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

For committee – contains ACIC information

5 October 2023

Chair: Peter Jackson

Lead team: Sarah Davis, Philip Beales, Tina Garvey

External assessment group: Kleijnen Systematic Reviews (KSR)

Technical team: Luke Cowie, Mary Hughes, Ian Watson

Company: Britannia

Background on immunoglobulin A nephropathy (IgAN)

Causes

- IgAN is a progressive chronic kidney disease (CKD). It is caused by IgA antibodies building up in the kidney causing inflammation and scarring. In primary IgAN there is no obvious initiating or underlying cause.

Epidemiology

- IgAN is estimated to affect 14,372 people in England. It can present at any age, with mean age of 41 at diagnosis in the UK. More common in males (ratio estimated to be up to 6:1 in northern Europe), and more common in Caucasian and Asian populations.

Diagnosis and classification

- IgAN is asymptomatic in early stages. Urine protein and kidney function tests often first indication, but definitive diagnosis through renal biopsy to detect IgA deposition.

Symptoms and prognosis

- Most people with IgAN progress to kidney failure within 10–15 years from diagnosis. CKD is associated with a wide range of clinical symptoms including pain, fatigue, muscle cramps and shortness of breath.

Treatment pathway

Currently no NICE guidance or guidelines for the treatment of IgAN, KDIGO guidelines widely used

Persistent proteinuria >1g/day (despite 3-6 months of optimised supportive care)

Goal of treatment is to control blood pressure and reduce proteinuria to slow rate of renal function decline

1L

Initial therapy maximum tolerated RAS blockade with ACEi or ARB (not both)
Blood pressure management
Lifestyle modification
Address cardiovascular risk (SLGT2i and statins)
TRF-budesonide to be used here as add-on treatment alongside SoC

2L

Consider enrolment in a clinical trial

Company state corticosteroids and mycophenolate mofetil (MMF) not widely used:

- UK clinical experts reported that in practice, corticosteroids are used sparingly/only in severe disease where risk/benefit is acceptable.
- MMF may be used in Chinese people only (KDIGO 2021). Lack of effectiveness evidence in other groups.

NICE

Abbreviations: ACEi, angiotensin converting enzyme inhibitor; RAS, renin-angiotensin system; ARB, angiotensin receptor blockers; SLGT2, Sodium-glucose cotransporter-2 inhibitor; SoC, standard of care; KDIGO, Kidney Disease Improving Global Outcomes

TRF-budesonide (Kinpeygo, Britannia)

Marketing authorisation	• 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 • Granted February 2023 (MHRA)
Mechanism of action	• Targeted suppression of mucosal B-cells in the ileum, a primary site of IgA antibody production. Reducing circulating IgA antibodies in blood may prevent the effects of their build-up in the kidneys, such as kidney inflammation, damage and loss of function
Administration	• Recommended dose is 16 mg (four 4 mg capsules) once daily in the morning, at least one hour before a meal, for 9 months • Re-treatment may be considered at the discretion of the treating physician
Price	• The company has a simple patient access scheme (PAS) discount, updated during technical engagement. Results in company TE response and EAG post-TE addendum include the updated PAS

NICE

Abbreviations: TRF, targeted-release formulation; MHRA, Medicines and Healthcare Products Regulatory Agency; gd-IgA1, galactose-deficient immunoglobulin A; UPCR, urine protein to creatinine ratio

Patient perspectives

IgAN is associated with high prognostic uncertainty and poor quality of life

Submissions from Kidney Research UK & UK Kidney Association

- IgAN mainly affects young adults: big impact on quality of life, ability to work, and is associated with mental ill-health, such as depression
- Realisation that there are no specific disease-modifying therapies which slow or prevent decline in kidney function can be difficult to accept and takes a big toll on wellbeing
- Transplantation and dialysis are extremely gruelling, and not a cure
- Dialysis can mean people leave their jobs or are often absent
- Corticosteroids can have significant side effects
- Welcome a treatment that could slow down progression could delay or prevent high costs and quality of life burden associated with dialysis, transplantation and treatment for chronic conditions associated with ESRD

"If Budesonide can slow down the IgAN pathway then the benefits to a younger patient population are obvious"

"...needing to go to hospital for four-hour dialysis sessions, three times a week, so a machine can keep you alive..."

Abbreviations: ESRD, end-stage renal disease

Clinical perspectives

Submission from University of Leicester UHL NHS Trust

- Main aim of treatment is to stop or slow progression to kidney failure requiring dialysis or a kidney transplant.
- TRF-budesonide would offer treatment choice for people who remain at high risk of progression despite maximal supportive care and avoid the significant side effects of systemic corticosteroids if used (estimated 1/3 of nephrologists will consider using corticosteroids).
- Data shows clear eGFR (kidney function) advantage over current optimised supportive care which will delay the time to kidney failure substantially for this group of young people.
- TRF-budesonide will extend the lifespan of people: kidney failure/dialysis/transplantation significantly increasing mortality/morbidity.

Is TRF-budesonide expected to have fewer side effects than systemic corticosteroids?

"First approved treatment for IgAN, it addresses the pathogenesis of the disease and is most definitely a 'step-change' in the management of the condition."

"The Phase 2 and Phase 3 data show that TRF-budesonide effectively reduces proteinuria in the short term and slows eGFR decline over 2 years"

NICE

Abbreviations: TRF, targeted-release formulation; eGFR, estimated glomerular filtration rate; UHL, University Hospitals of Leicester

Equality considerations

Use of TRF-budesonide is not expected to raise any equality issues

- Kidney disease disproportionally affects people from deprived communities and ethnic minority groups and people in these cohorts progress faster to end stage renal failure
- There is a higher prevalence of IgAN in East and South East Asians. In this population IgAN also tends to be a more aggressive disease carrying a greater risk of kidney failure
- 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

Abbreviations: TRF, targeted-release formulation

EAG key issues (1)

Issue	Resolved?	ICER impact
Issue 1: Applicability of trial evidence to those patients not on RASi therapy	No – for discussion	Unknown
Issue 2: Corticosteroids, MMF and SGLT2i may be relevant comparators for different subgroups	No – for discussion	Unknown
Issue 3: Short-term follow-up	Yes	Unknown
Issue 4: Omission of relevant evidence	Yes	Small
Issue 5: Exclusion of potentially relevant subgroup	Yes	Unknown
Issue 6: Possible selection bias	Yes	Unknown
Issue 7: Disease progression not reported	Yes	Unknown

Abbreviations: RASi, renin-angiotensin system inhibitor; SLGT2, Sodium-glucose cotransporter-2 inhibitor; MMF, mycophenolate mofetil; CKD, chronic kidney disease

Key issues (2)

Issue	Resolved?	ICER impact
Issue 8: Applicability of evidence	No – for discussion	Unknown 
Issue 9: Insufficient evidence regarding retreatment of patients	Partly – for discussion	Large 
Issue 10: Data source for estimating the transition from CKD 4 to CKD 5	Yes	Small 

Abbreviations: RASi, renin-angiotensin system inhibitor; SLGT2, Sodium-glucose cotransporter-2 inhibitor; MMF, mycophenolate mofetil; CKD, chronic kidney disease

Decision problem (1)

	Final scope	Company	EAG comments
Population	People with primary IgA nephropathy	Adult patients with primary IgAN who: • are on a stable dose of maximally tolerated RASi therapy • are at risk of rapid disease progression with a UPCR ≥1.5 g/g	Aligned with marketing authorisation and appropriate
Intervention	Targeted-release budesonide	As per scope	Notes budesonide is taken alongside standard of care (RASi therapy, lifestyle modification, blood pressure management, and addressing cardiovascular risk)

Abbreviations: RASi, renin-angiotensin system inhibitor; UPCR, urine protein to creatinine ratio

Decision problem (2)

	Final scope	Company	EAG comments
Comparators	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 • SGLT2i	Glucocorticoids/ corticosteroids are not included as part of standard care in the decision problem. UK clinical experts reported corticosteroids are used sparingly/only in people with severe kidney disease. SGLT2i is are given to patients with IgAN as part of SoC for cardiovascular protection	For the small subgroup who are eligible 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 (EAG key issue 2)

Abbreviations: ACE, angiotensin converting enzyme; ARBs, angiotensin receptor blockers; SLGT2, Sodium-glucose cotransporter-2 inhibitor; MMF, mycophenolate mofetil; SoC, standard of care

Decision problem (3)

	Final scope	Company	EAG comments
Outcomes	• 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.

Abbreviations: UPCR, urine protein to creatinine ratio

Key issue 2: Corticosteroids, MMF and SGLT2i may be relevant comparators for different subgroups (1)

Company submission

- Considers that corticosteroids (in addition to optimised SoC) are not relevant comparators for TRF-budesonide in addition to optimised SoC, based on feedback received by clinical experts that sparingly used. May only be considered in people with nephrotic syndrome.
- KDIGO guidelines highlight an “important risk of treatment-emergent toxicity” and the “clinical benefit of glucocorticoids in IgAN is not established and should be given with extreme caution”.
- KDIGO guidelines recommend mycophenolate mofetil (MMF) for Chinese people only,
- SGLT2i is not currently recommended for use in IgAN, but since approval of dapagliflozin for CKD (TA775) clinical experts expect it to be used as part of SoC for IgAN. Study of dapagliflozin in IgAN vs placebo (DAPA-CKD) showed it did not statistically significantly improve kidney function (eGFR) so efficacy of SoC not impacted by inclusion of SGLT2i.

Abbreviations: KDIGO, Kidney Disease Improving Global Outcomes; CS, corticosteroids; SLGT2, Sodium-glucose cotransporter-2 inhibitor; ITC, indirect treatment comparison; SoC, standard of care; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate

Key issue 2: Corticosteroids, MMF and SGLT2i may be relevant comparators for different subgroups (2)

EAG comments

- Still a small subgroup in KDIGO guidelines for whom CS and immunosuppressants are indicated, and who would receive TRF-budesonide, so a relevant comparator regardless of their limited use. Same for MMF.
- Little evidence to support company's claim no benefit of dapagliflozin in IgAN. Primary outcome showed statistically significant improvement vs. placebo. Numerical improvement in eGFR. Was not included as SoC in TRF-budesonide trial.

Company comments after TE

- Maintained original view, but provided 2 ITCs: of TRF-budesonide vs CS and immunosuppressants, and of TRF-budesonide vs dapagliflozin + SoC
- Clinical expert advice suggests MMF not used in clinical practice in England, so not included in the ITC
- Potential benefits from the addition of dapagliflozin to SoC expected to be additive to TRF-budesonide treatment effect, as no crossover between their mechanisms of action

Abbreviations: KDIGO, Kidney Disease Improving Global Outcomes; CS, corticosteroids; SLGT2, Sodium-glucose cotransporter-2 inhibitor; ITC, indirect treatment comparison; SoC, standard of care; eGFR, estimated glomerular filtration rate; MMF, mycophenolate mofetil

EAG Key issue 2: Corticosteroids, MMF and SGLT2i may be relevant comparators for different subgroups (3)

EAG comments after TE

- Overall, ITC results suggest that budesonide may be superior to both IS/CS and DAPA.
- Some uncertainty in ITC results: unclear whether all relevant studies were included.
- MMF not being commonly used in UK probably because the sub-group that respond to it are a minority. But this does not mean this sub-group should be ignored.

Clinical expert comments

- Use of SGLT2i is increasing in patients with non-diabetic kidney disease but is certainly not uniform. TRF-budesonide would be used in addition to SGLT2i so makes no sense to compare the two.
- DAPA-CKD [used in company ITC for DAPA] did not recruit the same population as a dedicated IgAN trial, so comparing data across these studies is challenging.
- CS and MMF are not part of SoC. Most UK nephrologists will not treat IgAN patients with these drugs.

Are corticosteroids, MMF and SGLT2i + SoC relevant comparators in whole population or any subgroup?

Abbreviations: SLGT2, Sodium-glucose cotransporter-2 inhibitor; MMF, mycophenolate mofetil; SoC, standard of care; TRF, targeted-release formulation; IS, immunosuppressants; CS, corticosteroids; ITC, indirect treatment comparison; DAPA, dapagliflozin

Clinical effectiveness

NICE National Institute for Health and Care Excellence

Clinical effectiveness data

NeflgArd Nef-301 (Part A) • **Key source of data in model**	• Phase 3, double-blind, RCT. • Patient follow up at 12 months. • Compared optimised RASi therapy plus TRF-budesonide 16 mg/day with optimised RASi therapy plus placebo.
NeflgArd Nef-301 (Part B) • **Not used by company in model, data became available during technical engagement**	• Phase 3, double-blind, RCT. • Extension of Part A up to 2 years (12 months of follow-up off drug.
NeflgArd NeF-202	• Phase 2b, double blind RCT. • Collected additional information supporting the safety profile of TRF-budesonide. • Compared optimised RASi therapy plus TRF-budesonide 16 mg/day, TRF-budesonide 8 mg/day, and placebo (1:1:1) • Had different eligibility criteria (kidney function measures) to 301. Company provided data for subgroup matching 301

Abbreviations: RCT, randomised controlled trial; TRF, targeted-release formulation; RASi, renin-angiotensin system inhibitor

Key clinical trial

NeflgArd Nef-301 is a double-blind RCT of TRF-budesonide vs placebo

Design	Phase 3, double-blind, RCT. International included UK sites
Population (N=199, Barratt et al 2022)	• ≥18 years with biopsy-confirmed primary IgAN • eGFR ≥35 and ≤90 mL/min per 1.73 m2 • Proteinuria ≥1 g/day or UPCR ≥0.8 g/g
Subgroup supporting MA. All data presented is for this subgroup ([redacted])	• adult patients with primary IgAN at risk of rapid disease progression with a UPCR ≥1.5 g/g (post hoc subgroup)
Intervention	Optimised RASi therapy plus TRF-budesonide 16 mg/day
Comparator	Optimised RASi therapy plus placebo
Duration	A 9-month blinded treatment period, and a 3-month follow-up period (including a 2-week tapering period)
Primary outcome	Ratio of UPCR at 9 months compared with baseline
Key secondary outcomes (* used in economic model)	**Ratio of eGFR at 9 and 12 months compared with baseline***, ratio of UACR at 9 months compared with baseline, 1-year eGFR slope, safety

NICE

Abbreviations: RCT, randomised controlled trial; eGFR, estimated glomerular filtration rate; TRF, targeted-release formulation; RASi, renin-angiotensin system inhibitor; UACR, urine albumin to creatinine ratio; UPCR, urine protein to creatinine ratio

NeflgArd Nef-301 baseline characteristics

EAG consider it is unclear whether the population informing the MA reflected the UK population eligible for TRF-budesonide

Characteristic	MA population subgroup [redacted]
Median age (range years)	[redacted]
Male n (%)	[redacted]
Female n(%)	[redacted]
Race n (%)	[redacted]
White	[redacted]
Asian	[redacted]
Black	[redacted]
Other	[redacted]
Baseline proteinuria g/day, median (IQR)	[redacted]
Baseline eGFR (CKD-EPI), mL/min/1.73 m^2, median (IQR)	[redacted]
Did not have RASi due to intolerance	6

Abbreviations: MA, marketing authorisation; RASi, renin-angiotensin system inhibitor; IQR, Interquartile range

Key issue 1: Applicability of trial evidence to those patients not on RASi therapy (1)

Company

- The company population is defined according to the marketing authorisation (MA) and people having TRF-budesonide should be on a stable dose of maximally tolerated RASi therapy.
- People who cannot tolerate RASi have very limited treatment options.

EAG comments

- Satisfied that the population aligns with the MA wording, and that a maximally tolerated dose of RASi therapy may be zero (not tolerated).
- But EAG concerned that the evidence presented is not applicable to this subpopulation [for whom any dose of RASi not tolerated] as there were only 6 people (4 in budesonide arm and 2 in placebo arm) who did not receive RASi therapy in NefIgArd Nef-301 trial.

Is the trial generalisable to UK target population, taking into account those not on RASi therapy due to intolerance?

Abbreviations: TRF, targeted release formulation; UPCR, urine protein to creatinine ratio; RASi, renin-angiotensin system inhibitor

Key issue 1: Applicability of trial evidence to those patients not on RASi therapy (2)

Company comments after TE

- People with IgAN who cannot tolerate RASi therapy have limited treatment options.
- Excluding these people may result in challenges to equitable access to treatment.

EAG comments after TE

- Notwithstanding challenges to equitable access to treatment for this subgroup, it remains true that the clinical evidence does not adequately cover this population group.

Clinical expert comments

- All IgAN patients should be on RASi - this would be an irrelevant comparison and would not reflect clinical practice anywhere in the world.
- There is no evidence to support the use of budesonide in patients not on RASi.

Is the trial generalisable to UK target population, taking into account those not on RASi therapy due to intolerance?

Abbreviations: IgAN, immunoglobulin A nephropathy; RASi, renin-angiotensin system inhibitor

Key issue 8: Applicability of evidence (1)

Company

- 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.

EAG comments

- Company claim not supported by evidence from UK RaDaR study: lack of detail in important variables, and only some variables are compared.
- Some possible differences in ethnicity and other variables between target [UK] and trial
- Subgroup data available for whole trial population. No company subgroup analysis restricted to those with UPCR >1.5g/g. Remains unclear whether any potential differences between target and trial population could have led to different outcomes.

Clinical expert comments

- Baseline features in company trial very similar to those in the UK RaDaR registry.
- Company trial data reflects treatments people have in the UK and the characteristics of people who would have targeted release budesonide in the NHS.

Is the trial population data sufficiently generalisable to UK clinical population?

Abbreviations: RaDaR, UK National Registry of Rare Kidney Diseases, UPCR, urine protein to creatinine ratio

Key issue 8: Applicability of evidence (2)

Company comments after TE

- Clinical experts reported trial population in NefIgArd Nef-301 to be representative of patients with primary IgAN in the UK RaDaR database, and those who would be treated with TRF-budesonide in clinical practice.
- Age at baseline in both treatment arms was considered to be in line with published data from UK RaDaR.
- Proportion of males, females, and race ratio aligned with target population in England.

EAG comments after TE

- A 17.6% difference in median UACR between trial and UK RaDaR.
- Remains unclear whether age, sex and ethnicity similar between trial and UK RaDaR.

Stakeholder comments

- Novartis agrees evidence generation in rare diseases such as IgAN is very challenging.
- Conclusions from subgroup analyses of a subgroup, as requested by the EAG, may not be meaningful given the small sample sizes available.

Is the trial population data sufficiently generalisable to UK clinical population?

Abbreviations: RaDaR, UK National Registry of Rare Kidney Diseases, UPCR, urine protein to creatinine ratio; TRF, targeted-release formulation; eGFR, estimated glomerular filtration rate

NeflgArd Nef-301 Part A results: UPCR

TRF-budesonide reduced urine protein to creatinine ratio at 9 months compared with placebo

UPCR (g/g) at 9 months compared with baseline in patients with a baseline UPCR ≥1.5 g/g

	TRF-budesonide† n=	Placebo† n=
Ratio of geometric LS mean UPCR at 9 months compared with baseline (95% CI)		
Corresponding % reduction (95% CI)		
TRF-budesonide versus placebo		
Ratio of geometric LS mean UPCR, TRF-budesonide vs placebo (95% CI)		
Corresponding % reduction (95% CI)		
P value		
† Treatment in addition to RAS inhibition		

NICE

Abbreviations: CI, confidence interval; LS, least squares; TRF, targeted-release formulation; UPCR, urine protein to creatinine ratio; RAS, renin-angiotensin system

NeflgArd Nef-301 Part B results: UPCR

At TE company presented data from more people and for an extended follow up after treatment. Treatment effect persisted after stopping treatment at 9 months

UPCR (g/g) using MMRM for patients with a baseline UPCR ≥1.5 g/g

Timepoint (months)	Ratio of geometric LS mean UPCR compared with baseline (95% CI)		TRF-budesonide 16 mg/day vs placebo; ratio of geometric LS means (95% CI); p value	% change versus placebo
	TRF-budesonide (n=[redacted])	Placebo (n=[redacted])		
3				
6				
9				
12				
18				
24				

Abbreviations: CI, confidence interval; LS, least squares; TRF, targeted-release formulation; UPCR, urine protein to creatinine ratio

NeflgArd Nef-301 results: eGFR

TRF-budesonide shows benefit on eGFR over 24 months compared with placebo

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)
Part A (used in company base case model)			
9 months	[redacted]		[redacted]
PART B presented after technical engagement			
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; LS, least squares; TRF, targeted-release formulation; eGFR, estimated glomerular filtration rate

ITC results: change from baseline to 12 months in UPCR

ITC suggests TRF-budesonide may be superior to corticosteroids/ immunosuppressive therapy, [redacted]

Mean treatment difference for CFB to 12 months in UPCR

	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]	–
Probability TRF-budesonide superior to comparator	[redacted]	[redacted]	–

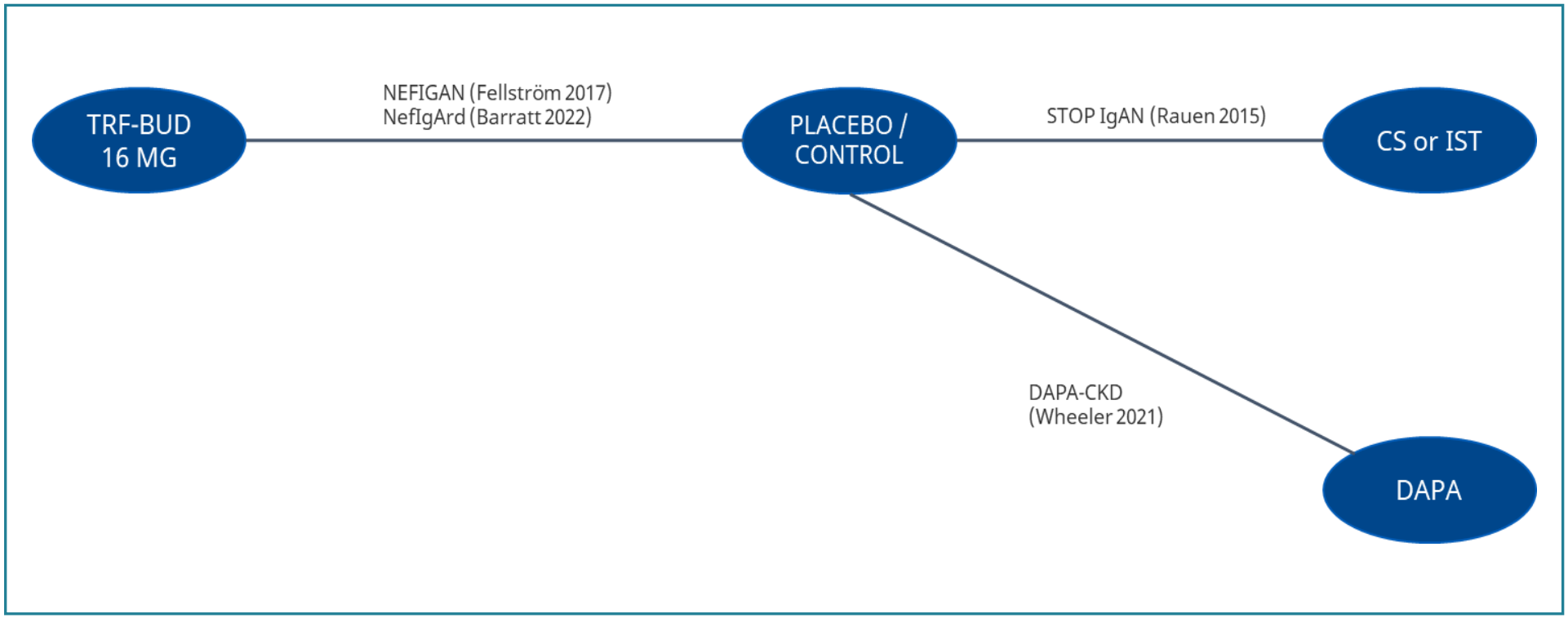
ITC network:

Abbreviations: CS, corticosteroids; IST, immunosuppressive therapy; TRF, targeted-release formulation; UPCR, urine protein to creatinine ratio; CFB, change from baseline; ITC, indirect treatment comparison

ITC results: change from baseline to 12 months in eGFR

ITC suggests TRF-budesonide may be superior to CS/IST and dapagliflozin

ITC network:



<u>EAG comment on ITCs</u>: For CS/IST + SoC versus SoC, there appears to have been no systematic basis to the selection of relevant trials. A transparent systematic review would have increased confidence that all relevant studies have been included in the ITC.

NICE

Abbreviations: CS, corticosteroids; IST, immunosuppressive therapy; TRF, targeted-release formulation; eGFR, estimated glomerular filtration rate; ITC, indirect treatment comparison

ITC results: change from baseline to 12 months in eGFR

ITC suggests TRF-budesonide may be superior to CS/IST and dapagliflozin

Mean treatment difference for CFB to 12 months in eGFR

	Placebo/ Control	CS or IST	Dapagliflozin	TRF-budesonide 16 mg/day
Placebo/ Control	–	[redacted]	[redacted]	[redacted]
CS or IST	[redacted]	–	1.89 [-1.56, 5.39]	[redacted]
Dapagliflozin	[redacted]	[redacted]	–	[redacted]
TRF-budesonide 16 mg/day	[redacted]	[redacted]	[redacted]	–
Probability TRF-budesonide) superior to comparator	[redacted]	[redacted]	[redacted]	–

Network:

NICE

Abbreviations: CI, confidence interval; CS, corticosteroids; IST, immunosuppressive therapy; TRF, targeted-release formulation; eGFR, estimated glomerular filtration rate; CFB, change from baseline; ITC, indirect treatment comparison

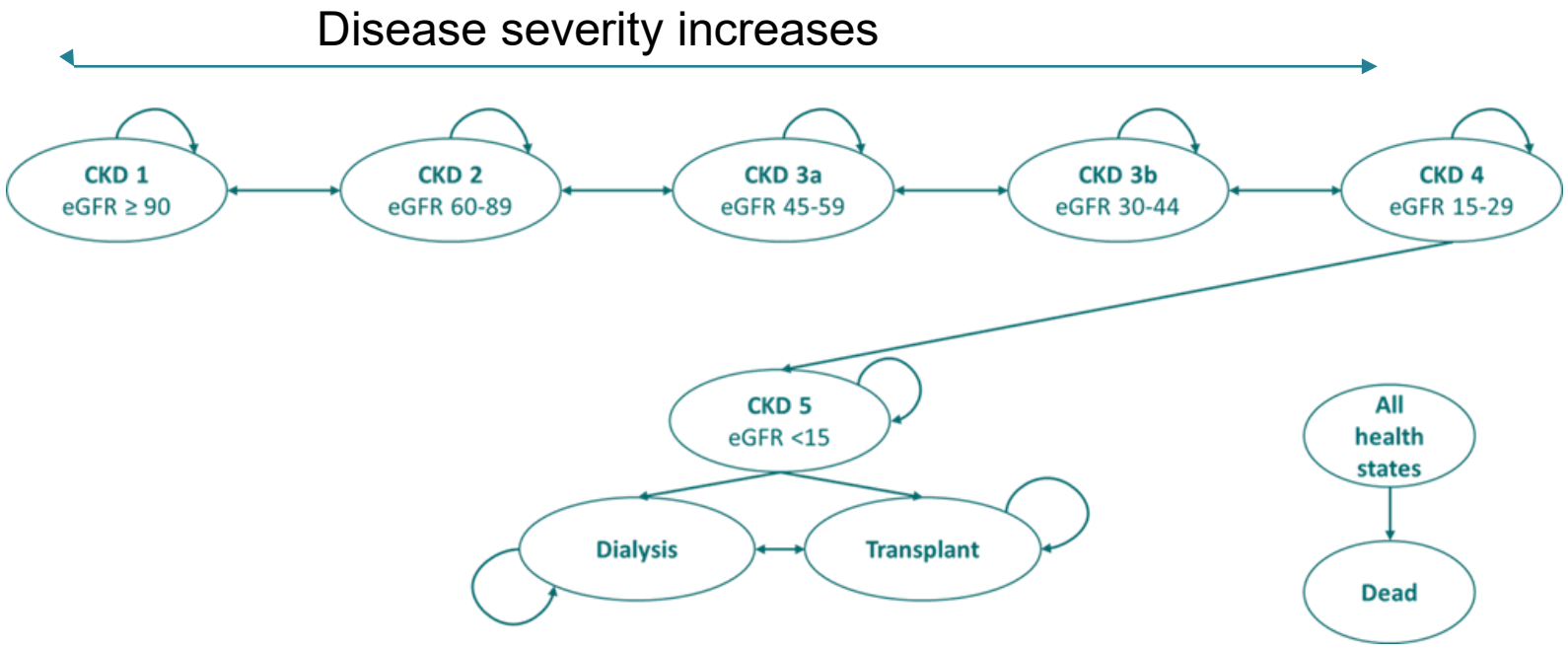
Cost effectiveness

NICE National Institute for Health and Care Excellence

Company's model overview

- Model consists of 8 mutually exclusive health states and an absorbing mortality state: 6 core health states defined by the level of CKD disease, and the health states of renal transplant and dialysis.
- Chronic kidney disease health states were populated using the baseline distribution of CKD states from NeflgArd Nef-301 Part A.

Model structure



EAG comments

- Main concern 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
- Nonetheless, company has clarified that this assumption was validated with clinical experts and further aligned with the model structure used in the previous TA775 NICE submission

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

How company incorporated evidence into model

Input and evidence sources

Input	Assumption and evidence source
Modelled cohort	NefIgArd Nef-301 Part A trial subgroup UPCR ≥1.5 g/g . CKD state distribution at baseline eGFR from this cohort
Transition probabilities CKD 1-4	Change from baseline eGFR to 9 months in TRF-budesonide + standard care arm and standard care arm used to determine probabilities of moving between CKD state for 1st 12 months then estimated transition probabilities for SoC applied to both arms
Transition probabilities 4 to 5 and death	For SoC transition probability CKD4→5 based on UK RaDaR data. Hazard ratio of [redacted] applied to SoC transition probabilities for 1st year based on treatment effect observed between arms in change from baseline eGFR. Probability of dying in any CKD state from RaDaR
Source of AE rates	NefIgArd Nef-301 Part A study
Source of utilities	Cooper et al. 2020 (a systematic review of CKD 1-5 utility values used in HTA submissions – not specific for IgAN population. AE disutility sourced from literature

Abbreviations: UPCR, urine protein to creatinine ratio; AE, adverse event; TRF, targeted-release formulation

Company assumptions on retreatment

Assumptions in company and EAG base case, post technical engagement

Assumption	Company/EAG base case (after TE)	Rationale
Number of treatment rounds in model	• 2 rounds of treatment with TRF-budesonide for 9 months each	2 clinical experts reported that people with primary IgAN expected to receive approximately 2 rounds of treatment with TRF-budesonide for 9 months each, provided an acceptable tolerability profile is maintained.
% receiving retreatment	• 75% of eligible patients would receive retreatment (originally company assumed 100%)	2 clinical experts predicted that 100% and 50% of people 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. 75% selected as midpoint between these estimates.
Retreatment efficacy	• Treatment effect of 90% in subsequent rounds (originally company assumed 100%)	Treatment effect from subsequent treatments updated to 90% as a conservative assumption, because of limited evidence to support 100% efficacy in subsequent rounds of treatment.

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

Key issue 9: Insufficient evidence regarding retreatment (1)

Company

- Option to retreat patients was included in the TRF-budesonide arm of the economic model, with 1 round of retreatment assumed in the base case.
- Transition probabilities for the retreated people in all CKD stages were set equal to the respective 12-months transition probabilities from the first round of treatment.
- Proportion of people on retreatment also informed by TTD curve observed in NefIgArd Nef-301 Part A trial.

EAG comments

- Data is lacking so there is much uncertainty regarding retreatment, specifically assumptions used to inform retreatment parameters: timing and effectiveness of retreatment, percentage of people that would have it.
- Asked company to explore impact of alternative options regarding time between treatment rounds and the proportion of people eligible for retreatment. Also to allow option for a reduced benefit of TRF-budesonide for retreated people in the model.
- Cost effectiveness outcomes were quite sensitive to the proportion of patients eligible for retreatment.
- Due to uncertainty, EAG preferred assumption is retreatment set to 0 in its base case.

Abbreviations: TRF, targeted-release formulation; CKD, chronic kidney disease; TTD, time to treatment discontinuation

Key issue 9: Insufficient evidence regarding retreatment (2)

Company comments after TE

- Clinical experts suggest people would receive 2 rounds of treatment with TRF-budesonide for 9 months.
- No resistance to TRF-budesonide or waning of treatment effect expected.
- Updated base case model to assume 75% will have retreatment (mid-point of 2 clinical opinions). Also assumed treatment effect of later rounds updated to 90% of the initial treatment effect due to lack of evidence that would be 100% effective.

EAG comments after TE

- EAG is happy to accept the company's suggested estimates for the base case.
- Still uncertain and has a relatively large impact on the ICER, so remains for discussion.

Stakeholder comments

- Clinical expert expects all patients will need re-treatment at some point, likely on a cyclical basis every 18-36 months. Predicts a response similar to that seen with initial treatment regimen.
- Despite uncertainty in efficacy and safety of retreatment, Novartis consider that EAG approach of setting retreatment probability to zero is not appropriate.

Are company's retreatment assumptions appropriate for decision making?

Abbreviations: TRF, targeted-release formulation; ICER, incremental cost effectiveness ratio

Company base case results (updated PAS price)

Deterministic incremental base case results*

Technology	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER incr. (£/QALY)
TRF-budesonide	[redacted]	16.049	[redacted]				
SoC	[redacted]	15.944	[redacted]	[redacted]	0.106	[redacted]	£4,672

Probabilistic incremental base case results (EAG preferred, with corrections)

Technology	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER incr. (£/QALY)
TRF-budesonide	[redacted]	15.852	[redacted]	-	-	-	-
SoC	[redacted]	15.725	[redacted]	[redacted]	0.127	[redacted]	£7,916

* Company base case uses results from Part A of NeflgArd Nef-301. When results from Part B used in the model the ICER becomes dominant.

EAG comment: satisfied with changes to company base case at TE, so no EAG preferred base case. EAG initially had some concerns about the probabilistic analyses, but discovered errors in the model which were then corrected.

Abbreviations: TRF, targeted release formulation; LYG, life years gained; QALY, quality-adjusted life years; ICER, incremental cost effectiveness ratio; SoC, standard of care; TE, technical engagement; PAS, patient access scheme

EAG corrected errors in the probabilistic analysis

- Company identified that transition between CKD 1 to CKD 2 in TRF-budesonide arm informed by data from 1 patient in Part A of NefIgArd Nef-301. Therefore, this transition often takes extreme values of either 0% or 100%, and so has a big impact on the ICER.
- When this transition excluded from the PSA, results were more aligned with the deterministic results, but still showed a higher difference than expected.
- EAG further explored possible reasons for this discrepancy and identified and corrected several errors in the PSA, pertaining to:
  - The HR for estimating the transition probability from CKD 4 to CKD 5 in the TRF-budesonide arm was incorrectly calculated as an HR of 1 in each iteration of PSA
  - Use of standard error of 10% of the mean values for slope, intercept, and treatment effect resulting in negative standard errors. EAG corrected to use observed standard errors
  - Use of standard error of 10% of the mean for proportion of dialysis patients receiving haemodialysis leading to proportions higher than 100% in some PSA iterations
- EAG preferred PSA includes these corrections for HR and proportion of dialysis patients

Abbreviations: PSA, probabilistic sensitivity analysis; ICER, incremental cost-effectiveness ratio; HR, hazard ratio

Subgroup analyses: TRF-budesonide vs corticosteroids and SGLT2i

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

EAG comment: Implementation of ITC results into the model required using estimated difference in eGFR after 1 year to find a factor to adjust transition probabilities between health states. The validity of this approach may be questioned, and so results of the subgroup analyses should be regarded as exploratory only.

Abbreviations: TRF, targeted release formulation; LYG, life years gained; QALY, quality-adjusted life years; ICER, incremental cost effectiveness ratio; SoC, standard of care; TE, technical engagement; PAS, patient access scheme; ; SLGT2i, Sodium-glucose cotransporter-2 inhibitor

Retreatment scenario analysis

Scenario	Assumption	Incr. costs	Incr. QALYs	ICER
Updated company base case		[redacted]	[redacted]	£4,672
TRF-budesonide retreatment **Base case:** • **1 round of retreatment at 14.75 months** • **[redacted] of patients have retreatment (75% of eligible)** • **90% initial effectiveness**	80% of initial effectiveness	[redacted]	[redacted]	£7,863
	100% of initial effectiveness	[redacted]	[redacted]	£1,748
	50% of eligible patients	[redacted]	[redacted]	£5,521
	100% of eligible patients	[redacted]	[redacted]	£4,456
	Retreatment at 24 months	[redacted]	[redacted]	Dominant
	80% of initial effectiveness & 50% of eligible patients	[redacted]	[redacted]	£8,026
	100% of initial effectiveness & 100% of eligible patients	[redacted]	[redacted]	£1,147
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

NICE

EAG comment: ICER is more sensitive to changes in the % of initial effectiveness achieved in retreatment than to changes in the percentage receiving retreatment.

EAG scenario analyses post technical engagement data

EAG note that company did not update base case using data from updated data available post TE

Scenario	EAG scenario Assumption	Incr. costs	Incr. QALYs	ICER
Updated company base case		[redacted]	[redacted]	£4,672
Data source treatment effectiveness Base case: NeflgArd Nef-301 Part A which was available at submission for transitions from CKD 1 – 3b, HR TRF-budesonide vs SoC for transition CKD4 to CKD 5 is [redacted]	NeflgArd Nef-301 updated post-TE data for calculating transitions from CKD 1 – 3b	[redacted]	[redacted]	Dominant
	As above and HR TRF-budesonide vs SoC for transition CKD4 to CKD 5 [redacted] (calculated by EAG using post-TE data and company formula)	[redacted]	[redacted]	Dominant

Abbreviations: CKD, chronic kidney disease; TRF, targeted release formulation; HR, hazard ratio; TE, technical engagement; QALY, quality-adjusted life year; ICER, incremental cost-effectiveness ratio

NICE National Institute for Health and Care Excellence

Back up slides

EAG key issue 3: Short-term follow-up (1)

Follow up restricted to 12 months, despite longer term follow-up data being available

Company

- Part A analysis was scheduled to occur once 201 randomised patients had completed their 9-month visit
- Longer-term data from NefIgArd Nef-301 (part B) not yet fully published, so detailed outcomes in the company submission are restricted to those at 9 months
- Economic model did not include extrapolations beyond one year, in line with the clinical data available

EAG comments

- The company reference some further additional data from part B of the trial, but these data are very limited in scope, and only for eGFR.
- This information is not sufficient to convince the EAG that long-term benefits for UPCR can be assumed.

Clinical expert comments

- 2 year follow up is the best we have for any therapy in a global IgAN study
- Data on >1M patients with CKD shows robust predictive value of eGFR slope on future risk of kidney failure

Abbreviations: eGFR, estimated glomerular filtration rate; UPCR, urine protein to creatinine ratio; CKD, chronic kidney disease

EAG key issue 3: Short-term follow-up (2)

Follow up restricted to 12 months, despite longer term follow-up data being available

Company comments after TE

- 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
- A reduction in UPCR from baseline with TRF-budesonide was seen at all timepoints in Part B

EAG comments after TE

- These data from Part B of NefIgArd Nef-301 demonstrate a continuation of clinical benefits to 24 months.
- This is therefore no longer deemed a key issue.

Stakeholder comments

- Novartis agree there remains uncertainty in long-term benefit beyond the 12-month follow-up timepoint.
- Uncertainty regarding potential retreatment and associated efficacy.

Abbreviations: UPCR, urine protein to creatinine ratio; TRF, targeted-release formulation

EAG Key issue 4: Omission of relevant evidence

Company

- Results from Phase 2 NEFIGAN Nef-202 were not included in the company submission because they aligned with those of the Phase 3 NefIgArd Nef-301 study
- So results from the more robust and recent NefIgArd Nef-301 were used to inform the economic model

EAG comments

- Budesonide effectiveness for UPCR and UACR in NEFIGAN Nef-202 slightly lower than in NefIgArd Nef-301, so omission of NEFIGAN Nef 202 results may have slightly overestimated efficacy of budesonide.
- Would prefer NEFIGAN Nef-202 results be incorporated into the final cost effectiveness analysis

Company comments after TE

- Ad-hoc analysis of 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 provided as new evidence.

EAG comments after TE

- 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.

Is the company's ad hoc analysis of NEFIGAN Nef-202 appropriate for decision making?

Abbreviations: UPCR, urine protein to creatinine ratio; UACR, urine albumin to creatinine ratio; TRF, targeted-release formulation

EAG Key issue 5: Exclusion of potentially relevant subgroup

Company

- KDIGO guidelines warn of 'point of no return' where kidney injury is so extensive and irreversible that no treatment expected to alter the natural course of the disease (eGFR <20–30 mL/min per 1.73 m2).
- People with an eGFR of <35 mL/min/1.73 m2 were not considered for inclusion in NeflgArd Nef-301 to prevent diluting treatment effect and adversely affecting the power of the study.

EAG comments

- Assumed by company that this group will not respond to treatment, but this is untested
- Inclusion of this group in the trial, where clinically indicated, would have allowed an evidence-based recommendation to be made for this group.

Clinical expert comments

- Reasonable to exclude these people
- TRF-budesonide would not be used in people with greater renal failure than were included in the trial

Stakeholder comments

- Unreasonable to request a trial to be conducted in a population with high likelihood of therapeutic futility,
- KDIGO guidelines do not define precise point at which people with IgAN expected to be 'non-responders'.

Abbreviations: TRF, targeted-release formulation; eGFR, estimated glomerular filtration rate; KDIGO, Kidney Disease Improving Global Outcomes

EAG Key issue 6: Possible selection bias (1)

Company

- Minimal differences between treatment arms in the baseline characteristics.
- Those reported are likely a result of random variation that can take place in small sample sizes.
- Clinical experts suggest differences in age and time from diagnosis unlikely to have influenced trial results.
- Small imbalances in percentages of patients on ACEIs or ARBs between treatment arms, but overall RAS inhibition was similar.

EAG comments

- Agrees that such baseline differences probably random (small sample size), but still possible that difference in baseline proteinuria had some effect on outcome.
- Also threats to internal validity resulting from differences in SoC across trial arms.

Clinical expert comments

- None of the differences between trial arms identified suggest a risk of bias in the trial outcomes.

Is there a high risk of selection bias in the baseline characteristics of the trial arms?

Abbreviations: ACEi, angiotensin converting enzyme inhibitor; RAS, renin-angiotensin system; ARB, angiotensin receptor blockers; SoC, standard of care

EAG Key issue 6: Possible selection bias (2)

Company comments after TE

- Clinical expert opinion considers differences in the baseline characteristics between treatment arms not expected to impact the results of trial.
- Blood pressure controlled in both treatment arms at baseline, validating that differences in ACEi/ARB therapy are not expected to affect outcomes
- Age at baseline in both treatment arms considered to be in line with published data from UK RaDaR
- UPCR values in Part A and Part B similar to those in people with UPCR ≥1.5 g/g in RaDaR study

EAG comments after TE

- main concern was in the differences in baseline proteinuria.
- But given that the other indices of proteinuria (UPCR and UACR) were very similar between arms, the EAG considers this issue resolved.

Stakeholder comments

- Novartis do not anticipate difference in proportion of people receiving ACE inhibitors or ARBs between the two trial arms would have a major effect on clinical outcomes

Is there a high risk of selection bias in the baseline characteristics of the trial arms?

Abbreviations: ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blockers; UPCR, urine protein to creatinine ratio; RaDaR, UK National Registry of Rare Kidney Diseases

NeflgArd Nef-301 baseline characteristics (1)

EAG consider there are some imbalances between trial arms

Characteristic	TRF-budesonide 16 mg (n=[redacted])	Placebo (n=[redacted])	EAG comment
Median age (range)	[redacted]	[redacted]	Placebo group younger
Proteinuria (quantities)			
Proteinuria, g/day, median (IQR)	[redacted]	[redacted]	Placebo group had worse baseline proteinuria
<2 g/day	[redacted]	[redacted]	
³2 and ≤3.5 g/day	[redacted]	[redacted]	
>3.5 g/day	[redacted]	[redacted]	
Time from IgAN diagnosis to trial entry, years			
Median (IQR)	[redacted]	[redacted]	Placebo group longer

NICE

Abbreviations: TRF, targeted release formulation; IQR, Interquartile range

NeflgArd Nef-301 baseline characteristics (2)

EAG consider there are some imbalances between trial arms

Characteristic	TRF-budesonide 16 mg (n=[redacted])	Placebo (n=[redacted])	EAG comment
Prior corticosteroids or immunosuppressive use			
Patients with prior corticosteroids or immunosuppressive use, n (%)	[redacted]	[redacted]	Lower previous use in placebo group
Use of any RASi therapy, n (%)			
Patients on either ACEi or ARB	[redacted]	[redacted]	Usage of ACEi and ARBs differed
Patients on ACEi alone	[redacted]	[redacted]	
Patients on ARB alone	[redacted]	[redacted]	
Patients on both ACEi and ARB	[redacted]	[redacted]	

NICE

Abbreviations: ACE, angiotensin converting enzyme; ARBs, angiotensin receptor blockers; RASi, renin-angiotensin system inhibitor

NeflgArd Nef-301 concomitant medications (1)

EAG consider there are some imbalances between trial arms

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]

NeflgArd Nef-301 concomitant medications (2)

EAG consider there are some imbalances between trial arms

ATC Class	TRF-budesonide 16 mg/day (N=[redacted]), n (%)	Placebo (N=[redacted]), n (%)
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]

EAG Key issue 7: Disease progression not reported (1)

Company

- Assessing efficacy of treatments for IgAN is complicated by long-term nature of disease progression, so relies on use of surrogate endpoints, such as UPCR, UACR and eGFR.
- Associations between reduced proteinuria and a lower risk of decline in kidney function, progression to ESRD, and mortality in people with IgAN and CKD have been consistently demonstrated.

EAG comments

- Accepts points about surrogate endpoints, but still question why disease progression was not included.
- Company's assumption that disease progression events would not have happened in the trial is not certain.

Clinical expert comments

- Relationship between UPCR and eGFR is strong and linear.
- Appropriate to use eGFR data from the trial as a surrogate endpoint to estimate disease progression.

Is it appropriate to exclude disease progression as an outcome in NeflgArd Nef-301?

NICE

Abbreviations: eGFR, estimated glomerular filtration rate; UPCR, urine protein to creatinine ratio; UACR, urine albumin to creatinine ratioESRD, end-stage renal disease; CKD, chronic kidney disease

EAG Key issue 7: Disease progression not reported (2)

Company comments after TE

- Clinical experts considered that disease progression to dialysis or transplant would not be expected within the 12-month timeframe of Part A of the NeflgArd Nef-301 trial.
- Reductions in proteinuria (UPCR, and/or UACR) are accepted as a surrogate endpoint for improved outcomes in IgAN by KDIGO, the EMA, and clinical experts in England.

EAG comments after TE

- 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.

Stakeholder comments

- NHS England agree UPCR and eGFR decline recognised as valid surrogates for disease progression to dialysis/transplantation by regulatory authorities such as the FDA
- Novartis agree information on events such as receipt of transplant or initiation of dialysis should be collected, but very few of these events would likely occur within trial timeframe of a 9-month trial.

Is it appropriate to exclude disease progression as an outcome in NeflgArd Nef-301?

Abbreviations: eGFR, estimated glomerular filtration rate; UPCR, urine protein to creatinine ratio; UACR, urine albumin to creatinine ratio; ESRD, end-stage renal disease; FDA, Food and Drug Administration, EMA, European Medicines Agency; KDIGO, Kidney Disease Improving Global Outcomes

EAG Key issue 10: Data source for estimating the transition from CKD 4 to CKD 5 (1)

Company

- CKD 4 patients were not eligible for NefIgArd Nef-301, so transition probability from CKD 4 to CKD 5 in the SoC arm informed using RWE from people with IgAN and UPCR ≥1.5 g/g from UK RaDaR database.
- 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, which were then used to fit different parametric survival models.

EAG comments

- Data from UK RaDaR does not properly distinguish between ESRD or death event cases, so estimated transition probabilities from CKD 4 to CKD 5 not appropriately defined.
- This data is likely overestimating the risk of ESRD as they are also accounting for the risk of death and so are not considered to be appropriate for the base case analysis.
- Additional survival data provided by the company at clarification stage revealed inconsistencies that were difficult to explain, and EAG suspects that this analysis was implemented incorrectly.
- So EAG prefers company scenario using RWE from Leicester General Hospital (LGH) patient registry for its base case analysis.

Abbreviations: CKD, chronic kidney disease; UPCR, urine protein to creatinine ratio; RWE, real world evidence; RaDaR, UK National Registry of Rare Kidney Diseases; ESRD, end-stage renal disease

EAG Key issue 10: Data source for estimating the transition from CKD 4 to CKD 5 (2)

Company comments after TE

- Maintains that 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 (alleviating concerns of double counting mortality in model)
  - additional assumptions required to adjust the LGH data from all patients transitioning to ESRD, not just CKD 4 patients, introduces more uncertainty in model due to additional source required to estimate
  - population from the RaDaR registry considered more reflective of the England population as data are received from multiple sites, compared to LGH data taken from a single site.

EAG comments after TE

- Based on the company's response, EAG is happy to accept the company's choice as the appropriate base case.

Which is the preferred data source for estimating transitions between CKD 4 to CKD 5?

Abbreviations: CKD, chronic kidney disease; RaDaR, UK National Registry of Rare Kidney Diseases; LGH, Leicester General Hospital

Company deterministic scenario analysis (1)

Scenario	Assumption	Incr. costs	Incr. QALYs	ICER per QALY
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
	50 years	[redacted]	[redacted]	£4,672
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

Company deterministic scenario analysis (2)

Scenario	Assumption	Incr. costs	Incr. QALYs	ICER per QALY
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
	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

Company deterministic scenario analysis (3)

Scenario	Assumption	Incr. costs	Incr. QALYs	ICER per QALY
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