESRD and death cases to define the event outcome are likely overestimating the risk of ESRD as they are also accounting for the risk of death and are not considered to be appropriate for the base case analysis. The survival analysis conducted in the clarification phase using the UK RaDaR data for patients with IgAN and UPCR ≥1.5 g/g and ESRD only to define the event outcome could address this limitation, but based on the EAG concerns above, this analysis is thought to be conducted incorrectly. The UK RaDaR data using all patients with IgAN, UPCR ≥1.5 g/g and ACEi and/or ARBs at baseline and ESRD and death cases to define the event outcome is also suffering from the same limitations similar to the company's preferred option for the base case analysis, although this patient subgroup is more representative of the trial population (see comments in Section 4.2.3), considering that about 41% of patients with IgAN and UPCR ≥1.5 g/g will be using ACEi and/or ARBs at baseline according to the UK RaDaR database. Matching real-world data to trial data as done with the LGH survival analysis can address some of the limitations in the UK RaDaR database producing a higher sample size population, although the EAG agrees with the company that assuming the increased risk of death for patients in CKD 4 versus CKD 1-4 is equal to the increased risk of transitioning from CKD 4 versus CKD 1-4 to CKD 5 is subject to uncertainty. The EAG also considered that the CKD 4 to CKD 5 transitions using the LGH data and the UK RaDaR data with baseline ACEi and/or ARBs are more aligned than when using all patients from the UK RaDaR database as per company's preferred option. This is also evident in the impact of those two scenarios on the cost effectiveness outcomes with both scenarios increasing the company's base case ICER by about a similar order of magnitude.

4.2.6.3 Transition probabilities between CKD 5, dialysis, and kidney transplant health states

Transition probabilities between CKD 5, dialysis, and transplant health states were sourced from NICE TA775 and were assumed equal for both the TRF-budesonide and SoC arms, indicating that patients in CKD 5 health state do not encounter any treatment benefit from TRF-budesonide compared to SoC.[24]

The transitions from CKD 5 to dialysis and transplant health states in TA775 were informed from the DAPA-CKD trial whereas the transitions from dialysis and transplant health states were obtained from a systematic literature review by Sugrue 2019.[28]

EAG comment: In question B10 of the clarification letter the EAG asked after the face validity of the monthly transition probability from CKD 5 to dialysis of 4.5%, which results in a probability of still being in CKD 5 without dialysis after one year of >50%.

The company indicated that, in the absence of trial data from NefIgArd Nef-301, and as the model health states are based on eGFR values, the data from the DAPA-CKD trial was considered appropriate to inform this transition. They argued that although the face validity of this transition probability was not assessed in the Advisory Board, the same transition is applied to both the TRF-budesonide and SoC arm of the model. Additionally, previous engagements with clinicians have indicated that, as CKD 5 is distinct from ESRD and does not always require renal replacement therapies (i.e., dialysis), patients with CKD 5 can experience long durations without requiring such therapies.

Nonetheless, the company provided an additional scenario analysis which demonstrated that increasing the transition probability such that the majority of patients with CKD 5 will receive dialysis after 1 year causes the ICER to decrease (See Table 18, clarification letter). Therefore, the transition probability in DAPA-CKD is considered a conservative and appropriate data source given the lack of alternative data sources.

The EAG agrees that increasing the probability of dialysis will lead to a lower ICER. At the same time, the EAG would like to point out some inconsistency regarding the health states CKD 5 and ESRD, as at various points in the company submission it is remarked that CKD 5 will be considered equivalent to ESRD, whereas in their response to this question it was remarked that CKD 5 is distinct from ESRD. A more consistent terminology would enhance the clarity of what each health state entails.

4.2.6.4 Treatment effectiveness for retreated patients

As discussed in Section 4.2.4, the company included in the model the option to retreat patients in the TRF-budesonide arm. The transition probabilities for the retreated patients with TRF-budesonide in all CKD stages were set equal to the respective 12-months transition probabilities from the first round of treatment, and this assumption was implemented in the model to any round of retreatment, even though in the base case analysis only one retreatment round was assumed. The transition probabilities beyond 12 months in the retreated patients with TRF-budesonide were dependent on the selected duration of the TRF-budesonide treatment effect. The proportion of patients on retreatment [redacted] was also informed by the time-to-treatment discontinuation (TTD) curve observed in the NefIgArd Nef-301 Part A trial, as this was used to inform the proportion of patients in the first treatment round of TRF-budesonide (see Section 4.2.4 for further details).

EAG comment:

a) Considering the company's statement that patients discontinuing the TRF-budesonide treatment before 9 months were assumed to incur the same transition probabilities between CKD 1 to CKD 4 health states as those remaining in full treatment, the EAG asked the company to provide further details on the number of patients and reasoning for treatment discontinuation, and to re-estimate the transition probabilities between CKD 1 to CKD 4 health states while accounting for patients discontinuing treatment (see clarification question B5).[3] The company responded that four patients in the TRF-budesonide arm and seven in the placebo discontinued treatment due to adverse events [redacted], withdrawal of informed consent [redacted], pregnancy [redacted], and other reasons [redacted]. In the

response, it was explained that for the estimation of the transition probabilities the FAS dataset of the NefIgArd Nef-301 Part A trial was used, which included all patients who had received at least one dose of the study drug and who had the opportunity to receive the full 9-month treatment regimen. This is in essence patients that received at least one dose of treatment and had the opportunity to complete their 9-month visit (see response to clarification question A16). Consequently, the company clarified that these data inherently captured the impact of treatment discontinuation and the estimated transition probabilities also account for the disease progression of patients that discontinued treatment. The EAG considers this response sufficient.

b) The base case analysis of the company accounted for one retreatment round with TRF-budesonide, while the scenario analyses explored the impact of using no retreatment option or a higher number of retreatment rounds. The EAG observed some inconsistencies in the model outcomes to changes in the parameter that define the proportion of retreated patients which were explained in clarification question B11.[3] The company confirmed that inconsistencies were due to modelling errors in the implementation of the transition probability to CKD 5 in the TRF-budesonide arm for the retreatment rounds, the treatment effect on transitions from CKD 4 to CKD 5 for those receiving a retreatment, and the TRF-budesonide treatment effect on the risk of CKD 5 from CKD 4 health state. Following these corrections, the company's base case analysis led to an ICER change from £18,643 per QALY gained to £21,872 per QALY gained (response B11 in the clarification letter).

c) In the base case analysis, the company assumed that transition probabilities for patients in the retreatment round will follow the 0–12 month TRF-budesonide transition probabilities in the initial 12 months of treatment, so assuming that use of TRF-budesonide will have the same treatment benefit for the retreated patients. The EAG noticed that, in the absence of any data, there is much uncertainty regarding the retreatment of patients and specifically around the assumptions used to inform the retreatment parameters, such as the effectiveness of the retreatment option, the percentage of patients that would undergo retreatment and also the timing of the retreatment (14.75 months following the 9-month period), which was based on the starting point of the NefIgArd-OLE study and assumed to be the '*initial minimum time between treatment cycles'* as noted in response B11 of the clarification letter.[3] The uncertainties around the retreatment parameters have also been acknowledged by the company throughout the CS with some alternative number of retreatment rounds explored in the scenario analyses, even though scenarios exploring the impact of the timing between treatment rounds and the proportion of patients undergoing retreatment were not investigated. To address these uncertainties the EAG asked the company to explore the impact of alternative options regarding time between treatment rounds and the proportion of patients that are eligible for retreatment (clarification question B11). The EAG also asked the company to allow for a reduced benefit of TRF-budesonide for the retreated patients, by including in the model an additional parameter that accounts for a lower treatment effect in the TRF-budesonide retreated patient population (clarification question B12). As shown in these responses, the cost effectiveness outcomes were quite sensitive to the proportion of patients eligible for retreatment. Aligned with the input from clinicians the EAG agrees that, although still uncertain, in case of retreatment, 14.75 months would indeed be the initial minimum time between treatment cycles, aligning with the timing of the open-label extension trial. However, the company reported in Section B.2.11 of the CS that the preliminary data analyses from Part B of NefIgArd Nef-301 demonstrate a consistent and highly statistically significant benefit in eGFR for TRF-budesonide compared with placebo in the 15-months of follow-up observational study, as reported, the timing of the retreatment option may be shifted even further. The EAG considers the company's assumptions on the proportion of patients eligible for, and actually receiving, retreatment and the TRF-budesonide treatment effectiveness for the retreated patients optimistic, as they are not based on any evidence. As such, these assumptions are subject to considerable uncertainty. Therefore, the EAG will set retreatment

to 0 in an EAG preferred base case analysis, whilst also exploring the impact of alternative options in the scenario analysis as explained in Section 6.1.2.

4.2.6.5 Mortality

In absence of mortality data from the NefIgArd Nef-301 trial, data from the UK RaDaR database were used to inform the mortality rates from CKD stages 1–5 and dialysis by fitting Cox regression models using age, sex, and CKD stage as covariates. Background mortality was age- and sex-adjusted and estimated using UK life tables from the Office for National Statistics (ONS).[29] The impact of using alternative sources of mortality were explored by the company in the scenario analyses using the studies from Greene 2019[30] which assumed a linear relationship between the risk of death and eGFR levels to compute death rates per CKD stage and Hastings 2018,[27] a US study using patients with IgAN but not focussed on UPCR ≥1.5 g/g.

EAG comment: In general, the EAG agrees with the company that the UK RaDaR database is likely the best source of data to estimate mortality for the various health states. However, the EAG would have preferred to see more details about the population from which the data was extracted and more details about the Cox regression models.

4.2.7 Adverse events

Treatment adverse events used for both the TRF-budesonide and SoC arms were informed from the SAS of the NefIgArd Nef-301 trial. All commonly reported TEAEs that occurred in ≥4% of participants in either TRF-budesonide or SoC arms of the SAS were included in the model. Additionally, all treatment-emergent severe adverse events (TESAEs) occurring in more than one patient were also included in the analysis. The TESAEs according to the CS were pulmonary embolism and renal impairment. Table 23 of the CS shows the event rates for these AEs in each of the arms. For all included AEs the probability of occurrence is slightly higher in the TRF-budesonide arm than the comparator arm.[1]

4.2.8 Health-related quality of life

Utility values were collected for the CKD specific health states, namely: CKD 1, CKD 2, CKD 3a, CKD 3b, CKD 4 and CKD 5. In addition, utility values were collected for the treatment specific health states haemodialysis, peritoneal dialysis, and post-transplant.

4.2.8.1 Health-state utility values

Literature sources were consulted to inform the HSUVs in the model. According to the CS, this was the best approach in the absence of EQ-5D data in the NefIgArd Nef-301 trial and the concern that mapping the collected SF-36 trial data to the EQ-5D would introduce additional uncertainty due to the lack of IgAN-specific mapping studies.

No UK-specific EQ-5D studies were identified in the economic SLR for patients with IgAN. Therefore, references from recent CKD submissions to NICE were cross-checked. The TA775 NICE submission refers to Cooper 2020[21] which reports an SLR of HRQoL utility weights for CKD stages. From the overview presented by Cooper 2020 the utility values calculated using the European Quality of Life-5 Dimensions, 3 Levels (EQ-5D-3L) questionnaire from the study by Jesky 2016, performed in the UK, were selected for the utility values for patients in CKD 1 to CKD 5 health states.[22]

Utility values for patients in the dialysis and post-transplant health states were also extracted from Cooper 2020 using the UK-specific EQ-5D-3L values from Lee 2005.[23] For the utility value in the health state of dialysis, patients were assumed to receive either haemodialysis (86.5%) or peritoneal

dialysis (13.5%) distributed per the proportion reported in the United Kingdom Renal Registry (UKRR) 24th Annual Report.[29, 31]

The CS stated that not having utility values from patient groups with characteristics matched to NefIgArd Nef-301 patient characteristics is a limitation of the evidence. However, expert clinical opinion confirmed that the utility values used from the CKD studies were considered reasonable proxies.

A summary of all utility values used in the CEA is provided in Table 4.7 below.

Table 4.7: Health state utility values

Health state	Utility value	Reference	Justification
CKD 1	0.85	Cooper 2020.[21] From Cooper [21] only values from Jesky 2016 selected for CKD 1 to CKD 5 health states,[22] whereas for dialysis and post-transplant utility values from Lee 2005 were selected[23]	No UK-specific EQ-5D studies identified in the economic SLR for patient with IgAN. Cooper 2020[21] is a review paper and was identified in the TA775).[24]
CKD 2	0.85		
CKD 3a	0.80		
CKD 3b	0.80		
CKD 4	0.74		
CKD 5	0.73		
Haemodialysis	0.44		
Peritoneal dialysis	0.53		
Post-transplant	0.71		
Based on Table 25 and Table 26 CS.[1] CKD = chronic kidney disease; EQ-5D = EuroQoL-5 Dimensions; IgAN = immunoglobulin A nephropathy; SLR = systematic literature search; UK = United Kingdom			

4.2.8.2 Disutility values

In the cost effectiveness model (CEM) the disutilities due to AEs were applied as one-off utility decrements in the first on-treatment cycle to all patients in each arm. A targeted literature review provided information about the assumption of the duration and disutility of the AEs capture in the model. Only three out of the 13 included adverse events durations, namely upper respiratory tract infection (6.61 days), pulmonary embolism (6.61 days), and renal impairment (6.29 days), were informed by literature. For the other adverse events, a 1-week duration was assumed.

When no disutility could be found, a disutility of 0 was assumed. This happened for four out of the 13 included AEs, i.e., acne, weight increase, pulmonary embolism, and renal impairment (Table 4.8).

Table 4.8: Adverse event disutility values

Adverse event	Utility value	Source	Duration (days)	Source
Treatment-emergent adverse events				
Acne	-0.00	Assumption	7.0	Assumption
Cushingoid	-0.16	Sullivan 2011[32]		
Dyspepsia	-0.04			
Oedema peripheral	-0.16	Assumed same as cushingoid		
Face oedema	-0.16			
Headache	-0.04	Sullivan 2011[32]		

Adverse event	Utility value	Source	Duration (days)	Source
Hirsutism	-0.00			
Hypertension	-0.05			
Mood swings	-0.13			
Upper respiratory tract infection	-0.00	Sullivan 2006 [33]	6.61	NHS ref 17/18: Total HRG's - weighted average non-elective length of stay CB02A - CB02F [34]
Weight increase	-0.00	Assumption	7.00	Assumption
Treatment-emergent serious adverse events				
Pulmonary embolism	-0.00	Assumption	6.61	NHS ref 17/18: Total HRGs - weighted average non-elective length of stay DZ09J - DZ09Q [34]
Renal impairment	-0.00		6.29	NHS ref 17/18: Total HRGs - weighted average non-elective length of stay LA09J - LA09Q [34]

Based on Table 27 and 28 of the CS[1]
AE = adverse event; CS = company submission; HRG = health resource group; NHS = National Health Service

Total QALY loss attributed to each AE was estimated by combining the expected duration of the adverse event (in years) with each corresponding disutility value. These QALY loss per event values were then multiplied with the respective AE occurrence rates per treatment arm to estimate the total AE attributable QALYs lost per treatment arm (see CS Table 29). These total QALYs lost per treatment arm, 0.0156 for the TRF-budesonide arm and 0.0029 for the SoC arm, were applied in the model as one-off QALY decrement in the first model cycle of their respective treatment arm.

When retreatment with TRF-budesonide is enabled in the CEM, QALY decrements for the AE are applied in the first cycle of each retreatment round. The total QALY decrement at that point is estimated using the total QALYs lost per treatment arm for TRF-budesonide multiplied with the proportion of TRF-budesonide patients who are eligible to receive retreatment.

4.2.8.3 Age- and sex-adjusted utility decrements

The health state utility values were adjusted based on the expected utility decrement associated with aging. This age specific decrement was estimated using the algorithm published by Ara and Brazier[35] which estimate the age- and sex adjusted utility values for the general population. Based on the proportion of females in the study ([redacted]), a sex weighted age-specific utility for the general population was calculated. This value was divided by the base utility, to get an age-specific multiplier that can be used to adjust for the decrement over time.

The algorithm for the general utility weights reads:

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

EAG comment: The SF-36 data for health states CKD 1 to CKD 4 collected in the NefIgArd Nef-301 trial were effectively disregarded by the company, on the basis that SF-36 is not a disease-specific tool. In the clarification phase, the company were asked the reason behind not using a disease-specific tool instead (clarification letter question A19). As commented by the EAG in Section 3.2.5.5, the company did not respond to the question sufficiently, while only reiterating that the clinical benefits of TRF-budesonide in terms of QoL would be expected to be more evident in ESRD and dialysis in patients and as Part A of NefIgArd Nef-301 study only assessed 12 months of data, not many patients reached ESRD or dialysis health states. Given that QoL is a key outcome for establishing cost effectiveness, the EAG was concerned that no differences between arms were detected at the available follow-up, and thus asked the company to conduct a scenario analysis using the SF-36 data (clarification letter question B15). The company responded that considering the time frame of the clarification phase, they were not able to generate utility values using the SF-36 data and run a scenario analysis. Alternatively, they mentioned that the SF-36 data appears to demonstrate minimal differences in the QoL across health state CKD 1-4. Based on this, the company provided two scenario analyses assuming the health state utility in state CDK 1-4 (scenario 1) or CKD 1-3b (scenario 2) to be equivalent to the utility values for CKD 1. The respective ICERs decreased to £19,979 per QALY gained in scenario 1 and to £19,964 per QALY gained in scenario 2, compared to the company base case after clarification of £21,872. Although the EAG considers these scenarios informative at this point in time, when only evidence from part A is available, the QoL evidence from the trial becomes more important once evidence from Part B becomes available, as that data will presumably include more patients in ESRD or dialysis health states.

The EAG noted that the company in the base case analysis assigned a disutility value of zero to serious adverse events, i.e., the pulmonary embolism and renal impairment. In response to EAG's question (clarification letter question B13), the company responded that the initial targeted literature review did not yield disutility values or length of duration for pulmonary embolism or renal impairment. Further targeted literature reviews were since conducted which yielded disutility values of 0.018 for pulmonary embolism [34] and 0.0603 for renal impairment.[36] The targeted literature review also identified a disutility duration for pulmonary embolism of 1 month,[37] whilst assumed the same duration of 1 month for renal impairment in the absence of further evidence. The company included these values in a scenario analysis, which showed only a small impact. Nonetheless, the EAG considers the base case assumptions from the company unrealistic and will therefore include the newer estimates for the disutility and duration into an EAG preferred base case analysis.

4.2.9 Resources and costs

The cost categories included in the model were treatment acquisition costs for TRF-budesonide, standard of care costs, medical costs (secondary care, primary care, dialysis-related costs and transplantation costs), terminal care costs, and costs of managing adverse events.

Unit prices were based on the NHS reference prices, British National Formulary (BNF), Personal Social Services Research Unit (PSSRU) and electronic Market Information Tool (eMIT).

4.2.9.1 TRF-budesonide treatment costs

The company estimated a monthly cost of the TRF-budesonide treatment based on four 4 mg tablets administered OD for 9 months. TRF-budesonide was administered orally. The list price of TRF-budesonide is [redacted] for a package of 120 tablets of 4 mg. [redacted]. At the end of the 9-month treatment period, TRF-budesonide should be reduced to 8 mg OD for 2 weeks of therapy as per MHRA license. Following the MHRA license, TRF-budesonide can also be

administered at a dose tapering period of 4 mg OD for an additional 2 weeks following the end of the 9-month course and the 2-weeks period of reduced therapy. However, as the tapering treatment decision is at the discretion of the treating physician and based on clinical expert opinion, the company did not include the tapering option in the base case analysis, whilst exploring its impact on the cost effectiveness outcomes in the scenario analyses. Table 4.9 below presents the TRF-budesonide treatment costs per model cycle as used in the electronic model.

Table 4.9: TRF-budesonide treatment costs

Treatment period	Dose per day	Days per model cycle	Costs per model cycle
9-month treatment	4 x 4 mg	30.44	[redacted]
2-week reduced dose period	2 x 4 mg	14	[redacted]
2-week tapering period	1 x 4 mg	14	[redacted]

Based on the electronic model.[3]
mg = milligram; TRF = targeted-release formulation

To account for patients discontinuing treatment before 9 months and ensure that these patients did not incur the full treatment costs of TRF-budesonide, the number of patients that continued treatment each month was informed by the TTD data from Part A of the NefIgArd Nef-301 study (CS Figure 21). Considering the reduced-dose treatment period, all patients on treatment at the start of the last month of the 9-month treatment course were assumed to receive a reduced dose.

For patients undergoing retreatment, TRF-budesonide treatment costs were estimated based on the proportion of patients eligible for retreatment and the 9-month cost of TRF-budesonide treatment.

4.2.9.1.1 Wastage and relative dose intensity

The model assumed no wastage associated with the treatment of TRF-budesonide, as the cost of TRF-budesonide used a cost-per-mg approach in the calculations. According to the CS, this was justified as it is expected that [redacted].

Relative dose intensity (RDI) was also not part of the base case analysis. According to response to clarification question B18, the compliance rate in the FAS of Part A of the NefIgArd Nef-301 trial was [redacted] in patients receiving TRF-budesonide. However, the CS stated that it is anticipated in practice that any dose reductions or treatment breaks will have no consequence for treatment acquisition costs and considered the cost for the full TRF-budesonide treatment course relevant for the base case calculations.

EAG comment: The EAG agrees with the company that an RDI of [redacted] is unlikely to have consequences for the treatment acquisition costs but is not convinced that this is true for *any* dose reduction or treatment breaks unless the treatment were packaged per 9-month treatment course.

4.2.9.2 Standard of care treatment costs

Standard of care costs consisted of ACEi or ARBs, and treatments indicated for renal disease in adult patients with hypertension and type 2 diabetes mellitus and the SGLT2i dapagliflozin. The SoC treatment costs were applied to both the TRF-budesonide and SoC arms and were sourced from the eMIT.[38] For each treatment in the SoC the cost per month was calculated based on the number of tablets required per day, the cost per tablet (calculated as the pack price divided by the number of tablets per

pack) and the model cycle length (30.4375 days). For ACEi and ARBs, the average monthly cost was obtained producing a total SoC monthly cost of £63.71.

Table 4.1011: SoC treatment costs

Treatment period	Weights	Monthly cost	Weighted average cost
ACEi	50%	£3.45	£1.73
ARB	50%	£4.64	£2.32
SGLT2i	100%	£59.66	£59.66
Weighted average cost of SoC			**£63.71**

Based on Table 34 of the CS[1]
ACEi = angiotensin converting enzyme inhibitor; ARB = angiotensin receptor blockers; CS = company submission; SGLT2i = sodium-glucose cotransporter-2 inhibitors; SoC = Standard of care

EAG comment: The company included only two classes of drug treatment in their estimation of SoC treatment costs. In Table 4 in the response to the clarification letter, the company presented an overview of other classes of concomitant medication used by at least 10% of total patients in NefIgArd Nef-301 Part A with baseline UPCR ≥1.5 g/g. For completeness's sake, the EAG costed out the various classes of drugs, followed by the estimation of a weighted average, using the percentage of patients using a drug from a certain class as weights. This amounted to an estimated additional SoC costs of £3.67. This value will be added to the SoC costs in the EAG preferred base case. For details regarding the calculations see Appendix 1.

4.2.9.3 Health state costs

For each health state in the model a cycle cost for medical resource use (MRU) was estimated. For CKD stages 1 to 5, the cost of MRU was sourced from Kent 2015[39] which explored the impact of CKD stage and cardiovascular disease on the annual cost of hospital care in moderate to severe kidney disease. Kent 2015 estimated the cost of secondary care, including inpatient admissions, day cases and outpatient attendances. All costs were inflated to 2021 costs using the PSSRU inflation indices.[40] Primary care costs including general practitioner (GP) appointments and blood tests were sourced from the PSSRU and the NHS National Cost Collection 2021/22 data.[38, 41] GP appointments and blood tests were assumed to occur twice a year for CKD stages 1 to 3b and once every three months for CKD 4 and CKD 5.

For dialysis, 86.5% of patients were assumed to receive haemodialysis and 13.5% peritoneal dialysis based on the UKRR 24th Annual report.[31] Patients receiving haemodialysis were then further distributed across hospital haemodialysis (35.4%), satellite haemodialysis (58.9%) and home haemodialysis (5.7%), also sourced from the UKRR 24th Annual report. [31] The unit costs for haemodialysis were sourced from the NHS National Cost Collection 2021/22 data.[41] Hospital and satellite haemodialysis treatment patients were also assumed to incur a transportation cost sourced from Liu 2015.[42] Dialysis costs also accounted for the costs of nephrologist outpatient appointments, blood tests and hospitalisations. Nephrologist outpatient appointments and blood tests were assumed to occur quarterly, with one hospitalisation per year for 50% of all dialysis patients, which were validated by clinical experts.

For the transplant health state, MRU costs consisted of procedural and maintenance costs. Procedural costs included pre-assessment, transplant procedure, and post-transplant assessment and implemented

once patients received the transplant. For patients remaining in the transplant health state, the per cycle maintenance cost was equal to the costs of patients with CKD stage 3b, with additional nephrologist outpatient appointments, blood tests and immunosuppressive therapy. Following transplant, patients were assumed to receive immunosuppressive maintenance therapy, as recommended in NICE TA481.[43] Immunosuppressive therapy was assumed to apply for all patients following transplant and comprised of daily use of tacrolimus administered at 0.25 mg/kg. 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 were assumed to occur once annually for 50% of patients in the transplant health state, which was validated by clinical expert opinion. The unit cost for hospitalisation was calculated as the weighted average of health resource group **(**HRG**)** codes obtained from the NHS National Cost Collection 2021/22.[41]

The health state costs per cycle are summarised in Table 4.11 below.

Table 4.1213: Health state costs per cycle

Health state	Cost per cycle
CKD 1	£110.86
CKD 2	£110.86
CKD 3a	£110.86
CKD 3b	£110.86
CKD 4	£380.41
CKD 5	£1,307.94
Dialysis	£2,547.29
Transplantation maintenance	£1,366.27
One-off transplantation cost	
Transplantation procedural costs	£18,543.84
Based on Table 38 of the CS. [1] CKD = chronic kidney disease; CS = company submission	

4.2.9.4 Adverse events costs

Adverse event costs were sourced from the 2021/22 NHS National Cost Collection and were estimated using the weighted average of HRG codes.[44] The cost per AE is presented in Table 4.12 below.

Table 4.142: Adverse event costs

AE	Cost	Source
Treatment-emergent AE		
Acne	£0.00	Assumption
Cushingoid	£197.59	NHS 21/22: Total Outpatient Attendance - Service code 302, Endocrinology [41]
Dyspepsia	£148.93	NHS 21/22: Total Outpatient Attendance - Service code 301, Gastroenterology[41]
Oedema peripheral	£0.00	Assumption
Face oedema	£0.00	Assumption
Headache	£0.19	eMIT: Paracetamol 500 mg tablets, pack size 16[38]

AE	Cost	Source
Hirsutism	£0.00	Assumption
Hypertension	£196.88	NHS 21/22: Total Outpatient Attendance - Service code 361, Nephrology [41]
Mood swings	£0.00	Assumption
Upper respiratory tract infection	£1,273.39	NHS 21/22: Total HRG's - weighted average CB02A - CB02F [41]
Weight increase	£0.00	Assumption
Treatment emergent SAE		
Pulmonary embolism	£1,905.92	NHS 21/22: Total HRGs - weighted average DZ09J - DZ09Q [41]
Renal impairment	£1,757.91	NHS 21/22: Total HRGs - weighted average LA09J - LA09Q [41]

Based on Table 39 of the CS.[1]
AE = adverse event; CS = company submission; eMIT = electronic market information tool; HRG = health resource group; mg = milligram; NHS = National Health Service; SAE = serious adverse event

4.2.9.5 End of life costs

End of life care costs was £3,222.10 and was sourced from Kerr 2017[39] which reported the total hospital care cost for CKD patients by periods to death of 30 days, 3 months, and 12 months using data from the Hospital Episode Statistics data and ONS mortality data. The base case analysis used the 30-day cost to avoid potential double-counting with MRU costs, and was inflated to 2021 prices using PSSRU inflation indices.[40]

4.2.10 Disease severity

The new NICE process and methods manual describes disease severity as a decision modifier, i.e. depending on the severity of the disease, a higher threshold ICER may be used to consider if a new technology offers value for money.[45] According to the manual:

The committee will consider the severity of the condition, defined as the future health lost by people living with the condition with standard care in the NHS (including use of other available treatments, diagnostics, or best supportive care). The extent of unmet health need is reflected within the severity definition.

When assessing the severity of the condition in technology appraisals, the committee will consider the associated absolute and proportional QALY shortfall.

The QALY weightings for severity are applied based on absolute and proportional shortfall, whichever implies the greater severity level. If either the proportional or absolute QALY shortfall calculated falls on the cut-off between severity levels, the higher severity level will apply.

The cut-off point between severity levels are shown in Table 4.13.

Table 4.153: QALY weightings for severity

QALY weight	Proportional QALY shortfall	Absolute QALY shortfall
1	Less than 0.85	Less than 12
x 1.2	0.85 to 0.95	12 to 18
x 1.7	At least 0.95	At least 18

Based on NICE manual 2022[45]
NICE = National Institute for Health and Care Excellence; QALY = quality-adjusted life year

In their submission, the company stated that the technology is not expected to meet the criteria for a severity weight.

5. COST EFFECTIVENESS RESULTS

5.1 Company's cost effectiveness results

5.1.1 Main results original company submission

Table 5.1 shows the company's deterministic base case results from the original submission. The total discounted costs associated with TRF-budesonide treatment combined with established standard of care (TRF-budesonide + SoC) were estimated at [redacted] and total costs associated with SoC only were estimated at [redacted], indicating that addition of TRF-budesonide to the SoC treatment increases total costs by [redacted]. Total QALYs associated with TRF-budesonide + SoC were estimated at [redacted] and total QALYs associated with SoC were estimated at [redacted], indicating an incremental number of [redacted] QALYs gained for patients treated with TRF-budesonide + SoC. These give an ICER for TRF-budesonide + SoC versus SoC only of £18,643 per QALY gained.

Table 5.1: Company's base-case deterministic cost effectiveness results

Technologies	Total costs	Total LYG	Total QALYs	Incr. costs	Incr. LYG	Incr. QALYs	ICER (£/QALY)
TRF-budesonide	[redacted]	16.060	[redacted]				
SoC	[redacted]	15.958	[redacted]	[redacted]	0.102	[redacted]	£18,643

Based on: Table 42 in CS[1]
CS = company submission; ICER = incremental cost-effectiveness ratio; Incr. = incremental; LYG = life years gained; QALYs = quality-adjusted life years; SoC = standard of care; TRF = targeted-release formulation

5.1.2 Main results based on model after the request for clarification

During the clarification phase, the EAG asked the company about some inconsistencies between model results and expectations when varying the percentage of patients allowed to receive retreatment in the model (see question B11 in the clarification letter and Section 4.2.6 above for further details). During the clarification phase the company confirmed the inconsistencies were due to modelling errors and following their correction, updated base case results were provided in the clarification letter. With these changes, the revised company base case results are presented in Table 5.2. The total discounted costs associated with TRF-budesonide treatment combined with established standard of care (TRF-budesonide + SoC) were estimated at [redacted] and total costs associated with SoC only were estimated at [redacted], indicating that addition of TRF-budesonide to the SoC treatment increases total costs by [redacted]. Total QALYs associated with TRF-budesonide + SoC were estimated at [redacted] and total QALYs associated with SoC were estimated at [redacted], indicating an incremental number of [redacted] QALYs gained for patients treated with TRF-budesonide + SoC.

Table 5.2: Company's base-case deterministic cost effectiveness results

Technologies	Total costs	Total LYG	Total QALYs	Incr. costs	Incr. LYG	Incr. QALYs	ICER (£/QALY)
TRF-budesonide	[redacted]	16.065	[redacted]				
SoC	[redacted]	15.940	[redacted]	[redacted]	0.102	[redacted]	£21,872

Based on the electronic model submitted after the clarification phase [3]
CS = company submission; ICER = incremental cost-effectiveness ratio; Incr. = incremental; LYG = life years gained; QALYs = quality-adjusted life years; SoC = standard of care; TRF = targeted-release formulation

As a consequence of the revision, the ICER increased from £18,643 per QALY gained to £21,872 per QALY gained.[3]

5.2 Company's sensitivity analyses

In this section, only the results of the revised company analyses will be presented. The company performed and presented the updated results of probabilistic sensitivity analyses (PSA), while the deterministic sensitivity analyses (DSA) was extracted from the model submitted by the company following the clarification phase and the scenario analysis was updated by the EAG using this updated model version.

5.2.1 Probabilistic sensitivity analysis

After the corrections from the clarification phase, the PSA results from the base case analysis are presented in Table 5.3 below. The company presented two sets of probabilistic analysis one including and one excluding incorporation of the transition probability from CKD 1 to CKD 2 health states. This was because there was only one patient with CKD 1 at the start of the trial from which the transition was calculated. Therefore, in the PSA the transition probability from CKD 1 to CKD 2 was widely spread across iterations, highly influencing PSA outcomes. Table 5.3 below shows that when excluding the transition from CKD 1 to CKD 2 health states, the probabilistic results are aligning with the deterministic base case results. When excluding the transition probability of CKD 1 to CKD 2 health states from the PSA parameter list, the cost effectiveness acceptability curve (CEAC) in Figure 5.1 shows that the probability of TRF-budesonide combined with SoC to be cost effective at thresholds of £20,000 and £30,000 per QALY gained is 50.2% and 63.8%, respectively.

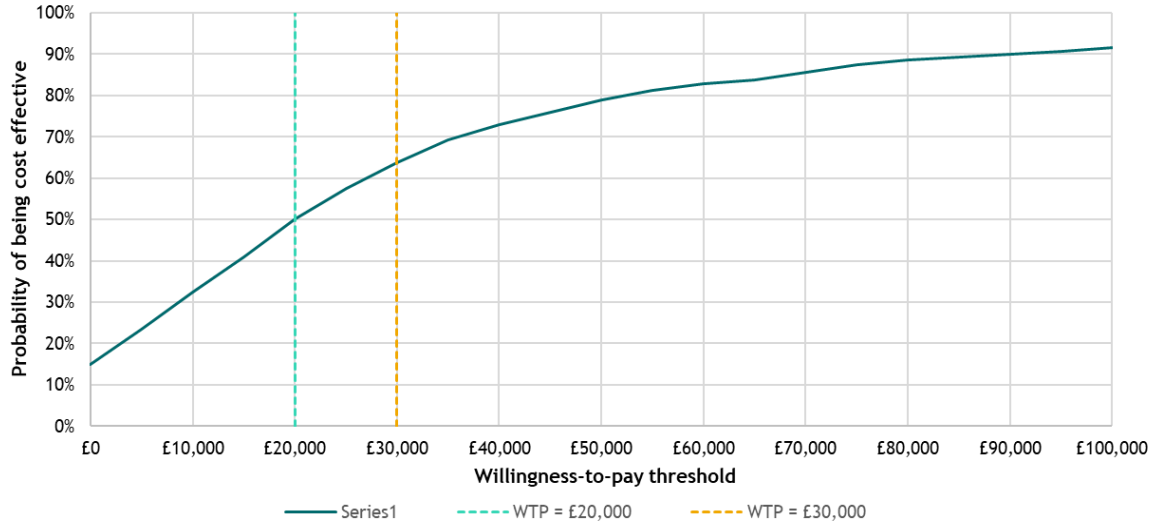
Table 5.3: Company base case probabilistic CE results after the clarification letter

Technologies	Total costs	Total LYG	Total QALYs	Incr. costs	Incr. LYG	Incr. QALYs	ICER (£/QALY)
Including CKD 1 to CKD 2 transition							
TRF-budesonide	[redacted]	16.596	[redacted]				
SoC	[redacted]	16.181	[redacted]	[redacted]	0.414	[redacted]	Dominant
Excluding CKD 1 to CKD 2 transition							
TRF-budesonide	[redacted]	16.205	[redacted]				
SoC	[redacted]	16.053	[redacted]	[redacted]	0.153	[redacted]	£20,177

Based on: Table 8 and Table 9 in CL[3]

CE = cost effectiveness; CKD; chronic kidney disease; CL = clarification letter; ICER = incremental cost-effectiveness ratio; Incr. = incremental; LYG = life years gained; QALYs = quality-adjusted life years; SoC = standard of care; TRF = targeted-release formulation

Figure 5.1: Cost effectiveness acceptability curve when the CKD 1 to CKD 2 transition in the TRF-budesonide arm is excluded (1,000 iterations)

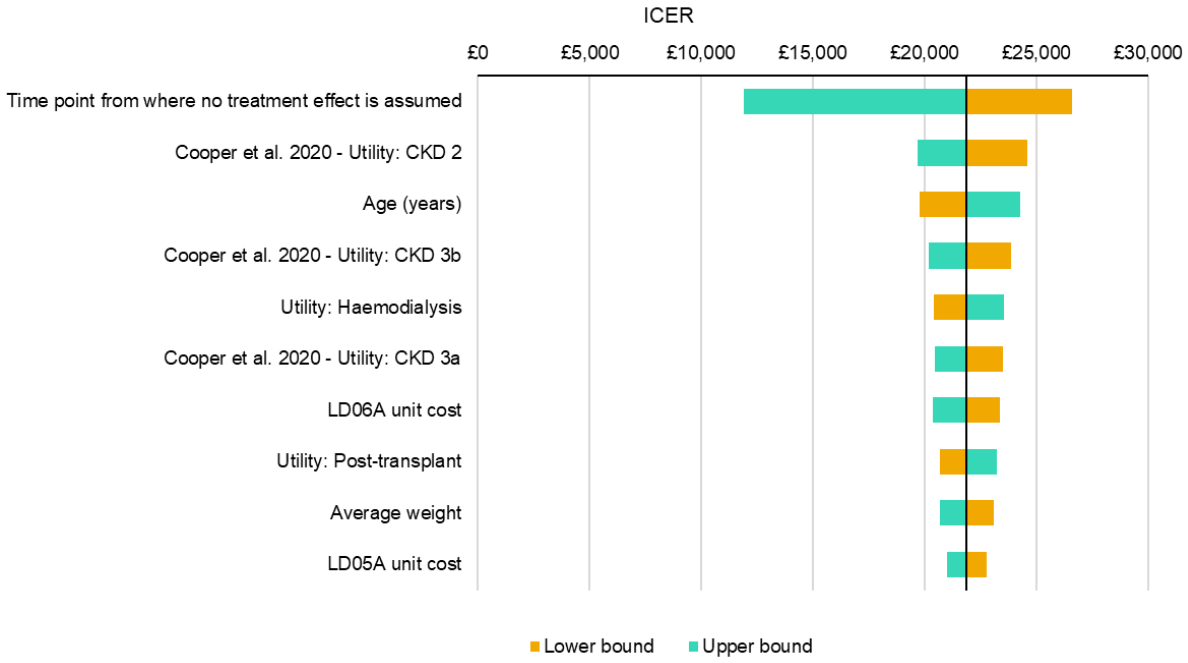


Based on the model submitted following the clarification phase [3]
CKD = chronic kidney disease; TRF = targeted-release formulation; WTP = willingness-to-pay threshold

5.2.2 Deterministic sensitivity analysis

The results of the company's DSA are displayed in Figure 5.2, which shows the impact of the 10 most influential parameters. Parameters relating to the time point from where no treatment effect for TRF-budesonide is assumed and the different health state utilities had the largest impact on the ICER, though without the ICER exceeding the willingness-to-pay threshold of £30,000/QALY.

Figure 5.2: Tornado plot showing the top 10 most influential parameters with an impact on ICER following the clarification phase



Based on the model submitted following the clarification phase [3]
CKD = chronic kidney disease; ICER = incremental cost-effectiveness ratio; WTP = willingness-to-pay threshold

5.2.3 Scenario analyses

Company scenario analysis results are presented in Table 5.3. The rationale for each scenario is outlined in Table 47 of the CS.[1] The scenarios leading to the highest increase on the ICER were changing the time horizon to 10 years and excluding the retreatment option for TRF-budesonide. These two scenarios led to respective ICER increase of £41,044 and £33,141 per QALY gained. Also, in the scenario where the study of Greene 2019[30] was used to inform mortality in the different CKD and dialysis health states, the ICER increased to £31,953 per QALY gained. In all other scenarios the ICER remained below £30,000 per QALY gained.

Table 5.4: Company scenario analyses after the clarification letter updated by the EAG

Scenario	Assumption	Incr. costs	Incr. QALYs	ICER per QALY
Base case		[redacted]	[redacted]	£21,872
Time horizon	10 years	[redacted]	[redacted]	£41,044
	20 years	[redacted]	[redacted]	£20,622
	30 years	[redacted]	[redacted]	£21,540
	40 years	[redacted]	[redacted]	£21,858
	50 years	[redacted]	[redacted]	£21,872
Distribution of patients across CKD states at baseline	UK RaDaR data	[redacted]	[redacted]	Dominant
	UK RaDaR data - apportioned to exclude CKD 4	[redacted]	[redacted]	£18,645
Parametric extrapolations to estimate time to CKD 5	Exponential	[redacted]	[redacted]	£24,988
	Generalised gamma	[redacted]	[redacted]	£24,573
	Gompertz	[redacted]	[redacted]	Dominant
	Log-logistic	[redacted]	[redacted]	Dominant
	Log-normal	[redacted]	[redacted]	£1,616
	Weibull	[redacted]	[redacted]	£17,022
Risk of ESRD	UK RaDaR data – ACEi and ARB patients	[redacted]	[redacted]	£25,921
	Leicester General Hospital data with HR applied	[redacted]	[redacted]	£27,429
SoC acquisition costs	£0	[redacted]	[redacted]	£19,499
Time point from where no treatment effect is assumed	1.5 year	[redacted]	[redacted]	Dominant
	2 years	[redacted]	[redacted]	Dominant
	2.5 years	[redacted]	[redacted]	Dominant
	5 years	[redacted]	[redacted]	Dominant
Mortality source	Greene 2019[30]	[redacted]	[redacted]	£31,953
	Hastings 2018[27]	[redacted]	[redacted]	£24,218
CKD stage utility source	Gorodetskaya 2005[46]	[redacted]	[redacted]	£18,687

Scenario	Assumption	Incr. costs	Incr. QALYs	ICER per QALY
Age-adjusted utilities	Excluded	[redacted]	[redacted]	£21,226
Treatment stopping approach	Use the TTD curve from the CSRs	[redacted]	[redacted]	£21,938
TRF-budesonide dose reduction	Excluded	[redacted]	[redacted]	£18,325
TRF-budesonide tapering period	Included	[redacted]	[redacted]	£22,400
TRF-budesonide retreatment	No retreatment	[redacted]	[redacted]	£33,141
	3 rounds of treatment	[redacted]	[redacted]	£14,810
	4 rounds of treatment	[redacted]	[redacted]	£9,569
	5 rounds of treatment	[redacted]	[redacted]	£5,381
	6 rounds of treatment	[redacted]	[redacted]	£2,464
Societal costs	Included	[redacted]	[redacted]	£17,912

Based on the model submitted following the clarification phase, the EAG run these scenarios[3]

ACEi = angiotensin converting enzyme inhibitors; ARB = angiotensin receptor blockers; CKD = chronic kidney disease; CSR = clinical study report; ESRD = end-stage renal disease; HR = hazard ratio; ICER = incremental cost-effectiveness ratio; Incr. = incremental; QALY = quality-adjusted life year; RaDaR = National Registry of Rare Kidney Diseases; SoC = standard of care; TRF = Targeted-release formulation; TTD = time to treatment discontinuation; UK = United Kingdom

5.3 Model validation and face validity check

Validation efforts conducted on the economic model were shortly discussed in the validation section of the CS (Section B.3.14).1 The company indicated in Section B.3.14 of the CS that internal validation process was conducted in line with the Professional Society for Health Economics and Outcomes Research (ISPOR) best practices guidance. The validation process consisted of an adapted form of the TECH-VER internal validity checklist. [47, 48]

The company further solicited expert opinion to validate key model inputs and assumptions from a clinical perspective. For instance, clinical opinion was requested to validate the current pathway of care for patients with IgAN. The model structure and inputs were also critiqued and validated in an HTA Advisory Board meeting consisting of external health economists and clinical advisor experts.[49] The goal of the Advisory Board was to assess the clinical evidence and clinical positioning of TRF-budesonide in the treatment pathway for IgAN in the UK and to validate the cost effectiveness model, inputs and assumptions. The CS states that overall, the validation process did not identify issues with the structural or computational accuracy of the model.

Unfortunately, at several points the EAG did encounter issues with the technical validity of the model; these issues have been raised in EAG comment in Section 4.

6. EVIDENCE REVIEW GROUP'S ADDITIONAL ANALYSES

6.1 Exploratory and sensitivity analyses undertaken by the EAG

6.1.1 Explanation of the EAG adjustments

The changes that the EAG made (to the model received with the response to the clarification letter[3]) can be subdivided into the following three categories (according to Kaltenthaler 2016[50]).

- Fixing errors (correcting the model where the company's electronic model is unequivocally wrong).
- Fixing violations (correcting the model where the EAG considers that the NICE reference case, scope or best practice has not been adhered to).
- Matters of judgement (amending the model where the EAG considers that reasonable alternative assumptions are preferred).

After the proposed changes were implemented in the company's model, additional scenario analyses were explored by the EAG in order to assess the impact of alternative assumptions on the CE results.

6.1.1.1 Fixing errors

The EAG identified some modelling errors following the clarification phase.

- The EAG noticed that for the transition probability for patients in the dialysis to transplant health state assumes a standard error of 0 (cell K140 on the 'Transitions' sheet). As a result of the set-up on the parameter sheet, during the PSA, this probability (base case 0.5%) becomes 100% in about 25% of the iterations. Therefore, the EAG assumed a standard error of 0.001 there, which solves this issue.
- Regarding the PSA analysis, the EAG also noticed that on the 'Parameters' sheet, the company allowed the HR of the transition probability from CKD 4 to CKD 5 to vary in the PSA by including two options in rows 460 and 461, of which the first was set to a fixed value and the second was allowed to vary based on a log normal distribution for the HR estimated using the LGH data (see Section 4.2.6). However, as these options were used to define the same parameter in the PSA outcomes, they were producing incorrect results. The EAG deactivated the second parameter in cell Y461 and made changes in row 460 similar to row 461 to allow for the parameter variation in the PSA outcomes.

6.1.1.2 Fixing violations

No violations were applicable to this appraisal.

6.1.1.3 Matters of judgement

The EAG's preferences regarding alternative assumptions led to the following changes to the company base case analysis:

- To inform the transition probability from CKD 4 to CKD 5, the EAG considers that data from patients at LGH in the UK between 1992 to 2020 is more appropriate than the UK RaDaR data (see Section 4.2.6.2), given problems with the implementation of the scenario using the ACEi and/or ARBs subgroup of the UK RaDaR data.
- The company assumed one round of retreatment. In the absence of any (be it real-world or trial) evidence to support the timing of the retreatment, the proportion of patients eligible for retreatment and the clinical benefit of TRF-budesonide for the retreated patients, the EAG considers the retreatment option uncertain and removed it from the base case analysis (see Section 4.2.6.2).

- The EAG does not agree with the company's approach in the base case analysis to assign a disutility value of zero to serious adverse events. Therefore, the EAG used the disutility values of 0.018 for pulmonary embolism[37] and 0.0603 for renal impairment[36] as presented by the company in the scenario analysis during the clarification phase. The disutility duration for both adverse events was set at 1 month (see Section 4.2.8).[37]
- For completeness, the EAG also adjusted the costs of SoC treatment in the model to account for concomitant medications costs that were missing from the company's calculations on the acquisition costs of SoC (see Section 4.2.9).

The overview of the changes and the bookmarks for the justification of the EAG changes are presented in Table 6.1.

Table 6.1: Company and EAG base case preferred assumptions

Base case preferred assumptions	Company	EAG	Justification for change
Transition probability from CKD 4 to CKD 5	UK RaDaR patients with IgAN and UPCR ≥1.5 g/g	Matched data from the LGH database to the NefIgArd Nef-301 trial patients	Section 4.2.6.2
Retreatment	1 round of retreatment	No retreatment	Section 4.2.6.2
Disutility scores to TESAEs	No disutility values for TESAEs	Disutility values of 0.018 for pulmonary embolism[37] and 0.0603 for renal impairment[36] and disutility duration at 1 month.[37]	Section 4.2.8
Cost of SoC	Included costs of ACEis/ARBs and SGLT2i	Incorporated costs of additional concomitant medications	Section 4.2.9

ACEi = angiotensin converting enzyme inhibitor; ARB = angiotensin receptor blockers; CKD = chronic kidney disease; EAG = Evidence Assessment Group; IgAN = immunoglobulin A nephropathy; RaDaR = National Registry of Rare Kidney Diseases; SGLT2i = sodium-glucose cotransporter-2 inhibitors; SoC = standard of care; TESAE = treatment-emergent serious adverse event; UK = United Kingdom; UPCR = urine protein to creatinine ratio

6.1.2 EAG exploratory scenario analyses

The EAG performed the following exploratory scenario analyses to explore the impact of alternative assumptions conditional on the EAG base case.

Scenario 1: Transition probabilities

The EAG explored the impact on the ICER of using alternative options to estimate transition probabilities from CKD 4 to CKD 5 as estimated based on the subgroups of the UK RaDaR data using all patients with IgAN and UPCR ≥1.5 g/g, patients with IgAN ≥1.5 g/g, and ACEis/ARBs at baseline as well as different parametric models to fit the available real-world data.

Scenario 2: Time point from where no treatment effect is assumed

Considering the promising preliminary data analyses from Part B of the NefIgArd Nef-301 trial showing a consistent and highly statistically significant benefit in eGFR for TRF-budesonide compared with placebo in the 15-months of follow-up observational study, as reported in Section B.2.11 of the CS, the EAG explored the impact on the ICER of extending the time points from which no treatment effect is assumed.

Scenario 3: CKD utility values

As per company's scenario analyses, the EAG also ran a scenario analysis in which utility values for CKD stages were extracted from Gorodetskaya 2005.[46]

Scenario 4: Treatment dose reduction period

In line with the company scenario analyses, the EAG excluded the treatment costs assigned to the 2-week dose reduction period (TRF-budesonide 8 mg OD for 2 weeks).

Scenario 5: Treatment tapering

Including the option of further treatment tapering, i.e.4 mg OD for an additional 2 weeks following the end of the 9-month course and the 2-weeks period of reduced therapy, was also explored in the EAG scenario analyses.

Scenario 6: Retreatment

The EAG explored the impact on the ICER of using one or two retreatment rounds with alternative options on the timing of the retreatment, the proportion of patients eligible for retreatment and the clinical benefit of TRF-budesonide for retreated patients as compared to no retreatment.

6.1.3 EAG subgroup analyses

No subgroup analyses were performed by the EAG.

6.2 Impact on the ICER of additional clinical and economic analyses undertaken by the EAG

6.2.1 Results of the EAG preferred base case scenario

Table 6.2 shows the deterministic CE results of the EAG preferred base case analysis. All results are discounted. The total costs of TRF-budesonide treatment combined with established standard of care (TRF-budesonide + SoC) were estimated at [redacted] and total costs associated with SoC only were estimated at [redacted], indicating that addition of TRF-budesonide to the SoC treatment increases total costs by [redacted]. Total QALYs associated with TRF-budesonide + SoC were estimated at [redacted] and total QALYs associated with SoC were estimated at [redacted], indicating an incremental number of [redacted] QALYs gained for patients treated with TRF-budesonide + SoC. Therefore, the ICER was £41,598 per QALY gained. Table 6.2: EAG preferred base case deterministic cost effectiveness results

Technologies	Total costs	Total LYG	Total QALYs	Incr. costs	Incr. LYG	Incr. QALYs	ICER (£/QALY)
TRF-budesonide	[redacted]	16.024	[redacted]				
SoC	[redacted]	15.950	[redacted]	[redacted]	0.075	[redacted]	£41,598
Based on the EAG preferred assumptions in the electronic model following the clarification question							

Technologies	Total costs	Total LYG	Total QALYs	Incr. costs	Incr. LYG	Incr. QALYs	ICER (£/QALY)
EAG = Evidence Assessment Group; ICER = incremental cost-effectiveness ratio; Incr. = incremental; LYG = gained; QALYs = quality-adjusted life years; SoC = standard of care; TRF = targeted-release formulation							

Results of the PSA are given in Table 6.3 below. As explained in Section 5.2.1, the company presented two sets of probabilistic analyses, one including and one excluding incorporation of the transition probability from CKD 1 to CKD 2 health states, because of the high uncertainty around the transition probability of this parameter. Similarly, the Table 6.3 below presents three sets of probabilistic analyses, the first two based on the correction made to the SE of the probability of moving from dialysis to transplantation, and the latter where the SE has been set to 0 again, as in the company's model. Table 6.3 shows that EAG probabilistic results are quite different from the EAG deterministic base case. The difference between including CKD 1 to CKD 2 transitions and excluding it is very large, as was also observed in the company base case. However, we now also see a significant difference between the deterministic base case and the probabilistic base case excluding the CKD 1 to CKD 2 transition. In general, such gap between deterministic and probabilistic ICER can either be a bug or a feature. That is, there may be more issues than discovered so far with the workings of the PSA, leading to unforeseen and unwanted results. However, it is also possible that there are non-linearities in the model that are intended, explaining this gap. Whilst the EAG did find some issues, time constraints did not allow for a more thorough investigation. When we set the SE of the probability of moving from dialysis to transplantation to 0 again, as per the company base case, we see that the probabilistic ICER moves closer to the deterministic ICER. However, this version is known to be incorrect (see also Section 6.1.1). The CE plane in Figure 6.1 shows that most of the simulations fell in the north-east quadrant. Based on the CEAC in Figure 6.2, the probability that is cost effective at thresholds of £20,000 and £30,000 per QALY gained are 10.0% and 22.1%, respectively, using the EAG base case assumptions.

Table 6.3: EAG base case probabilistic CE results

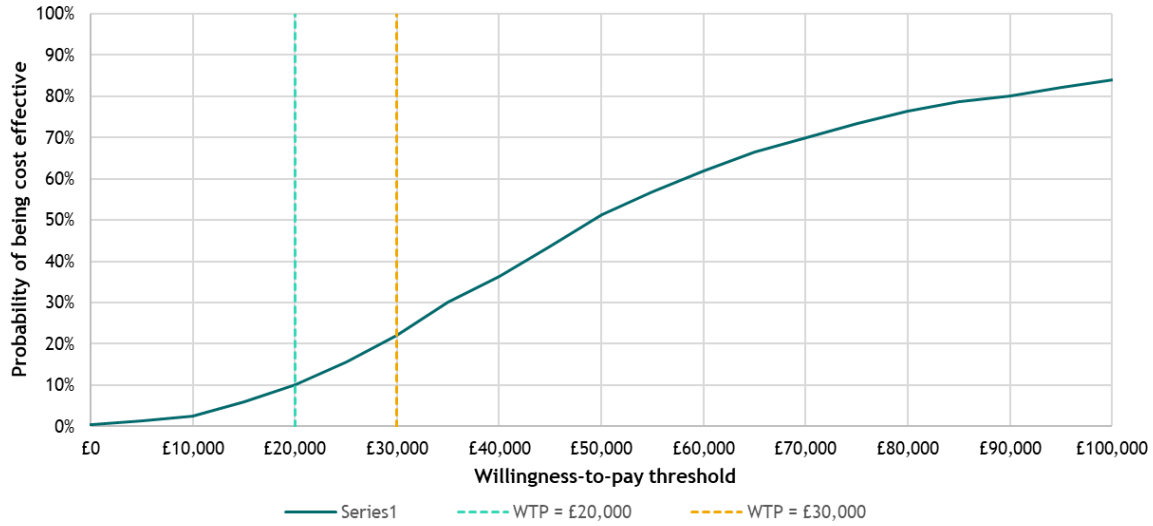
Technologies	Total costs	Total LYG	Total QALYs	Incr. costs	Incr. LYG	Incr. QALYs	ICER (£/QALY)
Including CKD 1 to CKD 2 transition							
TRF-budesonide	[redacted]	16.188	9.972				
SoC	[redacted]	15.895	[redacted]	[redacted]	0.294	[redacted]	Dominant
Excluding CKD 1 to CKD 2 transition							
TRF-budesonide	[redacted]	16.220	[redacted]				
SoC	[redacted]	16.138	[redacted]	[redacted]	0.082	[redacted]	£49,821
Excluding CKD 1 to CKD 2 transition and excluding the uncertainty around dialysis to transplant transition							
TRF-budesonide	[redacted]	15.911	[redacted]				
SoC	[redacted]	15.826	[redacted]	[redacted]	0.085	[redacted]	£39,442
Based on the EAG preferred assumptions in the electronic model following the clarification question							

Technologies	Total costs	Total LYG	Total QALYs	Incr. costs	Incr. LYG	Incr. QALYs	ICER (£/QALY)
CE = cost effectiveness; CKD = chronic kidney disease; EAG = Evidence Assessment Group; ICER = incremental cost-effectiveness ratio; Incr. = incremental; LYG = life years gained; QALYs = quality-adjusted life years; SoC = standard of care; TRF = targeted-release formulation							

Figure 6.1: EAG PSA cost effectiveness plane

EAG = Evidence Assessment Group; PSA = probabilistic sensitivity analysis; QALY = quality-adjusted life year; SoC = standard of care

Figure 6.2: EAG PSA cost effectiveness acceptability curve



EAG = Evidence Assessment Group; PSA = probabilistic sensitivity analysis; WTP = willingness-to-pay

6.2.2 Results of the EAG additional exploratory scenario analyses

The results of the scenario analyses are provided in Table 6.4.

Table 6.4: Results of exploratory scenario analyses by the EAG

Scenario	Assumption	Incr. costs	Incr. QALYs	ICER per QALY
EAG base case		[redacted]	[redacted]	£41,598
Scenario 1a: Parametric extrapolations to estimate time to CKD 5 based on the LGH data	Gamma	[redacted]	[redacted]	£47,993
	Generalised gamma	[redacted]	[redacted]	£42,820
	Gompertz	[redacted]	[redacted]	£49,589
	Log-logistic	[redacted]	[redacted]	£38,314
	Log-normal	[redacted]	[redacted]	£30,371
	Weibull	[redacted]	[redacted]	£49,009
Scenario 1b: Data source used to estimate time to CKD 5	UK RaDaR data all patients with gamma extrapolation option	[redacted]	[redacted]	£33,695
	UK RaDaR data all patients with generalised gamma extrapolation option	[redacted]	[redacted]	£36,793
	UK RaDaR data all patients with exponential extrapolation option	[redacted]	[redacted]	£38,572
	UK RaDaR data - limited to ACEis/ARBs at baseline with exponential extrapolation option	[redacted]	[redacted]	£39,763
	UK RaDaR data - limited to ACEis/ARBs at baseline with Weibull extrapolation option	[redacted]	[redacted]	£48,113
	UK RaDaR data - limited to ACEis/ARBs at baseline with Gompertz extrapolation option	[redacted]	[redacted]	£63,410
Scenario 2: Time point from where no treatment effect is assumed	1.5 year	[redacted]	[redacted]	£4,423
	2 years	[redacted]	[redacted]	Dominant
Scenario 3: CKD stage utility source	Gorodetskaya 2005[46]	[redacted]	[redacted]	£36,711
Scenario 4: TRF-budesonide dose reduction	Excluded	[redacted]	[redacted]	£37,383
Scenario 5: TRF-budesonide tapering period	Included	[redacted]	[redacted]	£42,225
Scenario 6: TRF-budesonide retreatment	1 round of retreatment at 14.75 months for [redacted] of patients as per company's base case assumption	[redacted]	[redacted]	£27,886

Scenario	Assumption	Incr. costs	Incr. QALYs	ICER per QALY
	1 round of retreatment at 14.75 months for 50.0% of patients	[redacted]	[redacted]	£30,456
	1 round of retreatment at 14.75 months for 25.0% of patients	[redacted]	[redacted]	£34,388
	1 round of retreatment at 24 months for 50.0% of patients	[redacted]	[redacted]	£25,621
	1 round of retreatment at 24 months for 25.0% of patients	[redacted]	[redacted]	£31,724
	2 rounds of retreatment at 24 months for 50.0% of patients	[redacted]	[redacted]	£15,177
	2 rounds of retreatment at 24 months for 25.0% of patients	[redacted]	[redacted]	£19,868
	1 round of retreatment at 14.75 months for 25.0% of patients and 75% clinical benefit	[redacted]	[redacted]	£40,085
	1 round of retreatment at 14.75 months for 25.0% of patients 50% clinical benefit	[redacted]	[redacted]	£46,379
	1 round of retreatment at 24 months for 25.0% of patients and 75% clinical benefit	[redacted]	[redacted]	£37,011
	1 round of retreatment at 24 months for 25.0% of patients 50% clinical benefit	[redacted]	[redacted]	£42,756

Based on the model submitted following the clarification phase[3]
ACEi = angiotensin converting enzyme inhibitor; ARB = angiotensin receptor blocker; CKD = chronic kidney disease; EAG = Evidence Assessment Group; ICER = incremental cost-effectiveness ratio; Incr. = incremental; LGH = Leicester General Hospital; QALY = quality-adjusted life year; RaDaR = National Registry of Rare Kidney Diseases; TRF = targeted-release formulation; TTD = time to treatment discontinuation; UK = United Kingdom;

6.3 EAG's preferred assumptions

Adjustments made by the EAG, to derive the EAG base-case using the CS base case and the electronic model submitted following the clarification as starting point are listed below. Table 6.5 shows the step-by-step changes made by the EAG to the company base case. The change with by far the largest impact on the results was omitting the retreatment option for TRF-budesonide. This change leads to increase of the ICER to over £30,000. Also important is the source used to inform the transition probability for

patients in CKD 4 to CKD 5. The impact of incorporating disutilities for TESAEs and additional costs for concomitant medication is relatively small, with the first change leading to a decrease in the number of QALYs gained and the second to an increase in the incremental costs.

Table 6.55: Individual impact of EAG preferred assumptions

Preferred assumption	TRF-Budesonide + SoC		SoC		Incr. Costs (£)	Incr. QALYs	ICER (£/QALY)
	Costs (£)	QALYs	Costs (£)	QALYs			
Company base case (original)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£18,643
Company base case (after clarification)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£21,872**
EAG change on the source used to estimate transition probability from CKD 4 to CKD 5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£27,429
EAG change on retreatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£33,141
EAG change on disutility of TESAEs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£22,122
EAG change on cost of SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£22,009

Based on the EAG preferred assumptions in the electronic model following the clarification question
CKD = chronic kidney disease; EAG = Evidence Assessment Group; ICER = incremental cost-effectiveness ratio; Incr. = incremental; QALY = quality-adjusted life year; SoC = standard of care; TESAE = treatment-emergent serious adverse event; TRF = targeted-release formulation

6.4 Conclusions of the cost effectiveness section

The company developed a Markov model in Microsoft Excel® to assess the CE of TRF-budesonide for the treatment of adult patients with primary IgAN who are at risk of rapid disease progression with a UPCR ≥1.5 g/g. The model consists of eight mutually exclusive health states and an absorbing mortality state. The eight mutually exclusive health states are six core health states defined by the level of CKD disease (i.e., CKD 1, CKD 2, CKD 3a, CKD 3b, CKD 4, and CKD 5), and the health states of renal transplant and dialysis.

The EAG considers that the model structure adequately reflects clinical issues related to patients with primary IgAN who are at risk of rapid disease progression with a UPCR ≥1.5 g/g. Therefore, the model structure appears to be appropriate and fit for purpose. The CE analysis was performed in line with the NICE Reference Case in terms of perspective, time horizon and discounting.

The population in the company's analysis are adult patients receiving SoC, defined as a stable dose of maximally tolerated RASi therapy, where SoC is insufficient in delaying progression through CKD stages. The treatments compared were TRF-budesonide with SoC versus SoC alone.

The model is structured based on a 1-month cycle length, while the impact of TRF-budesonide is evaluated based on a 9-month follow-up period using data from Part A of the NefIgArd Nef-301 trial. Transition probabilities between CKD 1 and CKD 4 health states for both the TRF-budesonide and SoC arms were estimated by comparing the eGFR values at baseline and after 9 months of treatment which

were then mapped to reflect patients in different CKD health states. From these 9-month transition probabilities monthly transition probabilities were derived, which were assumed to be applicable for a 1-year period. The transition probability from CKD 4 to CKD 5 in the SoC arm was informed using real-world evidence from patients with IgAN and UPCR ≥1.5 g/g from the UK RaDaR database and based on this the transition probability, the respective transition probability for the TRF-budesonide arm was estimated using a HR approach. Transition probabilities from CKD 1 to CKD 5 beyond 12 months in the TRF-budesonide arm were assumed to be equal to the transition probabilities in the SoC arm. Transition probabilities between CKD 5, dialysis, and transplant health states were sourced from NICE TA775 and were assumed equal for both the TRF-budesonide and SoC arms, indicating that patients in the CKD 5 health state do not have any treatment benefit from TRF-budesonide compared to SoC.

The EAG identified a strong limitation considering the use of the UK RaDaR data to estimate the transition probability from CKD 4 to CKD 5. That is related to the fact the UK RaDaR data used ESRD cases and death cases combined to define the event outcome, hence likely overestimating the risk of ESRD as the risk to ESRD is also accounting for the risk of death. During clarification, and as part of the scenario analyses the company also provided estimates of the transition probability from CKD 4 to CKD 5 using i) data from the UK RaDaR data that assessed the time from CKD 4 diagnosis to ESRD in patients with IgAN and UPCR ≥1.5 g/g, ii) data from the UK RaDaR data that assessed the time from CKD 4 diagnosis to ESRD or death in patients with IgAN, UPCR ≥1.5 g/g and use of ACEis/ARBs at baseline and iii) data from a real-world registry from patients at the LGH in the UK between 1992 to 2020. Following the evidence presented and considering the limitations of each of these approaches, the EAG considered that the LGH data were more appropriate for the base case analysis, whilst exploring the impact of the alternative data sources in a scenario analysis.

The model also included the option to retreat patients in the TRF-budesonide arm. For retreated patients and irrespective of the number of rounds of retreatment, the transition probabilities in all CKD stages were set equal to the respective 12-months transition probabilities from the first round of treatment, although in the base case analysis of the company only one retreatment round was assumed. It should be noted that currently no evidence is available to estimate the probability of retreatment, the time until retreatment, and the effectiveness of retreatment. Further, the EAG noted many inconsistencies in the model regarding the parameters used to define retreatment options, which the company resolved in the clarification phase. Following these and the uncertainties around the parameters used to inform the proportion of patients eligible for retreatment, the timing of the retreatment option and the clinical benefit of retreated patients with TRF-budesonide the EAG set the probability of retreatment to zero in the EAG base case analysis. The EAG considers that, given the lack of evidence, the impact of retreatment should not be part of the base case computations and instead should be only explored in the scenario analyses.

Mortality rates from CKD stages 1–5 and dialysis were informed from the UK RaDaR data by fitting Cox regression models using age, sex, and CKD stage as covariates. The EAG found the source of mortality data appropriate. However, the EAG would have preferred to see more details about the population from which the data was extracted and more details about the Cox regression models as it was missing from the company submission and the clarification response.

The EAG has concerns around the preference-based measures of health which were collected in the NefIgArd Nef-301 trial using the SF-36 tool, but the results were disregarded by the company. The company argued that considering the time frame of the clarification phase, they were not able to generate utility values using the SF-36 data and run a scenario analysis. They also mentioned that the

SF-36 data appears to demonstrate minimal differences in the QoL across health state CKD 1-4 and presented some additional scenarios assuming the health state utility in state CDK 1-4 (scenario 1) or CKD 1-3b (scenario 2) to be equivalent to the utility values for CKD 1. Although the EAG considers these scenarios informative given the currently available evidence from part A, the QoL evidence from Part B will be important as that data will presumably include more patients in ESRD or dialysis health states once available.

The cost categories included in the model were treatment acquisition costs for TRF-budesonide, standard of care costs, medical costs (secondary care, primary care, dialysis-related costs and transplantation costs), terminal care costs, and costs of managing adverse events.

The company estimated a monthly cost of the TRF-budesonide treatment based on four 4 mg tablets administered OD for 9 months. TRF-budesonide was administered orally. The list price of TRF-budesonide is [redacted] for a package of 120 tablets of 4 mg. [redacted] and a cost per month of [redacted].

At the end of the 9-month treatment period, TRF-budesonide should be reduced to 8 mg OD for 2 weeks of therapy as per MHRA license, with the option of an additional dose tapering period of 4 mg OD for 2 weeks following the end of the 9-month course and the 2-weeks period of reduced therapy. However, as the tapering treatment decision is at the discretion of the treating physician and based on clinical expert opinion, the company did not include the tapering option in the base case analysis.

The SoC costs consisted of ACEi or ARBs and the SGLT2i dapagliflozin. Standard of care treatment costs were applied to both the TRF-budesonide and SoC arms. For each health state in the model a cycle cost for MRU was estimated. For CKD stages 1 to 5, the**se** cost**s** included the cost of secondary care, including inpatient admissions, day cases and outpatient attendances, and primary care**,** including GP appointments and blood tests**.**

For dialysis, 86.5% of patients were assumed to receive haemodialysis and 13.5% peritoneal dialysis based on the UKRR 24th Annual report.[31] Hospital and satellite haemodialysis treatment patients were also assumed to incur a transportation cost sourced from Liu 2015.[51] Dialysis costs also accounted for the costs of nephrologist outpatient appointments, blood tests and hospitalisations. For the transplant health state, costs consisted of procedural and maintenance costs. Procedural costs included pre-assessment, transplant procedure, and post-transplant. Following transplant, patients were assumed to receive immunosuppressive maintenance therapy, as recommended in NICE TA481.[43]

The company's deterministic base case analysis showed that the total costs associated with TRF-budesonide treatment combined with SoC were estimated at [redacted] and total costs associated with SoC only were estimated at [redacted], indicating that addition of TRF-budesonide to SoC treatment increases total costs by [redacted]. Total QALYs associated with TRF-budesonide + SoC were estimated at [redacted] and total QALYs associated with SoC were estimated at [redacted], indicating an incremental number of [redacted] QALYs gained for patients treated with TRF-budesonide + SoC. These give an ICER for TRF-budesonide + SoC versus SoC only of £21,872 per QALY gained. All results are discounted and include a single PAS discount value of [redacted] for TRF-budesonide.

The PSA provided by the company showed that the probability that TRF-budesonide combined with SoC is cost effective at thresholds of £20,000 and £30,000 per QALY gained is 50.2% and 63.8%, respectively.

The company performed various scenario analyses to assess the impact of alternative assumptions on the ICER. For most scenarios the ICER was close to the base case ICER. There were two scenarios with a slightly larger impact. The scenarios leading to the highest increase on the ICER were changing the time horizon to 10 years and excluding the retreatment option for TRF-budesonide. These two scenarios led to respective ICER increases of £41,044 and £33,141 per QALY gained. Also, in the scenario where the study of Greene 2019[30] was used to inform mortality in the different CKD and dialysis health states, the ICER increased to £31,953 per QALY gained. In all other scenarios the ICER remained below £30,000 per QALY gained

The EAG's preferences regarding alternative assumptions for the model led to a number of changes to the company base case analysis. Most importantly, the EAG prefers to use data from patients at LGH in the UK between 1992 to 2020 to inform the transition probability from CKD 4 to CKD 5. In the absence of any (be it real-world or trial) evidence to support the timing of the retreatment, the proportion of patients eligible for retreatment and the clinical benefit of TRF-budesonide for the retreated patients, the EAG also considers the retreatment option uncertain and removed it from the base case analysis. Some additional adjustments which had a smaller impact on results included incorporation of disutility values for TESAEs and adjustment on the costs of SoC to account for concomitant medications costs that were missing from the company's calculations on the acquisition costs of SoC.

These changes in the model lead to the following EAG preferred base case incremental cost effectiveness results. The total costs for TRF-budesonide amount to [redacted], versus [redacted] for SoC. At the same time [redacted] and [redacted] QALYs are accumulated, for TRF-budesonide and SoC, respectively. This leads to an ICER of £41,598, which is higher than the company ICER of £21,872 per QALY gained.

The company presented two sets of probabilistic analyses, one including and one excluding incorporation of the transition probability from CKD 1 to CKD 2 health states, because of the high uncertainty around the transition probability of this parameter. Similarly, the EAG estimated three sets of probabilistic analyses, the first two based on the correction made to the SE of the probability of moving from dialysis to transplantation as the company had assumed a zero SE for this parameter in the base case analysis. Therefore, the third set of the EAG PSA analysis assumed a SE of 0 again, as in the company's model. The EAG probabilistic results were quite different from the EAG deterministic base case. The difference between including CKD 1 to CKD 2 transitions and excluding was very large, as was also observed in the company base case. However, the EAG also noted a significant difference between the deterministic base case and the probabilistic base case when excluding the CKD 1 to CKD 2 transition. The probabilistic ICERs were estimated as: TRF-budesonide produced more QALYs at a lower cost versus SoC (dominant), when CKD 1 to CKD 2 transition probability was included, £49,821 per QALY gained when CKD 1 to CKD 2 transition probability was excluded, and £39,442 when the SE is set to zero for the probability of moving from dialysis to transplantation. Therefore, the PSA ICER of £39,442 per QALY gained is much higher than the EAG deterministic base case. In general, such gap between deterministic and probabilistic ICER can either be a bug or a feature. That is, there may be more issues than discovered so far with the workings of the PSA, leading to unforeseen and unwanted results. The EAG thinks that there is a possibility that there are non-linearities in the model that are intended explaining this gap. Whilst the EAG did find some issues, time constraints did not allow for a more thorough investigation. When we set the SE of the probability of moving from dialysis to transplantation to 0 again, as per the company base case, the probabilistic ICER moves closer to the deterministic ICER. However, this version is known to be incorrect. The PSA shows that the probability that TRF-budesonide is cost effective at thresholds of £20,000 and £30,000 per QALY gained are 10.0% and 22.1%, respectively, using the EAG base case assumptions.

The EAG explored several scenarios, and most of these led to modest changes in the ICER. The most substantial change occurred when the time point from where no treatment effect is increased, in which scenario TRF-budesonide would be the dominant treatment. Using alternative options to estimate transition probabilities from CKD 4 to CKD 5 based on different parametric models to fit the available real-world data from LGH as well as data from different subpopulations of the UK RaDaR database combined with different parametric models showed the ICER was sensitive to these assumptions varying from £30,371 to £[redacted]. Various scenarios regarding percentage of patients being retreated, duration until retreatment starts, and the percentage of the original effectiveness obtained during retreatment were run, yielding ICERs ranging from £15,177 to £46,379 per QALY gained.

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APPENDIX 1: CALCULATION ADDITIONAL STANDARD OF CARE COSTS

For the below table, for each Anatomical Therapeutic Chemical (ATC) group all drugs in eMIT were identified, but only tablet and capsule formulation. Injections and intravenous (IV) fluid were excluded, as these will in generally not be used long-term if good alternatives in tablet or capsule form are available. The quantities reported in eMIT were used to calculate a weighted average cost per month per ATC group. Finally, the average cost per ATC group was adjusted for the percentage of patients using drugs from that ATC category and then summed (see also Question 5, Response to the Clarification letter).[3]

ATC group	DDD	Quantity	Daily tablets required for DDD†	Pack price	Cost per tablet‡	Cost per day§	Cost per month¶
HMG CoA reductase inhibitors							
Atorvastatin 10 mg tablets/Pack size 28	20 mg	119493	2	£0.25	£0.01	£0.02	£0.55
Atorvastatin 20 mg tablets/Pack size 28		272446	1	£0.30	£0.01	£0.01	£0.33
Pravastatin 10 mg tablets/Pack size 28	30 mg	9758	3	£0.46	£0.02	£0.05	£1.50
Rosuvastatin 5 mg tablets/Pack size 28	10 mg	21251	2	£0.57	£0.02	£0.04	£1.23
Simvastatin 10 mg tablets/Pack size 28	30 mg	20203	3	£0.20	£0.01	£0.02	£0.66
Weighted average							£0.47
Adjusted for % patients		*48%*					£0.23
Dihydropyridine derivatives							
Amlodipine 5 mg tablets/Pack size 28	5 mg	388655	1	£0.20	£0.01	£0.01	£0.21
Felodipine 2.5 mg modified-release tablets/Pack size 28	5 mg	18464	2	£1.13	£0.04	£0.08	£2.46
Felodipine 5 mg modified-release tablets/Pack size 28		17922	1	£1.50	£0.05	£0.05	£1.63
Lacidipine 2 mg tablets/Pack size 28	4 mg	2910	2	£3.06	£0.11	£0.22	£6.65
Lacidipine 4 mg tablets/Pack size 28		2294	1	£3.09	£0.11	£0.11	£3.36
Lercanidipine 10 mg tablets/Pack size 28	10 mg	32167	1	£0.75	£0.03	£0.03	£0.82
Nifedipine 10 mg capsules/Pack size 90	30 mg	1835	3	£54.45	£0.60	£1.81	£55.24
Nifedipine 5 mg capsules/Pack size 90		2587	6	£47.25	£0.52	£3.15	£95.87
Weighted average							£1.20
Adjusted for % patients		*41%*					£0.50
Preparations inhibiting uric acid production							
Allopurinol 100 mg tablets/Pack size 28	400 mg	117757	4	£0.32	£0.01	£0.05	£1.41
Febuxostat 80 mg tablets/Pack size 28	80 mg	3996	1	£5.35	£0.19	£0.19	£5.82
Weighted average							£1.55
Adjusted for % patients		*35%*					£0.54
Vitamin D and analogues							
Calcitriol 250 nanogram capsules/Pack size 30	1 mcg	837	4	£3.29	£0.11	£0.44	£13.35
Calcitriol 500 nanogram capsules/Pack size 30		270	2	£5.82	£0.19	£0.39	£11.81

ATC group	DDD	Quantity	Daily tablets required for DDD†	Pack price	Cost per tablet‡	Cost per day§	Cost per month¶
Colecalciferol 800 unit capsules/Pack size 30	20 mcg	194131	1	£1.51	£0.05	£0.05	£1.53
Colecalciferol 800 unit tablets/Pack size 30		40047	1	£3.00	£0.10	£0.10	£3.04
Weighted average							£1.84
Adjusted for % patients		*27%*					£0.49
Beta blocking agents, selective							
Atenolol 25 mg tablets/Pack size 28	75 mg	35756	3	£0.54	£0.02	£0.06	£1.74
Bisoprolol 1.25 mg tablets/Pack size 28	10 mg	340089	8	£0.26	£0.01	£0.07	£2.25
Bisoprolol 10 mg tablets/Pack size 28		31430	1	£0.30	£0.01	£0.01	£0.32
Bisoprolol 2.5 mg tablets/Pack size 28		400416	4	£0.21	£0.01	£0.03	£0.91
Bisoprolol 5 mg tablets/Pack size 28		197793	2	£0.23	£0.01	£0.02	£0.49
Celiprolol 200 mg tablets/Pack size 30	200 mg	80	1	£5.43	£0.18	£0.18	£5.51
Metoprolol 50 mg tablets/Pack size 28	150 mg	14855	3	£0.59	£0.02	£0.06	£1.93
Nebivolol 5 mg tablets/Pack size 28	5 mg	14763	1	£0.86	£0.03	£0.03	£0.93
Weighted average							£1.30
Adjusted for % patients		*21%*					£0.28
Proton pump inhibitors							
Lansoprazole 15 mg gastro-resistant capsules/Pack size 28	30 mg	314807	2	£0.44	£0.02	£0.03	£0.96
Lansoprazole 15 mg orodispersible tablets/Pack size 28		59748	2	£2.15	£0.08	£0.15	£4.66
Lansoprazole 30 mg gastro-resistant capsules/Pack size 28		671342	1	£0.63	£0.02	£0.02	£0.68
Lansoprazole 30 mg orodispersible tablets/Pack size 28		119029	1	£2.81	£0.10	£0.10	£3.05
Omeprazole 10 mg gastro-resistant capsules/Pack size 28	20 mg	40150	2	£0.51	£0.02	£0.04	£1.11
Omeprazole 20 mg gastro-resistant capsules/Pack size 28		1151554	1	£0.39	£0.01	£0.01	£0.42
Pantoprazole 20 mg gastro-resistant tablets/Pack size 28	40 mg	20256	2	£0.42	£0.01	£0.03	£0.90
Pantoprazole 40 mg gastro-resistant tablets/Pack size 28		14227	1	£0.55	£0.02	£0.02	£0.60
Rabeprazole 10 mg gastro-resistant tablets/Pack size 28	20 mg	1702	2	£1.49	£0.05	£0.11	£3.24
Rabeprazole 20 mg gastro-resistant tablets/Pack size 28		1872	1	£2.56	£0.09	£0.09	£2.78
Weighted average							£0.82
Adjusted for % patients		*20%*					£0.16
Glucocorticoids							
Hydrocortisone 10 mg tablets/Pack size 30	30 mg	50571	3	£1.24	£0.04	£0.12	£3.78
Prednisolone 1 mg tablets/Pack size 28	10 mg	133254	10	£0.20	£0.01	£0.07	£2.17
Prednisolone 2.5 mg gastro-resistant tablets/Pack size 28		18214	4	£0.64	£0.02	£0.09	£2.79
Prednisolone 2.5 mg gastro-resistant tablets/Pack size 30		1896	4	£0.64	£0.02	£0.09	£2.60
Prednisolone 5 mg gastro-resistant tablets/Pack size 28		30302	2	£1.23	£0.04	£0.09	£2.66

ATC group	DDD	Quantity	Daily tablets required for DDD†	Pack price	Cost per tablet‡	Cost per day§	Cost per month¶
Prednisolone 5 mg soluble tablets/Pack size 30		28799	2	£7.83	£0.26	£0.52	£15.88
Prednisolone 5 mg tablets/Pack size 28		2042999	2	£0.30	£0.01	£0.02	£0.66
Weighted average							£1.05
Adjusted for % patients		*19%*					£0.20
Other antihistamines for systemic use							
Desloratadine 5 mg tablets/Pack size 30	10 mg	1455	2	£0.94	£0.03	£0.06	£1.91
Fexofenadine 120 mg tablets/Pack size 30	120 mg	27550	1	£1.41	£0.05	£0.05	£1.43
Loratadine 10 mg tablets/Pack size 30	10 mg	42096	1	£0.32	£0.01	£0.01	£0.32
Weighted average							£0.78
Adjusted for % patients		*15%*					£0.12
Alpha-adrenoreceptor antagonists							
Doxazosin 1 mg tablets/Pack size 28	4 mg	28144	4	£0.28	£0.01	£0.04	£1.21
Doxazosin 2 mg tablets/Pack size 28		64936	2	£0.28	£0.01	£0.02	£0.60
Doxazosin 4 mg modified-release tablets/Pack size 28		4205	1	£2.06	£0.07	£0.07	£2.24
Doxazosin 4 mg tablets/Pack size 28		99278	1	£0.39	£0.01	£0.01	£0.42
Weighted average							£0.63
Adjusted for % patients		*13%*					£0.08
Imidazoline receptor agonists							
Moxonidine 300 microgram tablets/Pack size 28	300 mcg	1784	1	£4.33	£0.15	£0.15	£4.71
Adjusted for % patients		*11%*					£0.50
Other lipid modifying agents							
Ezetimibe 10 mg tablets/Pack size 28	10 mg	47218	1	£1.01	£0.04	£0.04	£1.10
Omega-3 Ethyl Ester 1 g capsules/Pack size 28	4 g	5301	4	£8.07	£0.29	£1.15	£35.10
Weighted average							£4.53
Adjusted for % patients		*12%*					£0.54
Thiazides, plain							
Bendroflumethiazide 2.5 mg tablets/Pack size 28	2.5 mg	42304	1	£0.32	£0.01	£0.01	£0.34
Adjusted for % patients		*11%*					£0.04
Total costs							**£3.67**

† Calculated as the defined daily dose divided by the tablet size; ‡ Calculated as the pack price divided by the pack size; § Calculated as the cost per tablet multiplied by the number of daily tablets required for DDD; ¶ Calculated as the cost per day multiplied by 30.4375 days.
ATC = Anatomical Therapeutic Chemical; DDD = defined daily dose; HMG CoA = 3-hydroxy-3-methyl-glutaryl-coenzyme A

Single Technology Appraisal

Targeted-release budesonide for treating primary IgA nephropathy [ID1434]

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 Tuesday 11 July** 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 separately highlight information that is submitted as '[redacted]' in turquoise, all information submitted as '[redacted]' in yellow, and all information submitted as '[redacted]' in pink.

Issue 1 Treatment of patients who cannot tolerate RASi with TRF-budesonide

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
ID1434 budesonide EAG report pg 25, 85. EAG statement that treatment of patients who cannot tolerate RASi with TRF-budesonide is a contradiction of the licensed indication.	Removal of statement.	The licensed indication of TRF-budesonide is for the treatment of primary IgAN in adults at risk of rapid disease progression with a UPCR ≥1.5 g/g. The NefIgArd Nef-301 trial required patients to be receiving a stable dose of RAS inhibitor therapy (ACEIs and/or ARBs) at the maximum allowed dose or maximum tolerated dose, according to the 2012 KDIGO guideline, for at least 3 months prior to randomisation. As not all patients tolerate RASi therapy, the maximally tolerated RASi dose of such patients may be zero. As such, treatment of patients who cannot tolerate RASi therapy with TRF-budesonide does not constitute a	Thank you. An amendment has been made to the report on p25 and p85
ID1434 budesonide EAG report pg 48. EAG statement that inclusion of patients not receiving RASi therapy in Nef-301 deviates from the study exclusion criterion.	Removal of statement.		Thank you. An amendment has been made to the report on p49

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
		contradiction to the licensed indication or a deviation from the exclusion criterion in Nef-301. Treatment of patients who cannot tolerate RASi therapy with TRF-budesonide is also in line with anticipated use in clinical practice.	

Issue 2 Terminology 'special circumstances'

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
ID1434 budesonide EAG report pg 26, 27 EAG use of the term 'special circumstances'	Amend wording to: 'corticosteroids and immunosuppressants are only recommended if a clinical trial is not accessible and the risk/benefit profile is considered to be acceptable, in line with the KDIGO guidelines'.	To accurately relay the KDIGO recommendations.	Thank you. The report has been amended on pages 26-27

Issue 3 Comparators

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
ID1434 budesonide EAG report pg 28 EAG comment that MMF is mentioned as an aspect of SoC by the Company.	Removal of statement.	MMF was not mentioned as a component of SoC by the Company. Specifically, in the Company submission, SoC is described as: blood pressure management; maximally tolerated dose of ACEi/ARB; lifestyle modification; and addressing cardiovascular risk. SGLT2is are also given to patients with IgAN as part of SoC.	Thank you – this has been amended by the removal of the phrase, “as an aspect of SoC”.
ID1434 budesonide EAG report pg 29 EAG comment that SGLT2i were included as comparators in the decision problem.	Removal of statement.	SGLT2is were not included as direct comparators in the decision problem. The company provided evidence, supported by clinical expert opinion, indicating that SGLT2is would be administered as a component of SoC for IgAN. Therefore, it is anticipated that in clinical practice TRF-budesonide will be used in combination with	This is not a factual inaccuracy. In Table 1 of the CS (Table 2.1 in the EAG report) the company indicates that SGLT2is are part of the SoC comparator.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
		SGLT2is as part of an SoC regimen.	
ID1434 budesonide EAG report pg 29, 74 EAG comment that no patients in the trial of budesonide + SoC versus SoC (Nef-301) received an SGLT2i.	Removal of statement.	SGLT2is were not excluded as concomitant medications in the NeflgArd Nef-301 trial. However, prevalent use was not observed as SGLT2is did not have a marketing authorisation (2021) in the treatment of CKD in adults until after trial initiation (2018). In total, [redacted] patients in the safety analysis set ([redacted] in the TRF-budesonide arm; [redacted] in the placebo arm) and [redacted] patient in the TRF-budesonide arm of the full analysis set received SGLT2i as part of SoC.	This is not a factual inaccuracy. The Table the company provided during clarification did not include any information on SGLT2is. Therefore, it was correct at the time for the EAG to assume that none were used.

Issue 4 Addressing 'disease progression' as an outcome of interest

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
ID1434 budesonide EAG report pg 32, 59 EAG claim that the trial evidence did not address 'disease progression', a highly patient-relevant outcome.	The pivotal trial for TRF-budesonide in IgAN, NefIgArd NEF-301, employed the use of previously validated and clinically accepted surrogate outcomes to address disease progression; the results were presented in the Company submission.	In the Company submission disease progression was assessed using surrogate outcomes accepted by KDIGO, the EMA, and clinical experts in England (details provided in Section B.2.3.2 of the original Company submission). Progression to ESRD/ dialysis/transplant is difficult to assess in rare orphan diseases as it requires a large patient sample and a long (several years) follow up to allow adequate statistical power for assessing significance.	This is not a factual inaccuracy. The EAG appreciates that clinical disease progression outcomes might have produced sparse data at this stage but nevertheless believes that such data would have been beneficial, as explained in the report on page 59.

Issue 5 Health-related quality of life data

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
ID1434 budesonide EAG report pg 60, 98 EAG claim that the Company did not respond to the question regarding use of a disease-specific HRQoL tool.	Amend statement to acknowledge that the Company provided the following response: '*The impact of IgAN on patient quality of life (QoL) has been reported to increase with disease progression, particularly when dialysis becomes necessary (24). A wide range of health-related quality of life (HRQoL) instruments, including short-form 36 (SF-36), have been used in assessments of the QoL of people with kidney disease (25) and IgAN (24). However, QoL has not been included as a primary outcome in clinical trials in IgAN (8, 10, 26) and, to our knowledge, there is no precedent for the use of a particular disease-specific assessment tool.* *QoL assessment using the SF-36 was included as a secondary outcome in the NefIgArd NEF-301 trial, and its use aimed to assess*	The Company provided a response which explained that there was no precedent where QoL was assessed as a primary outcome in clinical trials in patients with IgAN or where a particular disease-specific assessment tool was used. The company highlighted that due to the timeframe of Part A of Nef-301 (12 months), the lack of difference in QoL between treatment arms was not surprising. In addition, the Company also noted the 2-fold intention in using the QoL tool, to assess the impact of treatment with TRF-budesonide on QoL related to adverse events in addition to overall QoL.	The question posed to the company during clarification was: *The company effectively dismisses the non-significant SF-36v2 findings, on the basis that SF-36v2 is not a disease-specific tool. However, SF-36v2 was the outcome chosen pre-hoc by the company. Please explain why SF-36v2, and not a disease-specific tool, was measured in the trial if this was not deemed appropriate*? An important context to this question is that the company had previously commented on their non-conclusive QoL results in the CS (page 64) by stating that *"it should be noted that the SF-36 is a generic HRQoL measure without any domains specific to kidney disease, as opposed to [a] tool specific to people with kidney disease, which may be more sensitive to potential changes in response to therapy."* This

	the impact of TRF-budesonide treatment on QoL and safety. *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 HRQoL decline associated with end-stage renal disease (ESRD) and dialysis in patients with primary IgAN and a baseline UPCR ≥1.5 g/g. Since Part A of NefIgArd Nef-301 only assessed 12 months of data, it was not expected that a substantial proportion of patients would reach ESRD or require dialysis; therefore, the lack of difference in QoL between treatment arms is not surprising. In addition, the lack of significance in the SF-36 results demonstrates minimal impact of adverse events associated with TRF-budesonide on patients' QoL and further supports its good safety profile. TRF-budesonide is a well-tolerated treatment associated with mild or moderate TEAEs and no severe infections – which occur*		comment indicated that a more disease-specific tool may have been more sensitive. With that comment taken into consideration, the company's response to the EAG question does appear to evade the key clause of the question: "*if this was not deemed appropriate*". In other words, if the company felt that a generic tool was not appropriate, why was it used? The company's response does not answer this question properly, because their only justification for the use of what they themselves admitted was an insensitive generic tool was that there was *"no precedent for the use of a particular disease-specific assessment tool"*. In other words, the company used a possibly inappropriate tool because a potentially more appropriate alternative had not been used in a similar context before. This is an insufficiently strong response to convince the EAG, and so the EAG maintain that the question has not been *convincingly* answered. However, a qualifier has been

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
	frequently during treatment with the use of systemic corticosteroids (8, 10, 27).'		added to the text in the report to indicate that the answer has been answered to a certain extent, as well as additional explanatory sentences (p60).

Issue 6 Ongoing studies

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
ID1434 budesonide EAG report pg 73 EAG statement that there are no ongoing studies.	The NefIgArd-OLE open-label extension (OLE) study is an ongoing phase 3b, multicentre, open-label, single-arm extension trial to evaluate the efficacy and safety of TRF-budesonide 16 mg/day treatment in patients with IgAN who have completed the phase 3 NefIgArd Nef-301 trial. Trial completion is due in May 2024.	Accuracy change.	Thank you - the report has been amended. Please see Section 3.2.7 (page 73).

Issue 7 TRF-budesonide re-treatment

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
ID1434 budesonide EAG report pg 94 To summarise the issue, the EAG noticed that when the retreatment option is deactivated from the base case analysis, which is aligned with the EAG's preferred options for the base case analysis as explained below, there is still treatment benefit accounted for in the TRF-budesonide comparator option. To totally remove this treatment benefit, in addition to deselecting the retreatment option, the EAG had to explicitly omit the treatment effect during retreatment and set the timing between retreatments to zero.	To avoid underestimating the treatment benefit of the initial dose of TRF-budesonide, it is suggested to keep the time between treatments at 14.75 months as the formulae in "Risk_of_CKD5!R96:W3749" already account for the loss of treatment benefit at the user-defined time-point (in the base case this is 1-year).	As identified by the EAG "there is still treatment benefit accounted for in the TRF-budesonide comparator option". As specified elsewhere in the submission, this additional benefit is the assumed benefit from months 9–12 after the first treatment initiation. By setting the time between retreatments to 0 the EAG have removed the additional 3-months (month 9 to 12) of assumed treatment benefit after the initial 9-month treatment period. This is seen in the model graphically in the "Time to CKD 5 - Kinpeygo versus SoC" figure on the "Risk_of_CKD5"	Thank you for the clarification. The report has been amended and results have been updated accordingly.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
		worksheet. In this figure it is evident that the increase in the risk of progressing to CKD5 (the kink in the TRF-budesonide curve) happens at month-9, when time between treatments is set to zero. However, as the treatment effect of TRF-budesonide is assumed to be observed for 12-months after treatment initiation, the EAG base case has underestimated the benefits of TRF-budesonide.	
ID1434 budesonide EAG report pg 94 Total removal of retreatment with TRF-budesonide from the economic model.	A single round of retreatment is proposed given feedback received from clinical experts.	Based on clinical feedback from the advisory board, it was highlighted that retreatment was likely to be needed. Although uncertainty persists around the effect of subsequent treatment cycles, it was expected by clinicians that patients who	This is not a factual inaccuracy. The EAG considers the company's assumptions on the proportion of patients eligible for retreatment and the TRF-budesonide treatment effectiveness for the retreated patients

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
		had responded to initial treatment and were still eligible for treatment would be considered for retreatment in clinical practice, in line with the product label.	optimistic, as they are not based on any evidence. As such, these assumptions were subject to considerable uncertainty deeming inclusion of retreatment inappropriate for the base case analysis. These EAG's concerns are aligned with the input from the advisory board which flagged that 1) the efficacy of TRF-budesonide upon retreatment, 2) the timing of the retreatment, 3) the criteria for retreatment, and 4) the proportion of patients that may require retreatment are uncertain.{CS#2} We understand that when evidence is lacking but clinicians confirm that retreatment may be

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
			used, including this in the model is one alternative (more optimistic when treatment is assumed to have a similar health benefit as the original treatment round). However, given the lack of evidence the EAG thinks this is not appropriate for the base case analysis. The impact of retreatment has been addressed through multiple scenario analyses which covered a wide range of uncertainty in the input parameters.

Issue 8 PSA analysis

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
ID1434 budesonide EAG report pg 109 The transition probability for patients in the dialysis to transplant health state assumes a standard error of 0. The EAG assumed a standard error of 0.001, which solves this issue.	Based on the standard error (SE) published in the TA775 submission (0.000) the maximum SE this parameter could have been was 0.0004, if rounding to 4 decimal points instead of 3. As such, it is believed a SE value of 0.0004 for the probability of transitioning from dialysis to transplant is closer to the true value of uncertainty than the 0.001 proposed by the EAG.	The use of 0.001 as the standard error is expected to overestimate the uncertainty in the probability of transitioning from dialysis to transplant based on published values from TA775. Although it is agreed a SE other than 0 should be incorporated into the model, a value of 0.0004 is expected to be closer to the true value of the SE, if rounding to a greater degree is used.	The EAG thanks the company for providing this additional information. However, this is not a factual inaccuracy. The EAG is satisfied to see that the company agrees that using a SE of 0 is not an appropriate approach. However, the response of the company indicates that this issue is not a factual inaccuracy as at the time of the EAG report the SE was set to 0. Despite this, the EAG noticed that even when using the new proposed SE of the company of 0.0004 the probabilistic outcomes are similar to the probabilistic

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
			outcomes of the EAG base case.

Issue 9 Typographical errors

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
ID1434 budesonide EAG report pg 75	This could be derived from another trial, or indirectly via an ITC (using budesonide + SoC versus SoC and corticosteroids +SoC verseus SoC…	Accuracy change – correct typographical error	Thank you - amended
ID1434 budesonide EAG report pg 91	Based ~~Based~~	Accuracy change – delete repeated word	Thank you - amended
ID1434 budesonide EAG report pg 112, 119	… moving from ~~diabetes~~ dialysis to transplantation…	Accuracy change	Thank you - amended
ID1434 budesonide EAG report pg 117	Transition probabilities between CKD 1 and CKD 4 health states for both the TRF-budesonide and SoC arms were estimated by comparing the eGFR values at baseline and after 9 months of treatment which were then mapped to reflect patients in different CKD health states ~~these transitions~~	Delete unnecessary words	Thank you - amended

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
ID1434 budesonide EAG report pg 117	The EAG found the source of ~~morality~~ mortality data appropriate.	Accuracy change	Thank you - amended
ID1434 budesonide EAG report pg 119	the EAG ~~considers~~ also considers	Accuracy change – delete repeated word	Thank you - amended
ID1434 budesonide EAG report pg 120	The PSA shows that the probability that ~~the probability~~ that…	Accuracy change – delete repeated words	Thank you - amended

Issue 10 Errors in confidential marking

Location of incorrect marking	Description of incorrect marking	Amended marking	EAG response
ID1434 budesonide EAG report pg 26	Number and percentage of patients needs to be marked as AIC.	([redacted] in the TRF-budesonide 16 mg/day group and [redacted] in the placebo group experienced a severe treatment-emergent AE [TEAE])	Thank you - amended
ID1434 budesonide	Percentage of patients needs to be	Other than ARBs and ACEIs, the overall most common classes of concomitant medications were the following: Hydroxy-3-methyl-glutaryl-coenzyme A reductase inhibitors ([redacted] of patients in the TRF-budesonide 16 mg/day group and [redacted] of patients in the placebo group); Dihydropyridine derivatives ([redacted] of patients in	Thank you - amended

Location of incorrect marking	Description of incorrect marking	Amended marking	EAG response
EAG report pg 30	marked as AIC	the TRF-budesonide 16 mg/day group and [redacted] of patients in the placebo group); and Preparations inhibiting uric acid production ([redacted] of patients in the TRF-budesonide 16 mg/day group and [redacted]% of patients in the placebo group).	
ID1434 budesonide EAG report pg 49	Number and percentage of patients needs to be marked as AIC	In a subgroup analysis of patients with a UPCR of >1.5 g/g within the RaDaR cohort, [redacted]) of patients had an eGFR ≤30 mL/min/1.73 m^2 (CKD stages 4 and 5 at diagnosis).	Thank you - amended
ID1434 budesonide EAG report pg 49	Percentage of patients needs to be marked as AIC	The EAG think that [redacted] of patients with an eGFR of <30 ml/min/1.73 m^2 in the population of people with UPCR >1.5 g/g is significant, given the lack of treatment options available for that group.	Thank you - amended
ID1434 budesonide EAG report pg 54	Percentage of patients needs to be marked as AIC	In addition, although there were some small imbalances in the percentages of patients on ACEIs or ARBs between treatment groups, overall RAS inhibition was similar, with the majority of patients receiving at least 50% of the maximum allowed dose ([redacted] in the TRF-budesonide group vs [redacted] in the placebo group).	Thank you - amended

Location of incorrect marking	Description of incorrect marking	Amended marking	EAG response
ID1434 budesonide EAG report pg 56	Percentage of patients needs to be marked as AIC	Consistent with the primary endpoint, after 9 months of treatment, patients with a baseline UPCR ≥1.5 g/g treated with TRF-budesonide 16 mg per day showed a [redacted] reduction in UACR…	Thank you - amended
ID1434 budesonide EAG report pg 57	Values to be marked as AIC	The findings of Part A of the NeflgArd Nef-301 trial indicate a [redacted] mL/min/1.73 m^2 absolute change in eGFR from baseline following the 9-month treatment with TRF-budesonide (vs [redacted] mL/min/1.73 m^2 in the placebo arm), further indicating a reduction in the risk of progression to kidney failure.	Thank you - amended
ID1434 budesonide EAG report pg 63	Values to be marked as AIC	For example, although the proportion of white patients in the UK target population (77%) was reasonably close to that in the trial ([redacted]%), no information of the proportions of other ethnicities were given. In addition, the male proportion in the UK population (71%) appeared larger than that in the trial ([redacted]%).	Thank you - amended
ID1434 budesonide EAG report pg 63	Values to be marked as AIC	The TEAE incidence rates were slightly lower in the SAS with baseline UPCR ≥1.5 g/g; [redacted] of [redacted] ([redacted]%) patients in the TRF-budesonide 16 mg/day group and [redacted] of [redacted] ([redacted]%) patients in the placebo group reported AEs.	Thank you - amended
ID1434 budesonide	AIC not marked correctly, highlighted	To account for treatment discontinuation during the first round of treatment, the company base case assumed that [redacted] of TRF-budesonide patients would	Thank you - amended

Location of incorrect marking	Description of incorrect marking	Amended marking	EAG response
EAG report pg 85	but not underlined	undergo retreatment, based on the number of patients that completed the full treatment course in Part A of the NefIgArd Nef-301 study.	
ID1434 budesonide EAG report pg 85	Values to be marked as AIC	i) all patients in the UK RaDaR database who had IgAN and UPCR ≥1.5 g/g, consisting of [redacted] patients (Figure 17 of the CS[1]) ii) patients in the UK RaDaR database with IgAN who had a UPCR ≥1.5 g/g and were on ACEi and/or ARBs at baseline, consisting of [redacted] patients	Thank you - amended
ID1434 budesonide EAG report pg 85	Value to be marked as AIC	However, as mentioned above, in the NefIgArd Nef-301 trial only six patients in the SAS dataset (n=[redacted]) were not using RASi therapy at baseline, which raises concerns to the EAG about the representativeness of the trial population, especially if patients who cannot tolerate RAS blockade therapy are still eligible to receive TRF-budesonide treatment.	Thank you - amended
ID1434 budesonide EAG report pg 85	Values to be marked as AIC	In addition, the EAG would have liked to see the same patient characteristics as reported in Table 4.5 for the [redacted] and [redacted] selected patients from the UK RaDaR database, respectively.	Thank you - amended
ID1434 budesonide EAG report pg 86	AIC not marked correctly, highlighted but not underlined	… the percentage of patients receiving a second treatment round is [redacted]% (see response to clarification question B11a.3).	Thank you - amended

Location of incorrect marking	Description of incorrect marking	Amended marking	EAG response
ID1434 budesonide EAG report pg 87	Value to be marked as AIC	The model has a time horizon of 56 years that is considered appropriate as a lifetime horizon, in line with the NICE reference case, given that the average age of patients at the start of treatment is [redacted] years.	Thank you - amended
ID1434 budesonide EAG report pg 90	Values to be marked as AIC	However, it is presently unclear to the EAG why the number of patients at risk at t=0 in Figure 4.3 (n=[redacted]) is different than the same number in Figure 4.2 (n=[redacted]) above…	Thank you - amended
ID1434 budesonide EAG report pg 91	Values to be marked as AIC	According to this scenario, of the total number of [redacted] patients that were originally identified in the UK RaDaR database to have IgAN and UPCR ≥1.5 g/g presented in Figure 4.2 above, [redacted] patients would be on ACEi and/or ARBs at baseline	Thank you - amended
ID1434 budesonide EAG report pg. 91	AIC not marked correctly, highlighted but not underlined	Figure 4.4 KM curves estimating time from CKD 4 diagnosis to ESRD in patients with IgAN based on the survival data in the electronic model	Thank you - amended

Location of incorrect marking	Description of incorrect marking	Amended marking	EAG response
ID1434 budesonide EAG report pg. 93	Values to be marked as AIC	The company responded that [redacted] patients in the TRF-budesonide arm and seven in the placebo discontinued treatment due to adverse events (n=[redacted]), withdrawal of informed consent (n=[redacted]), pregnancy (n=[redacted]), and other reason (n=[redacted]).	Thank you - amended
ID1434 budesonide EAG report pg. 98	Value to be marked as AIC	Based on the proportion of females in the study ([redacted]%), a sex weighted age-specific utility for the general population was calculated.	Thank you - amended
ID1434 budesonide EAG report pg. 99	Text to be marked as CIC	According to the CS, this was justified as it is expected that [redacted].	Thank you - amended
ID1434 budesonide EAG report pg. 107 Table 5.4 Column ICER per QALY	Incorrect CIC marking, values underlined	Remove underline from all ICER per QALY value in Table 5.4	Thank you - amended

Location of incorrect marking	Description of incorrect marking	Amended marking	EAG response
ID1434 budesonide EAG report pg. 114 Table 6.4 Column ICER per QALY	Incorrect CIC marking, values underlined	Remove underline from all ICER per QALY value in Table 6.4	Thank you - amended

NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Targeted-release budesonide for treating primary IgA nephropathy [ID1434]

Technical engagement response form

As a stakeholder you have been invited to comment on the External Assessment Report (EAR) for this evaluation.

Your comments and feedback on the key issues below are really valued. The EAR and stakeholders' responses are used by the committee to help it make decisions at the committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form

We are asking for your views on key issues in the EAR that are likely to be discussed by the committee. The key issues in the EAR reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the EAR.

You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise.

If you would like to comment on issues in the EAR that have not been identified as key issues, you can do so in the 'Additional issues' section.

If you are the company involved in this evaluation, please complete the 'Summary of changes to the company's cost-effectiveness estimates(s)' section if your response includes changes to your cost-effectiveness evidence.

Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.

Do not include medical information about yourself or another person that could identify you or the other person.

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.

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 under [redacted], all information submitted under [redacted], and all information submitted under [redacted] in pink. If confidential information is submitted, please also send a second version of your comments with that information redacted. See the NICE health technology evaluation guidance development manual (sections 5.4.1 to 5.4.10) for more information.

The deadline for comments is **5pm** on **22 August 2023**. 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 during engagement, 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 during engagement 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.

Technical engagement response form

About you

Table 1. About you

Your name	[redacted]
Organisation name: stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder, please leave blank)	Britannia Pharmaceuticals Ltd.
Disclosure Please disclose any funding received from the company bringing the treatment to NICE for evaluation or from any of the comparator treatment companies in the last 12 months [Relevant companies are listed in the appraisal stakeholder list.] Please state: • the name of the company • the amount • the purpose of funding including whether it related to a product mentioned in the stakeholder list • whether it is ongoing or has ceased.	Employee of Britannia Pharmaceuticals Ltd., the company submitting for the current HTA
Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry	N/A

Key issues for engagement

All: Please use the table below to respond to the key issues raised in the EAR.

Table 2. Key issues

Key issue	Does this response contain new evidence, data or analyses?	Response
1. Applicability of the trial evidence to those patients not on RASi therapy	Yes	In the NefIgArd Nef-301 study, targeted-release formulation (TRF)-budesonide was administered in addition to standard of care (SoC), which includes lifestyle modification, blood pressure management, maximum-tolerated renin-angiotensin system (RAS) blockade (angiotensin-converting enzyme inhibitors [ACEi] or angiotensin receptor blockers [ARB]), and addressing cardiovascular risk in order to align with current clinical practice and the proposed positioning/indication of TRF-budesonide (1-3). Of note, patients who could not tolerate RAS blockade therapy (and for whom, therefore, the maximally tolerated RASi dose may be zero) were considered in the study, in line with anticipated use in clinical practice. In real-world clinical practice, a small proportion (~10%) of patients with IgAN with UPCR ≥1.5 g/g (an already small subgroup of patients with primary IgAN, an orphan disease) are intolerant to RASi therapy (4). This is most commonly because patients have low blood pressure at the time of initiating RASi therapy. Clinical expert opinion (submitted as new evidence (4)) indicated that patients who were not receiving RASi therapy in the NefIgArd Nef-301 study were likely to have had low blood pressure at the time of treatment with TRF-budesonide, and would therefore have been unable to tolerate further reductions in blood pressure induced by RASi therapy. In accordance, the 2021 KDIGO guidelines note that the use of RASi therapy in younger patients with low/normal blood pressure may increase the risk of orthostatic hypotension and advise that normotensive patients are started on low-dose

		therapy with dose escalation controlled so that the patient is treated with the maximal tolerated dose of RASi (balancing the benefits of treatment and minimising side effects) (1). The clinical expert indicated that TRF-budesonide does not affect blood pressure and so would be an appropriate treatment for patients who cannot tolerate RASi therapy and for whom limited alternative therapeutic options exist (4). Patients with IgAN who cannot tolerate RASi therapy (and who otherwise receive optimised SoC) have limited treatment options. The 2021 KDIGO guidelines recommend that patients at high risk of progressive CKD despite maximal supportive care (including maximum tolerated RASi therapy) are enrolled on a clinical trial (1). The use of immunosuppressants is cautiously recommended should a clinical trial not be accessible due to their adverse event profile (1). As such, excluding these patients (i.e. patients with primary IgAN who are intolerant to RASi therapies and who otherwise receive optimised SoC) from treatment with TRF-budesonide, a therapy that presents the potential to delay disease progression, may result in challenges to equitable access to treatment for these patients.
2. Corticosteroids, MMF and SGLT2i may be relevant comparators for different subgroups of patients	Yes	**Corticosteroids and immunosuppressants** The company maintains the position that corticosteroids (CS) and immunosuppressants (in addition to optimised SoC) are not relevant comparators for TRF-budesonide, based on feedback received by clinical experts (2). CS and immunosuppressants are only recommended if a clinical trial is not accessible and the risk/benefit profile is considered to be acceptable (1). UK clinical experts (2) reported that in practice, CS are used sparingly and only in patients with severe kidney disease (i.e. patients with nephrotic syndrome, defined by the KDIGO guidelines as those with proteinuria ≥3.5 g/day and PCR of ≥3,000 mg/g [≥300 mg/mmol], including oedema, hypoalbuminemia and hyperlipidaemia (1)). As noted by the KDIGO guidelines, patients with IgAN rarely present with nephrotic syndrome (including oedema and both hypoalbuminemia and nephrotic-range proteinuria >3.5 g/d) (1). To address and respond to the EAG's concerns, however, the company conducted an indirect treatment comparison (ITC) of TRF-budesonide vs CS and immunosuppressants (submitted as new evidence); the methodology and results of these analyses are presented below.

		Mycophenolate mofetil (MMF) Based on advice received by clinical experts (2, 4) and the 2021 KDIGO guidelines (1), the company also maintains the position that MMF (in addition to optimised SoC) is not a relevant comparator for TRF-budesonide. The 2021 KDIGO guidelines (1) highlight that there is insufficient evidence to support the use of MMF in IgAN; randomised controlled trials that investigated the efficacy of MMF monotherapy in IgAN versus placebo or other immunosuppressive treatment in cohorts including Asian and non-Asian patients demonstrated uncertain clinical benefits (5-7). Two trials were terminated early due to lack of treatment benefit (5, 7). The KDIGO guidelines (1) suggest that MMF may be used in Chinese patients only as a glucocorticoid-sparing agent, based on the results of one randomised controlled trial (8). Clinical experts advised that, due to the lack of other available treatment options and the adverse event profile of CS, MMF could be used as a steroid-sparing agent for patients with IgAN; however, MMF is not used in clinical practice in England (2, 4). As such, MMF was not included as a relevant comparator in the ITC that was conducted by the company. **Sodium-glucose cotransporter-2 inhibitors (SGLT2is)** There is as yet no clinical guidance for the use of SGLT2is specific to patients with IgAN by NICE. However, dapagliflozin has received NICE approval for the treatment of CKD (TA775) (9) and is also anticipated to be used as part of SoC in patients with IgAN, as indicated by clinical expert opinion (2). As such, it is anticipated that dapagliflozin will be administered in combination with TRF-budesonide as part of SoC. Any potential benefits that may be observed from the addition of dapagliflozin to SoC, are anticipated to be additive to the TRF-budesonide treatment effect, especially since there is no crossover between their mechanisms of action (as indicated by clinical expert opinion (2)). To address and respond to the EAG's concerns, however, the company conducted an ITC of TRF-budesonide vs dapagliflozin + SoC; the methodology and results of these analyses are presented below. **ITC methodology** A Bayesian network meta-analysis (NMA) approach was adopted for synthesis of the evidence base. Both random-effects (RE) and fixed-effect (FE) models were fitted to the data to estimate relative treatment-effects between TRF-budesonide and comparators of interest

		(CS and immunosuppressants + SoC; and dapagliflozin + SoC). Efficacy outcomes that were assessed included change from baseline (CFB) to 12 months in urine protein to creatinine ratio (UPCR) and estimated glomerular filtration rate (eGFR). Consistent with the target population for current appraisal of TRF-budesonide, the analyses were informed by a cohort from the NefIgAn Nef-202 (who received TRF-budesonide 16 mg/day) (10) and NefIgArd NEF-301 (11) trials who had a baseline UPCR of ≥1.5 g/g (which is the indicated population). However, the intention-to-treat population from all comparator studies was evaluated in all networks in the absence of results reported for UPCR ≥1.5 g/g subgroup; no other studies assess this population and therefore there are no study populations which are homogenous to the NefIgArd trial. This is a significant limitation of the analyses as baseline proteinuria is a significant predictor of patient outcomes, and further, analysis of differing trial populations may undermine the robustness of the NMA. The analyses for the CS and immunosuppressants arm (in addition to optimised SoC) of the ITC were informed by the STOP-IgAN trial (12, 13), a study conducted across 32 centres in Germany and which was, therefore, likely to evaluate a higher proportion of white/Caucasian patients, comparable to the population within the TRF-budesonide studies. A second study of CS in IgAN (TESTING (14, 15)) was considered in the ITC feasibility assessment; the study population, however, was found not to be homogeneous to the population of the TRF-budesonide as it primarily consisted of an Asian population. In addition, patients in the TESTING study received oral (full- or reduced-dose) methylprednisolone (15) (whereas patients in the STOP-IgAN received immunosuppressant therapy [oral cyclophosphamide for the first 3 months, switched to azathioprine for the next 3 years] together with oral prednisolone (12)); clinician feedback has indicated that methylprednisolone is not used to treat IgAN patients in the UK (4). As such, it was concluded that STOP-IgAN was more relevant than TESTING to UK clinical practice based on both the trial population and the treatments received. The TESTING study was not considered relevant to inform the CS arm of the ITC versus TRF-budesonide. The analyses for the dapagliflozin arm (in addition to optimised SoC) of the ITC were informed by a pre-specified analysis within the DAPA-CKD trial investigating the efficacy of dapagliflozin in IgAN (16).

ITC results – change from baseline to 12 months in eGFR

A total of three 2-arm studies were included in the analysis evaluating the CFB to 12 months in UPCR (Figure 1) (12, 15, 17). All studies reported data (either numerically or graphically) for changes in UPCR at 12 months post-baseline, or baseline and 12-month from which CFB estimates could be calculated. Based on the structure of the network, an ITC is possible between TRF-budesonide versus CS or immunosuppressants.

Figure 1. Network – CFB to 12 months in UPCR (N=3)

Abbreviations: CFB, change from baseline; CS, corticosteroid; IST, immunosuppressive therapy; N, number of studies; TRF-BUD, targeted-release formulation budesonide; UPCR, urine protein-creatinine ratio.

All pairwise treatment comparisons from the RE model (using Turner's prior distribution) are presented in Table 3; comparisons between TRF-budesonide and CS or immunosuppressants versus placebo/control were [redacted] both comparators over placebo/control. The comparison between TRF-budesonide and CS or immunosuppressants was [redacted]. The probability of TRF-budesonide being superior to each of the comparators is also presented, with probabilities of [redacted] and [redacted]

Table 3. Mean treatment difference for CFB to 12 months in UPCR (RE model using Turner's prior distribution)

	Placebo/Control	CS or IST	TRF-budesonide 16 mg/day
Placebo/Control	–	[redacted]	[redacted]
CS or IST	[redacted]	–	[redacted]

TRF-budesonide 16 mg/day	[redacted]	–
P(TRF-budesonide) superior to comparator*	[redacted]	–

Abbreviations: CFB, change from baseline; CrI, credible interval; CS, corticosteroid; IST, immunosuppressive therapy; MD, mean difference; RE, random-effects; TRF, targeted-release formulation; UPCR, urine protein-creatinine ratio.
Notes: NMA results are presented as the median and 95% CrI; results are interpreted as the MD between the therapy in the respective row versus the therapy in the respective column; bold denotes statistical significance at 5% level; green shading represents an improved treatment-effect (MD<0) for the comparator in the row versus the therapy in the respective column; orange shading represents a worse treatment-effect (MD>0) for the comparator in the row versus the therapy in the respective column. Studies included in the network are as follows: NEFIGAN, NefIgArd and STOP-IgAN.
*Posterior probability that TRF-budesonide is superior to comparator (MD<0).

ITC results – change from baseline to 12 months in eGFR

A total of four 2-arm studies were included in the analysis of change from baseline to 12 months in eGFR (Figure 2) (10, 12, 16, 17). All studies reported data (either numerically or graphically) for changes in UPCR at 12 months post-baseline, or baseline and 12-month from which CFB estimates could be calculated. Based on the structure of the network, an indirect comparison is possible between TRF-budesonide versus CS or immunosuppressants and dapagliflozin.

Figure 2. Network – CFB to 12 months in eGFR (N=4)

[redacted]

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

All pairwise treatment comparisons from the RE NMA (using Turner's prior distribution) are presented in Table 4. Comparisons between TRF-budesonide versus placebo/control, CS or immunosuppressants and dapagliflozin [redacted] TRF-budesonide; no other pairwise comparison was statistically significant. The probability of TRF-budesonide being superior to each of the comparators is also presented, with probabilities of [redacted] for TRF-budesonide being superior to placebo/control and dapagliflozin, and of [redacted]% for TRF-budesonide being superior to CS or immunosuppressants.

Table 4. Mean treatment difference for CFB to 12 months in eGFR (RE model using Turner's prior distribution)

	Placebo/ Control	CS or IST	DAPA	TRF-budesonide 16 mg/day
Placebo/ Control	—	[redacted]	[redacted]	[redacted]
CS or IST	[redacted]	—	1.89 [-1.56, 5.39]	[redacted]
DAPA	[redacted]	[redacted]	—	[redacted]
TRF-budesonide 16 mg/day	[redacted]	[redacted]	[redacted]	—
P(TRF-budesonide) superior to comparator*	[redacted]	[redacted]	[redacted]	–

Abbreviations: CFB, change from baseline; CrI, credible interval; CS, corticosteroid; DAPA, dapagliflozin; eGFR, estimated glomerular filtration rate; IST, immunosuppressive therapy; MD, mean difference; RE, random-effects; TRF, targeted-release formulation.

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

*Posterior probability that TRF-budesonide is superior to comparator (MD>0),

3. Short-term follow-up	Yes	The data presented in the company submission (NefIgArd Nef-301 Part A; 9 months of treatment with TRF-budesonide or placebo and 3 months of untreated follow-up) were the most mature available at the time of submission. In addition, the economic model did not include extrapolations beyond one year, in line with the clinical data available. The pre-planned Part A analysis was scheduled to occur once the first 201 patients randomised had had the opportunity to complete their 9-month visit and included [redacted] participants (TRF-budesonide 16 mg n=[redacted]; placebo n=[redacted]) with a baseline UPCR ≥1.5 g/g. Since the original company submission, data from Part B of NefIgArd Nef-301 have become available, providing 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 follow-up off drug (18). The Part B analysis included all patients randomised who completed the NefIgArd Nef-301 study (TRF-budesonide 16 mg n=[redacted] placebo n=[redacted]. **Change in UPCR from baseline** A reduction in UPCR from baseline with TRF-budesonide 16 mg/day was seen at all timepoints in NefIgArd Nef-301 Part B (Table 5). Following 9 months of treatment, the ratio of UPCR compared with baseline was [redacted] for patients treated with TRF-budesonide and [redacted] for those who received placebo. This equated to a statistically significant [redacted] reduction in UPCR for patients treated with TRF-budesonide 16 mg/day compared with placebo (p=[redacted]). Treatment with TRF-budesonide provided continued improvement compared with placebo up to the 12-month timepoint, with a [redacted] treatment difference at 3 months of untreated follow-up (ratio of UPCR compared with baseline of [redacted] and [redacted] for those treated with TRF-budesonide and placebo, respectively). At 24 months from baseline (15-months of follow-up off drug), the ratio of UPCR compared with baseline was [redacted] for patients treated with TRF-budesonide and [redacted] for those who received placebo. The reduction in UPCR was [redacted] greater for TRF-budesonide 16 mg/day compared with placebo at 24 months (p=[redacted]), demonstrating the durable benefit obtained at the end of 9 months of treatment with TRF-budesonide.

Table 5. Analysis of UPCR (g/g) using MMRM for patients with a baseline UPCR ≥1.5 g/g in NeflgArd Nef-301 Part B

Timepoint	Ratio of geometric LS mean UPCR compared with baseline (95% CI)		Comparison of TRF-budesonide 16 mg/day† vs placebo†; ratio of geometric LS means (95% CI); p value	Corresponding % change versus placebo‡
	TRF-budesonide† (n=[redacted])	Placebo† (n=[redacted])		
3 months	[redacted]	[redacted]	[redacted]	[redacted]
6 months	[redacted]	[redacted]	[redacted]	[redacted]
9 months	[redacted]	[redacted]	[redacted]	[redacted]
12 months	[redacted]	[redacted]	[redacted]	[redacted]
18 months	[redacted]	[redacted]	[redacted]	[redacted]
24 months	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CI, confidence interval; LS, least squares; MMRM, mixed-effects model for repeated measures; RAS, renin-angiotensin system; TRF, targeted-release formulation; UPCR, urine protein to creatinine ratio.
† Treatment in addition to RAS inhibition.
‡ Calculated as (1 – ratio) of LS means * 100.

Ratio of eGFR compared with baseline

After 9 months of treatment, a statistically significant [redacted] benefit on eGFR was observed with TRF-budesonide 16 mg/day compared with placebo (difference in absolute change in eGFR from baseline for TRF-budesonide vs placebo was [redacted] mL/min/1.73 m^2), demonstrating a delay in the progression of kidney disease compared with patients who received placebo (Table 6). The treatment benefit accrued by the end of 9 months of treatment with TRF-budesonide was continued after 15 months of observational follow-up; the estimated difference in absolute change in eGFR from baseline for TRF-budesonide vs placebo was [redacted] mL/min/1.73 m^2, equating to a [redacted] treatment benefit at the 24 month timepoint.

Table 6. Analysis of the ratio of eGFR (CKD-EPI) (mL/min/1.73 m^2) compared with placebo using robust regression in patients with a baseline UPCR ≥1.5 g/g in NeflgArd Nef-301 Part B

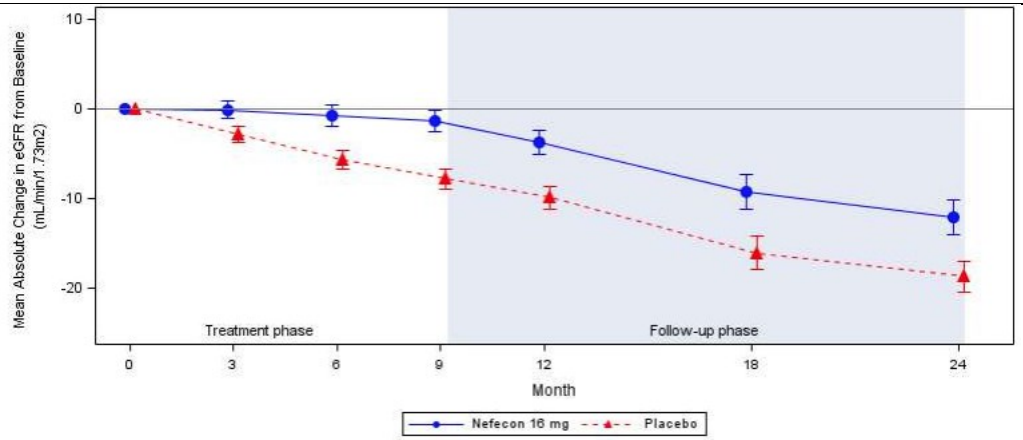
Timepoint	Comparison of TRF-budesonide 16 mg/day† vs placebo†		
	Ratio of geometric LS means (95% CI); p value	Corresponding % change‡	Difference in absolute change (mL/min/1.73 m²)
3 months	[redacted]	[redacted]	[redacted]
6 months	[redacted]	[redacted]	[redacted]
9 months	[redacted]	[redacted]	[redacted]
12 months	[redacted]	[redacted]	[redacted]
18 months	[redacted]	[redacted]	[redacted]
24 months	[redacted]	[redacted]	[redacted]

Abbreviations: CI, confidence interval; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; eGFR, estimated glomerular filtration rate; FAS, full analysis set; LS, least squares; RAS, renin-angiotensin system; TRF, targeted-release formulation. † Treatment in addition to RAS inhibition. ‡ Calculated as (1 – ratio) of LS means * 100.

Decline in eGFR (total slope)

In Part B of NefIgArd Nef-301, treatment with TRF-budesonide 16 mg/day provided an improvement in eGFR slope of [redacted] mL/min/1.73 m^2 per year compared with placebo (95% CI: [redacted]; p=[redacted]; Figure 3). This corresponded to a least squares mean 2-year eGFR slope of [redacted] mL/min/1.73 m^2 per year in the TRF-budesonide 16 mg/day group and of [redacted] mL/min/1.73 m^2 per year in the placebo group.

Figure 3. Change in eGFR (CKD-EPI) (mL/min/1.73 m^2) from baseline in patients with a baseline UPCR ≥1.5 g/g in NefIgArd Nef-301 Part B



Abbreviations: CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; eGFR, estimate glomerular filtration rate; od, once daily; UPCR, urine protein to creatinine ratio.
Source: Lafayette et al. 2023 (19).

4. Omission of relevant evidence	Yes	An ad-hoc analysis of the efficacy of TRF-budesonide in patients with primary IgAN with baseline UPCR ≥1.5 g/g using pooled data from NefIgAn Nef-202 and NefIgArd Nef-301 has been conducted and provided as new evidence. A summary of the efficacy results at 9 and 12 months from baseline is provided in Table 7. The outcomes for the pooled analysis were in line with those of NefIgArd Nef-301, supporting the efficacy of TRF-budesonide as a treatment for primary IgAN in patients with baseline UPCR ≥1.5 g/g and were used to inform the ITC (20).

Table 7. Summary of the ratio of geometric LS means of TRF-budesonide 16 mg vs placebo for selected efficacy outcomes at 9 and 12 months from baseline in patients with a baseline UPCR ≥1.5 g/g in NefIgArd Nef-301 Part A, NefIgAN Nef-202, and a pooled analysis

Outcome		Nef-301	Nef-202	Pooled
UPCR Ratio of Geometric LS Means TRF-budesonide 16	9 months	[redacted]	[redacted]	[redacted]

		mg vs placebo (95% CI), p-value; 12 months; [redacted] UACR Ratio of Geometric LS Means TRF-budesonide 16 mg vs placebo (95% CI), p-value; 9 months; [redacted] UACR Ratio of Geometric LS Means TRF-budesonide 16 mg vs placebo (95% CI), p-value; 12 months; [redacted] eGFR Ratio of Geometric LS Means TRF-budesonide 16 mg vs placebo (95% CI), p-value; 9 months; [redacted] eGFR Ratio of Geometric LS Means TRF-budesonide 16 mg vs placebo (95% CI), p-value; 12 months; [redacted] Abbreviations: CI, confidence interval; eGFR, estimated glomerular filtration rate; TFR, targeted-release formulation; UACR, urine albumin to creatinine ratio; UPCR, urine protein to creatinine ratio.
5. Exclusion of potentially relevant subgroup	Yes	Patients with an eGFR of <35 mL/min/1.73 m^2 were not considered for inclusion in the NefIgArd Nef-301 trial to prevent diluting any treatment effect and adversely affecting the power of the study. Patients with severe loss of kidney function (eGFR <20–30 mL/min per 1.73 m^2) may have such extensive and irreversible kidney injury that any therapeutic strategy being tested cannot reasonably be expected to alter the natural history of progressive deterioration in kidney function (therapeutic futility) (1). The presumption is that such patients should be excluded from clinical trials since they are expected to be “non-responders” and therefore

		may dilute any treatment effect and adversely affect the power of the study (1). In line with the 2021 KDIGO guidelines, a clinical expert indicated that an eGFR threshold >30 mL/min per 1.73 m^2 is typically used to define eligibility for treatment in most trials of immunomodulatory drugs as there is likely to be advanced and irreversible fibrosis below this level (1, 4). In NefIgArd Nef-301, this threshold was increased to an eGFR of <35 mL/min/1.73 m^2 for inclusion in the trial to mitigate the risk of participants developing an eGFR of <30 mL/min/1.73 m^2 early in the trial and obscuring the results.
6. Possible selection bias	Yes	Clinical expert opinion indicated that the differences in the baseline characteristics between treatment arms observed by the EAG are not expected to impact the results of Part A of the NefIgArd Nef-301 trial (4). Patients in both treatment arms were considered by clinical expert opinion to have comparable eGFR and UPCR, indicating that differences in time from diagnosis, proteinuria, UPCR, and eGFR levels would not be expected to affect treatment outcomes. Of note, UPCR analysis based on 24-hour collection, the approach utilised in NefIgArd Nef-301, is considered to be the gold standard for assessing proteinuria in clinical trials as this adjusts for urine concentration and any differences in patient approaches to collection (e.g. over/under collecting). In addition, clinical expert opinion indicated that proteinuria levels >3.5 g/day are considered to be high and that differences above this level are not expected to yield a further incremental increase in rate of disease progression (4). Clinical expert opinion indicated that blood pressure was controlled in both treatment arms of NefIgArd Nef-301 at baseline, which validates that the differences in the use of ACE/ARB therapy are not expected to affect outcomes (4). In addition, clinicians consider the characteristics of patients with UPCR ≥1.5 g/g in NefIgArd Nef-301 to be generalisable to the UK population and broadly similar to those of the UK RaDaR population (2). The age at baseline in both treatment arms was considered to be in line with published data from UK RaDaR (21). Similarly, the proportion of males, females, and race ratio were considered to be in line with what would be expected in the target treatment population in England (4). The median UPCR at baseline for patients in the UPCR ≥1.5 g/g subpopulation of the NefIgArd Nef-301 Part A trial (n=[redacted]) was [redacted] g/g, median UACR was [redacted] g/g, and kidney function was mildly-to-moderately impaired overall (median eGFR: [redacted] mL/min/1.73 m^2).

		Similar values were also observed at baseline for patients with UPCR ≥1.5 g/g at baseline in Part B of NefIgArd Nef-301, which included all randomised patients who completed the NefIgArd Nef-301 study (n=[redacted]; the median UPCR was [redacted] g/g and the median eGFR was [redacted] mL/min/1.73 m^2 at baseline (18). The values in the NefIgArd Nef-301 Part A and Part B are similar to those observed in patients with UPCR ≥1.5 g/g included in the RaDaR study, for whom the median UPCR at diagnosis was [redacted] g/g (n=[redacted]); the median UACR was [redacted] g/g (n=[redacted]); and the median eGFR at diagnosis was [redacted] mL/min/1.73 m^2 (n=[redacted]) (22).
7. Disease progression not reported	Yes	It was reported by the clinical experts that disease progression to dialysis or transplant would not be expected within the 12-month timeframe of Part A of the NefIgArd Nef-301 trial (4). The decline in eGFR in the placebo arm was [redacted] mL/min/1.73 m^2 at the 12 month timepoint of Part A of NefIgArd Nef-301. As such, this group would be expected to progress to ESRD in 3–5 years (aligned with the median time to ESRD or death in the RaDaR subpopulation with UPCR ≥1.76 g/g (21)), and the assessment of disease progression as an endpoint would require long trials with a large patient number to obtain statistical power. Due to the challenges associated with the evaluation of disease progression in patients with IgAN, surrogate endpoints (changes in proteinuria [UPCR and urine albumin to creatinine ratio (UACR)] and eGFR) accepted by regulatory bodies (EMA, FDA, KDIGO) and clinical experts were utilised to evaluate the impact of TRF-budesonide on disease progression in the pivotal Phase 3 trial (NefIgArd Nef-301) (1, 2, 23, 24). Reductions in proteinuria (assessed by measuring proteinuria over 24 hours, UPCR, and/or UACR) are accepted as a surrogate endpoint for improved outcomes in IgAN by KDIGO, the EMA, and clinical experts in England (1, 2, 23, 24). 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 (23), and are discussed in further detail in Section B2.3.2 of the company submission. Similarly, reductions in eGFR from baseline over a 2- to 3-year period are considered by regulatory authorities and clinical experts in England to be an acceptable surrogate outcome measure for kidney failure in clinical trials (1, 2, 24, 25), also discussed in further detail in Section B2.3.2 of the company submission.

8. Applicability of evidence	Yes	Clinical experts reported that the baseline characteristics for the trial population in NefIgArd Nef-301 were representative of patients with primary IgAN in the UK RaDaR database and those who would be treated with TRF-budesonide in clinical practice. Therefore, the NefIgArd Nef-301 trial results were considered to be applicable to the UK target population. The age at baseline in both treatment arms was considered to be in line with published data from UK RaDaR (21). Similarly, the proportion of males, females, and race ratio were considered to be in line with what would be expected in the target treatment population in England (21).The median UPCR at baseline for patients in the UPCR ≥1.5 g/g subpopulation of the NefIgArd Nef-301 Part A trial was [redacted] g/g, median UACR was [redacted] g/g, and kidney function was mildly-to-moderately impaired overall (median eGFR: [redacted] mL/min/1.73 m^2). Similar values were also observed at baseline for patients with UPCR ≥1.5 g/g at baseline in Part B of NefIgArd Nef-301, which included all randomised patients who completed the NefIgArd Nef-301 study (n=[redacted]; the median UPCR was [redacted] g/g and the median eGFR was [redacted] mL/min/1.73 m^2 at baseline (18). The values in the NefIgArd Nef-301 Part A and Part B are similar to those observed in patients with UPCR ≥1.5 g/g included in the RaDaR study, for whom the median UPCR at diagnosis was [redacted] g/g; the median UACR was [redacted] g/g; and the median eGFR at diagnosis was [redacted] mL/min/1.73 m^2 (22).
9. Insufficient evidence regarding retreatment of patients	Yes	The company maintains the position that retreatment should be included in the model base case. This position is in line with NICE routine practice to assess treatments with an ongoing treatment paradigm in such a way as to reflect the ongoing nature of these treatments within the assessment. Therefore, given the TRF-budesonide license permits retreatment (at the discretion of the treating physician), it is anticipated this should form part of the assessment. Additionally, to address the key issues outlined by the EAG, two clinical experts were consulted with regards to their expert opinion on the matter. The two experts reported that patients with primary IgAN would be expected to receive approximately two rounds of treatment with TRF-budesonide for 9 months each, provided an acceptable tolerability profile is maintained. Patients would not be expected to develop resistance to TRF-budesonide or to experience a waning of treatment effect if receiving multiple rounds of therapy (4).

		Overall, the two clinical experts predicted that 100% and 50% of patients who completed their initial treatment course of TRF-budesonide and were still classified as CKD 1–3b would be expected to be retreated in their lifetime (4). In light of the feedback received, the company's base case has been updated to include a single additional round of treatment. Of those that are eligible for retreatment, the model assumes 75% will undergo retreatment (mid-point of the two clinical opinions). Although not specified by the clinical experts, the assumed treatment effect from subsequent treatments has also been updated to 90% of the initial treatment effect, based on the limited evidence to support an assumption that 100% of efficacy is maintained with each treatment cycle.
10. Data source for estimating the transition from CKD 4 to CKD 5	Yes	The EAG expressed concerns about the company's use of survival probability for patients with IgAN and UPCR ≥1.5 g/g from the UK RaDaR database (22). In the company submission, survival probability from diagnosis of CKD 4 to ESRD or death was used to inform the risk of CKD 5 from CKD 4. During the clarification phase, additional survival data from the UK RaDaR database which assessed the time from CKD 4 diagnosis to ESRD in patients with IgAN and UPCR ≥1.5 g/g was included in a scenario analysis. However, the EAG identified an inconsistency in the number of patients at risk at baseline between the two sets of survival probability data. The number of patients at risk of ESRD or mortality was 63 at t=0 whereas the number at risk of ESRD was 26. After the clarification phase, it was discovered by the company that the survival probability data from diagnosis of CKD 4 to ESRD presented at the clarification stage was specific to a subgroup of patients that were receiving ACEi and/or ARBs at baseline, rather than all patients with IgAN and UPCR ≥1.5 g/g as the company had stated in the clarification phase. To correct this error, the company will submit new data from UK RaDaR which presents the survival probability from diagnosis of CKD 4 to ESRD for all patients with IgAN and UPCR ≥1.5 g/g. The same methods of digitalisation and extrapolation, as detailed in the clarification letter will be used to include this data in the model. However, as no patients in this RaDaR cohort died over the observed time period its inclusion is not anticipated to significantly impact the company's base case results, with any changes compared to the CKD4 to ESRD or mortality analysis likely caused by the human interpretation required when digitising the curves.

		The company maintains the opinion that the UK RaDaR data for all patients is the most appropriate data source to inform the risk of CKD 4 to CKD 5, due to: • No deaths occurring in the RaDaR analysis, thereby alleviating the EAG concerns that this analysis may lead to double counting of mortality within the model • For some patients 'maximally-tolerated' RAS inhibitor therapy would be no use of ACEi and/or ARBs as they may not be able to tolerate RAS inhibitors. Therefore, the RaDaR data using the sub-group of patients receiving ACEi and/or ARBs is more restrictive than the product label for TRF-budesonide 1. Additionally, ACEi and/or ARBs usage data within the RaDaR registry are incomplete, which resulted in a relatively small sample on which to perform analysis • The additional assumptions required to adjust the Leicester General Hospital data from all patients transitioning to ESRD, not just CKD 4 patients, introduces a greater level of uncertainty in the model based on the additional source required to estimate: 1. Hastings et al. (26) analysis looking at time to death was used, due to lack of information pertaining to time to ESRD • The population from the RaDaR registry is considered more reflective of the England population as data are received from multiple sites. Therefore, the data from RaDaR is also considered more reflective of the England population compared to the Leicester General Hospital data taken from a single site
Other issues identified by NICE technical team (not included in the EAR): The technical team note that the probabilistic and deterministic analyses give substantially different cost effectiveness estimates. Please provide an	Yes	Upon further investigation into this issue, it has been identified that the standard errors associated with pulmonary embolism and renal impairment adverse events were set to zero. As a result, the values for these inputs used in the PSA were varied significantly more than expected. As these inputs only impact the TRF-budesonide arm of the model, due to these adverse events only being experienced by these patients, the results from the PSA overestimated the impact these adverse events have on the TRF-budesonide arm quality-adjusted life years. Upon correcting these two standard errors in the latest version of the model the outcomes from the deterministic analysis and the PSA are more aligned with expectations.

explanation for these differences.		

Additional issues

No additional issues have been identified by the company.

Summary of changes to the company's cost-effectiveness estimate(s)

Company only: If you have made changes to the base-case cost-effectiveness estimate(s) in response to technical engagement, please complete the table below to summarise these changes. Please also provide sensitivity analyses around the revised base case. If there are sensitivity analyses around the original base case which remain relevant, please re-run these around the revised base case.

Table 8. Changes to the company's cost-effectiveness estimate

Key issue(s) in the EAR that the change relates to	Company's base case before technical engagement	Change(s) made in response to technical engagement	Impact on the company's base-case incremental cost-effectiveness ratio (ICER)
2. Corticosteroids, MMF and SGLT2i may be relevant comparators for different subgroups of patients	Prior to the technical engagement, the company base case included SoC as the only comparator in the model. SoC was assumed to represent optimised supportive care which the KDIGO 2021 guidelines describe as: blood pressure management; maximally tolerated dose of ACEi/ARB; lifestyle modification; and addressing cardiovascular risk (1). SGLT2is were also assumed to be a component of SoC, and would therefore be anticipated to be	In response to key issue 2, results of the cost-effectiveness of TRF-budesonide versus CS and immunosuppressants have been included as an additional scenario. To inform the 0–12-month CKD 1-3b transition probabilities in the CS arm, outcomes from the ITC were used to calculate a factor value that should be applied to the SoC transition probabilities. The ITC compared the change in eGFR at 12 months post baseline outcomes for patients	Including CS and immunosuppressants as a comparator increased the ICER from £21,872 cost/QALY to £39,137 cost/QALY. This is an increase of £17,265. Including dapagliflozin as a comparator in the model decreased the base case ICER from £21,872 cost/QALY to £16,885 cost/QALY. This is a decrease of £4,987.

	administered in combination with TRF-budesonide. Any potential benefits that may be observed from the addition of dapagliflozin to SoC, are anticipated to be additive to the TRF-budesonide treatment effect, especially since there is no crossover between their mechanisms of action (as indicated by clinical expert opinion (2)). As such, only the cost of SGLT2is were included in the model. CS and MMF were not considered relevant comparators.	receiving CS and immunosenescent in the STOP-IgAN trial to patients on SoC. The factor was calculated by observing the proportion of patients in each CKD health state at baseline and at 12-months in the SoC arm of the model, based on the control arm data from Part A of NefIgArd Nef-301. The midpoint of the eGFR range associated with each stage were multiplied by the proportion of patients in each stage to calculate a weighted average eGFR value at baseline and at 12-months. The weighted average eGFR value at baseline was subtracted from the average eGFR value at 12-months to calculate the change in eGFR in SoC. A goal-seek analysis was then run to see what factor needs to be applied to the SoC transition probabilities to change the 12-month change in eGFR by [redacted], based on the outcomes from the ITC. The goal-seek	

		analysis identified a factor of [redacted] The 1-year change in eGFR compared to SoC was also used to derive a hazard ratio, using the equation from Inker et al. 2019 (27), which was applied to the SoC risk of CKD 5. A hazard ratio of [redacted] was produced. In alignment with the dosing regimen of STOP-IgAN, patients receive CS and immunosuppressants for up to 36-months. A monthly cost of £5.64 was applied for 36-months to patients on CS and immunosuppressants. Since CS and immunosuppressants are given in conjunction with SoC, the monthly SoC was applied to all patients in the CS and immunosuppressants arm. Rauen et al. 2015 (12) identified that the CS and immunosuppressants treatment effect does not extend beyond 1-year. Therefore, the model assumes CS and immunosuppressants	

		have a treatment effect of 1 year. After 1 year, SoC transition probabilities are applied to the CS and immunosuppressant arm. The AE rates were sourced from the STOP-IgAN trial. The ITC also provided information on the SGLT2i dapagliflozin. The same goal-seek technique was used to derive a factor to apply to the SoC CKD 1-3b transition probabilities. Similarly, the ITC results informed the hazard ratio that was applied to the SoC risk of CKD 5. A factor of [redacted] and a hazard ratio of [redacted] were utilised. As the SoC arm already included dapagliflozin, the same monthly cost was assumed when dapagliflozin was considered as a comparator. Details on the exact adverse events from the IgAN sub-population in the DAPA-CKD trial could not be identified (16). Therefore, the model assumes the same adverse events as SoC data from Part A of NefIgArd Nef-301. It is acknowledged that	

		this may provide less conservative results for TRF-budesonide, as fewer severe adverse events were captured in the IgAN population of the DAPA-CKD trial receiving dapagliflozin. However, without data on the types of adverse events observed, it has not been possible to include this data in the model.	
3. Short-term follow-up	The company base case utilised the 9-month eGFR data from NefIgArd Nef-301 Part A to inform the CKD 1-3b transition probabilities in the TRF-budesonide and SoC arms. The base case assumed a treatment effect duration of 1-year for TRF-budesonide. Beyond 1-year, the SoC transition probabilities were applied to the SoC arm.	During technical engagement, 24-month eGFR data from Part B of NefIgArd Nef-301 for the UPCR ≥1.5 g/g trial subpopulation became available. This was used to inform the CKD 1-3b transition probabilities in the TRF-budesonide and SoC arms. The model assumed TRF-budesonide had a treatment effect duration of 2 years. However, the data from Part B of NefIgArd Nef-301 was not able to inform the transition from CKD 4 to CKD 5. Therefore, as per the submitted company base case, TRF-budesonide was assumed to have a 1-year treatment effect on the risk of	The incorporation of data from Part B of NefIgArd Nef-301 decreased the ICER from £21,872 cost/QALY to £14,778 cost/QALY. This is a decrease of £7,094.

		CKD 5 from CKD 4 based on the 12-month change in eGFR. It should also be noted that Rauen et al. 2015 (12) identified that the CS and immunosuppressants treatment effect does not extend beyond 1-year. Therefore, it is anticipated that the benefits of TRF-budesonide seen in Part B of NefIgArd Nef-301 would also indicate an improvement in the ICER when compared to CS, although the extent of this impact is unknown due to limitations with the current model structure, and current time constraints.	
9. Insufficient evidence regarding retreatment of patients	The company base case assumed two rounds of treatment with TRF-budesonide (1 round of retreatment). It was assumed all eligible patients would receive retreatment. Eligible patients included those who had completed the full initial treatment and were still in CKD1-CKD3b health states at the time of	Two rounds of treatment with TRF-budesonide were included. However, it was assumed that only 75% of eligible patients would receive retreatment. Eligible patients include those that had completed the full initial treatment course and were still in CKD1-CKD3b health states at the time of retreatment.	These changes resulted in an increase in the ICER from £21,872 cost/QALY to £26,371 cost/QALY. This is an increase of £4,499.

	retreatment. It was assumed patients receiving TRF-budesonide would not experience treatment effect waning in subsequent treatment cycles (100% treatment effect in subsequent treatments).	It was also assumed TRF-budesonide would have a conservative treatment effect of 90%, based on feedback from clinical experts, in subsequent rounds of treatment.	
10. Data source for estimating the transition from CKD 4 to CKD 5	In the company base case, the risk of CKD 5 was informed by real world evidence from patients with IgAN and UPCR ≥1.5 g/g collected in the UK RaDaR database (22). A Kaplan-Meier (KM) curve which estimates the probability of progressing to ESRD or mortality over time was digitalised using Engauge Digitizer 12.1 software (28) to generate pseudo patient-level data.	A KM curve obtained from UK RaDaR was digitalised using Engauge Digitizer 12.1 software (28) to generate pseudo patient-level data which informed the risk of CKD 5. The KM curve estimated the time from CKD 4 diagnosis to ESRD in patients with IgAN and UPCR ≥1.5 g/g. Based on AIC and BIC ranking, a gamma model was chosen as the best fitting parametric distribution.	These changes resulted in the ICER decreasing from £21,872 cost/QALY to £21,636 cost/QALY. This is a decrease of £236.
Other issues identified by NICE technical team (not included in the EAR): The technical team note that the probabilistic and deterministic analyses	In the company base case the standard errors associated with pulmonary embolism and renal impairment adverse events were set to zero.	The model was corrected to ensure standard errors associated with pulmonary embolism and renal impairment disutility were not set to 0, instead assuming 10% standard error.	These changes do not change the model's deterministic results (£21,872 cost/QALY). However, the changes impact the probabilistic outcome and make the ICER £40,056**.**

give substantially different cost effectiveness estimates. Please provide an explanation for these differences.			
Company's base case following technical engagement (or revised base case)	Incremental QALYs: [redacted]	Incremental costs: [redacted]	The company's revised base-case ICER is £4,672 cost/QALY. The following changes have been made to the company base case: • Two rounds of treatment with TRF-budesonide are considered. However, only 75% of eligible patients will be considered. This includes those who were still on treatment at month 8 and in CKD1 to CKD3b at time of retreatment. Furthermore, TRF-budesonide will be assumed to have a treatment effect of 90% in subsequent treatment cycles • The risk of CKD 5 is informed by a digitised KM curve which showed the time from CKD 4 diagnosis to ESRD in patients with IgAN and UPCR ≥1.5 g/g • The model has been corrected to ensure standard errors associated with pulmonary embolism and renal impairment disutility were not set to 0, instead assuming 10% standard error. • The utility values associated with pulmonary embolism and renal impairment

			have been updated to -0.018 and -0.0603. The duration of disutility is assumed to be one month. This aligns with EAG preferred assumptions • The SoC costs have been updated to £67.38 in line with EAG adjustments to account for concomitant medications costs originally missing from the company submission • After receiving the results of the ITC, the company [redacted]

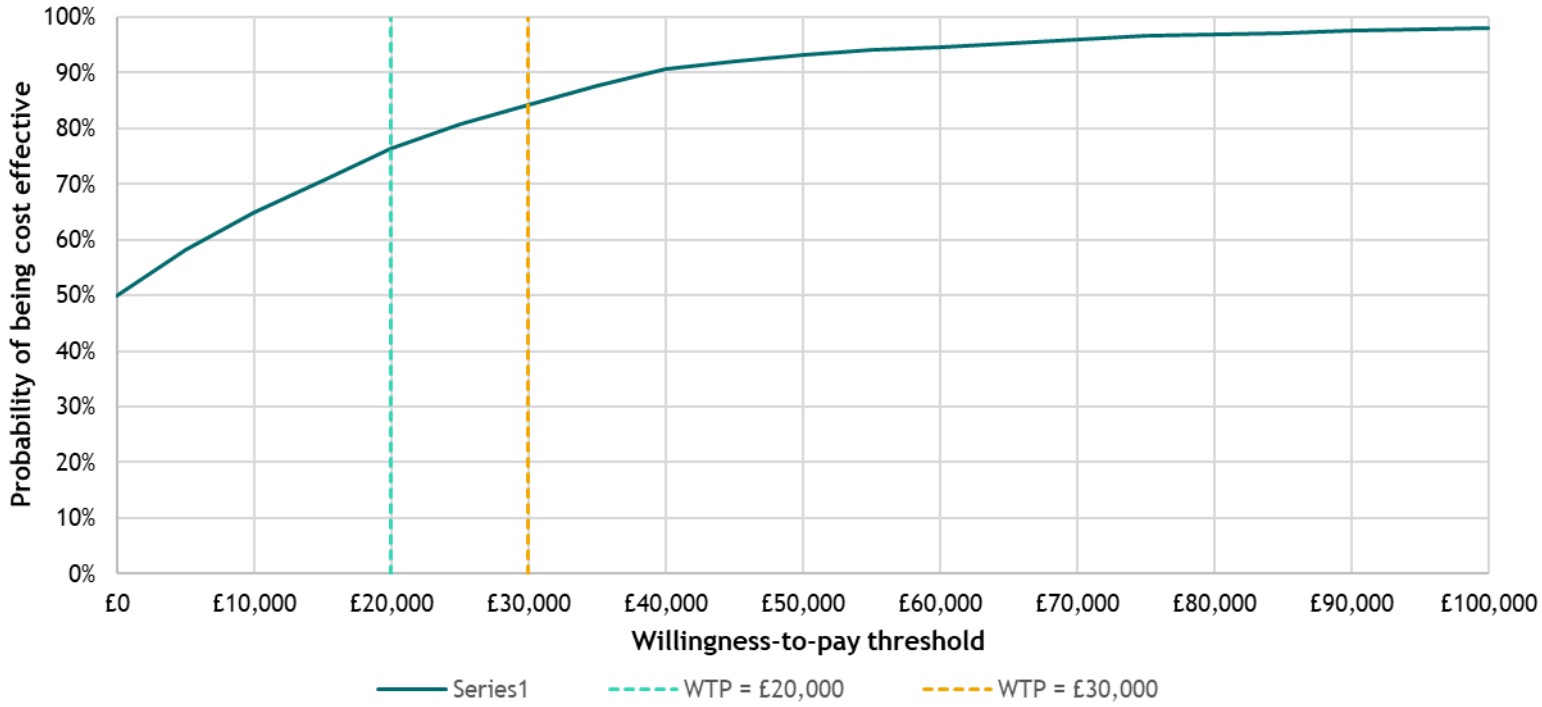
Sensitivity analyses around revised base case

Table 9 presents the results of the PSA. The cost-effectiveness acceptability curves are presented in Figure 4.

Table 9. 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]	16.479	[redacted]	-	-	-	-	-
SoC	[redacted]	16.104	[redacted]	[redacted]	0.376	[redacted]	Dominant	Dominant

Figure 4. Cost-effectiveness acceptability curve



Abbreviations: WTP, willingness-to-pay

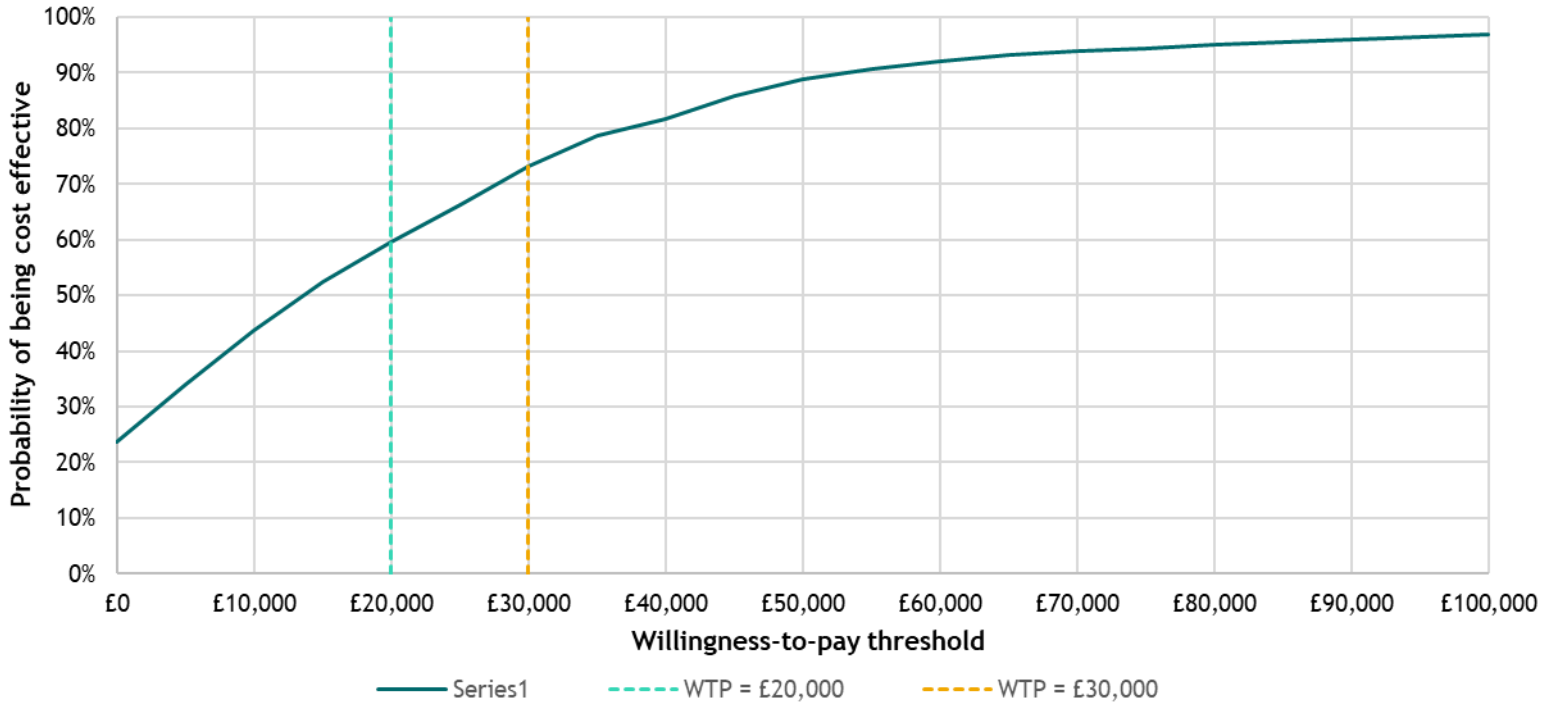
As reported in the company submission, the transition between CKD 1 to CKD 2 in the TRF-budesonide arm is informed by data from one patient in Part A of the NefIgArd Nef-301 study. Therefore, when this transition is varied in the PSA, it often takes extreme values of either 0% or 100% which has a significant impact on the ICER produced in the PSA. Therefore, a PSA that excluded this Technical engagement response form

transition was also run. The results of this PSA are presented in Table 10 and the cost-effectiveness acceptability cure is presented in Figure 5.

Table 10. 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]	15.953	[redacted]	-	-	-	-	-
SoC	[redacted]	15.823	[redacted]	[redacted]	0.130	[redacted]	£13,933	£13,933

Figure 5. Cost-effectiveness acceptability curve



Abbreviations: WTP, willingness-to-pay

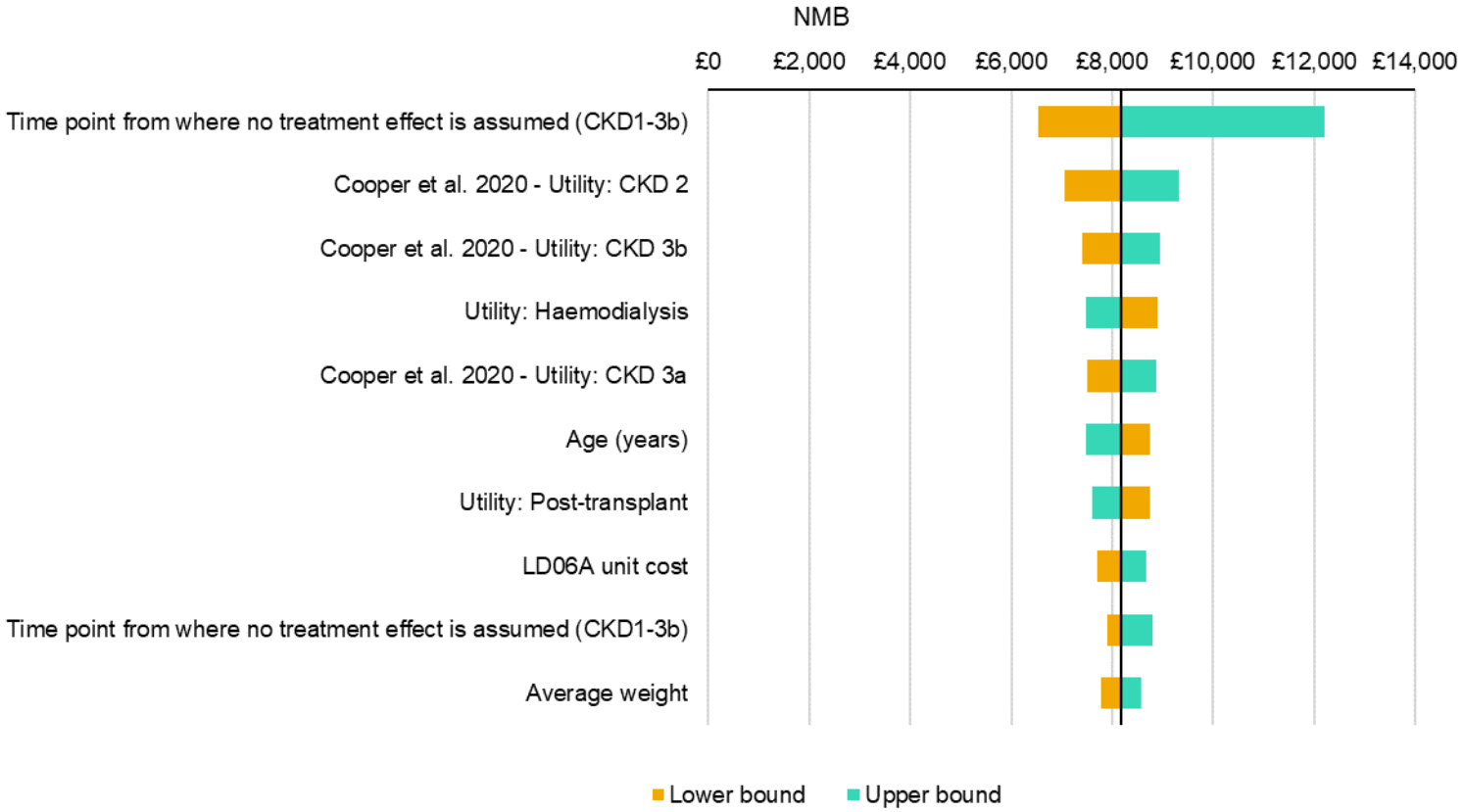
Table 11 presents the results of the deterministic sensitivity analysis. Figure 6 presents the tornado diagram.

Table 11. DSA results

Variable	Low NMB estimate	High NMB estimate	Change in NMB
Time point from where no treatment effect is assumed (CKD1-3b)	[redacted]	[redacted]	£5,670
Cooper et al. 2020 - Utility: CKD 2	[redacted]	[redacted]	£2,258
Cooper et al. 2020 - Utility: CKD 3b	[redacted]	[redacted]	£1,540
Utility: Haemodialysis	[redacted]	[redacted]	£1,407
Cooper et al. 2020 - Utility: CKD 3a	[redacted]	[redacted]	£1,374
Age (years)	[redacted]	[redacted]	£1,271
Utility: Post-transplant	[redacted]	[redacted]	£1,139
LD06A unit cost	[redacted]	[redacted]	£985
Time point from where no treatment effect is assumed (CKD1-3b)	[redacted]	[redacted]	£908
Average weight	[redacted]	[redacted]	£792

Abbreviations: CKD, chronic kidney disease; DSA, deterministic sensitivity analysis; NMB, net monetary benefit.

Figure 6. Tornado diagram



Abbreviations: CKD, chronic kidney disease; HR, hazard ratio: SoC, standard of care; NMB, net monetary benefit.

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NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Targeted-release budesonide for treating primary IgA nephropathy [ID1434]

Patient expert statement and technical engagement response form

Thank you for agreeing to give us your views on this treatment and its possible use in the NHS.

Your comments and feedback on the key issues below are really valued. You can provide a unique perspective on conditions and their treatment that is not typically available from other sources. The external assessment report (EAR) and stakeholder responses are used by the committee to help it make decisions at the committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

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 for your views on key issues in the EAR that are likely to be discussed by the committee. The key issues in the EAR reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the EAR, in sections 1.3-1.5.

A patient perspective could help either:

- resolve any uncertainty that has been identified OR
- provide missing or additional information that could help committee reach a collaborative decision in the face of uncertainty that cannot be resolved.

Patient expert statement

You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise. We have given guidance on the issues in which we expect this to be the case and advice on what you could consider when giving your response.

In part 3 we are asking you to provide 5 summary sentences on the main points contained in this document.

Help with completing this form

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Your response should not be longer than 15 pages.

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Patient expert statement

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Thank you for your time.

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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	Benjamin Stokes
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**	Having been diagnosed with IgA nephropathy at the age of 22, I've lived most of my adult life with the disease. At the point of diagnosis I was in Stage 3 of Chronic Kidney Disease, and over the past 12 years the condition has progressed to End-Stage Renal Disease. I am currently preparing transplantation, with the hope that this will take place pre-emptively to dialysis. My initial diagnosis was similar to what is described in the SIP. I had no noticeable symptoms until a sudden episode of unexplainable fluid retention led me to visiting the GP. A urine test identified high levels protein in my urine, and I was referred to Royal Berks immediately. Upon arrival, the consultant nephrologist quickly connected my symptoms to an episode of Henoch-Schonlein Purpura I had as a young child. At that point we had never heard of IgA nephropathy, and knew little of kidney disease in general. My family were never told that Henoch-Schonlein Purpura could contribute to kidney issues later down the line. A subsequent kidney biopsy then confirmed the diagnosis of IgA nephropathy. It was all very sudden, and came as a complete surprise to me and my family. I'll never forget being told that there wasn't anything they could do to directly treat IgA nephropathy, and that the only treatment would be to manage my blood pressure and live a healthy lifestyle. As a young man in my early twenties, about to enter what should have been the most exciting period of my life, this was devastating. The condition has had a massive impact on my mental health. I have had episodes of clinical depression, with the most recent being at the start of 2023. The prognosis of needed a transplant, and the uncertainty that brings, took me to a very difficult place. I was prescribed medication and have 6 months of intensive

	talking therapy through the NHS. Thankfully, my mental health is now in a much improved place, but I'm aware that it could quite easily have turned out differently.

Patient expert statement

	Over the first 8-10 years the condition remained relatively stable. Despite having few physical symptoms, it didn't reduce the anxiety and stress of living with a chronic health condition though. The disease has had an impact on all areas of my life because it carries a constant mental burden. Another difficulty is that a lack of understanding about the disease has made it almost impossible for anyone in my social circle to be able to relate, even those most close to me. The result being ongoing feelings of isolation and loneliness. As my condition has deteriorated over the past few years, the condition has begun to have more physical manifestation. I experience tiredness and severe fatigue, struggling to make it through most day without having a nap in the afternoon. As a result I've had to reduce my working hours significantly, and I've experienced financial difficulties as a result. It has also made socialising even more difficult.

7a. What do you think of the current treatments and care available for primary IgA nephropathy on the NHS? **7b. How do your views on these current treatments compare to those of other people that you may be aware of?**	There are currently no therapies licensed specifically for the treatment of IgAN. I think that says it all. Knowing there is no specific treatments has been one of the most challenging aspects of living with the disease.
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	
9a. If there are advantages of 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? **9b. If you have stated more than one advantage, which one(s) do you consider to be the most important, and why?** **9c. Does 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**	
10. If there are disadvantages of budesonide over current treatments on the NHS please describe these. For example, are there any risks with budesonide? If you are concerned about any potential side effects you have heard about, please describe them and explain why	

11. Are there any groups of patients who might benefit more from 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	
12. Are there any potential equality issues that should be taken into account when considering primary IgA nephropathy and budesonide? 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.	
13. Are there any other issues that you would like the committee to consider?	

Part 2: Technical engagement questions for patient experts

Issues arising from technical engagement

The issues raised in the EAR are listed in table 2. We welcome your comments on the issues, but you do not have to provide a response to every issue, such as the ones that are technical, that is, cost effectiveness-related issues. We have added a comment to the issues where we consider a patient perspective would be most relevant and valuable. If you think an issue that is important to patients has been missed in the EAR, please let us know in the space provided at the end of this section.

For information: the patient organisation that nominated you has also been sent a technical engagement response form (a separate document) which asks for comments on each of the key issues that have been raised in the EAR, the patient organisation responses will also be considered by the committee.

Table 2 Issues arising from technical engagement

1. Applicability of the trial evidence to those patients not on RASi therapy	
2. Corticosteroids, MMF and SGLT2i may be relevant comparators for different subgroups of patients	
3. Short-term follow-up	
4. Omission of relevant evidence	
5. Exclusion of potentially relevant subgroup	
6. Possible selection bias	
7. Disease progression not reported	
8. Applicability of evidence	

Patient expert statement

9. Insufficient evidence regarding retreatment of patients	
10. Data source for estimating the transition from CKD 4 to CKD 5	
Are there any important issues that have been missed in EAR?	

Part 3: Key messages
In up to 5 sentences, please summarise the key messages of your statement:

- Click or tap here to enter text.
- Click or tap here to enter text.
- Click or tap here to enter text.
- Click or tap here to enter text.
- Click or tap here to enter text.

Thank you for your time.

Your privacy

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Single Technology Appraisal

Targeted-release budesonide for treating primary IgA nephropathy [ID1434]

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Patient expert statement

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Patient expert statement

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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	Guy Hill
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	KidneyCare 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: From patient associations ☐ 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 diagnosed with IGAN after biopsy aged 36 after 6 months of severe headaches and subsequent diagnose of ultra high BP 210/150+ and admitted to hospital. Creatine level was 125 . once BP stabilised with pills the headaches subsided and I was informed that only 20% of patients progressed to ESRF. However within 2 years I was in ESRF and on PD . The 2 years decline was depressing and very disruptive to my lifestyle, work- days off and family life with wife and young children as I went through all the classic symptoms of pre dialysis ,tiredness, swelling ,appetite loss, sleep disorder , lack of appetite. My experience of meeting other IGAN patients is 'how young they are ' aged 20-30 and what a difficult time of life it is re economic and lifestyle , relationships etc, especially if they go to ESRF. Many do not report significant symptoms but just the frustration of a disease deteriorating kidney function from within and no obvious way like fitness or diet to stop it. These young patients will go on to be very expensive for the NHS with regard to dialysis and transplant costs over many years 50+
7a. What do you think of the current treatments and care available for primary IgA nephropathy on the NHS? **7b. How do your views on these current treatments compare to those of other people that you may be aware of?**	**There are no significant treatments for IGAN patients despite trials of steroids and immunosuppressive.** **We are all in utter frustration on having no treatments and no real understanding of how IGAN causes harm**
8. If there are disadvantages for patients of current NHS treatments for primary IgA nephropathy (for	With no treatments there are no effects either negative or positive . The patient undergoes all the typical issues of any patient with CKD leading to ESRF.

example, how they are given or taken, side effects of treatment, and any others) please describe these	
9a. If there are advantages of 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? **9b. If you have stated more than one advantage, which one(s) do you consider to be the most important, and why?** **9c. Does 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**	**If Budesonide can slow down the IGAN pathway then the benefits to a younger patient population are obvious . Completing education , achieving employment opportunities .creating relationships , marrying, having children . taking responsibility for family . keeping a patient within stage 2,3 CKD is not disabilitating and can allow most patients to function close to normal.** **Employment opportunities are the key to a stable lifestyle and confidence to cope with stable medical issues** **Against a non option of no treatments B. can offer a patient a real chance of stabilising or even reversing their IGAN progression. For any IGAN patient,It is a very positive drug specifically designed to treat IGAN**
10. If there are disadvantages of budesonide over current treatments on the NHS please describe these. For example, are there any risks with budesonide? If you are concerned about any potential side effects you have heard about, please describe them and explain why	From the study report The risks of B seem to be mainly comparable to typical CKD side effects that are associated with stage 3 CKD. Most of them tolerable and not significant to lifestyle . there appear to be no significant hospitalization or chronic risks associated with taking the drug. As an IGAN patient I would agree to take the drug with minimal fear of harm
11. Are there any groups of patients who might benefit more from 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	Asian patients are stated of being more susceptible to IGAN and will therefore find B of greater interest in their population. Younger patients with IGAN have the most to gain and also will be the most expensive for the NHS on ongoing life time treatments both renal and other linked chronic conditions. Any patients going to ESRF will experience severe limitations which will be greatly exaggerated if disabled in any way , physical or mental especially if dialysis is required and have limited dialysis options.
12. Are there any potential equality issues that should be taken into account when considering primary IgA nephropathy and budesonide? Please explain if you	Any patients going to ESRF will experience severe limitations which will be greatly exaggerated if disabled in any way , physical or mental especially if dialysis is required and have limited dialysis options

Patient expert statement

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.	
13. Are there any other issues that you would like the committee to consider?	I had acute IGAN with no apparent cause at age 36 in1996 , dialysis within 2 years , transplant after 2 years 2000, lasted 8 years 2008 , dialysis 4 years , 2nd transplant 2012 , lasted 4 years dialysis 4 years 3rd transplant 2019 still going aged 62 . I have tried at all times to remain as healthy as possible, fitness , diet, nocturnal dialysis but the suspicion / biopsies is the IGAN continues to affect my immune system and has played a part in my transplant failures. I have heart issues and skin issues now from renal failure . IGAN has been cruel to me and my family over a life time and of very significant cost to the NHS . If budesonide of today given its significant results or its subsequent development or sister drugs can go on to slow down or even retard IGAN then both the NHS & patients will avoid some or maybe all of my very typical renal journey as a result of IGAN.

Part 2: Technical engagement questions for patient experts

Issues arising from technical engagement

The issues raised in the EAR are listed in table 2. We welcome your comments on the issues, but you do not have to provide a response to every issue, such as the ones that are technical, that is, cost effectiveness-related issues. We have added a comment to the issues where we consider a patient perspective would be most relevant and valuable. If you think an issue that is important to patients has been missed in the EAR, please let us know in the space provided at the end of this section.

For information: the patient organisation that nominated you has also been sent a technical engagement response form (a separate document) which asks for comments on each of the key issues that have been raised in the EAR, the patient organisation responses will also be considered by the committee.

Table 2 Issues arising from technical engagement

1. Applicability of the trial evidence to those patients not on RASi therapy	
2. Corticosteroids, MMF and SGLT2i may be relevant comparators for different subgroups of patients	The apparent effectiveness of SGLT2I for CKD patients appears to imply going forward that these drugs will be very much part of patients treatment CKD pathways and should be viewed positively and not considered a hindrance to budesonide efficacy
3. Short-term follow-up	
4. Omission of relevant evidence	

Patient expert statement

5. Exclusion of potentially relevant subgroup	
6. Possible selection bias	I considered the patient selection to be reflective of IGAN patients eg younger than usual renal age profile
7. Disease progression not reported	As patients we would like to understand whether budesonide is a temporary effect or can expect a long term stability in CKD decline
8. Applicability of evidence	
9. Insufficient evidence regarding retreatment of patients	As patients we would like to understand whether budesonide is a temporary effect or can expect a long term stability in CKD decline and whether this is because of the need for re treatments
10. Data source for estimating the transition from CKD 4 to CKD 5	
Are there any important issues that have been missed in EAR?	

Part 3: Key messages
In up to 5 sentences, please summarise the key messages of your statement:

- Click or tap here to enter text.
- Click or tap here to enter text.
- Click or tap here to enter text.
- Click or tap here to enter text.
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NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Targeted-release budesonide for treating primary IgA nephropathy [ID1434]

Clinical expert statement and technical engagement response form

Thank you for agreeing to comment on the external assessment report (EAR) for this evaluation, and for providing your 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. The EAR and stakeholder responses are used by the committee to help it make decisions at the committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form

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A clinical perspective could help either:

- resolve any uncertainty that has been identified OR
- provide missing or additional information that could help committee reach a collaborative decision in the face of uncertainty that cannot be resolved.

In part 3 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 under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information redacted. See the NICE health technology evaluation guidance development manual (sections 5.4.1 to 5.4.10) for more information.

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The deadline for your response is **5pm** on **22 August 2023.** Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

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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 stop or slow progression to kidney failure requiring dialysis or a kidney transplant

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)	As an **early** marker a reduction in proteinuria, **medium term** a slowing in the rate of loss of eGFR (of at least 1ml/min/year compared to standard of care) and **long term** avoidance of kidney failure
10. In your view, is there an unmet need for patients and healthcare professionals in primary IgA nephropathy?	Yes, we have no safe and effective treatments above blood pressure control, RAS inhibition and possibly SGLT2 inhibitors
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?	KDIGO 2021 guidelines are adopted in the UK and there has been a UKKA commentary on these guidelines Major area of controversy is the use of systemic corticosteroids in IgAN-I would say that 2/3 UK nephrologists do not use systemic corticosteroids and 1/3 may try them. Due to the lack of safe & effective treatments most GN centres currently prefer to offer IgAN patients a clinical trial if they remain at high risk of progression despite maximal supportive care. Nefecon will offer a treatment choice for patients who remain at high risk of progression despite maximal supportive care and avoid the significant side effects of systemic corticosteroids offering those of us who do not use systemic corticosteroids a treatment for our patients and for those who use systemic corticosteroids an alternative.
12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice? • 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)	IgA nephropathy has to be diagnosed with a kidney biopsy and so all patients are at least initially under the care of a nephrologist. Any IgA nephropathy patient requiring additional treatment above maximal supportive care will be under the care of a nephrologist and ideally under the care of a dedicated GN service. IgAN will not be managed in primary care. No investment is needed to introduce Nefecon.

• What investment is needed to introduce the technology? (for example, for facilities, equipment, or training)	
13. Do you expect the technology 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- the P3 data clearly shows an eGFR advantage over current optimised supportive care which will delay the time to kidney failure substantially for this group of young (30-40s typically) patients. This will extend the life span of patients as kidney failure/dialysis/transplantation significantly increasing mortality and morbidity. For those who would have received systemic corticosteroids there will be a significant avoidance of side effects (all patient studies in IgAN report how much patients dislike systemic corticosteroids and how they reduce QoL). Delay in progression of kidney disease will improve QoL by delaying the onset of the many complications of progressive kidney failure (anaemia, bone disease, pruritis, nausea, appetite loss etc).
14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	No evidence any particular group of IgAN patients will respond differently.
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)	No issues- no particular monitoring required- straight forward to use.
16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	No- no additional testing required.

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	Major benefits will come from slowing of loss of kidney function and avoidance of systemic corticosteroids- both of which I think are included in the QALY calculation
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, it addresses the fundamentals of the pathogenesis of the disease and is most definitely a 'step-change' in the management of the condition. Unmet need=there are no approved therapies for IgAN
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?	There are some steroid related side effects in some patients and patients will need to be warned about this- but they are mild and reversible on stopping the medication- the treatment is a 9 month course.
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 the P2 and P3 trials are entirely consistent with UK practice and the UK contributed patients to both studies. The P3 trial has both proteinuria (published) and now 2 year eGFR data- presented at the ERA meeting in June 2023 and the P3 eGFR data will be published in the Lancet in the next few weeks (I am the senior author). eGFR is a surrogate for future kidney failure but there is international agreement that eGFR slope is highly predictive of future risk of kidney failure.

	No new adverse events reported as far as I am aware.
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
22. How do data on real-world experience compare with the trial data?	There is complete consistency in the placebo arms of all trials in IgAN (P2 & 3) regarding the rate of loss of eGFR and if you look at the baseline characteristic papers for the current P3 trials you will see highly consistent features confirming the applicability of this population to the patients we look after who remain at high risk of progression despite maximal supportive care.
23. 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 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	No potential equality issues. Worth noting data from the UK rare disease registry shows that the rate of loss of kidney function is greater in non-white IgAN patients and I have an abstract submitted to the ASN meeting showing that the rate of loss of kidney function is greater in those IgAN patients with a higher deprivation status. IgAN rarely affects patients of African descent, is more common in people from East and South Asia.

• 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: Technical engagement questions for clinical experts

We welcome your comments on the key issues below, but you may want to concentrate on issues that are in your field of expertise. If you think an issue that is important to clinicians or patients has been missed in the EAR, please also advise on this in the space provided at the end of this section.

The text boxes will expand as you type. Your responses to the following issues will be considered by the committee and may be summarised and presented in slides at the committee meeting.

For information: the professional organisation that nominated you has also been sent a technical engagement response form (a separate document) which asks for comments on each of the key issues that have been raised in the EAR. These will also be considered by the committee.

Table 2 Issues arising from technical engagement

1. Applicability of the trial evidence to those patients not on RASi therapy	All IgAN patients should be on RASi- this would be an irrelevant comparison and would not reflect clinical practice anywhere in the world
2. Corticosteroids, MMF and SGLT2i may be relevant comparators for different subgroups of patients	Systemic corticosteroids and MMF are NOT used by the majority of nephrologists in the UK and are not recommended routinely in international guidelines and so comparison is not justified- they are NOT standard of care. Use of SGLT2i is increasing in patients with non-diabetic kidney disease but is certainly not uniform. Nefecon would be used on top of SGLT2i and not instead of and so it makes no sense to look at comparing the two in my view. It is important to appreciate that both DAPACKD and EMPAKIDNEY did not recruit the same population of IgAN patients as a dedicated IgAN trial and therefore comparing data across these studies is challenging.

	Are corticosteroids, SGLT2i and MMF part of standard care for the whole population who would be treated with targeted release budesonide? **NO** *If not, which subgroups would receive these treatments,* **for most UK nephrologists no IgAN patient is treated with these drugs** *and would the clinical and/or cost effectiveness of budesonide in these groups be expected to be different to the whole population?* **Not relevant to common UK practice**
3. Short-term follow-up	2 year follow up is the best we have for any therapy in a global IgAN study- and there is data on >1M patients with CKD showing the robust predictive value of eGFR slope on future risk of kidney failure
4. Omission of relevant evidence	N/A
5. Exclusion of potentially relevant subgroup	Excluded patients with eGFR<30, proteinuria<1g/24h and those with an RPGN, nephrotic syndrome and secondary IgAN- I think this is reasonable and I do not think a clinically important group of IgAN patients have been unreasonably excluded from the trials. *Would TR budesonide be used in people with more severe renal failure than the who were people included in the trial?* **NO** *What is the relationship if any between UPCR and eGFR?* I can give you lots of references if needed-the relationship is linear and very strong (and these data are the basis for the FDA to agree proteinuria is a reasonably likely surrogate for eGFR decline).

	Is there any group who would be eligible for TR budesonide according to its marketing authorisation that was excluded from the trial? **NO** *Would you expect people with lower eGFR to have different treatment outcomes to people with higher eGFR?* There is no difference in the response to Nefecon for patients with eGFR 30-90. There is a lower likelihood of Nefecon improving rate of loss of eGFR decline in those with eGFR<30 as these patients are likely to have a significant degree of fixed scarring which will not be changed with Nefecon.
6. Possible selection bias	Global study- comparing the baseline characteristics published data for Nefigard/Protect/Applause they are all very similar not suggestive of significant bias. *Do any of the differences between trial arms identified in these tables suggest a risk of bias in the trial outcomes?* **NO**
7. Disease progression not reported	N/A -all have 2 year eGFR data- Lancet paper in press and presented at ERA meeting- happy to provide these data for the NICE panel- I think these data are essential for the evaluation and will answer a number of the EAGs questions. *What is the relationship between proteinuria and disease progression*? See answer to 5- happy to provide you with as many references as you would like on this. *Is using the eGFR data from the trial as a surrogate endpoint to estimate the disease progression through CKD states appropriate?* **YES** by definition they are completely interrelated

	Would you have expected to see disease progression reported as a specific separate outcome in the main clinical trial for TR budesonide? It is -reported in Lancet paper which is in press and can be provided.
8. Applicability of evidence	Outcomes measured highly relevant to the disease and future risk of kidney failure and baseline features very similar to those in the UK RaDaR registry data and publication-can provide if needed. *Do these tables reflect the treatments people have in the UK and the characteristics of people who would have targeted release budesonide in the NHS?* **YES** *Is the trial trial data generalisable to the UK target population?* **YES**
9. Insufficient evidence regarding retreatment of patients	There is an OLE ongoing and this data will be reported in due course and will include patients who receive a second 9 month course- but data are not available at present. *Please comment on the circumstances in which patients would be expected to be retreated with TR budesonide, the timing between treatment rounds, and the relative efficacy that would be expected from retreatment.* IgAN is a heterogeneous disease- retreatment will be individualised based on changes in proteinuria – I expect all patients will need re-treatment at some point likely on a cyclical basis every 18-36 months and I would predict a response similar to that seen with the initial treatment regimen.
10. Data source for estimating the transition from CKD 4 to CKD 5	These are reasonable
Questions from NICE relating to the EAGs identified issues. These have been	In relation to EAG issue 2: Are corticosteroids, SGLT2i and MMF part of standard care for the whole population who would be treated with targeted release budesonide? If not, which subgroups would

identified by the NICE technical team as questions which would be useful for you to address in your consideration of the EAG issues: • **EAG issue 2**	receive these treatments, and would the clinical and/or cost effectiveness of budesonide in these groups be expected to be different to the whole population? Does dapagliflozin have any treatment benefit in IgA nephropathy?
• **EAG issue 5**	In relation to EAG issue 5: Would TR budesonide be used in people with more severe renal failure than the who were people included in the trial? What is the relationship if any between UPCR and eGFR? Is there any group who would be eligible for TR budesonide according to its marketing authorisation that was excluded from the trial? Would you expect people with lower eGFR to have different treatment outcomes to people with higher eGFR?
• **EAG issue 6**	In relation to EAG issue 6: Table 2.2 in the EAG report gives details on concomitant medications by ATC class for both treatment arms of the main clinical trial, and Table 3.5 gives details on the baseline characteristics of patients in the trial with UPCR ≥1.5 g/g. Do any of the differences between trial arms identified in these tables suggest a risk of bias in the trial outcomes?
• **EAG issue 7**	In relation to EAG issue 7: What is the relationship between proteinuria and disease progression? Is using the eGFR data from the trial as a surrogate endpoint to estimate the disease progression through CKD states appropriate? Would you have expected to see disease progression reported as a specific separate outcome in the main clinical trial for TR budesonide?
• **EAG issue 8**	In relation to EAG issue 8: Table 2.2 in the EAG report gives details on concomitant medications by ATC class for both treatment arms of the main clinical trial, and Table 3.5 gives details on the baseline characteristics of patients in the trial with UPCR ≥1.5 g/g. Do these tables reflect the treatments people have in the UK and the characteristics of people who would have targeted release budesonide in the NHS? Is the trial trial data generalisable to the UK target population?

• **EAG issue 9**	In relation to EAG issue 9: There are some uncertainties around the retreatment with TR budesonide. Please comment on the circumstances in which patients would be expected to be retreated with TR budesonide, the timing between treatment rounds, and the relative efficacy that would be expected from retreatment.
Are there any important issues that have been missed in EAR?	

Part 3: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

There is a large unmet need for new safe, well tolerated and effective treatments for IgA nephropathy
The P2 and P3 data show that Nefecon effectively reduces proteinuria in the short term and slows eGFR decline over 2 years
Nefecon is well tolerated by patients with IgA nephropathy
Nefecon offers patients and nephrologists a new treatment choice to be given on top of maximal supportive care
The P3 clinical trial is well designed and the patient population representative of UK patients and UK clinical practice

Thank you for your time.

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

☐ **Please tick this box** if you would like to receive information about other NICE topics.

For more information about how we process your personal data please see our privacy notice.

NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Targeted-release budesonide for treating primary IgA nephropathy [ID1434]

Technical engagement response form

As a stakeholder you have been invited to comment on the External Assessment Report (EAR) for this evaluation.

Your comments and feedback on the key issues below are really valued. The EAR and stakeholders' responses are used by the committee to help it make decisions at the committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form

We are asking for your views on key issues in the EAR that are likely to be discussed by the committee. The key issues in the EAR reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the EAR.

You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise.

If you would like to comment on issues in the EAR that have not been identified as key issues, you can do so in the 'Additional issues' section.

If you are the company involved in this evaluation, please complete the 'Summary of changes to the company's cost-effectiveness estimates(s)' section if your response includes changes to your cost-effectiveness evidence.

Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.

Do not include medical information about yourself or another person that could identify you or the other person.

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.

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 under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information redacted. See the NICE health technology evaluation guidance development manual (sections 5.4.1 to 5.4.10) for more information.

The deadline for comments is **5pm** on **22 August 2023**. 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 during engagement, 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 during engagement 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.

Technical engagement response form

About you

Table 1 About you

Your name	[redacted]
Organisation name: stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder, please leave blank)	UK Kidney Association
Disclosure Please disclose any funding received from the company bringing the treatment to NICE for evaluation or from any of the comparator treatment companies in the last 12 months [Relevant companies are listed in the appraisal stakeholder list.] Please state: • the name of the company • the amount • the purpose of funding including whether it related to a product mentioned in the stakeholder list • whether it is ongoing or has ceased.	1) **Britannia Pharmaceuticals Ltd.** Ongoing consulting agreement (no funding received to date, under discussion). 2) **Stada Pharmaceuticals.** Delivered one-off industry sponsored symposium on new treatments in IgAN focusing on TRF-budesonide, for Romanian society of nephrology meeting, May 2023. 2251.13 EUR. 3) **Calliditas:** **a.** Educational podcast on immune complexes in IgAN. Jan 2023. $1575 USD **b.** Advisory board on TRF-budesonide and interpretation of Nefigard data. Nov 2022. $3653.21 USD **c.** UK Chief investigator and site PI for Nefigard Ph3 trial and open label extension study. Payments to institution (University Hospitals of Leicester NHS trust).
Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry	**No**

Key issues for engagement

All: Please use the table below to respond to the key issues raised in the EAR.

Table 2 Key issues

Key issue	Does this response contain new evidence, data or analyses?	Response
1. Applicability of the trial evidence to those patients not on RASi therapy	No	Single agent RASi therapy is considered globally as first line therapy in IgA nephropathy (IgAN) in those that tolerate this treatment and therefore in the Nefigard trial, use of RASi was mandated as standard of care. Due to TRF-budesonide's mechanism of action and working in a distinct manner to RASi, I do not believe this to be a concern.
2. Corticosteroids, MMF and SGLT2i may be relevant comparators for different subgroups of patients	No	In adults, corticosteroids are not generally used in the UK in the treatment of IgAN as they are poorly tolerated and have an unfavourable adverse effect/benefit profile. MMF is not routinely used in the UK for treatment of IgAN, and is not recommended outside China in the 2021 KDIGO guidelines due to a lack of evidence to support their use. The Nefigard trial was conducted before adoption of SGLT2i use in CKD and IgAN. TRF-budesonide has a distinct mechanism of action from SGLT2i which primarily act to reduce proteinuria by haemodynamic effects, and is therefore not a disease-specific treatment. Therefore I expect the two (SGLT2i and TRF-budesonide) will potentially be used in combination in clinical practice.

3. Short-term follow-up	No	Part B of the Nefigard study with 2-year data has recently been published: https://www.thelancet.com/cms/10.1016/S0140-6736(23)01554-4/attachment/c619bed2-d81b-486a-9f40-b9f09c4bebd8/mmc1.pdf
4. Omission of relevant evidence	No	No additional comments
5. Exclusion of potentially relevant subgroup	No	Further studies are required to assess whether people with an eGFR less than 35 mL/min/1.73m2 may benefit from TRF-budesonide. Most UK nephrologists would only consider treatments such as TRF-budesonide or other immunomodulatory agents if eGFR is above 30 mL/min, due to lack of evidence for their effect under this level and concern regarding irreversible kidney damage which would not respond to these therapies. This threshold is also stated in the 2021 KDIGO guidelines.
6. Possible selection bias	No	No additional comments
7. Disease progression not reported	No	IgAN is a disease that typically progresses over several years and therefore the number of events is likely to be very low in a 12-month study, especially as only patients with eGFR >35 mL/min were included.
8. Applicability of evidence	No	The population studied in the Nefigard trial is typical of a UK population with IgAN, and this trial did recruit study patients from the UK.
9. Insufficient evidence regarding retreatment of patients	No	By its mechanism of action, one may expect that retreatment would have similar effectiveness to initial treatment, but further data are required to demonstrate this.
10. Data source for estimating the transition from CKD 4 to CKD 5	No	No additional comments

Other issues identified by NICE technical team (not included in the EAR): The technical team note that the probabilistic and deterministic analyses give substantially different cost effectiveness estimates. Please provide an explanation for these differences.	No	No additional comments

NICE National Institute for Health and Care Excellence

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Targeted-release budesonide for treating primary IgA nephropathy [ID1434]

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Technical engagement response form

About you

Table 1 About you

Your name	[redacted] (on behalf of NHS England)
Organisation name: stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder, please leave blank)	NHS England Renal Services Clinical Reference Group
Disclosure Please disclose any funding received from the company bringing the treatment to NICE for evaluation or from any of the comparator treatment companies in the last 12 months [Relevant companies are listed in the appraisal stakeholder list.] Please state: • the name of the company • the amount • the purpose of funding including whether it related to a product mentioned in the stakeholder list • whether it is ongoing or has ceased.	**Nil**
Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry	

Key issues for engagement

All: Please use the table below to respond to the key issues raised in the EAR.

Table 2 Key issues

Key issue	Does this response contain new evidence, data or analyses?	Response
1. Applicability of the trial evidence to those patients not on RASi therapy	No	There is no substantive evidence to support the use of budesonide in patients not on RASi.
2. Corticosteroids, MMF and SGLT2i may be relevant comparators for different subgroups of patients	No	MMF has only been shown to be of benefit in an Asian (non-UK based) population and therefore the relevance of MMF as a comparator to budesonide in the UK is unclear. Dapaglifozin is licensed for ALL causes of albuminuric CKD irrespective of aetiology and therefore in practical terms it should be regarded as a standard of care therapy rather than a comparator to budesonide. Whilst it is theoretically logical to have corticosteroids as a comparator to budesonide, we note that the cumulative side-effect burden of systemic corticosteroids significantly limits their use in the real-world setting and therefore whether it can be seen as a genuine comparator to budesonide is uncertain. We note that the best evidence for the use of corticosteroids comes from the TESTING 2 study in which only 25 patients were Caucasian. Again, the relevance of this study and corticosteroid therapy in general to a UK population is questionable

3. Short-term follow-up	No	Although follow up is short we note that highly significant and that both proteinuria and eGFR are accepted as surrogates for long term kidney function decline. We agree that all term data should be available for analysis and in the submission
4. Omission of relevant evidence	No	We agree that NEFIGAN Nef 202 should comprise part of the analysis
5. Exclusion of potentially relevant subgroup	No	Although patients with an eGFR <35mls/min may benefit from budesonide the clinical relevance of this for the treatment pathway of patients with IgA nephropathy is uncertain given the likely presence of significant kidney fibrosis in such patients – ie irreversible kidney damage has already taken place. It would be important to have a clearer understanding of the potential benefit of budesonide in patients with proteinuria of between 1-1.5g/24 hours
6. Possible selection bias		Whilst there were differences in lipid-lowering therapy, dihydropyridine and uric acid lowering agents it is unlikely that these lead to significant selection bias given the baseline levels of BP, proteinuria, eGFR and RASi use were comparable between the 2 groups.
7. Disease progression not reported	No	uPCR and eGFR decline have been recognised as valid surrogates for disease progression (to dialysis/transplantation) by regulatory authorities such as the FDA
8. Applicability of evidence	No	This is an important area to modify disease natural history and avoid or delay the need for Renal Replacement Therapy. NHSE are unclear why the EAG deem the trial population as not being relevant to a UK population given the demographics and self-reported ethnicity within the study.
9. Insufficient evidence regarding retreatment of patients	No	Agree there is no clear evidence presented to support retreatment although there is a clinical rationale for this given the mechanism of action of budesonide in targeting the underlying problem galactose-deficient immunoglobulin A,
10. Data source for estimating the transition from CKD 4 to CKD 5	No	Nil to add
Other issues identified by NICE technical team (not included in the EAR):	No	Nil to add

The technical team note that the probabilistic and deterministic analyses give substantially different cost effectiveness estimates. Please provide an explanation for these differences.		

Additional issues

All: Please use the table below to respond to additional issues in the EAR that have not been identified as key issues. Please do **not** use this table to repeat issues or comments that have been raised at an earlier point in this evaluation (for example, at the clarification stage).

Table 3 Additional issues from the EAR

Issue from the EAR	Relevant section(s) and/or page(s)	Does this response contain new evidence, data or analyses?	Response
Additional issue 1: Insert additional issue	Please indicate the section(s) of the EAR that discuss this issue	Yes/No	Please include your response, including any new evidence, data or analyses, and a description of why you think this is an important issue for decision making
Additional issue 2: Insert additional issue	Please indicate the section(s) of the EAR that discuss this issue	Yes/No	Please include your response, including any new evidence, data or analyses, and a description of why you think this is an important issue for decision making
Additional issue N: Insert additional issue			[INSERT / DELETE ROWS AS REQUIRED]

Summary of changes to the company's cost-effectiveness estimate(s)

Company only: If you have made changes to the base-case cost-effectiveness estimate(s) in response to technical engagement, please complete the table below to summarise these changes. Please also provide sensitivity analyses around the revised base case. If there are sensitivity analyses around the original base case which remain relevant, please re-run these around the revised base case.

Table 4 Changes to the company's cost-effectiveness estimate

Key issue(s) in the EAR that the change relates to	Company's base case before technical engagement	Change(s) made in response to technical engagement	Impact on the company's base-case incremental cost-effectiveness ratio (ICER)
Insert key issue number and title as described in the EAR	Briefly describe the company's original preferred assumption or analysis	Briefly describe the change(s) made in response to the EAR	Please provide the ICER resulting from the change described (on its own), and the change from the company's original base-case ICER.
Insert key issue number and title as described in the EAR	…	…	[INSERT / DELETE ROWS AS REQUIRED]
Company's base case following technical engagement (or revised base case)	Incremental QALYs: [QQQ]	Incremental costs: [£££]	Please provide company revised base-case ICER

Sensitivity analyses around revised base case
PLEASE DESCRIBE HERE

NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Targeted-release budesonide for treating primary IgA nephropathy [ID1434]

Technical engagement response form

As a stakeholder you have been invited to comment on the External Assessment Report (EAR) for this evaluation.

Your comments and feedback on the key issues below are really valued. The EAR and stakeholders' responses are used by the committee to help it make decisions at the committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form

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Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.

Do not include medical information about yourself or another person that could identify you or the other person.

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.

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 under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information redacted. See the NICE health technology evaluation guidance development manual (sections 5.4.1 to 5.4.10) for more information.

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Thank you for your time.

We reserve the right to summarise and edit comments received during engagement, 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 during engagement 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.

About you

Table 1 About you

Your name	[redacted]
Organisation name: stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder, please leave blank)	Novartis Pharmaceuticals UK Limited
Disclosure Please disclose any funding received from the company bringing the treatment to NICE for evaluation or from any of the comparator treatment companies in the last 12 months [Relevant companies are listed in the appraisal stakeholder list.] Please state: • the name of the company • the amount • the purpose of funding including whether it related to a product mentioned in the stakeholder list • whether it is ongoing or has ceased.	N/A
Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry	**1)** Since April 2005, Novartis has exclusively licensed glycopyrronium bromide and certain intellectual property relating to its use and formulation from Vectura and its co-development partner, Sosei Heptares. The following inhaled medications are comprised of, or contain, glycopyrronium bromide:

	• Seebri® Breezhaler® (glycopyrronium bromide), used as a maintenance treatment for Chronic Obstructive Pulmonary Disease (COPD) • Ultibro® Breezhaler® (indacaterol/glycopyrronium bromide), used as a maintenance treatment for COPD • Enerzair® Breezhaler® (indacaterol/glycopyrronium bromide/mometasone furoate), used as a maintenance treatment for asthma uncontrolled with long-acting beta-agonist (LABA)/inhaled corticosteroid (ICS). Phillip Morris International (a tobacco company) has acquired Vectura Group Limited (formerly Vectura Group plc). **2)** Novartis has been granted with an exclusive license from Japan Tobacco Inc. (JT) under JT patents on a world-wide basis for commercial rights to trametinib (Mekinist®; TMT212). Trametinib is a kinase inhibitor indicated as a single agent or in combination with dabrafenib for the treatment of several oncology indications. In 2015, as part of its purchase of oncology products from GlaxoSmithKline, Novartis obtained the worldwide exclusive rights granted by JT to develop, manufacture, and commercialize trametinib. JT retains co-promotion rights in Japan.

Key issues for engagement

All: Please use the table below to respond to the key issues raised in the EAR.

Table 2 Key issues

Key issue	Does this response contain new evidence, data or analyses?	Response
1. Applicability of the trial evidence to those patients not on RASi therapy	No	Novartis would first like to highlight a point of clarification with regards to the licensed population for targeted release (TR)-budesonide and the target population described by the Company. Based on input received from the Company in response to the EAG clarification questions, the EAG report (page 85) summarises: "The company stated that according to the MHRA license of budesonide, the target population is limited to adult patients with primary IgAN who are on a stable dose of maximally tolerated RAS inhibitor therapy (ACEi or ARB)". However, Novartis note that the current MHRA license for TR-budesonide does not specify that patients must be receiving renin-angiotensin system inhibitor (RASi) therapy alongside TR-budesonide. Given the above, there is currently a lack of clarity between the licensed population and the target population addressed within the Company submission, which is important to clarify. With regards to the applicability of the pivotal trial evidence to those patients not on RASi therapy, Novartis agree that RASi therapy (with either an angiotensin-converting enzyme [ACE] inhibitor or angiotensin-receptor blocker [ARB]) represents the principal component of clinical management of immunoglobulin A (IgA) nephropathy for most patients, in line with Kidney

		Disease: Improving Global Outcomes (KDIGO) 2021 guidelines.[1] It is acknowledged that a small proportion of patients may not be able to tolerate or may be contraindicated to these therapies, and the very small number of participants in the NefIgArd Nef-301 trial not receiving RASi therapy due to intolerance or contraindication provides support for this. Novartis agree that, for these patients, the maximally tolerated dose of RASi therapy would be zero. Novartis consider that patients unable to tolerate or who are contraindicated to RASi therapy should not be excluded from receiving TR-budesonide. As these individuals are unable to receive the currently recommended therapy, there exists a high level of unmet need in this group, and Novartis believe that these patients should not be denied access to new, effective therapies. Furthermore, whilst the number of patients not receiving RASi therapy due to intolerance or contraindication in the NefIgArd Nef-301 trial was very small, at a level that would prevent results from this population being reliably analysed as a subgroup, data from this group nevertheless contributed evidence for the overall efficacy and safety of TR-budesonide. In the context of a rare disease, where small sample sizes are an inherent limitation, the data contributed by these patients within the NefIgArd Nef-301 trial should not be disregarded. Finally, the NICE recommendation made following the appraisal of dapagliflozin in chronic kidney disease (CKD) specifies that dapagliflozin is recommended as "an add-on to optimised standard care including the highest tolerated licensed dose of angiotensin-converting enzyme (ACE) inhibitors or angiotensin-receptor blockers (ARBs), *unless these are contraindicated*".[2] This recommendation was based on the DAPA-CKD trial in which only 3% of patients did not receive RASi background therapy.[3] Therefore, Novartis would suggest that a recommendation for TR-budesonide should similarly not exclude those patients unable to tolerate or who are contraindicated to RASi therapy.
2. Corticosteroids, MMF and SGLT2i may be relevant comparators for different subgroups of patients	No	**Corticosteroids** Novartis wish to reiterate earlier comments made on the draft scope of the present evaluation regarding the limited use of conventional corticosteroids in

		patients with IgA nephropathy in UK clinical practice, and the caution against their use in KDIGO guidelines, which highlight an "important risk of treatment-emergent toxicity" and that the "clinical benefit of glucocorticoids in IgAN is not established and should be given with extreme caution".[1] It is acknowledged that a small proportion of IgA nephropathy patients in the UK may still be eligible to receive corticosteroids; however, Novartis would like to reiterate that insights obtained from UK clinicians indicate that conventional corticosteroids are used very cautiously, given their adverse effects.[4] **Mycophenolate mofetil (MMF)** Novartis would like to reiterate earlier comments on the NICE draft scope regarding the limited use of MMF for IgA nephropathy in UK clinical practice. Use of MMF is not recommended by KDIGO guidelines, except for in Chinese patients.[1] As highlighted by the Company, the KDIGO guidelines also highlight the lack of evidence of efficacy in Caucasian patients.[1] Furthermore, it is noted that MMF was not included as a comparator in the final scope issued by NICE for this evaluation; Novartis agrees with this earlier decision, on the basis that MMF is rarely used in UK clinical practice. In addition, Novartis would like to note reservations with regards to any recommendation that may be based on patient ethnicity. **SGLT2 inhibitors (dapagliflozin)** It is important to note that the dapagliflozin data in IgA nephropathy patients referred to in the Company submission and EAG report are from a subgroup analysis of the DAPA-CKD trial which was not prospectively powered to demonstrate statistical significance; while the subgroup analysis was pre-specified, the number of patients with IgA nephropathy that would be enrolled was not known at the time of trial design.[5]
3. Short-term follow-up	No	Given that TR-budesonide is administered as a short-term, non-continuous treatment for 9 months only, Novartis agree that there remains uncertainty in the estimates of long-term benefit (beyond the 12-month follow-up timepoint). Furthermore, the uncertainty regarding potential retreatment and the

		associated efficacy (as discussed in Key Issue 9) contribute to the broader challenge of evaluating the long-term costs and benefits of the therapy. Consequently, Novartis share the view of the EAG that longer-term clinical data from Part B of the NefIgArd Nef-301 trial would be valuable in reducing uncertainty in the long-term benefits of TR-budesonide in patients with IgA nephropathy.
4. Omission of relevant evidence	No	No comments.
5. Exclusion of potentially relevant subgroup	No	Firstly, Novartis would like to highlight that clinical trials in CKD commonly specify eGFR cut-off values in the trial exclusion criteria. The rationale for excluding patients presenting with baseline eGFR values below a certain level is that very low eGFR levels are associated with a risk of therapeutic futility (alternatively described as the 'point of no return' with regards to the extent of disease). As outlined in the KDIGO guidelines,[1] this 'point of no return' describes a situation in which "…severe loss of kidney function (to an eGFR <20–30 ml/min/1.73 m^2) is accompanied by such extensive and irreversible kidney injury … that any therapeutic strategy being tested cannot reasonably be expected to alter the natural history of progressive deterioration in kidney function (therapeutic futility)…The presumption is that such patients should be excluded from clinical trials since they are expected to be 'non-responders'".[1] It also highlights that these patients with reduced kidney function may be at a higher risk of experiencing adverse effects when receiving new therapies.[1] Novartis believe that it would be unreasonable to request a clinical trial to be conducted in a population where a high likelihood of therapeutic futility, and potentially greater risk to patients, exists. However, KDIGO guidelines also emphasise that a precise definition does not yet exist for this point at which patients with CKD are expected to be 'non-responders' in a clinical trial.[1] Furthermore, in clinical practice, Novartis understand that decisions made by clinicians to determine whether CKD patients are likely to benefit from treatments are informed by broader, more holistic considerations (beyond the current eGFR level in isolation). These considerations may include clinical history of eGFR decline, the pace of that

		decline, as well as proteinuria level and biopsy findings, and the risk-benefit profile of the therapy being considered.
6. Possible selection bias	No	Novartis agree with the assessment of both the Company and the EAG that baseline differences in patient characteristics in the NefIgArd Nef-301 trial may reflect random differences secondary to the small sample sizes involved, as would be expected for a rare condition. Regarding the differences in the proportion of patients receiving ACE inhibitors or ARBs between the two trial arms, Novartis do not anticipate that these differences would exert a major effect on clinical outcomes. It is noted that the latest KDIGO guidelines continue to recommend both types of therapies in the treatment of IgA nephropathy,[1] indicating a lack of evidence of differences in their relative efficacy in this condition and other chronic kidney diseases; the same applies to the NICE clinical guideline for CKD.[6]
7. Disease progression not reported	No	With regards to direct measures of long-term disease progression outlined in the NICE final scope, such as rate of, or time to, progression to kidney transplant or dialysis, Novartis agree that the clinical trial evidence presented by the Company did not include these measures. Whilst information on events such as receipt of transplant or initiation of dialysis should be collected in clinical trials and reported on, very few of these events would likely occur within a trial timeframe, particularly a 9-month trial. Further, the inclusion criteria for the NefIgArd Nef-301 trial specified that patients were required to have a baseline eGFR ≥35 ml/min/1.73 m^2. As a result, patients with very low kidney function at baseline (in whom the abovementioned long-term disease progression events would be more likely to occur) were not included, limiting the likelihood of observing these events. Novartis would also like to highlight that a sustained decline in eGFR reflects a deterioration of kidney function and therefore eGFR endpoints reported in the Company submission of 'Ratio of eGFR compared with baseline' and 'Decline in eGFR at 1-year eGFR (total slope)' provide relevant information on the effect of TR-budesonide in terms of reducing the risk of disease progression. As also outlined in the Company submission, the use of surrogate outcomes – for instance eGFR, but also proteinuria – to predict long-term clinical outcomes

		such as kidney failure, is well established in CKD trials. A variety of published evidence also supports this specifically in IgA nephropathy,[7-9] including studies which can be categorised as providing 'Level 1' evidence, in line with the evidence framework for surrogate relationships defined in the NICE health technology evaluations manual.[10]
8. Applicability of evidence	No	Novartis would first like to emphasise the general challenge of evidence generation in rare diseases such as IgA nephropathy. Subgroup analyses of such trials should be done with caution, given that the small patient numbers involved will introduce substantial uncertainty. This challenge is prominent in the case of the present evaluation. The NefIgArd Nef-301 trial focused on patients at high risk of rapid disease progression (with included patients required to have proteinuria ≥1 g/day or urine protein creatinine ratio [UPCR] ≥0.8 g/g and to have been receiving optimised supportive care for at least 3 months prior to randomisation), which already represents a subgroup of the overall IgA nephropathy population. The TR-budesonide license and decision problem addressed within the Company submission then further restrict this population (to those patients with a UPCR ≥1.5 g/g), with a remaining sample size from the relevant trial of [redacted] patients for TR-budesonide and [redacted] patients for placebo. Conclusions from a potentially large number of further subgroup analyses of this subgroup, as requested by the EAG, may not be meaningful given the small sample sizes available. Moreover, in this rare disease indication where there are currently no treatments specifically licensed for IgA nephropathy (other than TR-budesonide), Novartis believe that a key priority should be to enable broad patient access to new treatment options, where efficacy, safety, and cost-effectiveness have been demonstrated.
9. Insufficient evidence regarding retreatment of patients	No	Novartis acknowledge the uncertainty surrounding retreatment with TR-budesonide, for example, the proportion of IgA nephropathy patients that would require and receive retreatment with TR-budesonide in UK clinical practice. However, given that the TR-budesonide license indicates that retreatment may be considered at the discretion of clinicians, it is expected that retreatment would occur in UK clinical practice to a certain degree. As such, whilst

		additional uncertainty introduced by the lack of efficacy and safety data for retreatment with TR-budesonide must be taken into account, Novartis consider that the EAG approach of setting the retreatment probability in the model to zero is not appropriate.
10. Data source for estimating the transition from CKD 4 to CKD 5	No	Novartis share the EAG's concern with regards to the data used to estimate the transition probability for patients in the SoC arm moving from the CKD stage 4 to CKD stage 5 health states in the Company base case analysis. Using data which combines end-stage renal disease (ESRD) and death cases will likely overestimate the risk of ESRD (CKD stage 5), given that the risk of death is incorporated into the analysis. In addition to the source utilised to estimate the probability of transition to CKD stage 5 for patients in the SoC arm, consideration must also be given to potential further uncertainty introduced by the source utilised to derive this transition probability for patients in the TR-budesonide arm of the model. Calculation of the hazard ratio for transition to CKD stage 5 was based on a CKD surrogate endpoint publication which included sustained doubling of serum creatinine, alongside ESRD (initiation of chronic dialysis or transplantation) and GFR <15 ml/min/1.73 m^2, in the composite clinical endpoint.[11] The R^2 value (0.50; 95% CrI 0.10, 0.80) of the utilised regression model indicated a borderline moderate trial-level association between the treatment effect on 1-year GFR slope and the treatment effect on the clinical endpoint, with the association becoming stronger with longer-term GFR slope data.[11, 12] The transition from CKD stage 4 to CKD stage 5 is an important aspect of the cost-effectiveness analysis, given the higher costs and quality of life (QoL) impact associated with ESRD, compared to earlier CKD stages. When considered in the context of the Company model structure, Novartis consider that the inability to use trial data to inform this transition could be viewed as a limitation in the Company modelling approach. More broadly, although the NefIgArd Nef-301 trial was utilised to inform transition probabilities between CKD stages 1–4, the small number of events informing these transitions could similarly be viewed as reflective of this limitation in the Company model

		structure. Alternative modelling approaches could ensure that trial data for the technology are better utilised to inform the modelling of later stage disease. Finally, Novartis would like to note that, in the context of a rare kidney disease indication, the UK RaDaR database represents a strong real-world data source. As a multi-centre database (collecting data from 107 UK sites),[13] the source provides longitudinal information on a large sample of patients with rare kidney diseases from across the UK (with patients included from 2010 onwards).[14]
Other issues identified by NICE technical team (not included in the EAR): The technical team note that the probabilistic and deterministic analyses give substantially different cost effectiveness estimates. Please provide an explanation for these differences.	No	Novartis note that a possible explanation for the discrepancy in the results of the probabilistic and deterministic cost-effectiveness analyses identified by the NICE technical team could be uncertainty in the transition probabilities between CKD health states in the Company model. The transition probabilities for CKD stages 1–4 for both the TR-budesonide and SoC arms used in the model were informed by eGFR data derived from the NefIgArd Nef-301 trial, with these data demonstrating how limited changes in kidney function were observed in patients receiving TR-budesonide versus SoC alone. These results are in line with expectations that the trial data would capture only a small number of transitions between stages, given the relatively short data collection period. Novartis note that this challenge was acknowledged by the Company in their submission, and that the transition probability for CKD stage 1 to CKD stage 2 in the TR-budesonide arm was informed by very limited data. This then resulted in high variation in outcomes across iterations of the PSA. As noted in Novartis's response to Key Issue 10, the limited availability of trial data to inform transitions between health states could be viewed as a limitation in the Company modelling approach, given the uncertainty that this introduces.

Additional issues

All: Please use the table below to respond to additional issues in the EAR that have not been identified as key issues. Please do **not** use this table to repeat issues or comments that have been raised at an earlier point in this evaluation (for example, at the clarification stage).

Table 3 Additional issues from the EAR

Issue from the EAR	Relevant section(s) and/or page(s)	Does this response contain new evidence, data or analyses?	Response
N/A	N/A	N/A	N/A

NICE National Institute for Health and Care Excellence

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N/A	N/A	N/A	N/A

Sensitivity analyses around revised base case
N/A

References

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13. UK Kidney Association. RaDaR Registry. Available at: https://ukkidney.org/rare-renal/radar [Last accessed Aug 23].
14. UK Kidney Association. Participating Renal Units. Available at: https://ukkidney.org/rare-renal/renal-units [Last accessed Aug 23].

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Technical engagement response form

About you

Key issues for engagement

All: Please use the table below to respond to the key issues raised in the EAR.

Table 1. Key issues

Key issue	Does this response contain new evidence, data or analyses?	Response	EAG comments
1. Applicability of the trial evidence to those patients not on RASi therapy	Yes	In the NefIgArd Nef-301 study, targeted-release formulation (TRF)-budesonide was administered in addition to standard of care (SoC), which includes lifestyle modification, blood pressure management, maximum-tolerated renin-angiotensin system (RAS) blockade (angiotensin-converting enzyme inhibitors [ACEi] or angiotensin receptor blockers [ARB]), and addressing cardiovascular risk in order to align with current clinical practice and the proposed positioning/indication of TRF-budesonide (1-3). Of note, patients who could not tolerate RAS blockade therapy (and for whom, therefore, the maximally tolerated RASi dose may be zero) were considered in the study, in line with anticipated use in clinical practice. In real-world clinical practice, a small proportion (~10%) of patients with IgAN with UPCR ≥1.5 g/g (an already small subgroup of patients with primary IgAN, an orphan disease) are intolerant to RASi therapy (4). This is most commonly because patients have low blood	Although the EAG agrees with the statement that withholding TRF budesonide from those patients who are intolerant to RAS blockade therapy may lead to challenges in equitable access to treatment, the

		pressure at the time of initiating RASi therapy. Clinical expert opinion (submitted as new evidence (4)) indicated that patients who were not receiving RASi therapy in the NefIgArd Nef-301 study were likely to have had low blood pressure at the time of treatment with TRF-budesonide, and would therefore have been unable to tolerate further reductions in blood pressure induced by RASi therapy. In accordance, the 2021 KDIGO guidelines note that the use of RASi therapy in younger patients with low/normal blood pressure may increase the risk of orthostatic hypotension and advise that normotensive patients are started on low-dose therapy with dose escalation controlled so that the patient is treated with the maximal tolerated dose of RASi (balancing the benefits of treatment and minimising side effects) (1). The clinical expert indicated that TRF-budesonide does not affect blood pressure and so would be an appropriate treatment for patients who cannot tolerate RASi therapy and for whom limited alternative therapeutic options exist (4). Patients with IgAN who cannot tolerate RASi therapy (and who otherwise receive optimised SoC) have limited treatment options. The 2021 KDIGO guidelines recommend that patients at high risk of progressive CKD despite maximal supportive care (including maximum tolerated RASi therapy) are enrolled on a clinical trial (1). The use of immunosuppressants is cautiously recommended should a clinical trial not be accessible due to their adverse event profile (1). As such, excluding these patients (i.e. patients with primary IgAN who are intolerant to RASi therapies and who otherwise receive optimised SoC) from treatment with TRF-budesonide, a therapy that presents the potential to delay disease progression, may result in challenges to equitable access to treatment for these patients.	fact remains that the clinical evidence does not adequately cover this population group. Therefore, it is still true to state that the applicability of the trial evidence to those patients not on RASi therapy is limited. This remains a key issue.
2. Corticosteroids, MMF and SGLT2i may be relevant comparators for different subgroups of patients	Yes	**Corticosteroids and immunosuppressants** The company maintains the position that corticosteroids (CS) and immunosuppressants (in addition to optimised SoC) are not relevant comparators for TRF-budesonide, based on feedback received by clinical experts (2). CS and immunosuppressants are only recommended if a clinical trial is not accessible and the risk/benefit profile is considered to be acceptable (1). UK clinical experts (2) reported that in practice, CS are used sparingly and only in patients with severe kidney disease (i.e. patients with nephrotic syndrome, defined by the KDIGO guidelines as those with proteinuria ≥3.5 g/day and PCR of ≥3,000 mg/g [≥300 mg/mmol], including oedema, hypoalbuminemia and hyperlipidaemia (1)). As	For MMF, the evidence base is described by the company as uncertain. This can be explained by MMF having been largely tested in an

		noted by the KDIGO guidelines, patients with IgAN rarely present with nephrotic syndrome (including oedema and both hypoalbuminemia and nephrotic-range proteinuria >3.5 g/d) (1). To address and respond to the EAG's concerns, however, the company conducted an indirect treatment comparison (ITC) of TRF-budesonide vs CS and immunosuppressants (submitted as new evidence); the methodology and results of these analyses are presented below. **Mycophenolate mofetil (MMF)** Based on advice received by clinical experts (2, 4) and the 2021 KDIGO guidelines (1), the company also maintains the position that MMF (in addition to optimised SoC) is not a relevant comparator for TRF-budesonide. The 2021 KDIGO guidelines (1) highlight that there is insufficient evidence to support the use of MMF in IgAN; randomised controlled trials that investigated the efficacy of MMF monotherapy in IgAN versus placebo or other immunosuppressive treatment in cohorts including Asian and non-Asian patients demonstrated uncertain clinical benefits (5-7). Two trials were terminated early due to lack of treatment benefit (5, 7). The KDIGO guidelines (1) suggest that MMF may be used in Chinese patients only as a glucocorticoid-sparing agent, based on the results of one randomised controlled trial (8). Clinical experts advised that, due to the lack of other available treatment options and the adverse event profile of CS, MMF could be used as a steroid-sparing agent for patients with IgAN; however, MMF is not used in clinical practice in England (2, 4). As such, MMF was not included as a relevant comparator in the ITC that was conducted by the company. **Sodium-glucose cotransporter-2 inhibitors (SGLT2is)** There is as yet no clinical guidance for the use of SGLT2is specific to patients with IgAN by NICE. However, dapagliflozin has received NICE approval for the treatment of CKD (TA775) (9) and is also anticipated to be used as part of SoC in patients with IgAN, as indicated by clinical expert opinion (2). As such, it is anticipated that dapagliflozin will be administered in combination with TRF-budesonide as part of SoC. Any potential benefits that may be observed from the addition of dapagliflozin to SoC, are anticipated to be	ethnically heterogeneous population (as seen in studies 5 to 7). In a more homogeneous Asian population, MMF appears to be more beneficial (as shown by study 8). Therefore, for the sub-group of patients who are eligible for budesonide and who may also respond to MMF, there is a need to establish efficacy of MMF + SoC relative to budesonide + SoC, so that the most clinically and cost-effective option for that sub-group can be ascertained. The company states that MMF is

		additive to the TRF-budesonide treatment effect, especially since there is no crossover between their mechanisms of action (as indicated by clinical expert opinion (2)). To address and respond to the EAG's concerns, however, the company conducted an ITC of TRF-budesonide vs dapagliflozin + SoC; the methodology and results of these analyses are presented below. **ITC methodology** A Bayesian network meta-analysis (NMA) approach was adopted for synthesis of the evidence base. Both random-effects (RE) and fixed-effect (FE) models were fitted to the data to estimate relative treatment-effects between TRF-budesonide and comparators of interest (CS and immunosuppressants + SoC; and dapagliflozin + SoC). Efficacy outcomes that were assessed included change from baseline (CFB) to 12 months in urine protein to creatinine ratio (UPCR) and estimated glomerular filtration rate (eGFR). Consistent with the target population for current appraisal of TRF-budesonide, the analyses were informed by a cohort from the NefIgAn Nef-202 (who received TRF-budesonide 16 mg/day) (10) and NefIgArd NEF-301 (11) trials who had a baseline UPCR of ≥1.5 g/g (which is the indicated population). However, the intention-to-treat population from all comparator studies was evaluated in all networks in the absence of results reported for UPCR ≥1.5 g/g subgroup; no other studies assess this population and therefore there are no study populations which are homogenous to the NefIgArd trial. This is a significant limitation of the analyses as baseline proteinuria is a significant predictor of patient outcomes, and further, analysis of differing trial populations may undermine the robustness of the NMA. The analyses for the CS and immunosuppressants arm (in addition to optimised SoC) of the ITC were informed by the STOP-IgAN trial (12, 13), a study conducted across 32 centres in Germany and which was, therefore, likely to evaluate a higher proportion of white/Caucasian patients, comparable to the population within the TRF-budesonide studies. A second study of CS in IgAN (TESTING (14, 15)) was considered in the ITC feasibility assessment; the study population, however, was found not to be homogeneous to the population of the TRF-budesonide as it primarily consisted of an Asian population. In addition, patients in the TESTING study received oral (full- or reduced-dose) methylprednisolone (15) (whereas patients in the STOP-IgAN received	not widely used in UK clinical practice. This may be true, but that is probably because the sub-group that respond to it are in a minority. However this does not mean that the needs of this sub-group should be ignored. This therefore remains as a key issue. Thank you for preparing the ITC analyses concerning 1) corticosteroids/ immunosuppresants (CS/IS) and 2) dapagliflozin (DAPA). These show that budesonide + SoC is [redacted] to both CS/IS + SoC and also DAPA + SoC, in terms of the change in

		immunosuppressant therapy [oral cyclophosphamide for the first 3 months, switched to azathioprine for the next 3 years] together with oral prednisolone (12)); clinician feedback has indicated that methylprednisolone is not used to treat IgAN patients in the UK (4). As such, it was concluded that STOP-IgAN was more relevant than TESTING to UK clinical practice based on both the trial population and the treatments received. The TESTING study was not considered relevant to inform the CS arm of the ITC versus TRF-budesonide. The analyses for the dapagliflozin arm (in addition to optimised SoC) of the ITC were informed by a pre-specified analysis within the DAPA-CKD trial investigating the efficacy of dapagliflozin in IgAN (16). **ITC results – change from baseline to 12 months in eGFR** A total of three 2-arm studies were included in the analysis evaluating the CFB to 12 months in UPCR (Figure 1) (12, 15, 17). All studies reported data (either numerically or graphically) for changes in UPCR at 12 months post-baseline, or baseline and 12-month from which CFB estimates could be calculated. Based on the structure of the network, an ITC is possible between TRF-budesonide versus CS or immunosuppressants. [redacted] **Figure 1. Network – CFB to 12 months in UPCR (N=3)** Abbreviations: CFB, change from baseline; CS, corticosteroid; IST, immunosuppressive therapy; N, number of studies; TRF-BUD, targeted-release formulation budesonide; UPCR, urine protein-creatinine ratio. All pairwise treatment comparisons from the RE model (using Turner's prior distribution) are presented in Table 2; comparisons between TRF-budesonide and CS or immunosuppressants versus placebo/control were [redacted] both comparators over placebo/control. The	eGFR. In terms of the change in UPCR, there is a [redacted] difference between budesonide + SoC and CS/IS + Soc, but the Bayesian probability of budesonide + SoC being [redacted]. DAPA is not included in the UPCR ITC. Overall, however, the available ITC results suggest that budesonide may be [redacted] to both IS/CS and DAPA. However the validity of this conclusion does depend on the studies chosen for the different treatment

comparison between TRF-budesonide and CS or immunosuppressants was [redacted]. The probability of TRF-budesonide being superior to each of the comparators is also presented, with probabilities of [redacted] and [redacted]

Table 2. Mean treatment difference for CFB to 12 months in UPCR (RE model using Turner's prior distribution)

	Placebo/Control	CS or IST	TRF-budesonide 16 mg/day
Placebo/Control	–	[redacted]	[redacted]
CS or IST	[redacted]	–	[redacted]
TRF-budesonide 16 mg/day	[redacted]	[redacted]	–
P(TRF-budesonide) superior to comparator*	[redacted]	[redacted]	–

Abbreviations: CFB, change from baseline; CrI, credible interval; CS, corticosteroid; IST, immunosuppressive therapy; MD, mean difference; RE, random-effects; TRF, targeted-release formulation; UPCR, urine protein-creatinine ratio.
Notes: NMA results are presented as the median and 95% CrI; results are interpreted as the MD between the therapy in the respective row versus the therapy in the respective column; bold denotes statistical significance at 5% level; green shading represents an improved treatment-effect (MD<0) for the comparator in the row versus the therapy in the respective column; orange shading represents a worse treatment-effect (MD>0) for the comparator in the row versus the therapy in the respective column. Studies included in the network are as follows: NEFIGAN, NefIgArd and STOP-IgAN.
*Posterior probability that TRF-budesonide is superior to comparator (MD<0).

ITC results – change from baseline to 12 months in eGFR

comparisons in the ITC.

The studies chosen for budesonide + SoC vs SoC are clearly correct, as they are the only relevant trials known.

For CS/IM + SoC versus SoC, the rationale given by the company for the omission of the TESTING trial from the CS/IM ITC appears to be valid – the ethnicity of participants was different, and methyl-prednisolone is not believed to be used in the UK. However, there appears to have been no systematic basis to the selection of relevant trials. For

		A total of four 2-arm studies were included in the analysis of change from baseline to 12 months in eGFR (Figure 2) (10, 12, 16, 17). All studies reported data (either numerically or graphically) for changes in UPCR at 12 months post-baseline, or baseline and 12-month from which CFB estimates could be calculated. Based on the structure of the network, an indirect comparison is possible between TRF-budesonide versus CS or immunosuppressants and dapagliflozin.  **Figure 2. Network – CFB to 12 months in eGFR (N=4)** Abbreviations: CFB, change from baseline; CS, corticosteroid; DAPA, dapagliflozin; eGFR, estimated glomerular filtration rate; IST, immunosuppressive therapy; N, number of studies; TRF-BUD, targeted-release formulation budesonide. All pairwise treatment comparisons from the RE NMA (using Turner's prior distribution) are presented in Table 3. Comparisons between TRF-budesonide versus placebo/control, CS or immunosuppressants and dapagliflozin [redacted] TRF-budesonide; no other pairwise comparison was statistically significant. The probability of TRF-budesonide being superior to each of the comparators is also presented, with probabilities of [redacted] for TRF-budesonide being superior to placebo/control and dapagliflozin, and of [redacted]% for TRF-budesonide being superior to CS or immunosuppressants.	example, the systematic review by Lv et al. [J AmSoC Nephrol 2012: 23(6):1108] suggests there may be 9 relevant RCTs, but no rationale is available from the company to explain their omission. For DAPA, the only trial considered was the DAPA-CKD trial, but again there was no explanation for the decision-making behind this. Some indication that no other relevant studies exist, based on a systematic search, would have been helpful. In summary, the EAG notes that the ITC suggests

Table 3. Mean treatment difference for CFB to 12 months in eGFR (RE model using Turner's prior distribution)

	Placebo/ Control	CS or IST	DAPA	TRF-budesonide 16 mg/day
Placebo/ Control	—	[redacted]	[redacted]	[redacted]
CS or IST	[redacted]	—	1.89 [-1.56, 5.39]	[redacted]
DAPA	[redacted]	[redacted]	—	[redacted]
TRF-budesonide 16 mg/day	[redacted]	[redacted]	[redacted]	—
P(TRF-budesonide) superior to comparator *	[redacted]	[redacted]	[redacted]	–

Abbreviations: CFB, change from baseline; CrI, credible interval; CS, corticosteroid; DAPA, dapagliflozin; eGFR, estimated glomerular filtration rate; IST, immunosuppressive therapy; MD, mean difference; RE, random-effects; TRF, targeted-release formulation.

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

			that budesonide may be [redacted] to CS and DAPA. However the EAG would also remind the committee that these ITC results are not backed up by a transparent systematic review to increase confidence that all relevant studies have been included in the ITC. As stated in the EAG report, there is also a question regarding the validity of the comparison if budesonide is to be added to DAPA instead of being a substitute for it in clinical practice. This therefore remains a key issue.
3. Short-term follow-up	Yes	The data presented in the company submission (NefIgArd Nef-301 Part A; 9 months of treatment with TRF-budesonide or placebo and 3 months of untreated follow-up) were the	Thank you for the longer-term data

		most mature available at the time of submission. In addition, the economic model did not include extrapolations beyond one year, in line with the clinical data available. The pre-planned Part A analysis was scheduled to occur once the first 201 patients randomised had had the opportunity to complete their 9-month visit and included [redacted] participants (TRF-budesonide 16 mg n=[redacted]; placebo n=[redacted]) with a baseline UPCR ≥1.5 g/g. Since the original company submission, data from Part B of NefIgArd Nef-301 have become available, providing 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 follow-up off drug (17). The Part B analysis included all patients randomised who completed the NefIgArd Nef-301 study (TRF-budesonide 16 mg n=[redacted] placebo n=[redacted]. **Change in UPCR from baseline** A reduction in UPCR from baseline with TRF-budesonide 16 mg/day was seen at all timepoints in NefIgArd Nef-301 Part B (Table 4). Following 9 months of treatment, the ratio of UPCR compared with baseline was [redacted] for patients treated with TRF-budesonide and [redacted] for those who received placebo. This equated to a statistically significant [redacted] reduction in UPCR for patients treated with TRF-budesonide 16 mg/day compared with placebo (p=[redacted]). Treatment with TRF-budesonide provided continued improvement compared with placebo up to the 12-month timepoint, with a [redacted] treatment difference at 3 months of untreated follow-up (ratio of UPCR compared with baseline of [redacted] and [redacted] for those treated with TRF-budesonide and placebo, respectively). At 24 months from baseline (15-months of follow-up off drug), the ratio of UPCR compared with baseline was [redacted] for patients treated with TRF-budesonide and [redacted] for those who received placebo. The reduction in UPCR was [redacted] greater for TRF-budesonide 16 mg/day compared with placebo at 24 months (p=[redacted]), demonstrating the durable benefit obtained at the end of 9 months of treatment with TRF-budesonide. **Table 4. Analysis of UPCR (g/g) using MMRM for patients with a baseline UPCR ≥1.5 g/g in NefIgArd Nef-301 Part B**	up to 24 months. These demonstrate a continuation of clinical benefits to 24 months. This is therefore no longer deemed a key issue.

Timepoint	Ratio of geometric LS mean UPCR compared with baseline (95% CI)		Comparison of TRF-budesonide 16 mg/day† vs placebo†; ratio of geometric LS means (95% CI); p value	Corresponding % change versus placebo‡
	TRF-budesonide† (n=[redacted])	Placebo† (n=[redacted])		
3 months	[redacted]	[redacted]	[redacted]	[redacted]
6 months	[redacted]	[redacted]	[redacted]	[redacted]
9 months	[redacted]	[redacted]	[redacted]	[redacted]
12 months	[redacted]	[redacted]	[redacted]	[redacted]
18 months	[redacted]	[redacted]	[redacted]	[redacted]
24 months	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CI, confidence interval; LS, least squares; MMRM, mixed-effects model for repeated measures; RAS, renin-angiotensin system; TRF, targeted-release formulation; UPCR, urine protein to creatinine ratio.
† Treatment in addition to RAS inhibition.
‡ Calculated as (1 – ratio) of LS means * 100.

Ratio of eGFR compared with baseline

After 9 months of treatment, a statistically significant [redacted] benefit on eGFR was observed with TRF-budesonide 16 mg/day compared with placebo (difference in absolute change in eGFR from baseline for TRF-budesonide vs placebo was [redacted] mL/min/1.73 m^2), demonstrating a delay in the progression of kidney disease compared with patients who received placebo (Table 5). The treatment benefit accrued by the end of 9 months of treatment with TRF-budesonide was continued after 15 months of observational follow-up; the estimated difference in absolute change in eGFR from baseline for TRF-budesonide vs

placebo was [redacted] mL/min/1.73 m^2, equating to a [redacted] treatment benefit at the 24 month timepoint.

Table 5. Analysis of the ratio of eGFR (CKD-EPI) (mL/min/1.73 m^2) compared with placebo using robust regression in patients with a baseline UPCR ≥1.5 g/g in NefIgArd Nef-301 Part B

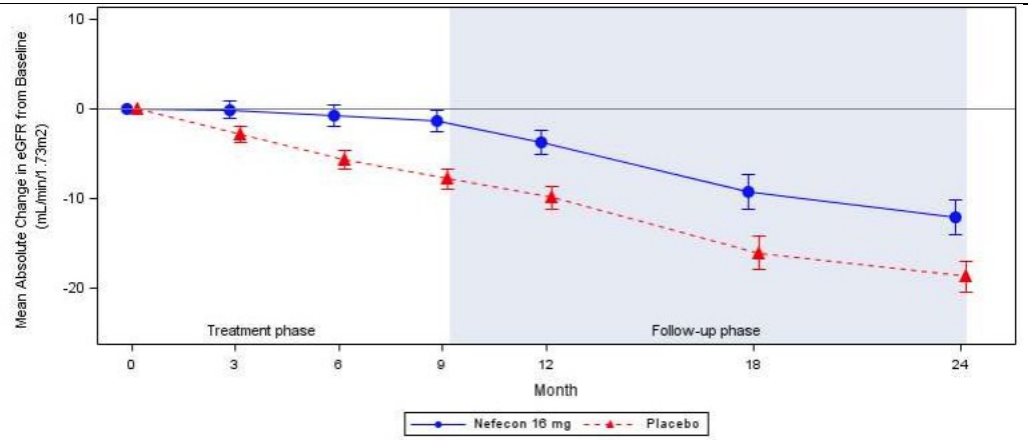
Timepoint	Comparison of TRF-budesonide 16 mg/day† vs placebo†		
	Ratio of geometric LS means (95% CI); p value	Corresponding % change‡	Difference in absolute change (mL/min/1.73 m^2)
3 months	[redacted]	[redacted]	[redacted]
6 months	[redacted]	[redacted]	[redacted]
9 months	[redacted]	[redacted]	[redacted]
12 months	[redacted]	[redacted]	[redacted]
18 months	[redacted]	[redacted]	[redacted]
24 months	[redacted]	[redacted]	[redacted]

Abbreviations: CI, confidence interval; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; eGFR, estimated glomerular filtration rate; FAS, full analysis set; LS, least squares; RAS, renin-angiotensin system; TRF, targeted-release formulation. † Treatment in addition to RAS inhibition. ‡ Calculated as (1 – ratio) of LS means * 100.

Decline in eGFR (total slope)

In Part B of NefIgArd Nef-301, treatment with TRF-budesonide 16 mg/day provided an improvement in eGFR slope of [redacted] mL/min/1.73 m^2 per year compared with placebo (95% CI: [redacted]; p=[redacted]; Figure 3). This corresponded to a least squares mean 2-year eGFR slope of [redacted] mL/min/1.73 m^2 per year in the TRF-budesonide 16 mg/day group and of [redacted] mL/min/1.73 m^2 per year in the placebo group.

Figure 3. Change in eGFR (CKD-EPI) (mL/min/1.73 m^2) from baseline in patients with a baseline UPCR ≥1.5 g/g in NefIgArd Nef-301 Part B



Abbreviations: CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; eGFR, estimate glomerular filtration rate; od, once daily; UPCR, urine protein to creatinine ratio.
Source: Lafayette et al. 2023 (18).

4. Omission of relevant evidence	Yes	An ad-hoc analysis of the efficacy of TRF-budesonide in patients with primary IgAN with baseline UPCR ≥1.5 g/g using pooled data from NefIgAn Nef-202 and NefIgArd Nef-301 has been conducted and provided as new evidence. A summary of the efficacy results at 9 and 12 months from baseline is provided in Table 6. The outcomes for the pooled analysis were in line with those of NefIgArd Nef-301, supporting the efficacy of TRF-budesonide as a treatment for primary IgAN in patients with baseline UPCR ≥1.5 g/g and were used to inform the ITC (19).	Thank you for including the new evidence. The pooled effects are heavily weighted towards Nef-301, secondary to greater imprecision in the Nef-202 data, leading to pooled results that closely resemble Nef-301. Repeating the pooling on RevMan by the

Table 6. Summary of the ratio of geometric LS means of TRF-budesonide 16 mg vs placebo for selected efficacy outcomes at 9 and 12 months from baseline in patients with a baseline UPCR ≥1.5 g/g in NefIgArd Nef-301 Part A, NefIgAN Nef-202, and a pooled analysis

Outcome		Nef-301	Nef-202	Pooled
UPCR Ratio of Geometric LS Means	9 months			

		TRF-budesonide 16 mg vs placebo (95% CI), p-value	12 months				EAG reproduced the same pooled results. The EAG agrees that the pooled results confirm that the Nef 202 results do not contradict those of Nef 301. This is therefore no longer a key issue.
		UACR Ratio of Geometric LS Means TRF-budesonide 16 mg vs placebo (95% CI), p-value	9 months				
			12 months				
		eGFR Ratio of Geometric LS Means TRF-budesonide 16 mg vs placebo (95% CI), p-value	9 months				
			12 months				
		Abbreviations: CI, confidence interval; eGFR, estimated glomerular filtration rate; TFR, targeted-release formulation; UACR, urine albumin to creatinine ratio; UPCR, urine protein to creatinine ratio.					
5. Exclusion of potentially relevant subgroup	Yes	Patients with an eGFR of <35 mL/min/1.73 m^2 were not considered for inclusion in the NefIgArd Nef-301 trial to prevent diluting any treatment effect and adversely affecting the power of the study. Patients with severe loss of kidney function (eGFR <20–30 mL/min per 1.73 m^2) may have such extensive and irreversible kidney injury that any therapeutic strategy being tested cannot reasonably be expected to alter the natural history of progressive deterioration in kidney function (therapeutic futility) (1). The presumption is that such patients should be					Thank you for this explanation. In view of the additional information received, the EAG agrees that it was reasonable for

		excluded from clinical trials since they are expected to be "non-responders" and therefore may dilute any treatment effect and adversely affect the power of the study (1). In line with the 2021 KDIGO guidelines, a clinical expert indicated that an eGFR threshold >30 mL/min per 1.73 m^2 is typically used to define eligibility for treatment in most trials of immunomodulatory drugs as there is likely to be advanced and irreversible fibrosis below this level (1, 4). In NefIgArd Nef-301, this threshold was increased to an eGFR of <35 mL/min/1.73 m^2 for inclusion in the trial to mitigate the risk of participants developing an eGFR of <30 mL/min/1.73 m^2 early in the trial and obscuring the results.	patients with an eGFR <35 ml/min/1.73 m^2 to have been excluded from the study. This does mean, however, that the trial results cannot be extended to apply to this group.
6. Possible selection bias	Yes	Clinical expert opinion indicated that the differences in the baseline characteristics between treatment arms observed by the EAG are not expected to impact the results of Part A of the NefIgArd Nef-301 trial (4). Patients in both treatment arms were considered by clinical expert opinion to have comparable eGFR and UPCR, indicating that differences in time from diagnosis, proteinuria, UPCR, and eGFR levels would not be expected to affect treatment outcomes. Of note, UPCR analysis based on 24-hour collection, the approach utilised in NefIgArd Nef-301, is considered to be the gold standard for assessing proteinuria in clinical trials as this adjusts for urine concentration and any differences in patient approaches to collection (e.g. over/under collecting). In addition, clinical expert opinion indicated that proteinuria levels >3.5 g/day are considered to be high and that differences above this level are not expected to yield a further incremental increase in rate of disease progression (4). Clinical expert opinion indicated that blood pressure was controlled in both treatment arms of NefIgArd Nef-301 at baseline, which validates that the differences in the use of ACE/ARB therapy are not expected to affect outcomes (4). In addition, clinicians consider the characteristics of patients with UPCR ≥1.5 g/g in NefIgArd Nef-301 to be generalisable to the UK population and broadly similar to those of the UK RaDaR population (2). The age at baseline in both treatment arms was considered to be in line with published data from UK RaDaR (20). Similarly, the proportion of males,	The EAG's main concern was in the differences in baseline proteinuria, based on the values for g/day [median [redacted] (IQR: [redacted]) for budesonide and [redacted] (IQR: [redacted]). However, given that the other indices of proteinuria (UPCR and UACR) were very similar between arms, the EAG considers this issue resolved.

		females, and race ratio were considered to be in line with what would be expected in the target treatment population in England (4). The median UPCR at baseline for patients in the UPCR ≥1.5 g/g subpopulation of the NefIgArd Nef-301 Part A trial (n=[redacted]) was [redacted] g/g, median UACR was [redacted] g/g, and kidney function was mildly-to-moderately impaired overall (median eGFR: [redacted] mL/min/1.73 m^2). Similar values were also observed at baseline for patients with UPCR ≥1.5 g/g at baseline in Part B of NefIgArd Nef-301, which included all randomised patients who completed the NefIgArd Nef-301 study (n=[redacted]; the median UPCR was [redacted] g/g and the median eGFR was [redacted] mL/min/1.73 m^2 at baseline (17). The values in the NefIgArd Nef-301 Part A and Part B are similar to those observed in patients with UPCR ≥1.5 g/g included in the RaDaR study, for whom the median UPCR at diagnosis was [redacted] g/g (n=[redacted]); the median UACR was [redacted] g/g (n=[redacted]); and the median eGFR at diagnosis was [redacted] mL/min/1.73 m^2 (n=[redacted]) (21).	
7. Disease progression not reported	Yes	It was reported by the clinical experts that disease progression to dialysis or transplant would not be expected within the 12-month timeframe of Part A of the NefIgArd Nef-301 trial (4). The decline in eGFR in the placebo arm was [redacted] mL/min/1.73 m^2 at the 12 month timepoint of Part A of NefIgArd Nef-301. As such, this group would be expected to progress to ESRD in 3–5 years (aligned with the median time to ESRD or death in the RaDaR subpopulation with UPCR ≥1.76 g/g (20)), and the assessment of disease progression as an endpoint would require long trials with a large patient number to obtain statistical power. Due to the challenges associated with the evaluation of disease progression in patients with IgAN, surrogate endpoints (changes in proteinuria [UPCR and urine albumin to creatinine ratio (UACR)] and eGFR) accepted by regulatory bodies (EMA, FDA, KDIGO) and clinical experts were utilised to evaluate the impact of TRF-budesonide on disease progression in the pivotal Phase 3 trial (NefIgArd Nef-301) (1, 2, 22, 23). Reductions in proteinuria (assessed by measuring proteinuria over 24 hours, UPCR, and/or UACR) are accepted as a surrogate endpoint for improved outcomes in IgAN by KDIGO, the EMA, and clinical experts in England (1, 2, 22, 23). Associations between reduced proteinuria and a lower risk of decline in kidney function, progression to ESRD, and	Based on the additional information received, the EAG understands why 'disease progression' was not included in the trial, given the statistical power considerations. This issue is therefore regarded as resolved.

		mortality in patients with IgAN and CKD have been consistently demonstrated (22), and are discussed in further detail in Section B2.3.2 of the company submission. Similarly, reductions in eGFR from baseline over a 2- to 3-year period are considered by regulatory authorities and clinical experts in England to be an acceptable surrogate outcome measure for kidney failure in clinical trials (1, 2, 23, 24), also discussed in further detail in Section B2.3.2 of the company submission.	
8. Applicability of evidence	Yes	Clinical experts reported that the baseline characteristics for the trial population in NefIgArd Nef-301 were representative of patients with primary IgAN in the UK RaDaR database and those who would be treated with TRF-budesonide in clinical practice. Therefore, the NefIgArd Nef-301 trial results were considered to be applicable to the UK target population. The age at baseline in both treatment arms was considered to be in line with published data from UK RaDaR (20). Similarly, the proportion of males, females, and race ratio were considered to be in line with what would be expected in the target treatment population in England (20).The median UPCR at baseline for patients in the UPCR ≥1.5 g/g subpopulation of the NefIgArd Nef-301 Part A trial was [redacted] g/g, median UACR was [redacted] g/g, and kidney function was mildly-to-moderately impaired overall (median eGFR: [redacted] mL/min/1.73 m^2). Similar values were also observed at baseline for patients with UPCR ≥1.5 g/g at baseline in Part B of NefIgArd Nef-301, which included all randomised patients who completed the NefIgArd Nef-301 study (n=[redacted]; the median UPCR was [redacted] g/g and the median eGFR was [redacted] mL/min/1.73 m^2 at baseline (17). The values in the NefIgArd Nef-301 Part A and Part B are similar to those observed in patients with UPCR ≥1.5 g/g included in the RaDaR study, for whom the median UPCR at diagnosis was [redacted] g/g; the median UACR was [redacted] g/g; and the median eGFR at diagnosis was [redacted] mL/min/1.73 m^2 (21).	Thank you for providing data from the UK RaDaR database, which do confirm similarity between the trial and UK target populations for median UPCR and eGFR. However, there is a 17.6% difference in median UACR. In addition, more information is required relating to the UK RaDaR data on age, sex and ethnicity, in order to confirm the claims that the trial data and UK RaDaR were similar in these respects. This

			remains a key issue.
9. Insufficient evidence regarding retreatment of patients	Yes	The company maintains the position that retreatment should be included in the model base case. This position is in line with NICE routine practice to assess treatments with an ongoing treatment paradigm in such a way as to reflect the ongoing nature of these treatments within the assessment. Therefore, given the TRF-budesonide license permits retreatment (at the discretion of the treating physician), it is anticipated this should form part of the assessment. Additionally, to address the key issues outlined by the EAG, two clinical experts were consulted with regards to their expert opinion on the matter. The two experts reported that patients with primary IgAN would be expected to receive approximately two rounds of treatment with TRF-budesonide for 9 months each, provided an acceptable tolerability profile is maintained. Patients would not be expected to develop resistance to TRF-budesonide or to experience a waning of treatment effect if receiving multiple rounds of therapy (4). Overall, the two clinical experts predicted that 100% and 50% of patients who completed their initial treatment course of TRF-budesonide and were still classified as CKD 1–3b would be expected to be retreated in their lifetime (4). In light of the feedback received, the company's base case has been updated to include a single additional round of treatment. Of those that are eligible for retreatment, the model assumes 75% will undergo retreatment (mid-point of the two clinical opinions). Although not specified by the clinical experts, the assumed treatment effect from subsequent treatments has also been updated to 90% of the initial treatment effect, based on the limited evidence to support an assumption that 100% of efficacy is maintained with each treatment cycle.	Thank you for providing more information through expert opinion. The EAG addendum contains a more elaborate response, main point is that the EAG is happy to accept the suggested estimates for the base case. Since these estimates are quite uncertain and have a relatively large impact on the ICER, we are inclined to keep it as a second-tier key issue.
10. Data source for estimating the transition from	Yes	The EAG expressed concerns about the company's use of survival probability for patients with IgAN and UPCR ≥1.5 g/g from the UK RaDaR database (21). In the company submission, survival probability from diagnosis of CKD 4 to ESRD or death was used to inform the risk of CKD 5 from CKD 4. During the clarification phase, additional survival data	The EAG was surprised to read that it was known to the company

CKD 4 to CKD 5		from the UK RaDaR database which assessed the time from CKD 4 diagnosis to ESRD in patients with IgAN and UPCR ≥1.5 g/g was included in a scenario analysis. However, the EAG identified an inconsistency in the number of patients at risk at baseline between the two sets of survival probability data. The number of patients at risk of ESRD or mortality was 63 at t=0 whereas the number at risk of ESRD was 26. After the clarification phase, it was discovered by the company that the survival probability data from diagnosis of CKD 4 to ESRD presented at the clarification stage was specific to a subgroup of patients that were receiving ACEi and/or ARBs at baseline, rather than all patients with IgAN and UPCR ≥1.5 g/g as the company had stated in the clarification phase. To correct this error, the company will submit new data from UK RaDaR which presents the survival probability from diagnosis of CKD 4 to ESRD for all patients with IgAN and UPCR ≥1.5 g/g. The same methods of digitalisation and extrapolation, as detailed in the clarification letter will be used to include this data in the model. However, as no patients in this RaDaR cohort died over the observed time period its inclusion is not anticipated to significantly impact the company's base case results, with any changes compared to the CKD4 to ESRD or mortality analysis likely caused by the human interpretation required when digitising the curves. The company maintains the opinion that the UK RaDaR data for all patients is the most appropriate data source to inform the risk of CKD 4 to CKD 5, due to: • No deaths occurring in the RaDaR analysis, thereby alleviating the EAG concerns that this analysis may lead to double counting of mortality within the model • For some patients 'maximally-tolerated' RAS inhibitor therapy would be no use of ACEi and/or ARBs as they may not be able to tolerate RAS inhibitors. Therefore, the RaDaR data using the sub-group of patients receiving ACEi and/or ARBs is more restrictive than the product label for TRF-budesonide 1. Additionally, ACEi and/or ARBs usage data within the RaDaR registry are incomplete, which resulted in a relatively small sample on which to perform analysis • The additional assumptions required to adjust the Leicester General Hospital data from all patients transitioning to ESRD, not just CKD 4 patients, introduces a greater	that no patients died from CKD4 in the UK RaDaR database, having sought this information from the company during the clarification phase. A detailed response is provided in the EAG addendum, but in summary the EAG is happy to accept the company's choice as the appropriate base case.

		level of uncertainty in the model based on the additional source required to estimate: 1. Hastings et al. (25) analysis looking at time to death was used, due to lack of information pertaining to time to ESRD • The population from the RaDaR registry is considered more reflective of the England population as data are received from multiple sites. Therefore, the data from RaDaR is also considered more reflective of the England population compared to the Leicester General Hospital data taken from a single site	
Other issues identified by NICE technical team (not included in the EAR): The technical team note that the probabilistic and deterministic analyses give substantially different cost effectiveness estimates. Please provide an explanation for these differences.	Yes	Upon further investigation into this issue, it has been identified that the standard errors associated with pulmonary embolism and renal impairment adverse events were set to zero. As a result, the values for these inputs used in the PSA were varied significantly more than expected. As these inputs only impact the TRF-budesonide arm of the model, due to these AEs only being experienced by these patients, the results from the PSA overestimated the impact these AEs have on the TRF-budesonide arm quality-adjusted life years. Upon correcting these two standard errors in the latest version of the model the outcomes from the deterministic analysis and the PSA are more aligned with expectations.	

Additional issues

No additional issues have been identified by the company.

Summary of changes to the company's cost-effectiveness estimate(s)

Company only: If you have made changes to the base-case cost-effectiveness estimate(s) in response to technical engagement, please complete the table below to summarise these changes. Please also provide sensitivity analyses around the revised base case. If there are sensitivity analyses around the original base case which remain relevant, please re-run these around the revised base case.

Table 7. Changes to the company's cost-effectiveness estimate

Key issue(s) in the EAR that the change relates to	Company's base case before technical engagement	Change(s) made in response to technical engagement	Impact on the company's base-case incremental cost-effectiveness ratio (ICER)
2. Corticosteroids, MMF and SGLT2i may be relevant comparators for different subgroups of patients	Prior to the technical engagement, the company base case included SoC as the only comparator in the model. SoC was assumed to represent optimised supportive care which the KDIGO 2021 guidelines describe as: blood pressure management; maximally tolerated dose of ACEi/ARB; lifestyle modification; and addressing cardiovascular risk (1).	In response to key issue 2, CS and immunosuppressants have been included as an additional comparator in the model. To inform the 0–12-month transition probabilities in the CS arm, outcomes from the ITC were used to calculate a factor value that should be applied to the SoC transition probabilities. The ITC compared the change in eGFR at 12 months post baseline outcomes for patients receiving	Including CS and immunosuppressants as a comparator increased the ICER from £21,872 cost/QALY to £39,137 cost/QALY. This is an increase of £17,265. Including dapagliflozin as a comparator in the model decreased the base case ICER from £21,872 cost/QALY to £16,885 cost/QALY. This is a decrease of £4,987.

	SGLT2is were also assumed to be a component of SoC, and would therefore be anticipated to be administered in combination with TRF-budesonide. Any potential benefits that may be observed from the addition of dapagliflozin to SoC, are anticipated to be additive to the TRF-budesonide treatment effect, especially since there is no crossover between their mechanisms of action (as indicated by clinical expert opinion (2)). As such, only the cost of SGLT2is were included in the model. CS and MMF were not considered relevant comparators.	CS and immunosenescent in the STOP-IgAN trial to patients on SoC. The factor was calculated by observing the proportion of patients in each CKD health state at baseline and at 12-months in the SoC arm. The midpoint of the eGFR range associated with each stage were multiplied by the proportion of patients in each stage to calculate a weighted average eGFR value at baseline and at 12-months. The weighted average eGFR value at baseline was subtracted from the average eGFR value at 12-months to calculate the change in eGFR in SoC. A goal-seek analysis was then run to see what factor needs to be applied to the SoC transition probabilities to change the 12-month change in eGFR by [redacted], based on the outcomes from the ITC. The goal-seek analysis identified a factor of [redacted] The 1-year change in eGFR compared to SoC was also used to derive a hazard ratio, using the equation from Inker et al. 2019 (27), which was applied to the	

		SoC risk of CKD 5. A hazard ratio of [redacted] was produced. In alignment with the dosing regimen of STOP-IgAN, patients receive CS and immunosuppressants for up to 36-months. A monthly cost of £5.64 was applied for 36-months to patients on CS and immunosuppressants. Since CS and immunosuppressants are given in conjunction with SoC, the monthly SoC was applied to all patients in the CS and immunosuppressants arm. Rauen et al. 2015 (12) identified that the CS and immunosuppressants treatment effect does not extend beyond 1-year. Therefore, the model assumes CS and immunosuppressants have a treatment effect of 1-year. After 1 year, SoC transition probabilities are applied to the CS and immunosuppressant arm. The AE rates were sourced from the STOP-IgAN trial.	

3. Short-term follow-up	The company base case utilised the 9-month eGFR data from NefIgArd Nef-301 Part A to inform the CKD 1-3b transition probabilities in the TRF-budesonide and SoC arms. The base case assumed a treatment effect duration of 1-year for TRF-budesonide. Beyond 1-year, the SoC transition probabilities were applied to the SoC arm.	During technical engagement, 24-month eGFR data from Part B of NefIgArd Nef-301 for the UPCR ≥1.5 g/g trial subpopulation became available. This was used to inform the CKD 1-3b transition probabilities in the TRF-budesonide and SoC arms. The model assumed TRF-budesonide had a treatment effect duration of 2 years. However, the data from Part B of NefIgArd Nef-301 was not able to inform the transition from CKD 4 to CKD 5. Therefore, as per the submitted company base case, TRF-budesonide was assumed to have a 1-year treatment effect on the risk of CKD 5 from CKD 4 based on the 12-month change in eGFR. It should also be noted that Rauen et al. 2015 (12) identified that the CS and immunosuppressants treatment effect does not extend beyond 1-year. Therefore, it is anticipated that the benefits of TRF-budesonide seen in Part B of NefIgArd Nef-301 would also indicate an improvement in the ICER when compared to CS, although the extent of this impact is unknown due to limitations with the current model structure, and current time constraints.	The incorporation of data from Part B of NefIgArd Nef-301 decreased the ICER from £21,872 cost/QALY to £14,778 cost/QALY. This is a decrease of £7,094.

9. Insufficient evidence regarding retreatment of patients	The company base case assumed two rounds of treatment with TRF-budesonide (1 round of retreatment). It was assumed all eligible patients would receive retreatment. Eligible patients included those who had completed the full initial treatment and were still in CKD1-CKD3b health states at the time of retreatment. It was assumed patients receiving TRF-budesonide would not experience treatment effect waning in subsequent treatment cycles (100% treatment effect in subsequent treatments).	Two rounds of treatment with TRF-budesonide were included. However, it was assumed that only 75% of eligible patients would receive retreatment. Eligible patients include those that had completed the full initial treatment course and were still in CKD1-CKD3b health states at the time of retreatment. It was also assumed TRF-budesonide would have a conservative treatment effect of 90%, based on feedback from clinical experts, in subsequent rounds of treatment.	These changes resulted in an increase in the ICER from £21,872 cost/QALY to £26,371 cost/QALY. This is an increase of £4,499.
10. Data source for estimating the transition from CKD 4 to CKD 5	In the company base case, the risk of CKD 5 was informed by real world evidence from patients with IgAN and UPCR ≥1.5 g/g collected in the UK RaDaR database (21). A Kaplan-Meier (KM) curve which estimates the probability of progressing to ESRD or mortality over time was digitalised using Engauge Digitizer 12.1 software (26) to generate pseudo patient-level data.	A KM curve obtained from UK RaDaR was digitalised using Engauge Digitizer 12.1 software (26) to generate pseudo patient-level data which informed the risk of CKD 5. The KM curve estimated the time from CKD 4 diagnosis to ESRD in patients with IgAN and UPCR ≥1.5 g/g. Based on AIC and BIC ranking, a gamma model was chosen as the best fitting parametric distribution.	These changes resulted in the ICER decreasing from £21,872 cost/QALY to £21,636 cost/QALY. This is a decrease of £236.

Other issues identified by NICE technical team (not included in the EAR): The technical team note that the probabilistic and deterministic analyses give substantially different cost effectiveness estimates. Please provide an explanation for these differences.	In the company base case the standard errors associated with pulmonary embolism and renal impairment adverse events were set to zero.	The model was corrected to ensure standard errors associated with pulmonary embolism and renal impairment disutility were not set to 0, instead assuming 10% standard error.	These changes do not change the model's deterministic results (£21,872 cost/QALY). However, the changes impact the probabilistic outcome and make the ICER £40,056.
Company's base case following technical engagement (or revised base case)	Incremental QALYs: [redacted]	Incremental costs: [redacted]	The company's revised base-case ICER is £26,575 cost/QALY. The following changes have been made to the company base case: • Two rounds of treatment with TRF-budesonide are considered. However, only 75% of eligible patients will be considered. This includes those who were still on treatment at month 8 and in CKD1 to CKD3b at time of retreatment. Furthermore, TRF-budesonide will be assumed to have a treatment effect of 90% in subsequent treatment cycles. • The risk of CKD 5 is informed by a digitized KM curve which showed the time from CKD 4

			diagnosis to ESRD in patients with IgAN and UPCR ≥1.5 g/g. • The model has been corrected to ensure standard errors associated with pulmonary embolism and renal impairment disutility were not set to 0, instead assuming 10% standard error. • The utility values associated with pulmonary embolism and renal impairment have been updated to -0.018 and -0.0603. The duration of disutility is assumed to be 1 month. This aligns with EAG preferred assumptions • The SoC costs have been updated to £67.38 in line with EAG adjustments to account for concomitant medications costs originally missing from the company submission

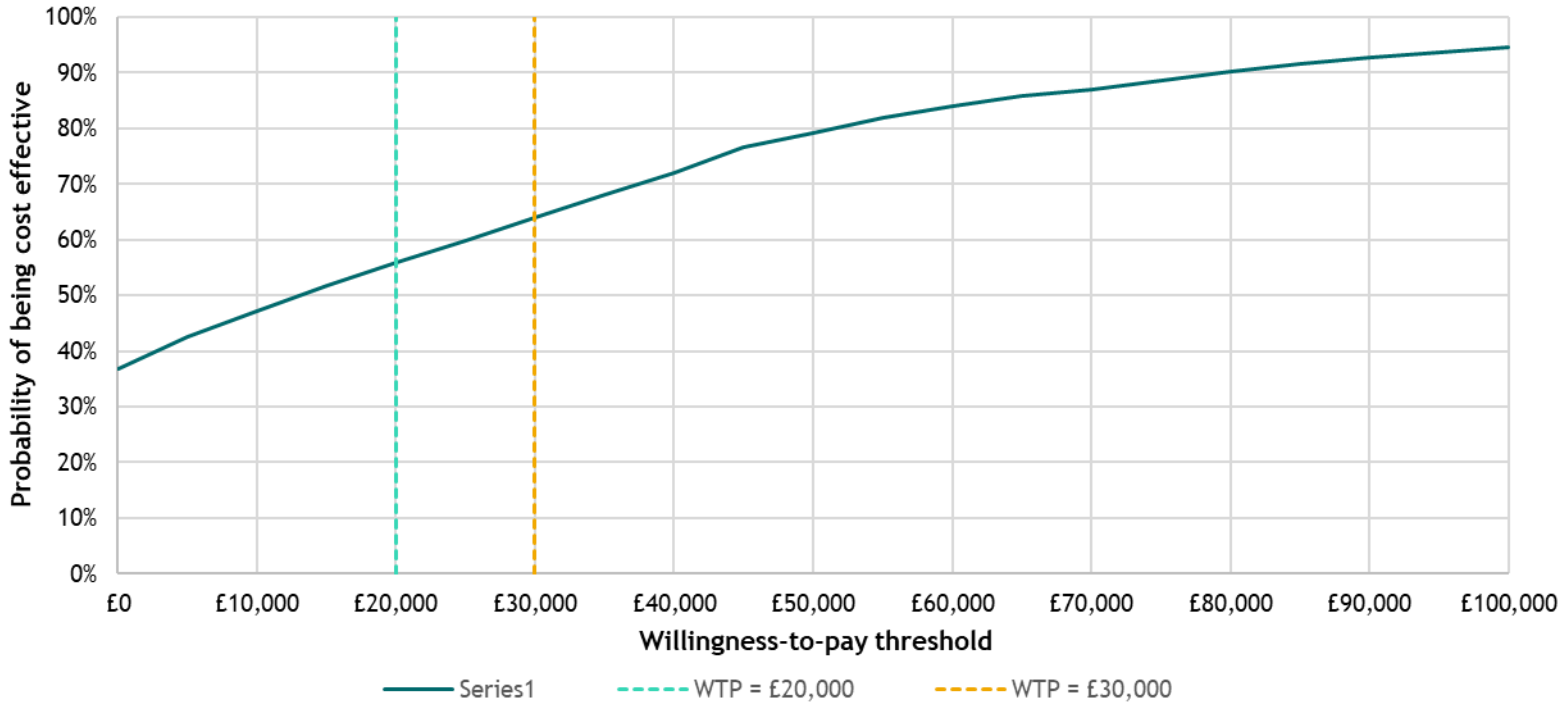
Sensitivity analyses around revised base case

Table 8 presents the results of the PSA. The cost-effectiveness acceptability curves are presented in Figure 4.

Table 8. 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]	Dominant	Dominant

Figure 4. Cost-effectiveness acceptability curve



Abbreviations: WTP, willingness-to-pay

As reported in the company submission, the transition between CKD 1 to CKD 2 in the TRF-budesonide arm is informed by data from one patient in Part A of the NefIgArd Nef-301 study. Therefore, when this transition is varied in the PSA, it often takes extreme values of either 0% or 100% which has a significant impact on the ICER produced in the PSA. Therefore, a PSA that excluded this Technical engagement response form

transition was also run. The results of this PSA are presented in Table 9 and the cost-effectiveness acceptability cure is presented in Figure 5.

Table 9. 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]	£40,056	£40,056

Figure 5. Cost-effectiveness acceptability curve

Abbreviations: WTP, willingness-to-pay

Table 10 presents the results of the deterministic sensitivity analysis. Figure 6 presents the tornado diagram.

Table 10. DSA results

Variable	Low NMB estimate	High NMB estimate	Change in NMB
Time point from where no treatment effect is assumed (TRF-budesonide)	[redacted]	[redacted]	£6,396
Cooper et al. 2020 - Utility: CKD 2	[redacted]	[redacted]	£2,258
Cooper et al. 2020 - Utility: CKD 3b	[redacted]	[redacted]	£1,540
Utility: Haemodialysis	[redacted]	[redacted]	£1,407
Cooper et al. 2020 - Utility: CKD 3a	[redacted]	[redacted]	£1,374
Age (years)	[redacted]	[redacted]	£1,262
Utility: Post-transplant	[redacted]	[redacted]	£1,139
LD06A unit cost	[redacted]	[redacted]	£985
Average weight	[redacted]	[redacted]	£792
LD05A unit cost	[redacted]	[redacted]	£587

Abbreviations: CKD, chronic kidney disease; DSA, deterministic sensitivity analysis; NMB, net monetary benefit.

Figure 6. Tornado diagram

Abbreviations: CKD, chronic kidney disease; HR, hazard ratio: SoC, standard of care; NMB, net monetary benefit.

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in collaboration with:

Erasmus School of Health Policy & Management

Maastricht University

Targeted-release budesonide for treating primary IgA nephropathy [ID1434]

Addendum Technical Engagement

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[redacted]

Introduction

This addendum contains the EAGs critique of the company's new evidence provided in the company's response to technical engagement (TE). The company's updated cost effectiveness results and scenarios are provided in Section 2, followed by various scenario analyses and subgroup analyses generated by the EAG using the company's updated model in Section 3. Note that the EAG was satisfied with the changes made to the company base case, and thus no EAG preferred base case results are presented.

1. Suggested changes for model input including key issues 3, 9, 10

Key Issue 3 – Short term follow up

In the EAG report, it was highlighted by the EAG that follow-up in the data used to show clinical efficacy was restricted to 12 months, making it difficult to form realistic evaluations of long-term benefit and cost.

In the original company submission (CS) data was presented from NefIgArd Nef-301 Part A, which covered 9 months of treatment with TRF-budesonide or placebo and 3 months of untreated follow-up, as the most mature data available at that time. The economic model consequently did not include extrapolations beyond one year. The pre-planned Part A analysis was scheduled to occur once the first 201 patients randomised had had the opportunity to complete their 9-month visit and included [redacted] participants (TRF-budesonide 16 mg n=[redacted]; placebo n=[redacted]) with a baseline UPCR ≥1.5 g/g.

At the time of technical engagement data from Part B of NefIgArd Nef-301 have become available, providing 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 follow-up off drug. The Part B analysis included all patients randomised who completed the NefIgArd Nef-301 study (TRF-budesonide 16 mg n=[redacted]; placebo n=[redacted] with a baseline UPCR ≥1.5 g/g).

In their TE response, the company presents the results of the analysis of urine protein to creatinine ratio and of the estimated glomerular filtration rate (eGFR), showing similar results at 12 months, and a sustained clinical effect at 24 months.

Using this newly available data, the company has re-estimated the CKD 1-3b transition probabilities for the health economic model and in addition, now assumes that the TRF-budesonide transition probabilities can be applied for 2 years, rather than 1 year. For the transition from CKD 4 to CKD 5, the treatment effect is assumed to apply only for 1 year, in line with the original CS.

EAG comment:

The EAG is pleased that the data from Part B have become available during the TE period so that the ICER is based on a larger sample size with a longer follow-up, thus decreasing the uncertainty around the effectiveness input parameters. It is not clear to the EAG why this dataset is not used for the company base case.

The EAG notes that at 3 points in the model input, no new estimates were derived based on the newly available data. This concerns a) incidence of adverse events, b) time to treatment discontinuation, and c) the hazard ratio that is used to estimate the transition probability from CKD 4 to CKD 5 in the TRF-budesonide arm.

Ideally, for all these 3 issues new estimates should be derived. However, it seems unlikely that updated estimates for adverse events will lead to an important change in the cost-effectiveness, as the incidences observed in Part A of the clinical study were quite low. We also expect little impact on the time to treatment discontinuation of the new evidence, as in the original CS it was observed that around 90% of patients receive the full course of 9 months, and it seems unlikely that this will be substantially different in the new data set.

For the last estimate, the one-year eGFR difference in absolute change that was used to derive the HR in the original CS was presented by the company for Part B (Table 6 TE response form), and amounted to 6.20 ml/min/1.73 m2. Using the equation as set out in the company submission section B.3.3.2.2., an updated HR of [redacted] is found (was [redacted]).

In Table 7, the revised company base case is compared to 1) a scenario where the transition probabilities from CKD 1-3b are based on the data from Part B and a hazard ratio of [redacted] to estimate the transition probability from CKD 4 to CKD 5 in the TRF-budesonide arm and 2) a similar scenario but now with an HR of [redacted].

Key issue 9: Insufficient evidence regarding retreatment of patients

In the EAG report the EAG was sceptical about the base case assumption of the company regarding retreatment of patients with TRF-budesonide. The initial treatment is 9 months and is not curative, so the company assumed that at some point in time all patients still eligible for treatment with TRF-budesonide would receive a new treatment course, and that this retreatment would have the same efficacy as the initial course. Whilst the EAG could indeed imagine some of the patients to receive retreatment. With at least some of the initial benefit, they considered that the estimates used by the company were not based on any evidence, and that in the absence of any evidence it would be better to set the retreatment percentage to 0, ensuring a conservative estimate of the ICER.

To address this issue, the company has consulted with two clinical experts, the results of which were presented in their TE response. The two experts reported that patients with primary IgAN would be expected to receive approximately two rounds of treatment with TRF-budesonide for 9 months each, provided an acceptable tolerability profile is maintained. Patients would not be expected to develop resistance to TRF-budesonide or to experience a waning of treatment effect if receiving multiple rounds of therapy.

The two clinical experts predicted that 100% and 50% of patients who completed their initial treatment course of TRF-budesonide and were still classified as CKD 1–3b would be expected to be retreated in their lifetime. Thus, in the model it has now been assumed that those eligible for retreatment, 75% will undergo retreatment (mid-point of the two clinical opinions). Although not specified by the clinical experts, the company also now assumes that during retreatment only 90% of the initial treatment effect will be achieved, given the limited evidence to support the original assumption that 100% of efficacy is maintained with each treatment cycle.

EAG comment:

Though the revised estimates are quite uncertain, the EAG considers them reasonable in light of the expert opinion. The EAG has explored a few extra scenarios, for example to see what the impact would be of changing the % of eligible patients receiving retreatment to the2 values suggested by the clinical experts, i.e. 50% and 100% (see Table 7).

Key issue 10: Data source for estimating the transition probability from CKD 4 to CKD 5.

In the EAG report, the EAG expressed concern regarding the use of a UK RaDaR data analysis, using all patients with IgAN and UPCR ≥1.5 g/g and with ESRD and death cases used to define the event outcome to estimate the transition probability from CKD 4 to CKD 5. The EAG expressed concern that this approach would likely overestimate the risk of ESRD as the company also incorporated the risk of death separately.

In addition, the EAG found that the alternative analysis that the company presented where only ESRD was used for the definition of an event was not correct. As a result, the EAG considered that data from patients at Leicester General Hospital (LGH) 1992 to 2020 would be more appropriate than the UK RaDaR data.

Patients from the LGH registry were matched to NefIgArd Nef-301 patients, using baseline eGFR between 35 and 90 mL/min/1.73 m2 and either proteinuria ≥1 g per day or UPCR ≥0.8 g/g. Patients were further selected for UPCR ≥1.5 g/g. The matching was done on a 5:1 ratio using a maximum of five LGH registry patients for each patient in the NefIgArd Nef-301 trial, leading to 294 matched records ready for analysis. The scenario using these data was limited by an assumption required to estimate the rate of movement from CKD 4 to CKD 5 based on the observed rate of movement from CKD 1-4 to CKD 5.

In their TE response, the company explained that they had rerun their analysis on the UK RaDaR data, presenting the survival probability from diagnosis of CKD 4 to ESRD for all patients with IgAN and UPCR ≥1.5 g/g. They also pointed out that no patients in this RaDaR cohort died over the observed time period, so the inclusion of this new analysis would not significantly impact the company's base case results, with any changes compared to the CKD4 to ESRD or mortality analysis likely caused by the human interpretation required when digitising the curves. The company further explained that this analysis should be preferred over one based on a subsample of patients receiving ACEi and/or ARBs, as a) it excludes patients who do not tolerate RAS inhibitors and b) data on ACEi and/or ARBs usage within the RaDaR registry are incomplete so the sample size would be, to some extend needlessly, reduced.

EAG comment:

During the clarification phase the EAG had asked the company "*Please explain how the two different events (ESRD or death) were distinguished"*. In their response the company explained that "*The events in Figure 17 (the KM curve) include both ESRD and death and no distinction was made between these events"*. They further stated that *"UK RaDaR data that assesses the time to ESRD from CKD in patients with IgAN and UPCR ≥1.5 g/g has since been attained" but pointed out that "However, in this analysis, patients that died were censored if they did not reach ESRD before their time of death. Due to this censoring, the number of ESRD events are inflated as they are based on a smaller sample of patients. As it seemed less clinically plausible that the risk of ESRD was greater than the risk of ESRD or mortality, UK RaDaR data that considered either ESRD or mortality as an event was used in the model base case."*

Thus, the EAG was surprised that the company was now able to confirm that in the group of patients in CKD4 with IgAN and UPCR ≥1.5 g/g, no patients died, meaning that the KM curve for the time to ESDR or death can be regarded as the KM curve for the time to ESDR.

In light of this knowledge, the EAG now agrees with the company that the use of this data is preferable above the use of the LGH data, given that the latter approach requires a strong assumption to estimate the time to event from CKD 4 to CKD 5 based on the time to event from CKD 1-4 to CKD 5.

Subgroup analyses based on ITC (key issue 2)

In the EAG report, the EAG indicated that corticosteroids, MMF and SGLT2i might be relevant comparators of TRF-budesonide in certain subgroups of patients. To address this, the company performed an indirect treatment comparison to inform the comparison TRF-budesonide + SoC versus corticosteroids + SoC and the comparison TRF-budesonide + SoC versus an SGLT2i + SoC. Using the results of this ITC, the company adjusted their model to allow for corticosteroids + SoC and SGLT2i + SoC as comparators. The results of these are presented in Table 8.

As indicated in the EAG comments in the TE response form, the EAG notes that the ITC suggests that TRF-budesonide may be [redacted] to CS and dapagliflozin, but these ITC results are not backed up by a transparent systematic review to increase confidence that all relevant studies have been included.

In addition, the EAG noticed that the outcomes of the ITC indicate a mean treatment difference for 12 months in eGFR in favour of placebo compared to dapagliflozin, where as the paper by Wheeler et al. 2021 reports: *"The least mean squares eGFR slopes from baseline to end of treatment in the dapagliflozin and placebo groups were -3.5 (SE, 0.5) and -4.7 (SE, 0.5) ml/min per 1.73 m2 per year, respectively, resulting in a between-group difference of 1.2 ml/min per 1.73 m2 per year (95% CI, -0.12 to 2.51 ml/min per 1.73 m2 per year; Figure 4a)."* Using these outcomes in the indirect comparison to TRF-budesonide + SoC would increase the ICER reported in Table 8.

In addition, some questions may be raised regarding the implementation of the ITC results into the model. The implementation required using the estimated difference in eGFR after 1 year to find a factor to adjust the transition probabilities between health states. In order to do this, it was necessary to assign each health state an average eGFR, for which the midpoint was chosen. For example, CKD 2 is defined as having an eGFR between 60 and 90, so the midpoint would be 75 (note that the company considered eGFR as an integer variable, and used a midpoint of 74.5 for the range 60 – 89). Based on this and the distribution of patients over the health states an overall average eGFR per cycle could be estimated. In their revised model, the company showed that after 1 year eGFR had declined by 0.93 ml/min per 1.73 m^2 in the TRF-budesonide + SoC arm, and by 12.52 ml/min per 1.73 m^2 in the SoC arm, yielding a difference of 11.59 ml/min per 1.73 m^2 between the treatment arms. This is substantially higher than the difference reported in the company submission, which is an improvement in slope of [redacted] mL/min/1.73 m^2 per year for TRF-budesonide compared with placebo (95% CI: [redacted]; p=[redacted]). Thus, the validity of the approach to convert the ITC results into transition probabilities may be questioned, and the results of the subgroup analyses should be regarded as exploratory only.

Another issue regarding the implementation relates to the inclusion/exclusion of certain drug costs. For example, the ITC provides estimates for the treatment effect for the comparison budesonide + SoC versus an SGLT2i + SoC. In the NefIgArd Nef-301 Part B study, [redacted] of patients used a SGLT2i, so effectively we may assume that the trial results reflect the comparison TRF-budesonide + SoC vs. SoC, both mostly not containing SGLT2i. Using the ITC results, this is now expanded to TRF-budesonide + SoC vs. SGLT2i + SoC. However, in the model, the costs of SGLT2i are included in both arms, meaning that in the TRF-budesonide + SoC arm, costs of SGLT2i are included without accounting for the potential impact of the drug. To explore the cost effectiveness of TRF-budesonide + SoC vs. SGLT2i + SoC without the costs of SGLT2i in the TRF-budesonide group, the EAG ran an extra scenario, presented in Table 8.

Of note, the current company base case analysis, essentially comparing TRF-budesonide + SGLT2i + SoC vs. SGLT2i + SoC assumes that the observed effects from the NefIgArd Nef-301 Part A study, where [redacted] of patients used a SGLT2i, can be applied.

For the comparison TRF-budesonide + SoC versus corticosteroids + SoC, the presented subgroup analysis again includes costs of corticosteroids in both arms. However, as these costs are much lower than the costs of SGLT2i, removing these costs in the TRF-budesonide arm will have very little impact on the results presented in Table 8.

2. Company's updated cost effectiveness results

The company provided updated cost effectiveness results. Of all the EAG preferred model changes as discussed in the EAG report, the company agreed with the following:

1. Inclusion of disutility for pulmonary embolism and for renal impairment
2. Including all concomitant drugs in estimation drug costs SOC

In addition, changes were made regarding key issues 9 and 10, as discussed in the previous section. Furthermore, the company implemented a new PAS discount. For key issue 3 (Short-term follow-up) a scenario analysis was done and for key issue 2 (Corticosteroids, MMF and SGLT2i may be relevant comparators for different subgroups of patients) subgroup analyses were done.

Table 1 presents the incremental impact of each model change implemented by the company in response to the technical engagement, as well as the aggregate impact on the model results. Note that the ICERs listed in Table 1 do not appear as such in the TE response, as changes were presented in a different order. E.g., where the company presents the impact of changes related to key issues, their results do not yet include the impact of the 2 minor changes suggested by the EAG.

Table 2 shows the full results for the new company base case, again derived by the EAG, as such a table with deterministic results were not presented in the TE response form.

Table 1 Changes to the company's deterministic cost-effectiveness estimate*

(Key) issue	ICER per QALY
Company base case after clarification	£21,872
Company BC + accepted EAG changes	£22,253
Adjusted BC + Key issue 9: Retreatment	£26,829
Adjusted BC + Key issue 8: Transition CKD 4 to CKD 5	£22,015
All company changes combined – old PAS	£26,580
All company changes combined – new PAS: Company base case	£4,672
* Derived by the EAG.	

Table 2 New deterministic base case, based on company model (not in TE response form)

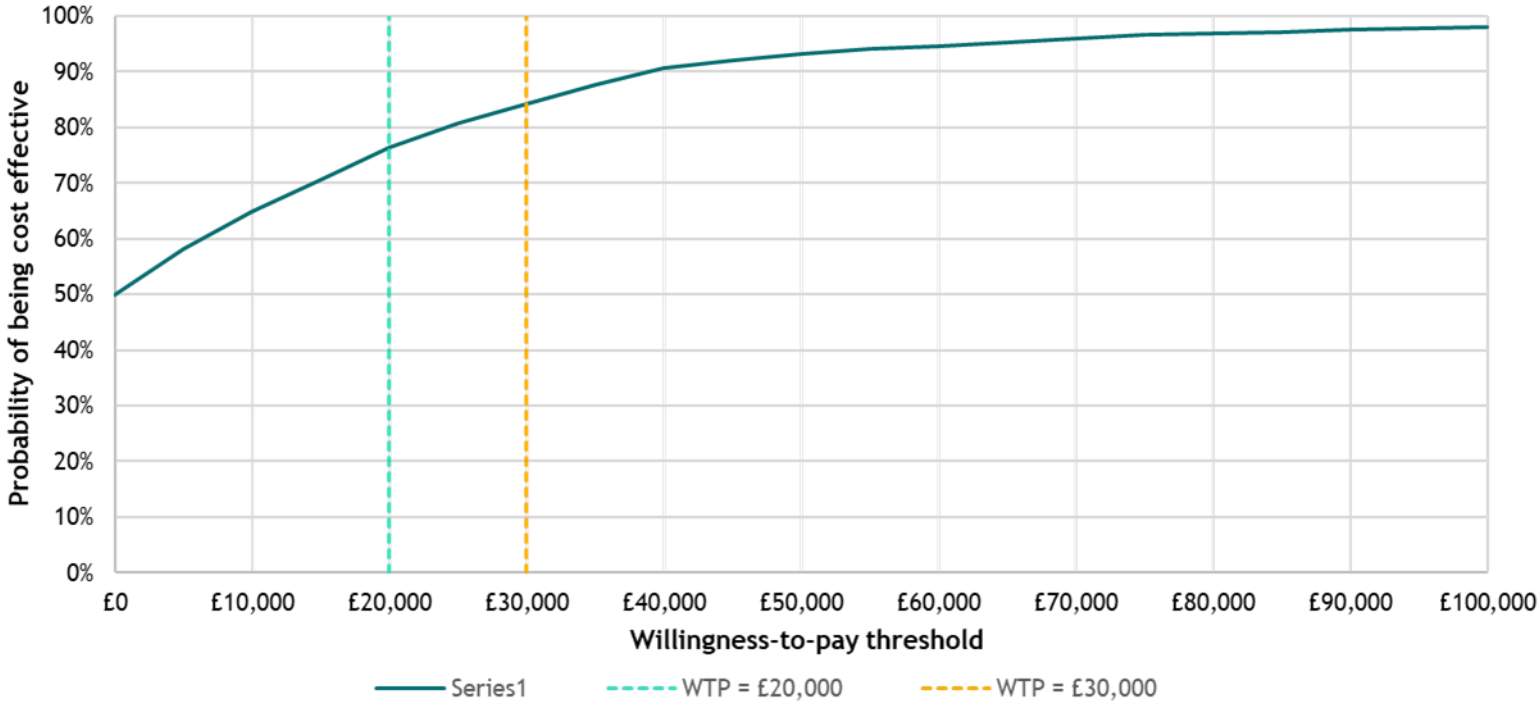
Arm	Total			Incremental			ICER
	Costs	LYs	QALYs	Costs	LYs	QALYs	
TRF-budesonide	[redacted]	16.049	[redacted]				
SoC	[redacted]	15.944	[redacted]	[redacted]	0.106	[redacted]	£4,672
ICER = incremental cost effectiveness ratio; LYG = life years gained; SoC = standard of care; QALY(s) = quality-adjusted life year(s); TRF = targeted-release formulation.							

Table 3. Base-case probabilistic incremental cost-effectiveness results, provided by company

Arm	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
TRF-budesonide	[redacted]	16.479	[redacted]	-	-	-	-
SoC	[redacted]	16.104	[redacted]	[redacted]	0.376	[redacted]	Dominant

ICER = incremental cost effectiveness ratio; LYG = life years gained; SoC = standard of care; QALY(s) = quality-adjusted life year(s); TRF = targeted-release formulation.

Figure 1. Cost-effectiveness acceptability curve



Abbreviations: WTP, willingness-to-pay

From Tables 2 and 3 it is clear that the results from the deterministic and probabilistic analyses differ substantially.

As reported in the company submission, the transition between CKD 1 to CKD 2 in the TRF-budesonide arm is informed by data from one patient in Part A of the NefIgArd Nef-301 study. Therefore, when this transition is varied in the PSA, it often takes extreme values of either 0% or 100% which has a significant impact on the ICER produced in the PSA. Therefore, a PSA that excluded this transition was also run. The results of this PSA are presented in Table 4 and the cost-effectiveness acceptability cure is presented in Figure 2. Comparing Tables 2, 3 and 4 it is clear that excluding the one patient from the analysis leads to probabilistic results that are more aligned with the deterministic results, though still quite different.

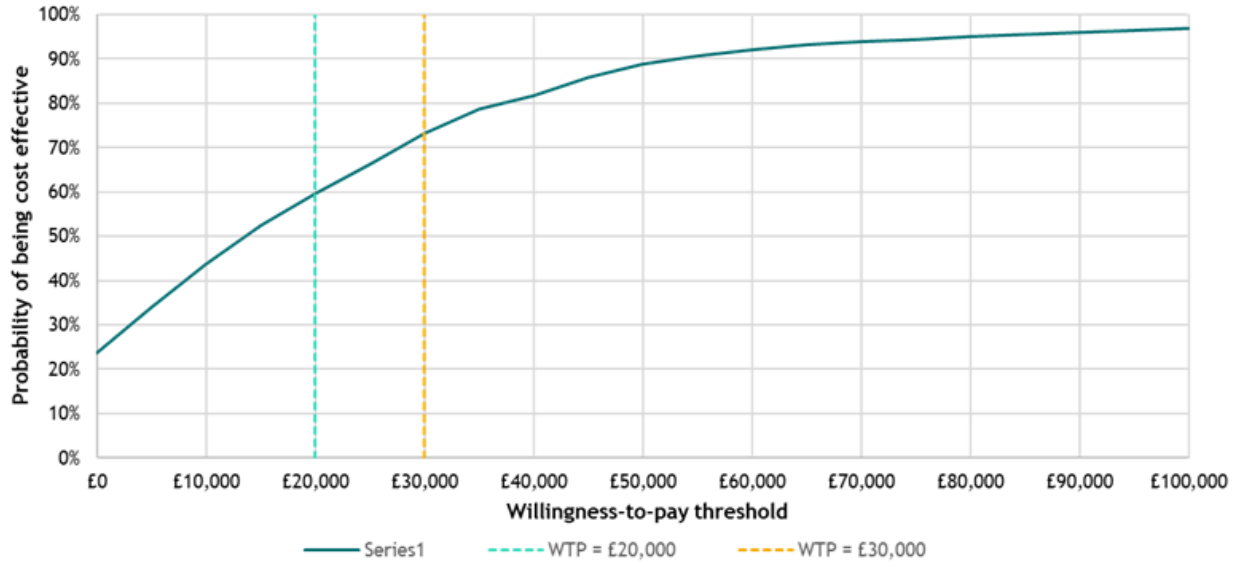
In general, such a discrepancy can either be due to the non-linearity of the model or due to issues in the set-up of the PSA. In the original EAG report, a few issues regarding the assumptions for the PSA were discussed, and the company has addressed these in the current submission. However, still a substantial difference between deterministic and probabilistic outcomes remains, for which the EAG has not yet found a good explanation.

Table 4. Base-case probabilistic incremental cost-effectiveness results, excluding transition between CKD 1 to CKD 2 TRF-budesonide arm

Arm	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
TRF-budesonide	[redacted]	15.953	[redacted]	-	-	-	-
SoC	[redacted]	15.823	[redacted]	[redacted]	0.130	[redacted]	£13,933

ICER = incremental cost effectiveness ratio; LYG = life years gained; SoC = standard of care; QALY(s) = quality-adjusted life year(s); TRF = targeted-release formulation.

Figure 2. Cost-effectiveness acceptability curve



Abbreviations: WTP, willingness-to-pay

From Figure 2 it can be concluded that, taking all parameter uncertainty into account, the probability that the ICER will be below £20,000 is 60% and below £30,000 around 72%.

Table 5 presents the results of the deterministic one-way sensitivity analyses. For all inputs, changing their value did not lead to negative net-monetary benefits.

Table 5. Results one-way deterministic sensitivity analysis (at threshold ICER £30,000)

Variable	Low NMB estimate	High NMB estimate	Change in NMB
Time point from where no treatment effect is assumed (CKD1-3b)	[redacted]	[redacted]	£5,670
Cooper et al. 2020 - Utility: CKD 2	[redacted]	[redacted]	£2,258
Cooper et al. 2020 - Utility: CKD 3b	[redacted]	[redacted]	£1,540
Utility: Haemodialysis	[redacted]	[redacted]	£1,407
Cooper et al. 2020 - Utility: CKD 3a	[redacted]	[redacted]	£1,374
Age (years)	[redacted]	[redacted]	£1,271
Utility: Post-transplant	[redacted]	[redacted]	£1,139
LD06A unit cost	[redacted]	[redacted]	£985
Time point from where no treatment effect is assumed (CKD1-3b)	[redacted]	[redacted]	£908
Average weight	[redacted]	[redacted]	£792

Abbreviations: CKD, chronic kidney disease; DSA, deterministic sensitivity analysis; NMB, net monetary benefit.

3. Scenario analyses and subgroup analyses generated by the EAG

In this section the results are presented from various scenario analyses, either earlier defined by the company in the original company submission, or defined based on the new evidence provided by the company during technical engagement.

The first set, presented in Table 6, shows that for most scenario's the ICER remains very low, or TNF-budesonide is even dominant, with the highest ICER being £17,316, when a time horizon of 10 years is assumed.

Table 6 Original set scenarios from company submission, using the updated company base case model

Scenario	Assumption	Deterministic		
		Incr. costs	Incr. QALYs	ICER
Updated company base case		[redacted]	[redacted]	£4,672
Time horizon	10 years	[redacted]	[redacted]	£17,316
	20 years	[redacted]	[redacted]	£2,840
	30 years	[redacted]	[redacted]	£4,236
	40 years	[redacted]	[redacted]	£4,653
Distribution of patients across CKD states at baseline	UK RaDaR data	[redacted]	[redacted]	Dominant
Parametric extrapolations to estimate time to CKD 5	Exponential	[redacted]	[redacted]	£8,069
	Generalised gamma	[redacted]	[redacted]	£8,755
	Gompertz	[redacted]	[redacted]	Dominant
	Log-logistic	[redacted]	[redacted]	Dominant
	Log-normal	[redacted]	[redacted]	Dominant
	Weibull	[redacted]	[redacted]	Dominant
Risk of ESRD	UK RaDaR data – ACEi and ARB patients	[redacted]	[redacted]	£9,038
	Leicester General Hospital data with HR applied	[redacted]	[redacted]	£10,375
SoC acquisition costs	£0	[redacted]	[redacted]	£2,130
Time point from where no treatment effect is assumed	1.5 year	[redacted]	[redacted]	Dominant
	2 years	[redacted]	[redacted]	Dominant

Scenario	Assumption	Deterministic		
		Incr. costs	Incr. QALYs	ICER
	2.5 years	[redacted]	[redacted]	Dominant
	5 years	[redacted]	[redacted]	Dominant
Mortality source	Greene 2019	[redacted]	[redacted]	£14,192
	Hastings 2018	[redacted]	[redacted]	£6,338
CKD stage utility source	Gorodetskaya 2005	[redacted]	[redacted]	£3,987
Age-adjusted utilities	Excluded	[redacted]	[redacted]	£4,536
Treatment stopping approach	Use the TTD curve from the CSRs	[redacted]	[redacted]	£4,726
TRF-budesonide dose reduction	Excluded	[redacted]	[redacted]	£1,757
TRF-budesonide tapering period	Included	[redacted]	[redacted]	£5,106
TRF-budesonide retreatment	No retreatment	[redacted]	[redacted]	£10,564
	3 rounds of treatment	[redacted]	[redacted]	Dominant
	4 rounds of treatment	[redacted]	[redacted]	Dominant
	5 rounds of treatment	[redacted]	[redacted]	Dominant
	6 rounds of treatment	[redacted]	[redacted]	Dominant
Societal costs	Included	[redacted]	[redacted]	£632

Based on the model submitted following the technical engagement phase, the EAG ran these scenarios

ACEi = angiotensin converting enzyme inhibitors; ARB = angiotensin receptor blockers; CKD = chronic kidney disease; CSR = clinical study report; ESRD = end-stage renal disease; HR = hazard ratio; ICER = incremental cost-effectiveness ratio; Incr. = incremental; QALY = quality-adjusted life year; RaDaR = National Registry of Rare Kidney Diseases; SoC = standard of care; TRF = Targeted-release formulation; TTD = time to treatment discontinuation; UK = United Kingdom

Table 7 shows the results of some additional scenario analyses. Some of the input parameters related to retreatment were varied. From these analyses, it is clear that the ICER is more sensitive to changes in the percentage of the initial effectiveness achieved during retreatment than to changes in the percentage patients receiving retreatment. For all scenarios explored, both regarding retreatment and regarding the longer term data, the ICER stays below £10,000.

Table 7: Results of exploratory scenario analyses by the EAG

Scenario	Assumption	Deterministic			Probabilistic (excl CKD1 to CKD2 transition)	
		Incr. costs	Incr. QALYs	ICER	ICER	Prob. ICER > £20,000/30.000
Updated company base case		[redacted]	[redacted]	£4,672	£13,933	60% / 72%
TRF-budesonide retreatment **Base case:** 1 round of retreatment at 14.75 months for [redacted] of patients (75% of eligible), at 90% initial effectiveness	80% of initial effectiveness	[redacted]	[redacted]	£7,863	£18,437	55% / 67%
	100% of initial effectiveness	[redacted]	[redacted]	£1,748	£11,421	67% / 80%
	50% of eligible patients	[redacted]	[redacted]	£5,521	£13,936	61% / 75%
	100% of eligible patients	[redacted]	[redacted]	£4,456	£15,337	60% / 74%
	Retreatment at 24 months	[redacted]	[redacted]	Dominant	£14,794	64% / 77%
	80% of initial effectiveness & 50% of eligible patients	[redacted]	[redacted]	£8,026	£19,003	54% / 70%
	100% of initial effectiveness & 100% of eligible patients	[redacted]	[redacted]	£1,147	£13,236	66% / 78%
Data source treatment effectiveness **Base case:** NefIgArd Nef-301 Part A for transitions from CKD 1 – 3b, HR TRF-budesonide vs SoC for transition CKD4 to CKD 5 is [redacted]	NefIgArd Nef-301 **Part B** for transitions from CKD 1 – 3b HR TRF-budesonide vs SoC for transition CKD4 to CKD 5 [redacted]	[redacted]	[redacted]	Dominant	£11,159	70% / 86%
	NefIgArd Nef-301 **Part B** for transitions from CKD 1 – 3b HR TRF-budesonide vs SoC for transition CKD4 to CKD 5 [redacted]	[redacted]	[redacted]	Dominant		88% / 95%

Based on the model submitted by the company during the technical engagement phase.

CKD = chronic kidney disease; EAG = Evidence Assessment Group; HR = hazard ratio; ICER = incremental cost-effectiveness ratio; Incr. = incremental; QALY = quality-adjusted life year; SoC = standard of care; TRF = targeted-release formulation; Prob. = probability

Finally, Table 8 shows the results of the subgroup analyses for TRF-budesonide + SoC vs corticosteroids + SoC and TRF-budesonide + SoC vs SGLT2i + SoC.

Table 8: Results of subgroup analyses

Subgroup	Assumption	Incr. costs	Incr. QALYs	ICER
Updated company base case		[redacted]	[redacted]	£4,672
TRF-budesonide + SoC versus corticosteroids + SoC		[redacted]	[redacted]	£25,000
TRF-budesonide + SoC versus an SGLT2i + SoC	Costs SGLT2i both arms (company version)	[redacted]	[redacted]	£11
	TNF-budesonide arm no costs SGLT2i	[redacted]	[redacted]	Dominant

Based on the model submitted by the company during the technical engagement phase.
ICER = incremental cost-effectiveness ratio; Incr. = incremental; QALY = quality adjusted life year; SGLT2i = sodium-glucose cotransporter-2 inhibitors; SoC = standard of care; TRF = targeted-release formulation;

in collaboration with:

Erasmus School of Health Policy & Management

Maastricht University

Targeted-release budesonide for treating primary IgA nephropathy [ID1434]

Second Addendum Technical Engagement

Produced by Kleijnen Systematic Reviews (KSR) Ltd. in collaboration with Erasmus University Rotterdam (EUR) and Maastricht University

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[redacted]

Introduction

This addendum should be read together with the addendum containing the EAGs critique of the company's new evidence provided in the company's response to technical engagement (TE).

In that earlier addendum (dated 8 September 2023), deterministic and probabilistic results were presented for the new company base case. Table 1 replicates the deterministic results.

Table 1 New deterministic base case, based on company model (not in TE response form)

Arm	Total			Incremental			ICER
	Costs	LYs	QALYs	Costs	LYs	QALYs	
TRF-budesonide	[redacted]	16.049	[redacted]				
SoC	[redacted]	15.944	[redacted]	[redacted]	0.106	[redacted]	£4,672

ICER = incremental cost effectiveness ratio; LYG = life years gained; SoC = standard of care; QALY(s) = quality-adjusted life year(s); TRF = targeted-release formulation.

It was then remarked that the results from the deterministic and probabilistic analyses differed substantially. In this addendum some of the causes for this discrepancy are discussed and new PSA results are presented.

Issues relating to the PSA

As reported in the company submission, the transition between CKD 1 to CKD 2 in the TRF-budesonide arm is informed by data from one patient in Part A of the NefIgArd Nef-301 study. Therefore, when this transition is varied in the PSA, it often takes extreme values of either 0% or 100% which has a significant impact on the ICER produced in the PSA. Therefore, the model allows for the option to excluded this transition from the PSA. When this was done for the new company base case, it was clear that excluding the one patient from the analysis lead to probabilistic results that are more aligned with the deterministic results, though still quite different.

In general, such a discrepancy can either be due to the non-linearity of the model or due to issues in the set-up of the PSA. In the original EAG report, a few issues regarding the assumptions for the PSA were discussed, and the company has addressed these in the current submission. However, still a substantial difference between deterministic and probabilistic outcomes remained.

After further exploration, the EAG found an error in the set-up of the PSA. For the transition from CKD 4 to CKD 5, the SoC arm was informed by data from the UK RaDaR database. In the TRF-budesonide arm, this transition probability was estimated by applying a HR of [redacted] to the respective risk in the SoC arm. This HR ratio was estimated using an intercept and a slope coefficient from a published meta-analysis, combined with the observed treatment effect on the 1-year eGFR total slope in the sub-population of patients from the NefIgArd Nef-301 trial with baseline UPCR ≥1.5 g/g. In the PSA, the slope, intercept, and observed treatment effect are all varied using a standard error of 10% of the mean value. However, as both the slope and the intercept have a negative mean value, this approach results in a negative standard error which is of course mathematically impossible. As a result, when drawing a random value from a normal distribution with the specified mean and standard error Excel produces an empty cell. In the subsequent calculation of the HR, this is interpreted by Excel as a zero, leading to an HR of 1 in each iteration of the PSA.

The simple solution for this is to take the absolute value of the calculated standard error (see Table 2 for the changes required in the model).

Table 2 Changes required in model to correct error in HR calculation

Sheet	Cell	Old code	New code
Company intended standard errors			
Parameters	O42	=AD42 * p_assumed_se	=ABS(AD42 * p_assumed_se)
	O43	=AD43 * p_assumed_se	=ABS(AD43 * p_assumed_se)
	O44	=AD44 * p_assumed_se	=ABS(AD44 * p_assumed_se)
EAG preferred standard errors			
Parameters	O42	=AD42 * p_assumed_se	= (U42-T42)/2/1.96
	O43	=AD43 * p_assumed_se	= (U43-T43)/2/1.96
	O44	=AD44 * p_assumed_se	= (U44-T44)/2/1.96

At this point the EAG became aware that the company did not use the observed standard errors for the slope, intercept, and treatment effect but a proxy standard error of 10% of the mean value. Thus, the EAG has also

used this occasion to present the PSA results if the observed standard errors are used, Table 2 shows how the code should be changed in Excel for this approach.

During the scrutiny of the PSA set up, the EAG also observed that the proportion of dialysis patients receiving haemodialysis is varied using a normal distribution with a standard error of 10% of the mean. This leads in about 4% of the PSA iterations to a proportion larger than 100% and thus to a negative proportion of patients receiving peritoneal dialysis. These proportions are only used in the calculation of the dialysis costs, but as these costs represent 60% of the total costs, the impact was uncertain. Thus, the EAG also corrected this error (see Table 3).

Table 3 Changes required in model to correct error proportion haemodialysis

Sheet	Cell	Old code	New code
Parameters	M34	-	25,221
	R34	-	=M34*J34
	S34	-	=M34-R34
	W34	=IFERROR(NORM.INV(V34,$AD34,$O34),0)	=BETA.INV(V34,$R34,$S34)

Another issue was found that might explain to some extend the difference between the deterministic and probabilistic results, which relates to the drawing of random values for the health state utilities. The deterministic utility for CKD 1 and CKD 2 is 0.85, for CKD 3a and 3b 0.80, for CKD 4 0.74, and for CKD 5 0.73. When drawing random values, first a value for CKD 1 and 2 is drawn, for example 0.82. Then a random value for CKD 3a and 3b is drawn. If this value is larger than our example of 0.82, the assigned utility is 0.82*(0.80/0.85), if it is smaller or equal the value drawn is used. This leads to an average utility for CKD 3a and 3b over all PSA iterations that is smaller than the deterministic value of 0.80. This will carry through to the total QALYs yielded in both arms. Thus, some of the difference in average QALYs per patient between deterministic and probabilistic results is an artefact of the aim to ensure that in the PSA worse health states always have a lower utility.

Results

Original PSAs with EAG corrections of errors

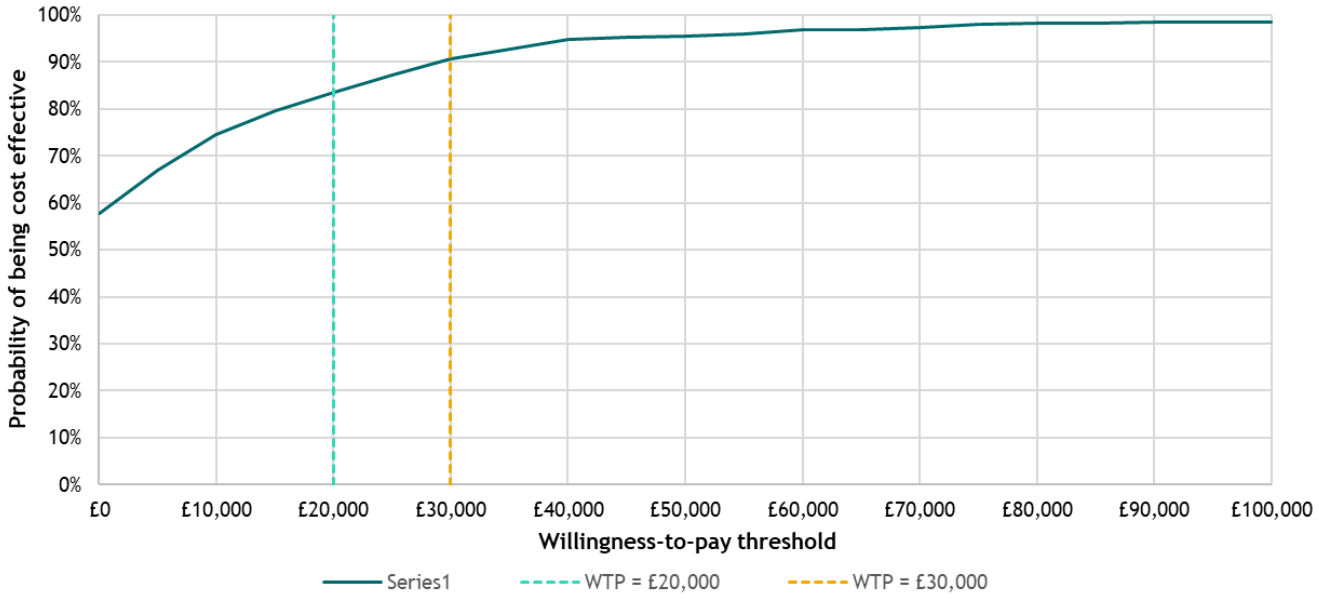
Running the PSA with the corrections set out in Tables 2 and 3, we find the results reported in Table 4 and Figure 1. These are not very different from what was seen before the corrections whilst they are quite different from the deterministic analysis (Table 1).

Table 4. Base-case probabilistic cost-effectiveness results, corrections for HR and proportion dialysis by EAG

Arm	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
TRF-budesonide	[redacted]	16.309	[redacted]	-	-	-	-
SoC	[redacted]	15.949	[redacted]	[redacted]	0.3593	[redacted]	Dominant

ICER = incremental cost effectiveness ratio; LYG = life years gained; SoC = standard of care; QALY(s) = quality-adjusted life year(s); TRF = targeted-release formulation.

Figure 1 Acceptability curve, corrections for HR and proportion dialysis by EAG



As reported in the company submission, the transition between CKD 1 to CKD 2 in the TRF-budesonide arm is informed by data from one patient in Part A of the NefIgArd Nef-301 study. Therefore, when this transition is varied in the PSA, it often takes extreme values of either 0% or 100% which has a significant impact on the ICER produced in the PSA. Therefore, a PSA that excluded this transition was also run. The results of this PSA are presented in Table 5 and the cost-effectiveness acceptability cure is presented in Figure 2. Comparing Tables 1, 4 and 5 it is clear that excluding the one patient from the analysis leads to

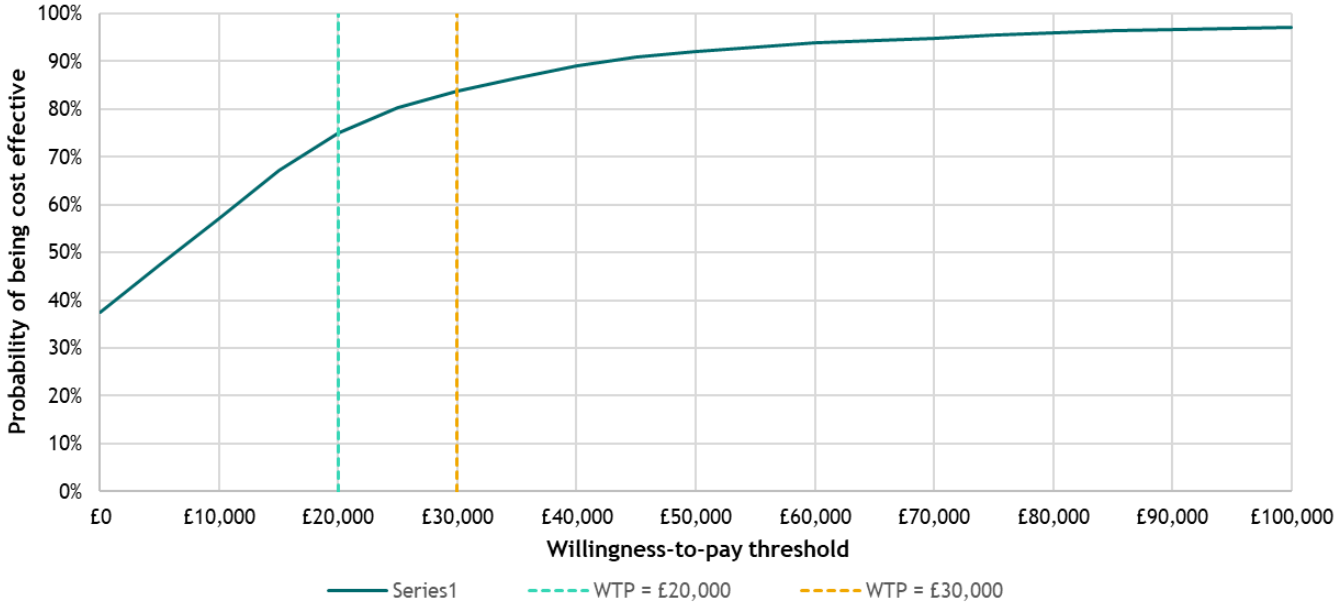
probabilistic results that are more aligned with the deterministic results, though the results per treatment arm are still quite different.

Table 5. Base-case probabilistic cost-effectiveness results, excluding transition between CKD 1 to CKD 2 TRF-budesonide arm, corrections for HR and proportion dialysis by EAG

Arm	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
TRF-budesonide	[redacted]	15.915	[redacted]	-	-	-	-
SoC	[redacted]	15.792	[redacted]	[redacted]	0.124	[redacted]	£6,924

ICER = incremental cost effectiveness ratio; LYG = life years gained; SoC = standard of care; QALY(s) = quality-adjusted life year(s); TRF = targeted-release formulation.

Figure 2 Acceptability curve, excluding transition between CKD 1 to CKD 2 TRF-budesonide arm, corrections for HR and proportion dialysis by EAG



Exploratory PSA (transitions between CKD 1 and CKD 4 all fixed)

Some further explorations by the EAG showed that keeping all transitions between CKD 1 to CKD 4 fixed leads to a further reduction in the difference between the deterministic and probabilistic, most notably now also in the per arm result, thus leading to the assumption that potentially the relatively small number of patients on which the estimation of the transition probabilities was based is causing the current gap between deterministic and probabilistic results.

Table 6. Base-case probabilistic cost-effectiveness results, all transitions between CKD 1 and CKD 4 fixed, corrections for HR and proportion dialysis

Arm	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
TRF-budesonide	[redacted]	15.807	[redacted]	-	-	-	-
SoC	[redacted]	15.683	[redacted]	[redacted]	0.124	[redacted]	£4,011
ICER = incremental cost effectiveness ratio; LYG = life years gained; SoC = standard of care; QALY(s) = quality-adjusted life year(s); TRF = targeted-release formulation.							

EAG preferred PSA

Here we present the PSA results if the observed standard errors of slope, intercept and treatment effect are used for the estimation of the HR for TRF-budesonide patient to transition from CKD 4 to CKD 5 compared to patients in the SoC arm. We also keep the transition from CKD 1 to CKD 2 TRF-budesonide arm fixed.

Table 2 shows how the code should be changed in Excel for this approach. If we compare these results to those presented in Table 5, we see that the ICER has increased by about £1,000 per QALY, and that the per arm estimates of costs, QALYs and life years have decreased slightly. The probability of being below a threshold of £20,000 and £30,000 is 72% and 83%, respectively.

Table 7. EAG preferred probabilistic cost-effectiveness results, excluding transition between CKD 1 to CKD 2 TRF-budesonide arm, corrections for HR and proportion dialysis

Arm	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
TRF-budesonide	[redacted]	15.852	[redacted]	-	-	-	-
SoC	[redacted]	15.725	[redacted]	[redacted]	0.127	[redacted]	£7,916
ICER = incremental cost effectiveness ratio; LYG = life years gained; SoC = standard of care; QALY(s) = quality-adjusted life year(s); TRF = targeted-release formulation.							

Figure 3 Acceptability curve for EAG preferred PSA, excluding transition between CKD 1 to CKD 2 TRF-budesonide arm corrections for HR and proportion dialysis