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

Contains no ACIC information

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Key issues

EAG issue number	Description
2	Corticosteroids, MMF (mycophenolate mofetil) and SGLT2i may be relevant comparators for different subgroups
1	Applicability of trial evidence to those patients not on RASi therapy because of intolerance
8	Applicability of evidence – baseline characteristics
9	Insufficient evidence regarding retreatment of patients

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.

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.

Symptoms and prognosis

- Asymptomatic in early stages. 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 & technology

No NICE guidance 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)
- Corticosteroids not commonly used due to side effects
- **TRF-budesonide to be used here as add-on treatment alongside SoC**

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
Mechanism of action	• Targeted suppression of mucosal B-cells in the ileum, a primary site of IgA antibody production, reducing effects of IgA build-up in the kidneys
Administration	• 16 mg once daily for 9 months • Re-treatment may be considered by treating physician
Price	• Company has a simple patient access scheme (PAS) discount, which is included in the cost effectiveness results

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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

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"

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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

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

Background

- Company consider corticosteroids not relevant comparator: used only rarely due to "important risk of treatment-emergent toxicity" (KDIGO guidelines).
- Mycophenolate mofetil (MMF) an option for Chinese people only (KDIGO guidelines).
- SGLT2i not currently recommended for use in IgAN, but dapagliflozin approved for CKD (TA775) and clinical experts expect it to be used as part of SoC for IgAN.

EAG comments

- Still a small subgroup for whom corticosteroids/immunosuppressants are indicated, and who would receive TRF-budesonide, so a relevant comparator regardless of their limited use. Same for MMF.

Clinical expert comments

- CS and MMF not part of SoC. Most UK nephrologists will not use these for IgAN.

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

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Abbreviations: KDIGO, Kidney Disease Improving Global Outcomes; CS, corticosteroids; SLGT2i, Sodium-glucose cotransporter-2 inhibitor; SoC, standard of care; CKD, chronic kidney disease; MMF, mycophenolate mofetil

Clinical effectiveness

NICE National Institute for Health and Care Excellence

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

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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

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

Background

- Company population defined according to marketing authorisation (MA), people having TRF-budesonide should be on a stable dose of maximally tolerated RASi therapy.

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 concerned that evidence presented not applicable to people for whom any dose of RASi not tolerated because only 6 people who did not receive RASi therapy in the trial.

Clinical expert comments

- All IgAN patients should be on RASi.

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

Abbreviations: TRF, targeted release formulation; RASi, renin-angiotensin system inhibitor

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; eGFR, estimated glomerular filtration rate

Key issue 8: Applicability of evidence

Background

- Company considers demographic and disease characteristics of trial population broadly reflect those of UK target population, as confirmed by UK clinical expert opinion.
- Proportion of males, females, and race ratio aligned with target population in England.

EAG comments

- Company claim not supported by evidence from UK RaDaR study.
- 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.
- 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

NeflgArd Nef-301 Part A and B results: UPCR and eGFR

TRF-budesonide shows benefit on UPCR and eGFR at 9 months and this benefit is maintained after stopping treatment

UPCR (g/g) in patients with a baseline UPCR ≥1.5 g/g

Timepoint (months)	TRF-budesonide vs placebo; ratio of geometric LS means (95% CI); p value	% change vs placebo
9 (part A [redacted])	[redacted]	[redacted]
9 (part B [redacted])		
24		

eGFR (mL/min/1.73 m2) in patients with a baseline UPCR ≥1.5 g/g

Timepoint (months)	TRF-budesonide vs placebo. Ratio of geometric LS means (95% CI); p value	% change vs placebo
9 (part A [redacted])	[redacted]	[redacted]
9 (part B [redacted])		
24		

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

	CS or IST
TRF-budesonide 16 mg/day	[redacted]

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

	CS or IST	Dapagliflozin
TRF-budesonide 16 mg/day	[redacted]	[redacted]

EAG noted concerns with selection of studies for ITCs not being systematic

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

Cost effectiveness

NICE National Institute for Health and Care Excellence

How company incorporated evidence into model

Company used a 7-state transition model. Health states defined by kidney disease severity

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; eGFR, estimated glomerular filtration rate; RaDaR, UK National Registry of Rare Kidney Diseases; HTA, health technology assessment; CKD, chronic kidney disease; SoC, standard of care

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

Background

- 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.
- Proportion of people on retreatment informed by TTD curve observed in the trial.

EAG comments

- Uncertainty regarding retreatment, specifically assumptions used to inform retreatment parameters: timing and effectiveness of retreatment, percentage of people retreated.
- Asked company to explore impact of alternative assumptions.
- Agree with updated company base case model: 75% will have retreatment (mid-point of 2 clinical opinions), assumed treatment effect of later rounds updated to 90% to reflect uncertainty that it will be equally effective as first round of treatment.
- Still uncertain and has a relatively large impact on the ICER, so remains for discussion.

Stakeholder comments

- Clinical expert expects all patients will be retreated, likely every 18-36 months. Predicts a response similar to that seen with initial treatment regimen.

Are company's retreatment assumptions appropriate for decision making?

Abbreviations: TRF, targeted-release formulation; TTD, time to treatment discontinuation; 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

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			£7,863
	100% of initial effectiveness			£1,748
	50% of eligible patients			£5,521
	100% of eligible patients			£4,456
	Retreatment at 24 months			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

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

Key issues

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