Voclosporin with immunosuppressives for treating lupus nephritis

For public observers – ACIC information redacted [redacted]

Slides 21, 24, 30, 39 and 40 updated post ACM1

Technology appraisal committee D [02 November 2022]

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Updated approach to health technology evaluations: new methods and processes

This topic uses NICE's updated methods for health technology evaluations, 2022: https://www.nice.org.uk/process/pmg36/chapter/introduction-to-health-technology-evaluation

Updates fall under 5 headings:

- Valuing the benefits of health technologies
- Understanding & improving the evidence base
- Structured decision making
- Challenging circumstances and evaluations
- Aligning methods across programmes

Including:

- Severe and end-of-life conditions ("modifiers")
- Presenting and considering uncertainty
- Technical updates – including comprehensive evidence base
- Consolidation and alignment for different technology types (medicines, devices, diagnostics)

Background on lupus nephritis

LN is divided into classes and can lead to increased risk of ESRD and death

Causes

- Systemic lupus erythematosus (SLE) is a chronic condition that causes inflammation in connective tissues, occurring when the immune system attacks the body's tissues and organs
- Lupus nephritis (LN) happens when SLE involves the kidneys, specifically glomeruli cells

Epidemiology

- Each year around 3,000 people will be diagnosed with SLE in England and Wales, about 40% to 60% of whom will develop LN
- Women with Indian-Asian, African-Caribbean or Chinese family backgrounds are most diagnosed

Diagnosis, symptoms and prognosis

- LN is divided into classes (1 to 6) based on glomerular pathology
- Symptoms of LN include blood or foam in urine, swelling in extremities and high blood pressure
- Untreated LN can permanently damage kidneys, leading to increased risk of ESRD and mortality
- There is no cure for LN, treatment aims to preserve renal function and prevent disease flares

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Abbreviations: ESRD, end-stage renal disease; LN, lupus nephritis; SLE, systemic lupus erythematosus

Voclosporin (Lupkynis, Otsuka Pharmaceuticals)

Table 1 Technology details

Marketing authorisation	• Voclosporin in combination with MMF for the treatment of adult patients with active class 3, 4 or 5 (including mixed class 3/5 and 4/5) LN • EMA licence granted in September 2022, MHRA licence expected soon via EU reliance procedure, guidance will only be published once MHRA licence received
Mechanism of action	• Voclosporin is a CNI immunosuppressant which inhibits lymphocyte proliferation, T-cell cytokine production and expression of T-cell activation surface antigens • The mechanism potentially reduces in kidney inflammation and tissue damage
Administration	• The recommended dose of voclosporin + MMF is 23.7mg of voclosporin twice daily and 1g of MMF twice daily, both self-administered as oral capsules • Treatment continuation informed by risk-benefit analysis at 24 weeks (at least)
Price	• List price for voclosporin of [redacted] per 180 pack of 7.9 mg soft capsules • List price for MMF of £6.83 per 50 pack of 500 mg tablets • 12-month list price of voclosporin and MMF: [redacted] • A patient access scheme is available for voclosporin

Abbreviations: CNI, calcinerium inhibitor; EC, European Commision; EMA, European Medicines Agency; LN, lupus nephritis; MHRA, Medicines and Health Regulatory Agency; MMF, mycophenolate mofetil

Decision problem

Comparators are uncertain and discussed on the next slide

Table 2 Population, intervention, comparators and outcomes from the scope

	Final scope	Company	EAG comments
Population	Adults with active LN	Same as final scope	-
Intervention	Voclosporin with immunosuppressive therapies	Same as final scope	-
Comparators	Standard therapy for LN without voclosporin: • including the following induction treatments MMF, CYC, AZA, RTX, a CNI plus MMF (typically given with corticosteroids) • followed by maintenance treatment with MMF or AZA plus corticosteroids	Same as final scope	MMF considered main comparator but uncertainty remains
Outcomes	• Renal response, remission and renal events • Incidence of end-stage renal disease • Corticosteroid use • Mortality • Adverse events • Health-related quality of life	Same as final scope	-

Abbreviations: AZA, azathioprine; CNI, calcinerium inhibitor; CYC, cyclophosphamide; LN, lupus nephritis; MMF, mycophenolate mofetil; RTX, rituximab

Key issues

Some areas of uncertainty may be unresolvable and are for discussion

Table 3 Key issues not resolved during technical engagement for discussion

Issue	ICER impact
What is the appropriate positioning for voclosporin + MMF in practice?	Unknown
Is the company's model appropriate for decision-making?	Large
Is a stopping rule for voclosporin + MMF appropriate?	Unknown

Table 4 Additional areas of uncertainty for discussion that currently cannot be resolved

Area of uncertainty	ICER impact
Are the pivotal AURORA trials generalisable to the NHS?	Unknown
Are fixed effects or random effects NMAs more appropriate for decision-making?	Small
Can long-term treatment effects be estimated from short-term data?	Unknown

Abbreviations: MMF, mycophenolate mofetil; NHS, National Health Service

Patient perspectives

LN is debilitating and current treatments offer limited choices

Submissions from patient experts, AOFAC Foundation and Lupus UK

- Most challenging aspects of LN are the symptoms and the subsequent impact on ability to work and mental wellbeing
- Fatigue (81%) and joint pain/swelling (60%) reported as the most difficult symptoms to live with: “Daily, I have to push myself”
- LN significantly impacts independence as 58% of people with LN need help with household care, 1 in 3 need help with personal care
- Significant impact on carers for people with LN due to helping with daily tasks, socialising and working less, constant worry for their health
- 57% of people with LN feel isolated once a week
- Current treatments mostly have debilitating side effects leading to other illnesses, especially with steroids
- Oral administration of voclosporin a real benefit in reducing hospital visits but the need to swallow a whole tablet may be a barrier for some

“[Being a carer] can be difficult at times…you feel so helpless…there are days when their joints are so swollen that I need to do everything; bathe, help dress, prepare meals”

“My care has always been great but it was trying to choose the lesser evil…led to further illnesses and burdens…destroyed my immune system”

Abbreviations: AOFAC, Athonia Oyindamola Folakemi Afelumo Coshare; LN, lupus nephritis

Clinical perspectives

Treatments take time to improve outcomes, but cause adverse effects

Submissions from clinical experts, BSR, UKKA and UK RPG

- High unmet need as LN is not curable, leads to a cycle of relapsing and remitting and some patients disease does not respond leading to ESRD
- Initial treatments aim to induce remission, with maintenance treatments given to maintain remission. Also aim to reduce organ damage and adverse events, improve symptoms and quality of life
- Recently steroids have been suggested as the cause of side effects, use is therefore tapered/stopped. Ideal dosage is uncertain
- Treatment response measured in imperfect ways, can take a year or more for meaningful disease marker changes
- Current treatments have adverse effects causing direct morbidities, contributing to non-compliance, some people do not respond
- Voclosporin may be less effective for some people due to high pill burden impacting adherence and swallowing difficulty

"There are problems with adverse effects of current therapies which have direct morbidities and also contribute to non-compliance"

"Voclosporin + MMF would be a triple therapy as a first option rather than MMF dual therapy"

Abbreviations: BSR; British Society for Rheumatology; ESRD, end-stage renal disease; RPG, Renal Pharmacy Group; LN, lupus nephritis; MMF, mycophenolate mofetil; UKKA, United Kingdom Kidney Association

Equality considerations

Poorer outcomes for some people and fertility concerns

- People with Indian-Asian, African-Caribbean and Chinese family backgrounds are more likely to have poorer outcomes
- SLE disproportionately affects women and commonly presents in those of childbearing age
- Risk of infertility from cyclophosphamide (though use in the NHS is limited for this reason) and risk of teratogenicity (birth defects in a developing foetus) from cyclophosphamide and MMF*
- Some people living in more remote parts of the country, those with mobility issues, or those on lower incomes may have difficulties travelling to treatment centres. Orally administered treatments such as voclosporin may present fewer barriers to access

Does the committee consider that there are any relevant equality or health inequality issues that it should consider in its decision making, and if so how?

*Note that voclosporin will also be given with MMF

Abbreviations: MMF, mycophenolate mofetil; SLE, systemic lupus erythematosus

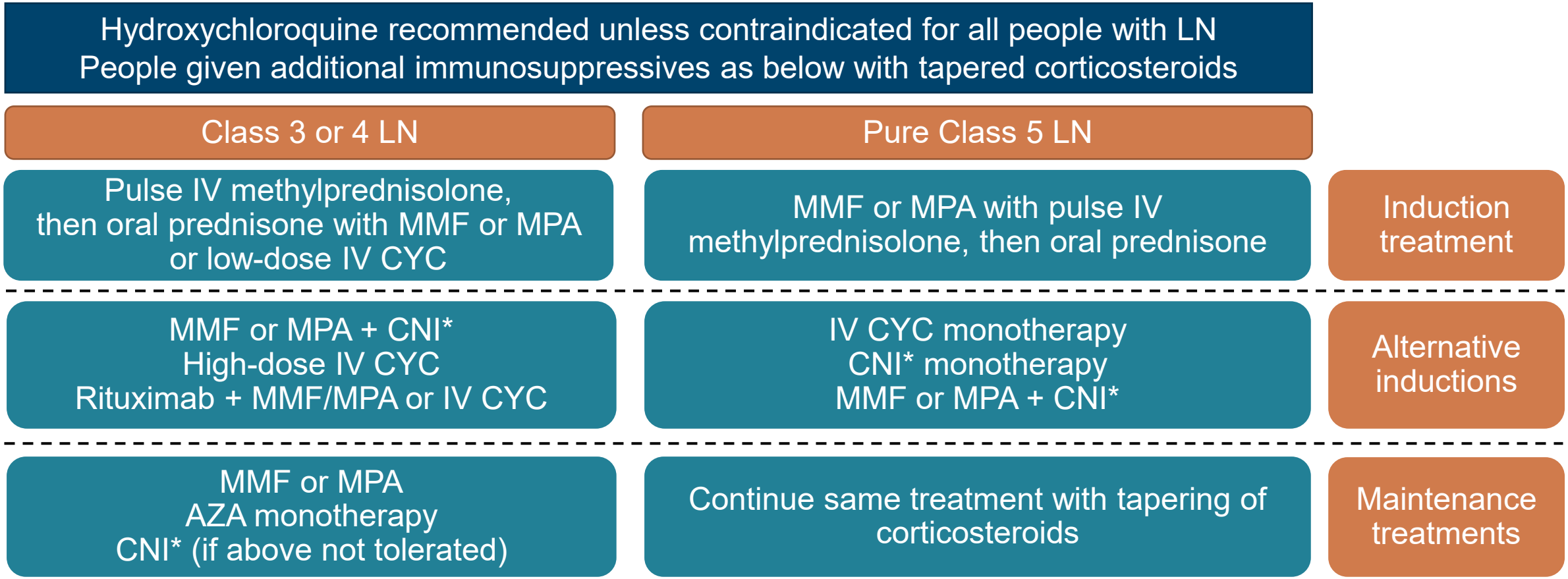
Clinical effectiveness

NICE National Institute for Health and Care Excellence

Treatment pathway

Treatments vary by LN class and are given with tapered corticosteroids

Figure 1 Treatment pathway



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Abbreviations: AZA, azathioprine; CNI, calcinerium inhibitor; CYC, cyclophosphamide; IV, intravenous; LN, lupus nephritis; MMF, mycophenolate mofetil; MPA, mycophenolic acid

***CNI = tacrolimus or ciclosporin**

Key issue: Clinical positioning of voclosporin

Stakeholders disagree on voclosporin's primary treatment line

Background

- LN is highly heterogeneous, the way in which people receive treatment in NHS varies significantly
- Voclosporin treatment line may impact clinical and cost effectiveness

Company

- Noted that marketing authorisation does not specify a treatment line for voclosporin
- Highlight the pivotal trial results (notably CRR) include participants at differing treatment lines

Stakeholder comments

- **BSR/clinical expert:** expect to be used as per trial (first-line and add-on for those who fail on MMF)
- **NHSE:** hesitation for first-line use as lack of long-term evidence, refractory use more likely

EAG comments

- Stakeholders disagree on voclosporin's main treatment line (first or second), EAG unable to resolve
- Stakeholders agree with EAG that voclosporin positioning will affect its cost-effectiveness
- MMF alone suitable first-line comparator, tacrolimus + MMF likely suitable second-line comparator

What is the appropriate position for voclosporin + MMF?
How is voclosporin likely to be used in clinical practice?

Abbreviations: BSR, British Society for Rheumatology; CRR, complete renal response; EAG, evidence assessment group; LN, lupus nephritis; MMF, mycophenolate mofetil; NHSE, National Health Service in England

Key clinical trials

Primary evidence is from two trials, the second a continuation of the first

Table 5 Clinical trial designs and outcomes

	AURORA 1 (N=357)	AURORA 2 (N=216)
Design	Phase 3, multicentre, double-blind, placebo-controlled, randomised trial	Phase 3, multicentre, double-blind, placebo-controlled, randomised, 24-month long-term continuation study for AURORA 1 patients who completed study and were not expected to require renal dialysis or kidney transplant. Primary outcomes were safety, efficacy and HRQoL are secondary outcomes.
Population	Adults with active LN	
Intervention	Voclosporin + MMF and low-dose corticosteroids	
Comparator(s)	Placebo + MMF and low-dose corticosteroids	
Duration	52 weeks (12 months)	
Primary outcome	CRR at 52 weeks	
Key secondary outcomes	Time to changes in UPCR; PRR at 24 and 52 weeks; CRR at 24 weeks; HRQoL; adverse events	
Locations	142 sites in 27 countries (none in UK)	
Used in model?	Baseline characteristics; transition probabilities; utilities; costs and resource use, adverse events	

Abbreviations: CRR, complete renal response; HRQoL, health-related quality of life; LN, lupus nephritis; MMF, mycophenolate mofetil; N, number of patients; PRR, partial renal response; UPCR, urine protein creatinine ratio

AURORA 1 trial results

Voclosporin significantly improves renal response up to 52 weeks

Table 6 AURORA 1 response outcomes results

	Voclopsorin + MMF (N=179)	Placebo + MMF (N=178)	Odds Ratio [95% CI]
CRR at 24 weeks	32.4%	19.7%	2.23 [1.3, 3.7]
CRR at 52 weeks	40.8%	22.5%	2.65 [1.6, 4.3]
PRR at 24 weeks	70.4%	50.0%	2.43 [1.56, 3.79]
PRR at 52 weeks	69.8%	51.7%	2.26 [1.45, 3.51]

Urine protein creatinine ratio (UPCR) measures the levels of protein and creatinine in urine, UPCR ≤0.5mg/mg can be a component of CRR

Figure 2 Probability of UPCR ≤0.5mg/mg

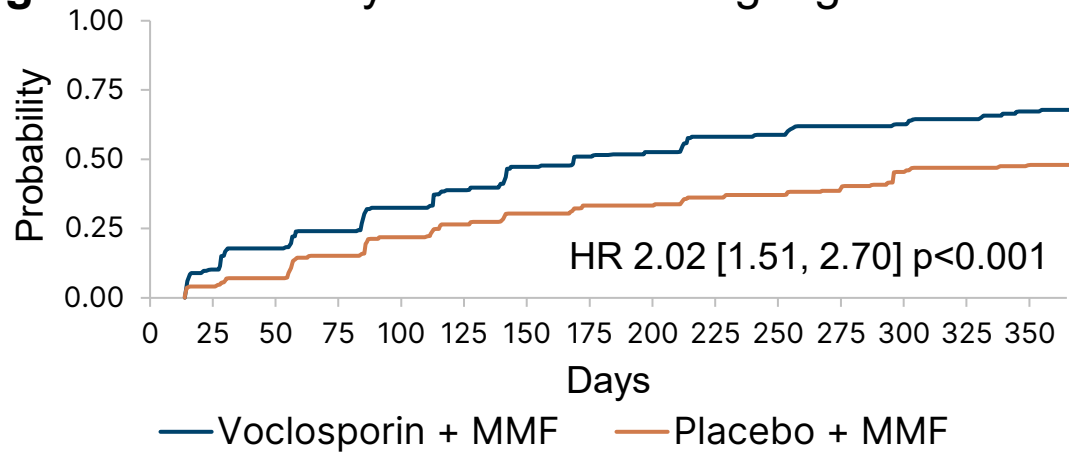
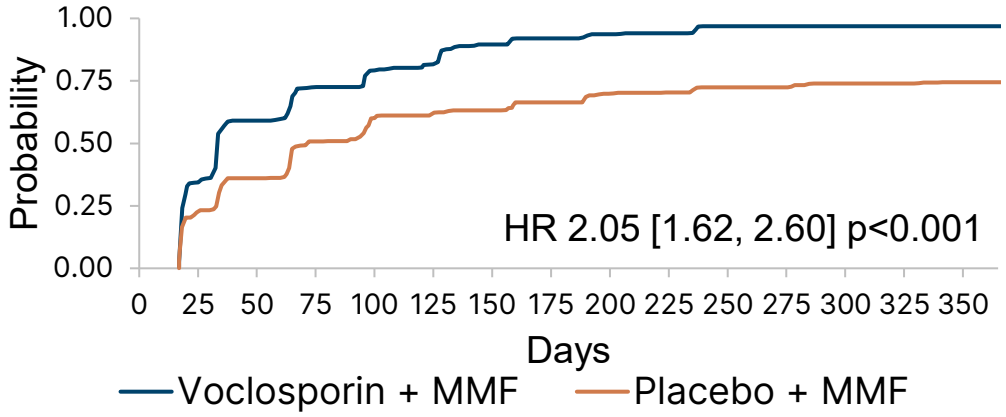


Figure 3 Probability of 50% reduction in UPCR



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Abbreviations: CI, confidence interval; CRR, complete renal response; HR, hazard ratio; MMF, mycophenolate mofetil; N, number of patients; PRR, partial renal response; UPCR, urine protein creatinine ratio

AURORA 2 trial results

Voclosporin improves renal response up to 30 months, less clear after

Table 7 AURORA 2 response outcomes results

	Voclosporin + MMF (N=116)	Placebo + MMF (N=100)	Odds Ratio [95% CI]
CRR at 18 months	[redacted]	[redacted]	[redacted]
CRR at 24 months	[redacted]	[redacted]	[redacted]
CRR at 30 months	[redacted]	[redacted]	[redacted]
CRR at 36 months	[redacted]	[redacted]	[redacted]
PRR at 18 months	[redacted]	[redacted]	[redacted]
PRR at 24 months	[redacted]	[redacted]	[redacted]
PRR at 30 months	[redacted]	[redacted]	[redacted]
PRR at 36 months	[redacted]	[redacted]	[redacted]

CRR is defined as a composite of UPCR of ≤0.5 mg/mg, eGFR of ≥60 ml/min/1.73^2 or no confirmed eGFR decrease of >20% from baseline, no rescue medication, and no more than 10 mg prednisone equivalent per day for ≥3 consecutive days or for ≥7 days in total during weeks 44–52

PRR defined as ≥50% reduction in UPCR from baseline

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Abbreviations: CI, confidence interval; CRR, complete renal response; eGFR, estimated glomerular filtration rate; MMF, mycophenolate mofetil; N, number of patients; PRR, partial renal response

NMA methodology: comparators

The NMA included CRR and PRR data for most comparators

Table 8 Comparators included in NMA and implied voclosporin treatment line

Comparator	NMA outcome	Implied voclosporin treatment line	Other considerations
MMF	Reference treatment for the NMA	1. Induction first-line 3. Maintenance	**Considered relevant comparator by EAG**
Voclosporin + MMF	CRR and PRR	-	Intervention
Azathioprine	CRR only	3. Maintenance	
High-dose cyclophosphamide	CRR and PRR	2. Induction alternative	Stakeholders suggest rarely used in NHS due to toxicity
Low-dose cyclophosphamide	CRR and PRR	1. Induction first-line	
Rituximab + MMF	CRR and PRR	2. Induction alternative	First-line use prohibited in current NHSE guidance
Tacrolimus	CRR and PRR	2. Induction alternative 3. Maintenance	Other CNI ciclosporin less used
Tacrolimus + MMF	CRR only	2. Induction alternative	**Considered relevant comparator by EAG**

Abbreviations: CRR, complete renal response; MMF, mycophenolate mofetil; NMA, network meta-analysis; PRR, partial renal response

Cost effectiveness

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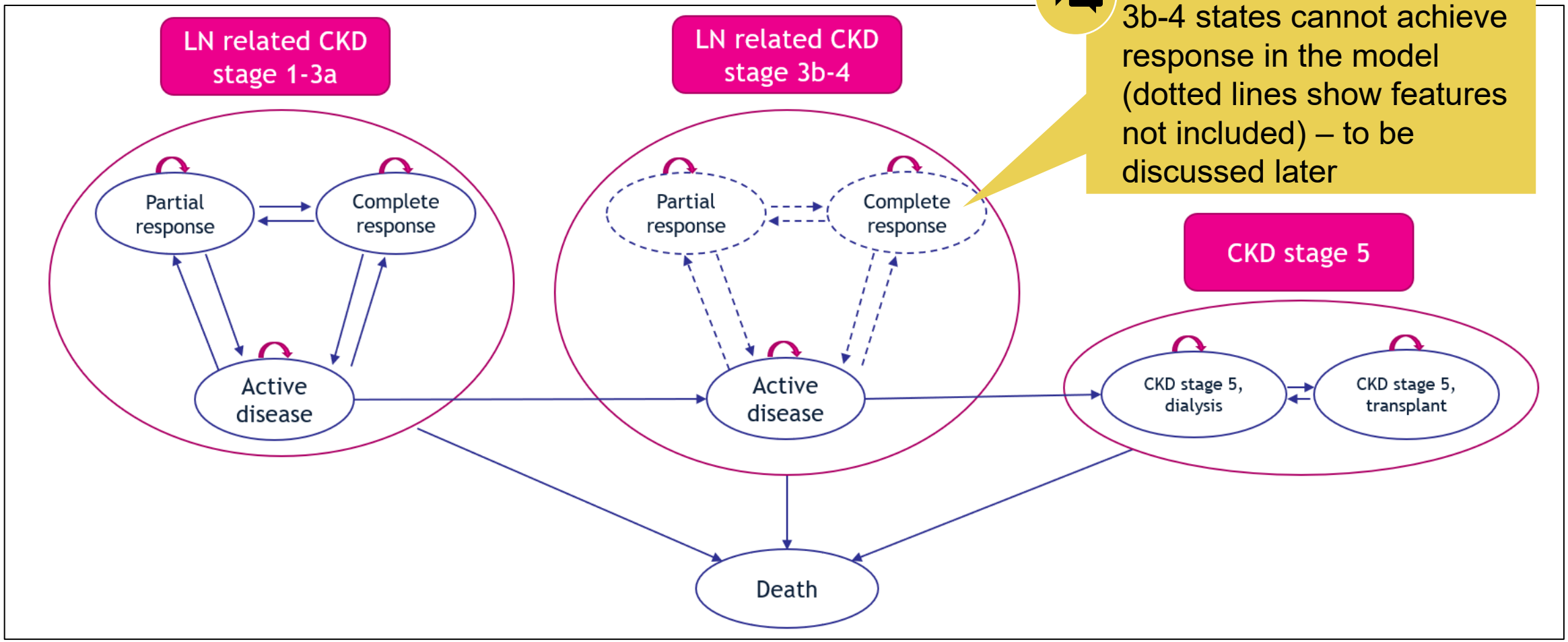
Company's model overview (1)

The company developed a cohort-level state-transition Markov model

Figure 4 Model structure



Abbreviations: CKD, chronic kidney disease; LN, lupus nephritis

Company's model overview (2)

Inputs and assumptions that affects costs and QALYs

- **Technology affects costs by:**
  - Drug costs for voclopsorin
  - Delaying/avoiding time spent in more expensive CKD health states (e.g., CKD 5)

- **Technology affects QALYs by:**
  - Increasing the rate of CRR
  - Increasing the rate of PRR
  - Reducing the risk of CKD progression

- **Assumptions with greatest ICER effect:**
  - Absolute and relative short term treatment effects can inform long term treatment effects

Abbreviations: CKD, chronic kidney disease; CRR, complete renal response; ICER, incremental cost-effectiveness ratio; LN, lupus nephritis; QALY, quality-adjusted life year

How company incorporated evidence into model

AURORA 1 and 2 data contributed most evidence used in the model

Table 9 Input and evidence sources for non-efficacy inputs

Input	Assumption and evidence source
Baseline characteristics	AURORA 1 and AURORA 2 patient data
Transition probabilities	AURORA 1 and 2 data; NMA; literature; expert opinion; assumptions
Utilities	AURORA 1/2 data for health states CKD 1-3a, literature for CKD 3b-5
Costs and resource use	NHS reference costs, PSSRU Unit Costs of Health and Social Care, previous NICE appraisals, clinical trial and observational data, disease treatment guidelines
Adverse events	AURORA 1 for voclosporin + MMF and MMF, literature for others

Abbreviations: CKD, chronic kidney disease; MMF, mycophenolate mofetil; NHS, national health service; NMA, network meta-analysis; PPSRU, Personal Social Services Research Unit

Key issue: The company's model (1)

Issues with the company's model raised prior to technical engagement

Model structure

- People in CKD 3b-4 states cannot achieve response in the model
- CKD progression only possible from AD state, patients with response at no risk of CKD progression
- No CKD progression events in AURORA trials so CKD progression was disabled in the company's base-case analysis for the first 3 years, not expected in clinical practice
- Transition probabilities were derived via count method and may be overestimated
- Very few within-trial deaths, cause of death not captured but is modelled to incur differential costs

Model transparency

- EAG: several input transparency issues including inputs which did not match source material, inconsistent inflation of costs, and non-systematic identification of drug costs
  - Also identified modelling issues related to coding and formulas for transition probabilities

Modelled costs

- EAG: fundamental misinterpretation between RDI and TTD – treatment discontinuation is captured via TTD but dose adjustments are not reflected through RDI
- Incorrect dose of MMF used and costed for in the model
- TTD assumed to be 100% for non-trial comparators, inappropriate as some people will discontinue
- Therapeutic drug monitoring costs for the voclosporin arm were excluded (in contrast to tacrolimus)

Abbreviations: AD, active disease; CKD, chronic kidney disease; EAG, evidence assessment group; MCAR, missing completely at random; MMF, mycophenolate mofetil; RDI, relative dosing intensity; TTD, time to treatment discontinuation

Key issue: The company's model (2)

Justifications and revisions made to the company base case

Model structure

- Aligned with EAG on CKD progression from stage 1-3a to stage 3b-4 ✓
- Only ~2.5% of people in CKD 3b-4 states would achieve response so not included in model ?
- CKD progression only possible from AD states, is a simplification but no supportive data otherwise ?
- Maintain the count method for transition probabilities, other statistical approaches failed ?
- LN-related death costs were updated in CKD stages 1-3a for background mortality costs instead, LN-related deaths from CR and PR health states removed ✓

Model transparency

- Corrected the modelling errors identified by the EAG and checked input alignment with sources ✓
- Assert that model input parameters are verified and accurate to inform decision making ✓

Modelled costs

- Agree with EAG changes to RDI percentages for non-trial comparators (apart from tacrolimus) ✓
- Wastage costs and MMF doses updated as per EAG suggestions ✓
- No change to TTD for non-trial comparators with no discontinuation assumed for these treatments ?
- Extra CNI monitoring cost for voclosporin not added (to align with tacrolimus) due to improved immunosuppressive potency and safety profile and broader therapeutic index of voclosporin ?

NICE ✓ Resolved – company aligned with EAG ? Not resolved, disputed with EAG

Abbreviations: AD, active disease; CKD, chronic kidney disease; CNI, calcinerium inhibitor; CR, complete response; EAG, evidence assessment group; LN, lupus nephritis; MMF, mycophenolate mofetil; PR, partial response; RDI, relative dosing intensity; TTD, time to treatment discontinuation

Key issue: The company's model (3)

Issues that are still considered unresolved by the EAG

Model structure

- Stakeholder uncertainty: progression/response assumptions, uncaptured effects on immunity and fertility
- People in CKD 3b-4 states still cannot achieve response in the model, should be included
- Transition probabilities still derived via count method and may be overestimated
- Kidney transplantation rates are too high in the company model compared to clinical advice to EAG

Model transparency

- Found additional issue affecting AE disutility calculations, cannot say there are no further accuracy edits

Modelled costs

- Clinical advice to EAG was to include drug monitoring costs for all CNI inhibitors, monitoring of kidney function and blood results would be anticipated for people treated with voclosporin
- SmPC for voclosporin says "careful monitoring of renal function is recommended"
- Company model discontinuation for MMF (using AURORA data) but assume no discontinuation for other comparators, EAG argue not reflective of clinical practice and is implausible
- **Stakeholders/NHSE comments:** disagree on monitoring costs – some agree with the same costs for voclosporin as for tacrolimus, others think not needed for voclosporin, just regular eGFR tests

Is the company's model appropriate for decision-making?

Abbreviations: AE, adverse event; CKD, chronic kidney disease; CNI, calcinerium inhibitor; EAG, evidence assessment group; eGFR, estimated glomerular filtration rate; MMF, mycophenolate mofetil; SmPC, Summary of Product Characteristics

Key issue: Estimating long-term outcomes

Long-term outcomes are uncertain and unlikely to be resolved

Background

- Lack of long-term trial data requires extrapolated data for approx. 69 years (3 years to 72 years)
- Assumption that short-term on-treatment data is reflective of long-term off-treatment outcomes

Company

- Added treatment waning assumption to long-term transition probabilities by combining 30- and 36-month transition probabilities for all disease states to reflect post-treatment outcomes
- For AD and PR, assume voclosporin + MMF transitions match MMF alone transitions
- For CR, assume voclosporin + MMF transitions equal average of voclosporin + MMF and MMF alone
- Other comparators' long-term outcomes are informed by AD health state from the NMA

EAG comments

- For all states, voclosporin and MMF are equivalent, using 30 and 36-month transition average of both arms
- Still considerable uncertainty in using short-term data for long-term outcomes, unlikely to be resolved without long-term data and/or input from clinical experts
- Stakeholders highlight that a long-term treatment effect is an unproven assumption, short-term benefits may not persist but are associated with better long-term outcomes

NICE Is the level of uncertainty associated with long-term extrapolations acceptable?

Abbreviations: AD, active disease; CR, complete response; MMF, mycophenolate mofetil; NMA, network meta-analysis; PR, partial response

Key issue: Duration of treatment

The company's modelled stopping rule is uncertain

Background

- MA for voclosporin specifies no explicit stopping rule, suggests risk-benefit analysis at 24 weeks
- Company's model stops treatment at 36-months, in line with availability of AURORA trial data

Company

- Notes in AURORA 2 that 87.1% of voclosporin patients reached Month 36 of treatment
- Clinical expert advice supported a 36-month stopping rule

EAG comments

- Tentatively accepts 36-month stopping rule in model based on company and EAG clinical advice
- Notes differing stakeholder opinions, treatment length may also be key cost-effectiveness driver
- Links closely to key issue on estimating long-term outcomes due to assuming time on treatment

Stakeholder comments

- Treatment duration will vary a lot by person but expect two years to be sufficient for response
- Some patients will be treated beyond 36-months but would be MMF alone and not in combination
- Would be illogical to stop a treatment if response is being achieved, can take time to respond

NICE

Does a 36-month treatment duration reflect expected use in NHS practice?
Is it appropriate for a 36-month stopping rule to be implemented into guidance?

Abbreviations: EAG, evidence assessment group; MA, marketing authorisation

Other issues for committee's attention

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Key issue: Generalisability of AURORA trials

Uncertain steroid use and no UK centres in AURORA trials

Background

- AURORA trials did not include any UK centres or patients
- Clinical expert advice to NICE is that steroid use in trials is lower than NHS practice, may also disadvantage comparator arm due to sub-optimal dosing

EAG comments

- Generalisability of AURORA data unknown as trial did not have any UK centres
- Clinical advice to the EAG agrees that steroid dose is lower than typical practice but the dose is still efficacious and consistent with guidelines for reducing dose to reduce AEs
- No quality evidence for optimal steroid use, voclosporin may provide AE benefit with low steroid use

Clinical expert advice to NICE

- Clinical practice does not always follow steroid use as in clinical trials
- Steroid use in trial is less than previously recommended by KDIGO guidelines, also emphasise that there are no data to recommend what lower dose should be used
- Stand alone steroid use lower than usual, suspect this favours additional agent (voclosporin)

Are the pivotal AURORA trials generalisable to the NHS?

Abbreviations: AE, adverse event; EAG, evidence assessment group; KDIGO, Kidney Disease Improving Global Outcomes; NHS, National Health Service

Key issue: Accounting for heterogeneity in the NMA

The company presented fixed effects and random effects NMAs

Background

- The company presented fixed effects NMAs noting random effects NMAs were not converging
- EAG suggested using informative priors to show random effects NMAs were not converging
- Company presented random effects NMA for CRR/PRR during technical engagement, but did not use the new NMAs in their base case citing little impact to results and increased PSA uncertainty
- Odds ratios change little with random effects but wider confidence intervals increase uncertainty

EAG comments

- Implementation of the informative priors has generated more credible NMAs
- Issue not resolved as company did not use new NMAs, EAG prefers random effects NMAs
- Little impact between NMAs to the odds ratios for voclosporin + MMF vs MMF but impact likely to be escalated on the rest of the network estimates

Table 10 Fixed effects and random effects NMA odds ratios for voclosporin vs MMF

Outcome	Fixed effects	Random effects (general prior)	Random effects (subjective prior)
CRR	[redacted]	[redacted]	[redacted]
PRR	[redacted]	[redacted]	[redacted]

NICE Are fixed effects or random effects NMAs more appropriate for decision-making?

Abbreviations: CRR, complete renal response; EAG, evidence assessment group; MMF, mycophenolate mofetil; NMA, network meta-analysis; PRR, partial renal response

Cost-effectiveness results

All ICERs are reported in PART 2 slides

because they include confidential

comparator discounts

Summary

- Company's base case ICER against MMF is **within the range** that would usually be considered a cost-effective use of NHS resources
- EAG's base case ICER against MMF is **higher** than what would usually be considered a cost-effective use of NHS resources

Abbreviations: EAG, evidence assessment group; ICER, incremental cost-effectiveness ratio; MMF, mycophenolate mofetil; NHS, national health service

Company and EAG base cases and scenarios

Table 11 Key scenarios for committee to consider in decision making

Key issue/scenario	Company base case	EAG base case	ICER impact*
Model transparency: Fix issue affecting AE disutility calculations	All modelling and input errors are corrected	Additional issue found affecting AE disutility calculations	~-£100 ↓
Long-term effects: Transition probabilities after 36 months	**AD/PR states:** Voclosporin = MMF **CR state:** Voclosporin = MMF alone, using the 30- and 36-month average of both arms	Voclosporin = MMF alone, using 30/36-month average of both for all states	~+£6,000 ↑
Model structure: Percentage reduction in transplantation rates	90% within 2 years	65% within 2 years	~-£1,000 ↓
Treatment costs: Extra monitoring costs for CNIs	Extra cost for tacrolimus but not voclosporin	Extra cost for voclosporin not added but uncertain	~+£2,000 ↑

*Impact rounded to nearest £1,000 as confidential ICERs are shown in Part 2

Abbreviations: AD, active disease; AE, adverse event; CNI, calcinerium inhibitor; CR, complete response; ICER, incremental cost-effectiveness ratio; MMF, mycophenolate mofetil; PR, partial response; RDI, reduce dosing intensity

Key areas of uncertainty for committee to consider

Table 12 Key areas of uncertainty for committee to consider in decision making

Key issue/scenario	Uncertainty
What is the appropriate positioning for voclosporin + MMF in practice?	EAG consider uncertain
Is the company's model appropriate for decision-making? • Uncertainty in model structure, response unachievable from CKD 3b-4 • EAG do not consider model to be transparent • Uncertainty in additional monitoring costs for voclosporin	Alternative model not provided/cannot be provided
Can long-term treatment effects be estimated from short-term data?	EAG consider unresolvable
Is a stopping rule for voclosporin + MMF appropriate? • Does a 36-month treatment duration reflect expected use in NHS? • Is it appropriate for a 36-month stopping rule to be in guidance?	ICERs will increase but magnitude uncertain
Are fixed or random effects NMAs appropriate for decision-making? • Company used fixed effects NMA but EAG prefers random effects	Random effects NMA not used in model
Are the pivotal AURORA trials generalisable to the NHS? • No UK centres and lower steroid use than clinical practice	Clinical effects may lack external validity

Abbreviations: CKD, chronic kidney disease; EAG, evidence assessment group; ICER, incremental cost-effectiveness ratio; MMF, mycophenolate mofetil; NHS, national health service; NMA, network meta-analysis

Uncertainty in the new methods and processes : maintaining and updating our approach

Understanding and presenting uncertainty

- Improvements to ensure uncertainty is thoroughly characterised, clearly presented and fully understood

Considering uncertainty in decision making

- Retain critical consideration of uncertainty and decision risk
- Ensure no inappropriate barriers, through formalised flexibility with uncertainty

Maintain key principle: more caution when there is less certainty about the evidence

Low uncertainty, low decision risk = **more likely to recommend**	High uncertainty, high decision risk = **less likely to recommend**

Clarify and formalise flexibility: higher uncertainty may be considered when evidence generation is difficult:

- Rare diseases
- Populations including children
- Innovative and complex technologies

Other considerations

Uncaptured benefits raised by the company

- Reduced monitoring burden compared to current CNIs (disputed by EAG)
- Oral administration reduces hospital visits and improves quality of life for people with lupus nephritis

Are there any benefits not captured in the QALY calculation?

Abbreviations: CNI, calcinerium inhibitor; EAG, evidence assessment group

NICE National Institute for Health and Care Excellence

Thank you.

Back up slides

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NMA methodology

RCTs included in the NMA were identified by SLR

SLR conducted identified 44 RCTs that evaluated the efficacy and safety of active treatments in people with active LN

Studies screened to identify those reporting CRR and PRR for comparators, to inform short term efficacy inputs in the model

17 RCTs reporting on 8 treatments for CRR

10 RCTS reporting on 6 treatments for PRR

NICE

Abbreviations: CRR, complete renal response; LN, lupus nephritis; NMA, network meta-analysis; PRR, partial renal response; RCT, randomised controlled trial; SLR, systematic literature review

NMA network diagrams

Systematic literature review identified 17 RCTs reporting on 8 treatments for CRR and 10 RCTS reporting on 6 treatments for PRR which were used in CRR and PRR NMAs

Figure 5 NMA network for CRR

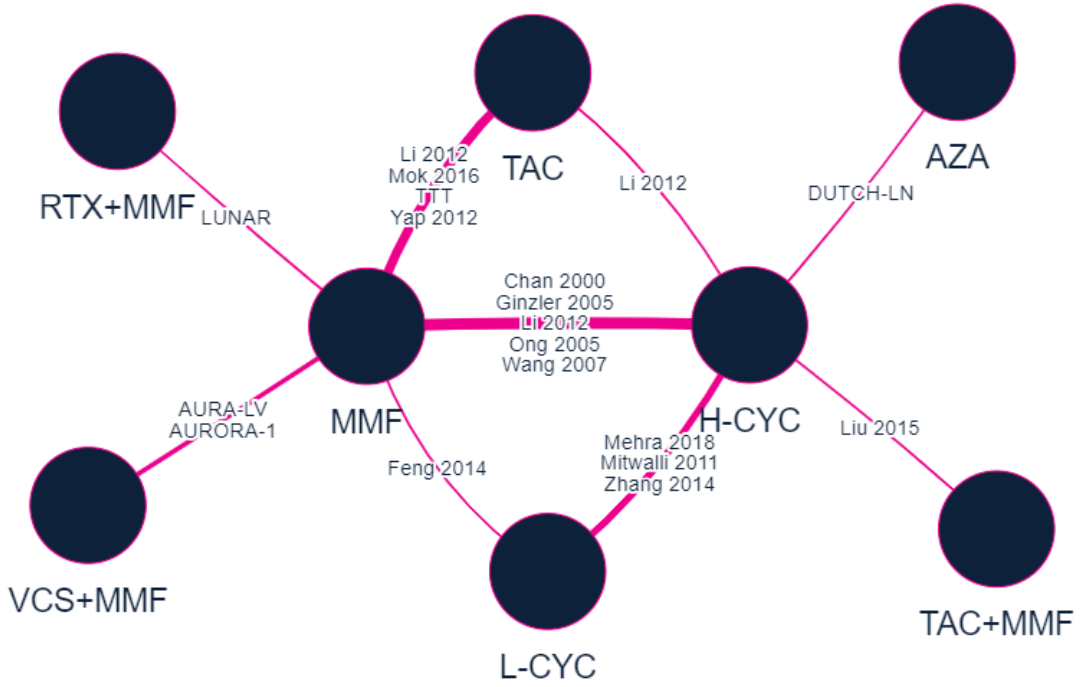
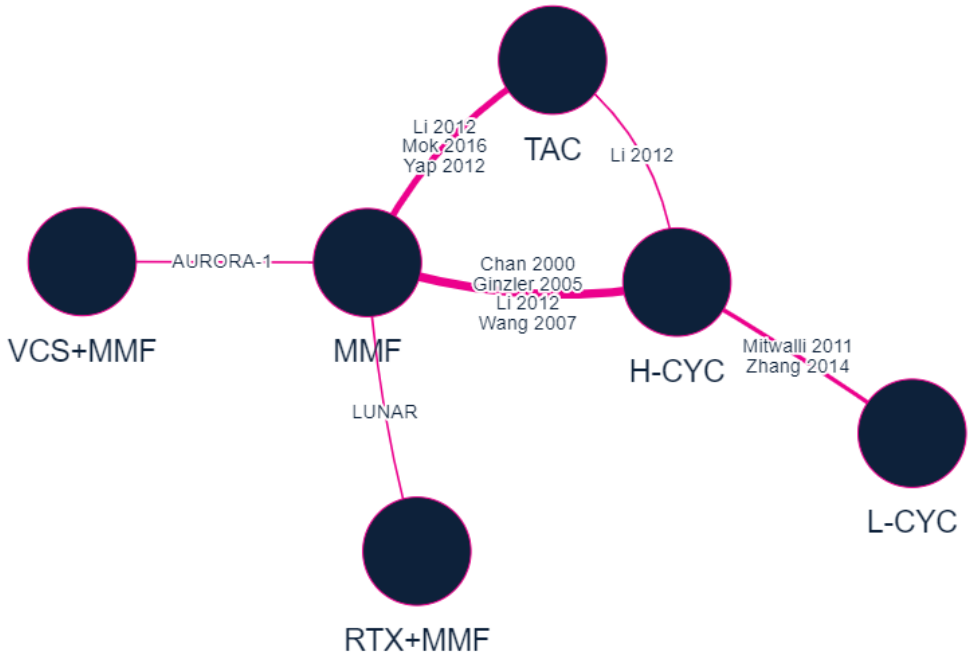


Figure 6 NMA network for PRR



Abbreviations: AZA, azathioprine; CRR, complete renal response; H-CYC, high-dose cyclophosphamide; L-CYC, low-dose cyclophosphamide; MMF, mycophenolate mofetil; NMA, network meta-analysis; PRR, partial renal response; RCTs, randomised controlled trials; RTX, rituximab; TAC, tacrolimus; VCS, voclosporin

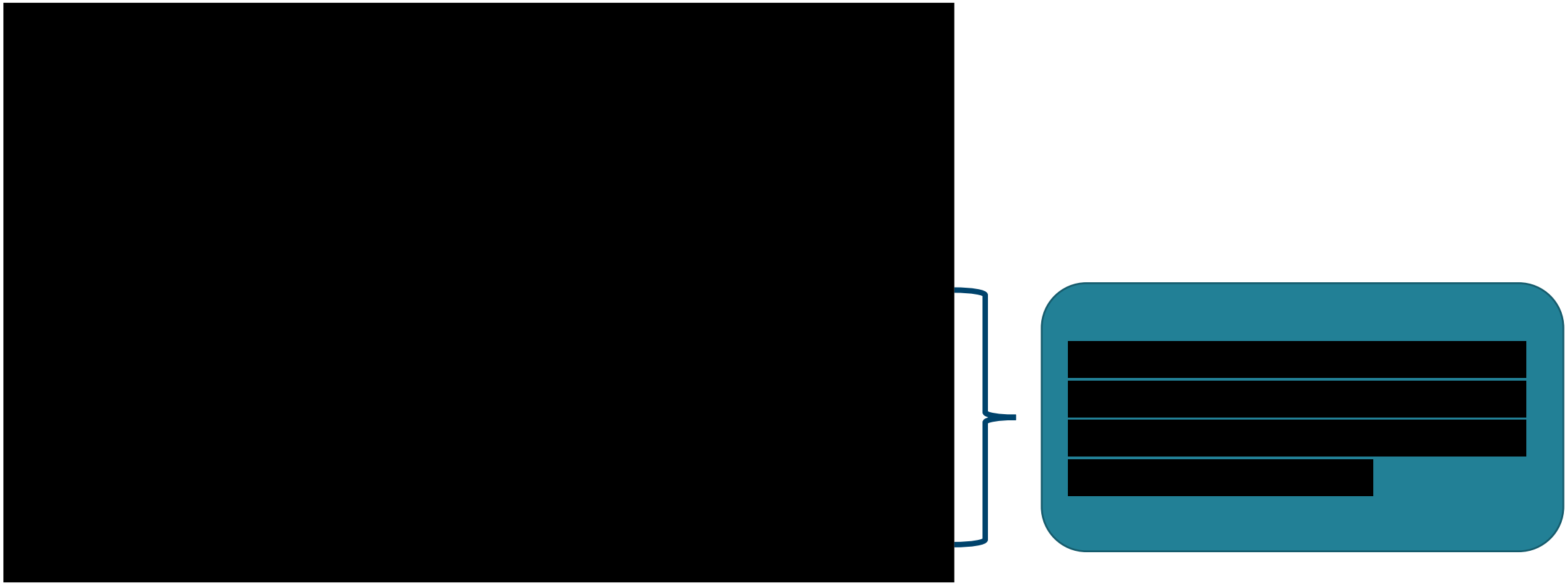
NMA results for CRR

Figure 7 Forest plot for posterior median ORs for CRR

Abbreviations: AZA, azathioprine; CRR, complete renal response; H-CYC, high-dose cyclophosphamide; L-CYC, low-dose cyclophosphamide; MMF, mycophenolate mofetil; NMA, network meta-analysis; OR, odds ratio; RTX, rituximab; TAC, tacrolimus; VCS, voclosporin

NMA results for PRR

Figure 8 Forest plot for posterior median ORs for PRR

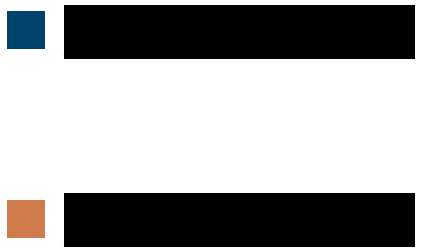


Abbreviations: H-CYC, high-dose cyclophosphamide; L-CYC, low-dose cyclophosphamide; MMF, mycophenolate mofetil; NMA, network meta-analysis; OR, odds ratio; PRR, partial renal response; RTX, rituximab; TAC, tacrolimus; VCS, voclosporin

NMA results

Table 13 AURORA 2 response outcomes results

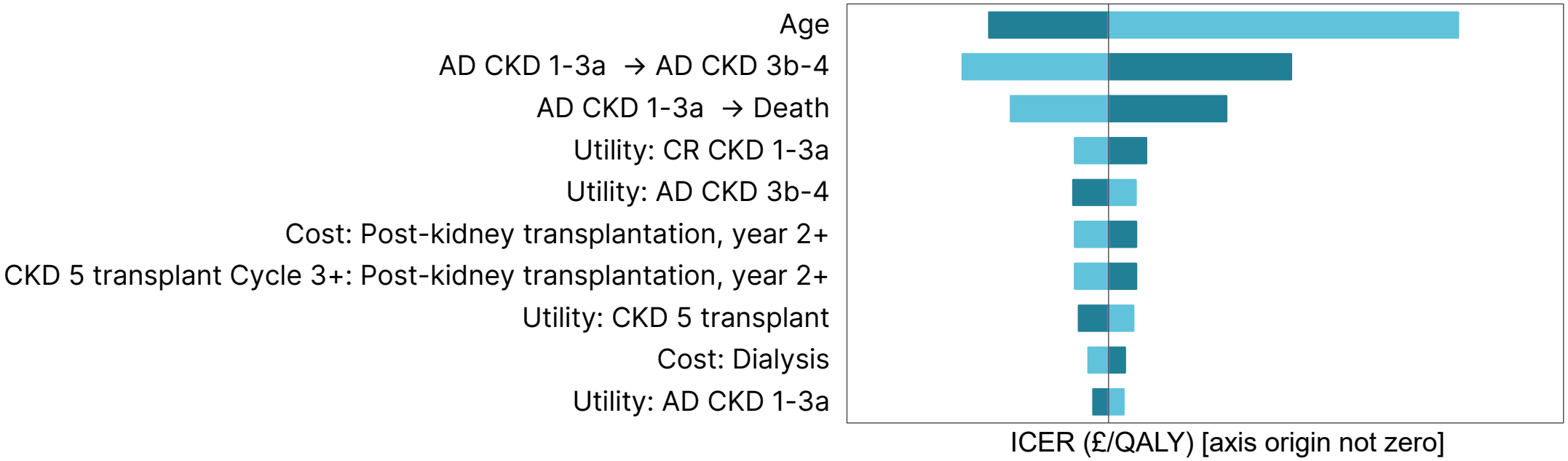
	Median odds ratio for CRR	Median odds ratio for PRR
MMF	Reference	Reference
Voclosporin + MMF	[redacted]	[redacted]
Azathioprine	[redacted]	-
High dose CYC	[redacted]	[redacted]
Low dose CYC	[redacted]	[redacted]
Rituximab + MMF	[redacted]	[redacted]
Tacrolimus	[redacted]	[redacted]
Tacrolimus + MMF	[redacted]	-



Abbreviations: CRR, complete renal response; CYC, cyclophosphamide; MMF, mycophenolate mofetil; PRR, partial renal response

One-way sensitivity analysis on company base case

Figure 9 One-way sensitivity analysis showing sensitivity of ICER versus MMF to different inputs



Abbreviations: AD, active disease; CKD, chronic kidney disease; ICER, incremental cost-effectiveness ratio; MMF, mycophenolate mofetil; QALY, quality-adjusted life year