Single Technology Appraisal

Voclosporin with immunosuppressive therapies for treating lupus nephritis [ID3962]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Voclosporin with immunosuppressive therapies for treating lupus nephritis [ID3962]

Contents:

The following documents are made available to stakeholders:

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

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2. **Clarification questions and company responses**

3. **Patient group, professional group, and NHS organisation submissions** from:
   a. AOFAC Foundation
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4. **External Assessment Report** prepared by Peninsula Technology Assessment Group (PenTAG)

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   a. Sian Brennan – patient expert, nominated by LUPUS UK
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   b. NHS England
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   d. Novartis

9. **External Assessment Group critique of company response to technical engagement** prepared by Peninsula Technology Assessment Group (PenTAG)

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

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Voclosporin with immunosuppressive therapies for treating lupus nephritis [ID3962]

Document B

Company evidence submission

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Abbreviations

Abbreviation	Definition
ACE	Angiotensin Converting Enzyme
ACEI	Angiotensin Converting Enzyme Inhibitor
ACR	American College of Rheumatology
AD	Active Disease
AIC	Akaike's Information Criterion
AE	Adverse Event
ANCOVA	Analysis Of Covariance
anti-dsDNA	Anti-Double Stranded Deoxyribonucleic Acid
APC	Antigen-Presenting Cell
ARB	Angiotensin Receptor Blocker
AZA	Azathioprine
BCC	Basal Cell Carcinoma
BEL	Belimumab
BIC	Bayesian Information Criterion
BID	Twice Daily
BNF	British National Formulary
BSR	British Society for Rheumatology
C1/2+/3+	Cycle 1, Cycle 2+ Or Cycle 3+
C3	Complement 3
C4	Complement 4
CC	Clinical Coding
CEC	Clinical Endpoints Committee
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
CKD	Chronic Kidney Disease
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CN¥	Chinese Yuan
CNI	Calcineurin Inhibitor
CR	Complete Response
CrI	Credible Interval
CRO	Contract Research Organisation
CRR	Complete Renal Response
CsA	Ciclosporin
CSR	Clinical Study Report
CYC	Cyclophosphamide
DIC	Deviance Information Criterion
dL	Decilitre
DSA	Deterministic sensitivity analysis
DSU	Decision Support Unit
ECG	Electrocardiogram
eGFR	Estimated Glomerular Filtration Rate
EMA	European Medicines Agency
eMIT	Electronic Market Information Tool
EPO	Erythropoietin
EQ-5D	Euroqol 5-Dimension
ESA	Erythropoiesis-Stimulating Agents
ESRD	End-stage renal disease
EULAR	European Alliance of Associations for Rheumatology
FAS	Full Analysis Set
FMV	First Morning Void
g	Grams
G-CSF	Granulocyte Colony-Stimulating Factor
GDP	Gross Domestic Product
GFR	Glomerular filtration rate

H-CYC	High-Dose Cyclophosphamide
HR	Hazard Ratio
HRQoL	Health-Related Quality Of Life
HRU	Healthcare Resource Utilisation
IBD	Inflammatory Bowel Disease
IC	Immune Complex
ICER	Incremental Cost Effectiveness Ratio
IL	Interleukin
Ig	Immunoglobulin
IQR	Interquartile Range
IRT	Interactive Response Technologies
ISN/RPS	International Society of Nephrology/Renal Pathology Society
ITC	Indirect treatment comparison
ITT	Intention-To-Treat
IV	Intravenous
KDIGO	Kidney Disease: Improving Global Outcomes
kg	Kilograms
KOL	Key Opinion Leader
KT	Kidney Transplant
L-CYC	Low-Dose Cyclophosphamide
LMMs	Linear mixed effects models
LN	Lupus Nephritis
LYG	Life Years Gained
LYs	Life years
m2	Metres Squared
MAA	Marketing Authorisation Application
maint.	Maintenance
Max	Maximum
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
MHRA	Medicines and Healthcare Products Regulatory Agency
Min	Minimum
mITT	Modified Intention-To-Treat
mL	Millilitre
MMF	Mycophenolate Mofetil
MMRM	Mixed effect model repeated measures
mo.	Months
MPA	Mycophenolic Acid
msec	Milliseconds
N/A	Not Applicable
N/n	Number Of Patients Evaluable
NFAT	Nuclear Factor of Activated T-Cells
NHB	Net Health Benefit
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NMA	Network meta-analysis
NR	Not Reported
NSAIDs	Non-steroidal anti-inflammatory drug
ONS	Office For National Statistics
OR	Odds Ratio
PAS	Patient Access Scheme
pD	Parameters
PH	Proportional hazards
PICOS	Population, intervention, comparator, outcome, study design
PP	Per protocol
PPS	Per protocol set
PR	Partial Response
PRO	Patient-Reported Outcome

PRR	Partial Renal Response
PSA	Probabilistic sensitivity analysis
PSM	Partitioned survival model
PSS	Personal Social Services
PSSRU	Personal Social Services Research Unit
PT	Preferred term
PTR	Prior To Randomisation
PTS	Prior To Screening
Q1	First Quartile
Q2W	Every 2 Weeks
Q3	Third Quartile
Q4W	Every 4 Weeks
QALY	Quality-Adjusted Life Year
QTcf	QT Interval Duration Corrected For Heart Rate Using Method Of Fridericia
RBC	Red Blood Cell
RCT	Randomised Controlled Trials
RTX	Rituximab
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS	Safety Analysis Set
SCC	Squamous Cell Carcinoma
SD	Standard Deviation
SE	Standard Error
SELENA-SLEDAI	Safety Of Estrogens In Lupus Nephritis National Assessment - Systemic Lupus Erythematosus Disease Activity Index
SF-36	Short Form 36 Health Survey Questionnaire
SIM	Serum Immunoglobulin Measurement
SLE	Systemic Lupus Erythematosus
SLR	Systematic literature review
SmPC	Summary of Product Characteristics
SoC	Standard of Care
SS	Safety Set
SUCRA	Surface Under the Cumulative Ranking Curve
TA	Technology Appraisal
TAC	Tacrolimus
TEAE	Treatment-Emergent Adverse Event
TNF	Tumour Necrosis Factor
TRAE	Treatment-Related Adverse Event
TSD	Technical Support Document
UK	United Kingdom
US	United States
UPCR	Urine Protein Creatinine Ratio
URTI	Upper Respiratory Tract Infection
UTI	Urinary Tract Infection
VCS	Voclosporin
yrs	Years

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

B.1.1 Decision problem

The submission covers the technology's full marketing authorisation for the following indication:

- Voclosporin is indicated in combination with background immunosuppressive therapies for the treatment of adult patients with active class III, IV or V (including mixed class III/V and IV/V) lupus nephritis (LN)

A summary of the decision problem is provided in Table B.1-1.

Table B.1-1. The decision problem

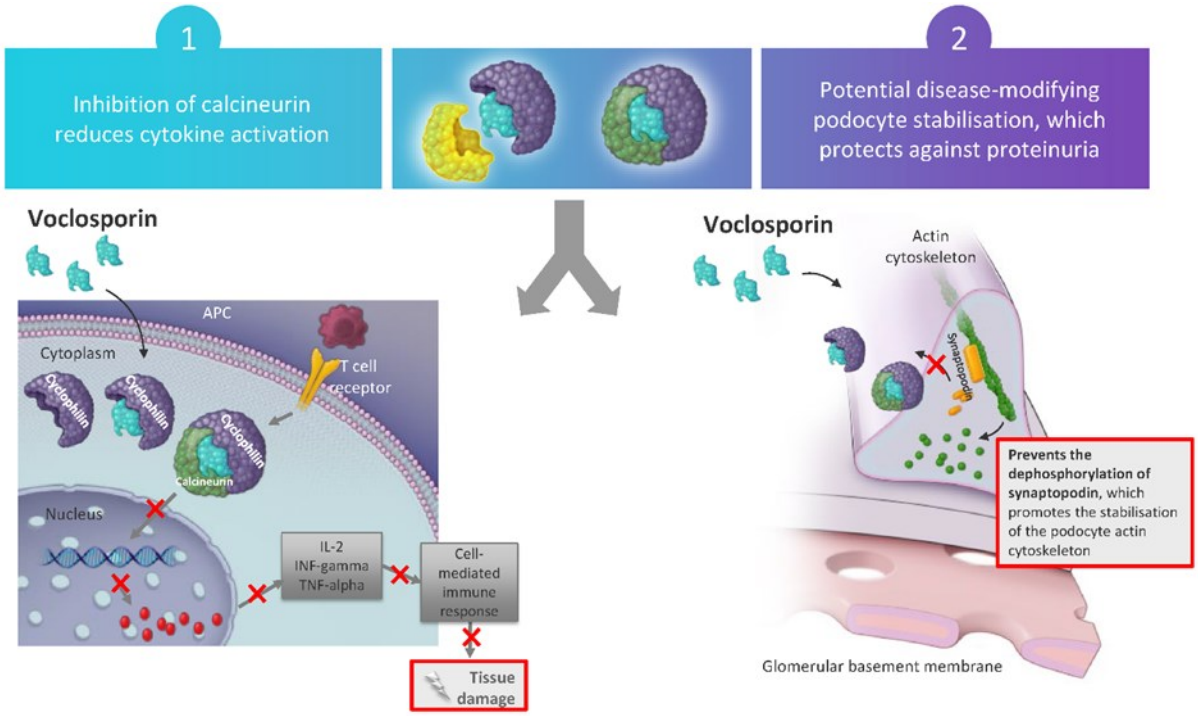
	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	Adults with active lupus nephritis	As per scope	N/A
Intervention	Voclosporin with immunosuppressive therapies	As per scope	N/A
Comparator(s)	Standard therapy for lupus nephritis without voclosporin including the following induction treatments, followed by maintenance treatment with mycophenolate plus corticosteroids or azathioprine plus corticosteroids: • mycophenolate plus corticosteroids • cyclophosphamide plus corticosteroids • azathioprine plus corticosteroids • rituximab • a calcineurin inhibitor plus mycophenolate and corticosteroids.	As per scope	N/A
Outcomes	The outcome measures to be considered include: • renal response • rate and severity of renal-related events (e.g., flares) • rate and duration of remission • incidence of end-stage renal disease • corticosteroid use • mortality • adverse effects of treatment • health-related quality of life	As per scope	N/A

B.1.2 Description of the technology being evaluated

Voclosporin (Lupkynis™) is a novel orally administered next generation calcineurin inhibitor (CNI) immunosuppressant with a dual mechanism of action which reduces proinflammatory T-cell mediated immune responses linked to kidney inflammation,[1] and protects renal podocytes from damage (Figure B.1-1).[2]

Specifically, voclosporin binds to calcineurin and blocks calcineurin-mediated activation of Nuclear Factor of Activated T-Cells (NFAT), a transcription factor which drives T-cell immune response.[1,3-6] CNI immunosuppressive activity results in inhibition of lymphocyte proliferation, T-cell cytokine production, and expression of T-cell activation surface antigens.[1] In addition, studies in animal models indicate that voclosporin stabilises actin cytoskeleton and stress fibres in renal podocytes, leading to increased podocyte integrity in glomeruli.[1] Podocytes are specialised epithelial cells that are a key component of the glomerular filtration barrier, and their cytoskeletal integrity is critical to ensure healthy kidney function.[4-7]

Figure B.1-1. Voclosporin mechanism of action



Abbreviations: APC = antigen-presenting cell; IL = interleukin; LN = lupus nephritis; TNF = tumour necrosis factor

Voclosporin's novel molecular structure and mechanism of action may eliminate the need for regular therapeutic drug monitoring required with currently available CNIs (ciclosporin and tacrolimus), and potentially minimise the risk of CNI-associated side effects such as diabetes, kidney dysfunction, and hypertension (Section B.1.3.7 and Section B.2.10). Voclosporin is structurally similar to ciclosporin, but incorporates a modification to a functional group on amino acid-1 of the molecule.[8] This modification changes both how voclosporin binds to calcineurin and its metabolic profile, leading to a four-fold increase in immunosuppressive potency compared to ciclosporin and fewer CNI-associated side effects due to the rapid elimination of voclosporin metabolites.[8] In addition, the combination of increased potency and decreased metabolite exposure gives voclosporin a more predictable pharmacokinetic and

pharmacodynamic profile compared to currently used CNIs, eliminating the need for intensive therapeutic monitoring.[8-11]

A summary of the technology being appraised, voclosporin, is provided in Table B.1-2.

Table B.1-2. Technology being evaluated

UK approved name and brand name	Voclosporin (Lupkynis™)
Mechanism of action	Voclosporin is a novel, orally administered next generation CNI immunosuppressant with a dual mechanism of action: • Voclosporin binds to calcineurin, and blocks calcineurin-mediated activation of NFAT, a transcription factor which drives T-cell immune response. The immunosuppressant mechanism blocks T-cell-mediated immune activity (IL-2 expression, cytokine production, lymphocyte proliferation, expression of T-cell surface antigens), leading to a reduction in kidney inflammation and tissue damage • Voclosporin stabilises the actin cytoskeleton and stress fibres in renal podocyte cells, leading to increased glomerular podocyte integrity and protection against proteinuria
Marketing authorisation/CE mark status	Voclosporin does not currently have a marketing authorisation in the UK for any indication. However, voclosporin is currently being reviewed by the EMA for the treatment of adults with LN. [redacted]
Indications and any restriction(s) as described in the SmPC	Voclosporin is indicated in combination with background immunosuppressive therapies for the treatment of adult patients with active class III, IV and V (including mixed class III/V and IV/V) LN
Method of administration and dosage	Oral, 23.7 mg (three 7.9 mg soft capsules) BID
Additional tests or investigations	The applicant does not expect any additional tests or investigations to be required beyond routine care in the management of LN
List price and average cost of a course of treatment	[redacted] per pack of 180 soft capsules, equating to a price of [redacted] for a 23.7mg dose
Patient access scheme (if applicable)	Simple PAS discount of [redacted] applied to the list price of voclosporin

Abbreviations: BID: twice daily; CHMP = Committee for Medicinal Products for Human Use; CNI = calcineurin inhibitors; EMA = European Medicines Agency; IL = interleukin; LN = lupus nephritis; MAA = marketing authorisation application; MMF = mycophenolate mofetil; MHRA = Medicines and Healthcare products Regulatory Agency; NFAT = nuclear factor of activated T-Cells; PAS = Patient Access Scheme; SmPC = summary of product characteristics; UK = United Kingdom

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

B.1.3.1 Disease overview

Systemic lupus erythematosus (SLE) is a chronic and complex autoimmune disease that can affect any organ in the body.[12] In SLE, abnormal and persistent immune system reactions to autologous nucleic acids result in the formation of damaging deposits of immune cell and autologous cellular materials called immune complex deposits.[13,14] These immune complexes form within organ systems throughout the body (e.g. skin, joints, kidney, and central nervous system).[13]

Lupus nephritis (LN) is the most common serious manifestation of SLE, affecting at least a third of patients,[15] although this may be as high as 60% among those with Black or Hispanic family backgrounds.[16-18] LN is characterised by the formation of immune complex deposits within renal tissues, leading to inflammation of the kidneys, renal damage, proteinuria and impaired renal function.[12,14]

LN-associated renal inflammation and structural/functional damage to renal cells is caused by the production of local cytokines, chemokines and adhesion molecules, along with an ensuing influx of inflammatory cells and proinflammatory cytokines.[14] T-cells play a major role in the pathogenesis and progression of LN, and contribute to renal tissue injury both directly and indirectly.[19-23] T-cells amplify inflammation by producing inflammatory cytokines, and also cause renal cell damage either by direct cytotoxicity, or through activation of macrophages, natural killer cells, dendritic cells and/or nephritogenic auto-antibody producing B cells.[23-25] LN is also associated with the disruption of podocyte function. Podocytes are highly specialised epithelial cells which form part of the filtration barrier in the kidneys, and are important in the regulation of glomerular filtration and regulation of protein loss.[26]

LN is an incurable, debilitating and potentially life-threatening disease that can cause permanent kidney damage.[12,27] If LN is left untreated, patients will progress through the stages of chronic kidney disease (CKD1-5), and may even go on to develop end-stage renal disease (ESRD) i.e. CKD5.[12,27] Overall, ESRD develops in 10–30% of patients with LN.[18,28] ESRD has particularly severe clinical consequences for patients, including high mortality rates and the need for invasive kidney replacement therapy, such as dialysis and/or kidney transplantation.[27]

B.1.3.2 Epidemiology

SLE is estimated to be prevalent in around 60,000 people in England and Wales and there are around 3,000 new SLE diagnoses each year (based on data collected within a retrospective cohort between 1999–2012 [LN data not available]).[29,30] Between 7–31% of patients with SLE have LN at diagnosis, and many go on to develop LN during the course of SLE disease (~30% within 1 year, ~40% within 5 years, and 40–48% within 15 years).[18] Guidelines from the British Society for Rheumatology (BSR) state that about one-third of SLE patients in the United Kingdom (UK) develop LN.[15]

Data describing the prevalence and incidence of LN in the UK are currently limited. Among publicly available data, the most recent UK-specific study was a 2001 retrospective analysis conducted in England, which reported overall LN prevalence and incidence rates of 4.4 and 0.4 per 100,000 of the population, respectively.[31]

Prevalence and incidence rates are also known to be higher among certain subsets of the UK population. According to the same English study, approximately 85% of LN cases were in women (female vs male prevalence: 7.1 and 1.4 per 100,000; female vs male incidence: 0.7 vs 0.1 per 100,000, respectively [2001]) and most developed the disease when they were of childbearing age (age 18–39: 7.7 per 100,000; 40–59: 9.6 per 100,000; ≥60: 3.5 per 100,000).[31,32] LN was also more prevalent in Indo-Asian (12.6 per 100,000), African-Caribbean (60.8 per 100,000) and Chinese (65.5 per 100,000) populations compared to those of White ethnicity (3.5 per 100,000).[31]

In the absence of more recent published epidemiology data in England and Wales; overall LN incidence and prevalence can instead be estimated by considering the proportion of the total population who have SLE, the proportion of patients with SLE diagnosed with LN, and also the proportion of patients with SLE and LN who have class III–V active LN specifically. Based on a total population of 59,719,724 people in England and Wales (2020), this would equate to a prevalence of 13,521 patients with active class III, IV or V LN and an incidence of 684 new diagnoses per year. A summary of this calculation is presented in Table B.1-3.

Table B.1-3. LN epidemiology estimates for England and Wales in 2020

	Population size	Calculation	Sources
Total population of England and Wales (2020)	59,719,724	N/A	ONS 2021[30]
Prevalence			
Prevalent cases of SLE	57,952	59,719,724[30] x 0.097% [29]	ONS 2021,[30] Rees et al., 2016[29]
Prevalent cases of LN	19,315	57,952 x 33.3%[15]	Gordon et al., 2018[15]
Prevalent cases of active class III, IV or V LN	13,521	13,521 x 70.0%[18]	Mahajan et al., 2020[18]
Incidence			
Incident cases of SLE	2,932	59,719,724 x 0.0049%[29]	Rees et al., 2016[29]
Incident cases of LN	977	2,932 x 33.3%[15]	Gordon et al., 2018[15]
Incident cases of active class III, IV or V LN	684	977 x 70.0%[18]	Mahajan et al., 2020[18]

Abbreviations: LN = lupus nephritis; ONS = Office for National Statistics
Source: Office for National statistics 2021[30]

B.1.3.3 Symptomatology and clinical presentation

Clinical presentation of LN is often subtle, and most commonly revealed by examination of the urine and blood.[12] Proteinuria is the defining aspect of LN and indicates both disease activity and kidney damage. Therefore, once proteinuria is clinically apparent, kidney tissues are already inflamed and damaged.[12,27] The most common clinical signs of LN (and approximate

prevalence) include proteinuria (100%), microscopic haematuria (80%), renal insufficiency (60%), nephrotic syndrome (50%), red blood cells (30%) or other cellular casts in urine (30%), and hypertension (30%).[12] Although patients with LN may experience few or no accompanying symptoms, a substantial proportion of patients may also experience skin rash across the nose and cheeks (~31%), photosensitivity (~8%), oral ulcer (~12%), arthritis (~6%), serositis (~24%), neurologic disorder (~1%), hematologic disorder (~89%), and/or immunologic disorder (~93%).[33-35]

The overarching goal of LN treatment is to quickly reduce proteinuria and inflammation to prevent further kidney damage.[12,27] However, renal flares occur in approximately 27–66% of LN patients,[36] usually within 5 to 6 years following the start of treatment.[27] The European Alliance of Associations for Rheumatology (previously European League Against Rheumatism) and European Renal Association–European Dialysis and Transplant Association (EULAR/ERA-EDTA) define a renal flare as an increase in proteinuria or serum creatinine level, an abnormal urinary sediment, or a reduction in creatinine clearance due to active disease.[15] Renal flares can be subdivided into proteinuric or nephritic flares:[36]

- Proteinuric flares – persistently increased proteinuria (>0.5–1.0 g daily) after a complete response (CR), or doubling of proteinuria (to >1.0 g daily) after a partial response (PR)
- Nephritic flares – an increase or recurrence of urinary sediment with or without increased proteinuria and are usually associated with a decline in renal function

Thus, renal flares result in histological progression to more severe disease (i.e. further kidney damage and decreased renal function) in 40–76% of patients, with rates of progression varying according to LN class (see section B.1.3.4).[18,27,37]

B.1.3.4 Disease classifications

LN severity is classified into LN class I to VI, by kidney biopsy according to the International Society of Nephrology/Renal Pathology Society (ISN/RPS) 2003 classification system (summarised in Table B.1-4). In some cases, biopsies may show mixed histological findings, warranting a combination of classifications (e.g. classes III + V, or class IV + V).[38] At initial LN diagnosis, the majority of patients are diagnosed with class III (10–25%), class IV (35–60%), and class V (5–30%) disease; while fewer patients are diagnosed at classes I, II, and VI (class I: 0–6%; class II: 1–20%; class VI: <5%).[18] Treatment decisions are largely based on the type and extent of renal damage.[28,39] For example, patients in classes I and II generally do not require treatment, while those in classes III, IV, and V benefit from potent immunosuppression and patients in class VI are considered for renal replacement therapy.[27]

Table B.1-4. Summary of ISN/RPS classification of LN

Pathology	Class	Class Overview
Minimal mesangial LN	Class I	Most glomeruli are healthy and unaffected Minimal IC deposits
Mesangial proliferative LN	Class II	
Focal LN	Class III	An increasing number of glomeruli are damaged relative to class I and II but >50% of glomeruli are healthy IC deposits apparent in outer layer/s of glomerulus tissue
Diffuse segmental (IV-S) or global (IV-G) LN	Class IV	More substantial numbers (≥50%) of glomeruli show damage IC deposits appear in deeper layers of tissue and outer layers may show structural changes
Membranous LN	Class V	IC deposits have infiltrated extensively deep within kidney tissues Structural irregularities may be apparent
Advanced sclerosing LN	Class VI	Fewer than 10% of glomeruli are functional Extensive damage and loss-of-function apparent in kidney tissues

Abbreviations: IC = immune complex; ISN/RPS = International Society of Nephrology/Renal Pathology Society; LN = lupus nephritis
Source: Weening 2004[40]

Furthermore, patients may be classified according to their level of renal function (i.e. estimated glomerular filtration rate [eGFR]). If disease remains uncontrolled, patients with LN will progress through the stages of CKD (CKD1: >90 ml/min/1.73m^2; CKD2: 60–89 ml/min/1.73m^2; CKD3: 30–59 ml/min/1.73m^2; CKD4: 15–29 ml/min/1.73m^2) to ESRD (CKD5: <15 ml/min/1.73m^2).[12,41-43]

B.1.3.5 Burden to patients, carers and society

B.1.3.5.1 *Clinical burden*

B.1.3.5.1.1 Disease progression and mortality risk

Progressive, uncontrolled kidney damage drives the clinical burden of LN.[44-46] Despite treatment, patients remain at high risk of renal flares, which may cause further renal damage and increase the likelihood of progression to CKD and ESRD.[36,47] In England, a retrospective analysis indicates that around 8% of patients with LN develop ESRD within 5 years of diagnosis (n=86; 1996–2005); while up to 20% of patients develop ESRD within three decades (n=154; 1975–2005).[48] More recently, studies outside of the UK (including a comprehensive literature review and meta-analysis) have reported even higher rates of progression to ESRD for patients with LN (10–50%).[16,18,28,49,50]

LN is associated with considerable mortality risk; however, progression to ESRD has particularly severe clinical consequences, including higher mortality rates and the need for invasive kidney replacement therapy (i.e. dialysis and/or kidney transplantation).[27] Although there are limited mortality data for LN in the UK, studies outside the UK associate LN with a 6–9-fold increase in mortality risk relative to a general population, which increases to a 26-fold-greater risk if the disease progresses to ESRD.[28,44,45] Similarly, a multi-national cohort study which included patients from England and Wales suggests that that LN is significantly more lethal than SLE alone (hazard ratio [HR] = 2.98 [95% CI: 1.48, 5.99]; p=0.002; n=1,827).[16,51] In England, five-year mortality rates increase substantially from 4.7% for patients

with LN (1996–2005 [n=86])[48] to 36.5% of patients with ESRD (2003–2005 [n=750]).[52] Although dialysis and kidney transplantation are effective in reducing mortality among patients with ESRD, most patients receive dialysis in a clinic which requires a 4–8-hour procedure at least 3 times per week until a kidney donor becomes available (2.5–3 years average waiting time).[27,53,54] In some cases, patients may receive dialysis at home.[55] However, these patients would still be limited to the confines of their home for extended periods of time, with duration and intensity dependent on the patient's needs. The National Health Service (NHS) recommend a variety of home dialysis schedules such as four days a week for four hours; five days a week for three hours; and six days a week for eight hours overnight.[55]

B.1.3.5.1.2 Pregnancy

As well as disease progression and mortality, LN is linked with poor maternal and foetal outcomes.[56] This is particularly important, given that the majority of patients with LN are women (~85%) (Section B.1.3.2) and most develop the disease when they are of childbearing age.[32,57,58] LN at the time of conception, or a history of prior LN, are both significantly associated with maternal hypertension ($p<0.001$), while prior LN is associated with an increased risk for preeclampsia.[59] High rates of preterm birth (39.4%), intrauterine growth restriction (12.7%), stillbirth (3.6%), and neonatal death (2.5%) have also been reported among LN-associated pregnancies.[59,60] LN-related kidney impairment may even cause infertility due to hypothalamic–pituitary dysfunction, and manifest as menstrual irregularity (including anovulatory cycles) in women or erectile dysfunction with reduced spermatogenesis in men.[61] Disease-related pregnancy concerns are further exacerbated by the use of treatments which may impair fertility and/or be harmful to a foetus.[62,63]

B.1.3.5.2 ***Humanistic burden***

Although there are limited UK-specific data, LN is generally associated with poor health-related quality of life (HRQoL)[64-67] due to both the symptomatic burden of LN (Section B.1.3.3)[33] and adverse effects associated with treatments (see Section B.1.3.7).[64] Patients with LN have reported HRQoL impairments in terms of physical functioning ($p<0.01$), social functioning ($p<0.001$), emotional role limitations ($p<0.05$), and general health ($p<0.001$) using the 36-Item Short Form Survey (SF-36).[64] HRQoL impairment is particularly pronounced if disease activity is not well-controlled.[65,66,68] Significantly poorer HRQoL has also been observed for patients with active LN compared to those with inactive disease (using LupusPRO);[66] and HRQoL worsens significantly as renal flares become more frequent (lupus impact tracker).[65] Impaired HRQoL is generally correlated with onset of symptoms (fatigue being the most burdensome) and deteriorates as patients progress to severe/advanced LN (i.e. greater renal insufficiency).[16,64,67] Treatments capable of achieving rapid renal remission may therefore be able to prevent or delay HRQoL decrements associated with disease progression.[16,64,67] However, while treatments may achieve renal remission, the systemic nature of underlying SLE means that it is particularly challenging to improve patient HRQoL due to other adversely affected organs/regions of the body.[69,70]

For these reasons, LN negatively impacts patient day-to-day activities (personal or work/study-related) and may even progress to short- or long-term disability (especially if patients develop ESRD).[54,71] Wider societal consequences are therefore expected for patients, their family, and caregivers as LN onset typically occurs at peak education/working age (18–59).[12,31,32] In a UK-based survey of patients with SLE (n=121) and their carers (n=31; LN data not available); 52% of patients had ceased work completely, while a substantial proportion of

carers reported time off work (52%), negative financial implications (55%), and interference with social activities (87%).[67] In addition to the impact of LN on general day-to-day life, active LN is associated with poor maternal and foetal outcomes (Section B.1.3.5.1)[56,72] and pregnant patients have reported emotional turmoil in the form of anxiety, depression, feelings of bitterness, and worry related to renal flares during pregnancy.[73]

B.1.3.5.3 *Economic burden*

Patients with LN are associated with substantial healthcare resource use (HRU) due to both treatment costs, and high rates of physician, inpatient and outpatient visits.[17] Patients with LN may require clinical visits for a variety of reasons that include; delivery of intravenous (IV) treatments, follow-up visits due to renal flares including repeat biopsy to assess disease progression, dialysis procedures, kidney transplantation, complications associated with long-term exposure to steroids, and/or adverse reactions to therapy.[12,27] As such, LN is known to have an even greater economic burden than patients with SLE only, particularly in terms of direct costs.[17,46,74]

Although there are no available data describing the economic burden of LN specifically in the UK, the economic burden of LN has been assessed globally across 32 clinics in 11 countries within North America, Latin America, Europe and Asia between 1999–2013 (n=1,545).[17] Ten-year cumulative direct costs were over 15-fold higher in patients with LN and poor kidney function (eGFR <30ml/min) compared to patients without LN (eGFR >60ml/min) (2015 Canadian dollars: $310,579 [approx. £207,640 in 2022] vs $19,987 [approx. £13,362 in 2022], respectively).[17] Unadjusted annual costs per patient with LN increased substantially with disease progression, increasing from $3,799 (approx. £2,542 in 2022) for patients with CKD1/2 to $50,614 (approx. £33,867 in 2022) for patients with CKD5 disease (i.e. ESRD).[17]

B.1.3.6 Clinical pathway of care

B.1.3.6.1 *Clinical guidelines for LN in the UK*

Currently, there are no available National Institute for Health and Care Excellence (NICE) guidelines for the diagnosis and management of LN, nor have any NICE technology appraisals been completed for this indication.

In the UK, the BSR have published the only national guideline for the management of mild, moderate, and severe SLE in adults as part of a NICE-accredited process (2018). Within this guideline, the BSR recommended that patients with LN should be managed according to clinical guidelines published by the EULAR/ERA-EDTA.[13,15,27] Beyond BSR/EULAR/ERA-EDTA recommendations, the most up-to-date guidelines for the treatment of LN were published by the Kidney Disease: Improving Global Outcomes (KDIGO) Glomerular Diseases Work Group (October 2021).[43] KDIGO 2021 guidelines have an international perspective, but largely reflect the BSR/EULAR/ERA-EDTA guidelines. Together, BSR/EULAR ERA-EDTA and KDIGO guidelines inform the management of LN in England and Wales.

B.1.3.6.2 *Diagnostic pathway*

Early diagnosis and management of LN is critical to preserve kidney function and associated with improved prognosis.[28] According to BSR/EULAR/ERA-EDTA and KDIGO guidelines, kidney involvement can be identified by urinalysis or blood tests and includes patients with: glomerular haematuria, cellular casts in the urine, proteinuria >0.5 g/24 hours, spot urine

protein to creatinine ratio (UPCR) >500mg/g, and/or an unexplained decrease in glomerular filtration rate (GFR).[15,27,39,43] The NHS and UK Kidney Association indicate that an eGFR of <60 ml/min/1.73 m^2 may be classified as CKD; while normal eGFR is ≥90 ml/min/1.73 m^2, or 60–89 ml/min/1.73 m^2 in the absence of kidney damage.[41,42] Patients with SLE that have persistent proteinuria ≥0.5g/day (or spot UPCR ≥500mg/g) and/or unexplained decreases in GFR should be referred for kidney biopsy to confirm and identify the extent of renal damage according to the ISN/RPS 2003 classification system (Section B.1.3.4).[27,43]

For patients with LN, glomerulonephritis due to immune complex deposits is the most common histology type, although other etiopathogenetic mechanisms may include podocytopathy or thrombotic microangiopathy.[12,39] To better differentiate among these mechanisms, patients with suspected kidney involvement may be tested for complement levels (C3 and C4); anti-double-stranded deoxyribonucleic acid (anti-dsDNA) and anti-C1q autoantibodies; and antiphospholipid antibodies, which may have prognostic implications.[27]

B.1.3.6.3 *Treatment pathway*

In the absence of a cure, LN treatment goals include the preservation or improvement of kidney function (i.e. the normalisation/stabilisation of eGFR) and the prevention of disease progression to more advanced stages of CKD.[12,27,43] Although there are no universally accepted criteria for the level of improvement required, treatments traditionally aim to achieve a 'CR' in terms of a reduction of proteinuria (EULAR/ERA-EDTA definition: UPCR below 500–700 mg/g by 12 months; KDIGO definition: UPCR 500 mg/g and/or stabilisation/improvement in kidney function [±10-15% of baseline] within 6–12 months).[27,43] In some cases, patients may require an additional 6-12 months of treatment to achieve CR (e.g. patients with nephrotic-range proteinuria [UPCR ≥3000 mg/g]).[27,43]

For all patients with LN, hydroxychloroquine is recommended unless contraindicated.[28,39,43] However, patients with class III, IV or V LN may benefit from additional immunosuppressive therapy, which traditionally involves an induction phase (initial treatment) to treat patients with active LN and a follow-up maintenance phase (subsequent treatment) once the disease is adequately controlled.[13,27,43]

EULAR/ERA-EDTA and KDIGO recommend initial treatments in terms of preferred first-line treatment options and alternative treatment options which may be considered under specific circumstances (summarised in Table B.1-5).[13,27] Available treatments include immunosuppressant agents such as mycophenolate mofetil (MMF), mycophenolic acid (MPA) and azathioprine; cyclophosphamide (an immunosuppressive form of chemotherapy), and CNIs (tacrolimus or ciclosporin).[13,27,43] In addition, treatments are typically used in combination with corticosteroids during the initial treatment phase, which are then tapered to the lowest possible dose or may even be discontinued during the subsequent maintenance phase.[13,27,43]

For the initial treatment of active class III–IV LN specifically, KDIGO recommend CNIs as a triple-combination therapy with reduced-dose MMF/MPA and corticosteroids for patients who are not suitable for standard-dose MMF/MPA or cyclophosphamide (KDIGO). EULAR/ERA-EDTA suggest this regimen may be particularly useful in those with nephrotic-range proteinuria (EULAR/ERA-EDTA).[13,27,43] CNIs may also be used as an initial treatment for class V LN, either with MMF/MPA and corticosteroids or with corticosteroids alone.[13,27,43] Among the two currently available CNIs (tacrolimus and ciclosporin), EULAR/ERA–EDTA guidelines and feedback from clinical experts suggest that tacrolimus is the most widely used CNI;[13,27] with

EULAR guidelines excluding ciclosporin from the recommended treatment algorithm for patients with class III–IV LN.[13]

Notably, although voclosporin has not yet received marketing authorisation in the European Union (EU), it is already licensed in the United States (US) for the treatment of active LN and KDIGO guidelines suggest that voclosporin can be added to MMF/MPA and corticosteroids as an initial therapy for up to one year.[75]

Table B.1-5. Summary of LN treatments by treatment phase and disease class according to EULAR/ERA-EDTA and KDIGO guidelines

		Treatment by disease severity	
		Class III or IV LN	Pure class V LN†
Initial treatment	First-line	MMF or MPA *OR* Low-dose IV CYC	MMF or MPA with pulse IV methylprednisolone, followed by oral prednisone
	Alternatives	MMF or MPA + CNI *OR* High-dose IV CYC *OR* Belimumab + MMF/MPA or IV CYC* *OR* Rituximab + MMF or IV CYC*‡	IV CYC monotherapy *OR* CNI monotherapy *OR* MMF or MPA + CNI
Subsequent treatment	First-line	MMF or MPA *OR* AZA monotherapy§ *OR* CNI (if above not tolerated)*	Continue same treatment with gradual tapering of corticosteroids

*KDIGO-recommendation only; †EULAR/ERA-EDTA-recommendation only (KDIGO guidelines for pure class V LN are less explicit than EULAR/ERA-EDTA recommendations and generally recommend management with combined immunosuppressive treatment (i.e MMF/MPA with CYC/CNI/AZA or rituximab); ‡for corticosteroid minimisation only; §preferred if pregnancy contemplated, or following first-line CYC (EULAR/ERA-EDTA)
Abbreviations: AZA = azathioprine; CNI = calcineurin inhibitor; CYC = cyclophosphamide; g = grams; GFR = glomerular filtration rate; KDIGO = Kidney Disease: Improving Global Outcomes; IV = intravenous; LN = lupus nephritis; MMF = mycophenolate mofetil; MPA = mycophenolic acid
Source: Fanouriakis et al., 2020; Fanouriakis et al., 2021; KDIGO 2021[13,27,43]

Non-responding/refractory patients may be considered for treatment with MMF/MPA, cyclophosphamide, CNIs (especially tacrolimus), belimumab, and/or rituximab either as monotherapy or part 'multitarget' therapy.[27,43]

Despite the above recommendations, most immunosuppressive treatments are not indicated for SLE, and only two treatments are indicated for LN specifically: cyclophosphamide as a treatment of life-threatening, severe progressive forms of LN only;[63] and belimumab in combination with background immunosuppressive therapies, for the treatment of adult patients with active LN (licensed by the European Medicines Agency [EMA], but does not currently have marketing authorisation in the UK for LN).[76,77] Therefore, almost all treatments currently used for LN are prescribed off-label. A summary of treatments currently used for LN and within the scope of this appraisal is presented in (Table B.1-6).

Table B.1-6. Summary of therapeutic indications for current LN treatments

	Treatment	Indication	Guidance for the treatment of LN*
Initial/ subsequent treatment	MMF/ MPA	Indicated for: • Prophylaxis of acute rejection in renal transplantation (in combination with a corticosteroid and CsA) • Prophylaxis of acute rejection in cardiac transplantation (in combination with a corticosteroid and CsA) • Prophylaxis of acute rejection in hepatic transplantation (in combination with a corticosteroid and CsA)	Offer Class III and IV LN patients 2–3 g/day in combination with corticosteroids. To reduce cumulative corticosteroid dose, the use of intravenous pulses methylprednisolone (total dose 500–2500 mg, depending on disease severity) is recommended, followed by oral prednisone (0.3–0.5 mg/kg/day) for up to 4 weeks, tapered to ≤7.5 mg/day by 3 to 6 months In pure class V LN, offer 2–3 g/day, in combination with pulse intravenous methylprednisolone (total dose 500–2500 mg, depending on disease severity) followed by oral prednisone (20 mg/day, tapered to ≤5 mg/day by 3 months) If improvement after initial treatment is achieved, subsequent immunosuppression is recommended with MMF/MPA (1–2 g/day) Gradual withdrawal of treatment (corticosteroids first, then immunosuppressive drugs) can be attempted after at least 3–5 years therapy in complete clinical response
Initial treatment only	CYC	Indicated for: • Life-threatening autoimmune diseases: severe progressive forms of LN and Wegener's granulomatosis • In combination with other agents for treating a wide range of malignancies, including leukaemia, lymphomas, and solid tumours	Offer Class III and IV LN patients low-dose intravenous CYC (500 mg every 2 weeks for a total of 6 doses) in combination with corticosteroids. To reduce cumulative corticosteroid dose, the use of intravenous pulses methylprednisolone (total dose 500–2500 mg, depending on disease severity) is recommended, followed by oral prednisone (0.3–0.5 mg/kg/day) for up to 4 weeks, tapered to ≤7.5 mg/day by 3 to 6 months Patients with high risk for kidney failure (reduced GFR, histological presence of crescents or fibrinoid necrosis or severe interstitial inflammation) can be treated with high-dose intravenous CYC (0.5–0.75 g/m^2 monthly for 6 months) in combination with corticosteroids

Initial/ maintenance	CNI (TAC)	Indicated for: • Prophylaxis of transplant rejection in liver, renal or cardiac allograft recipients • Treatment of allograft rejection resistant to treatment with other immunosuppressive medicinal products	Offered in combination with MMF (target dose: 1–2 g/day) and corticosteroids as an alternative in Class III and IV LN patients, particularly in patients with nephrotic-range proteinuria CNIs (especially TAC) can be offered as a monotherapy for treatment of Class V LN. Alternative treatment option for Class V LN, particularly with nephrotic range-proteinuria: MMF/MPA combined with CNI (especially TAC) Continuation, switching to or addition of CNIs can be considered in pure class V nephritis at the lowest effective dose and after considering nephrotoxicity risks
Initial/ subsequent treatment	CNI (CsA)	Indicated for: • Organ and bone marrow transplantation • Sight-threatening intermediate or posterior uveitis of non-infectious aetiology in patients in whom conventional therapy has failed or caused unacceptable side effects • Steroid-dependent and steroid-resistant nephrotic syndrome, due to primary glomerular diseases such as minimal change nephropathy, focal and segmental glomerulosclerosis, or membranous glomerulonephritis • Severe active rheumatoid arthritis • Short-term treatment of severe (and very severe) atopic dermatitis, where conventional therapy is ineffective or inappropriate • Severe psoriasis, where conventional therapy is ineffective or inappropriate	
Initial/ maintenance	AZA	Indicated for: • Enhancing the survival of organ transplants (such as renal, cardiac and hepatic transplants). It also reduces the corticosteroid requirements of renal transplant recipients • Moderate to severe IBD (Crohn's disease or ulcerative colitis) in patients in whom corticosteroid therapy is required, in patients who cannot tolerate corticosteroid therapy, or in patients whose disease is refractory to other standard first line therapy • Severe refractory eczema	Offered (2 mg/kg/day) instead of MMF/MPA, in combination with corticosteroid (low-dose prednisone [2.5–5 mg/day]) - preferred if pregnancy is contemplated, when needed to control disease activity (EULAR/ERA-EDTA only) Offered as an add-on treatment option for class V active LN only (KDIGO only)

NR/R	RTX	Indicated for: • Rheumatoid arthritis • Non-Hodgkin's lymphoma (specialist use only), • Chronic lymphocytic leukaemia (specialist use only), • Granulomatosis with polyangiitis and microscopic polyangiitis • Pemphigus vulgaris	Offered (1000 mg on days 0 and 14) as monotherapy (EULAR/ERA-EDTA only) or an add-on therapy to MMF/MPA or CYC (EULAR/ERA-EDTA and KDIGO) RTX may be offered for purpose of corticosteroid minimisation in active III–V LN (KDIGO only)

*Guidance relates to both EULAR/ERA-EDTA and KDIGO recommendations, unless otherwise stated

Abbreviations: AZA = azathioprine; BEL = belimumab; CNI = calcineurin inhibitor; CsA = ciclosporin; CYC = cyclophosphamide; GFR = glomerular filtration rate; IBD = inflammatory bowel disease; LN = lupus nephritis; MMF = mycophenolate mofetil; MPA = mycophenolic acid; NR/R = non-responding/refractory disease; RTX = rituximab; SLE = systemic lupus erythematosus; TAC = tacrolimus

Source:, Fanouriakis et al., 2020 and the Electronic Medicines Compendium[27,43,62,63,76,78-81]

B.1.3.7 Unmet need

Uncontrolled, active LN causes the irreversible loss of kidney nephrons,[82] resulting in the earlier onset of ESRD and a reduction in the overall lifespan of the kidneys.[83] For this reason, patients with LN who do not respond to treatment within 12 months are around five times more likely to develop CKD (HR 5.2 [95% CI: 2.8–7.6]).[84] It is therefore critical to achieve treatment response to prevent further organ damage accrual, and improve renal prognosis.[27,28,39,84-86]

Despite currently available treatments, many patients with LN continue to develop ESRD, where almost two-thirds of patients die within five years (Section B.1.3.5.1.1).[48,50,52] Standard of care (SoC) treatment with traditional immunosuppressants (MMF or cyclophosphamide; Section B.1.3.5.1.1) is associated with sub-optimal and slow clinical response, thereby extending the length of time that a patient is exposed to active LN and nephron damage (Rovin et al., 2021).[13,27,43] Phase 3 randomised trials report CR rates of only 8.6%–30.6% for MMF and 8.1% for cyclophosphamide (Appendix M). [2,87,88] Furthermore, various studies have reported high rates of renal flare after long-term follow-up following both MMF (19% after 48 months; ~45% after 110 months [Phase 3]),[89,90] and cyclophosphamide (29% after 41 months [Phase unspecified]).[91]

CNIs have demonstrated greater efficacy than traditional immunosuppressive agents, both as monotherapy and in combination with MMF.[92-94] In particular, meta-analyses of randomised trials demonstrate that tacrolimus monotherapy is significantly more effective than cyclophosphamide at achieving CR (51% vs 31%, respectively [p=0.004]; n=225);[95] and overall response (odds ratio [OR] 2.4 [95% CI: 1.0–5.5]; n=972).[96] Similarly, a randomised trial (n=368) report significantly higher complete clearance for tacrolimus with MMF vs cyclophosphamide only (45.9% vs 25.6%, respectively; p<0.001), and significantly shorter median time to overall response (4.1 fewer weeks [95% CI: -7.9 to -2.1 weeks]).[92] Despite promising efficacy, currently available CNIs have additional safety limitations. Tacrolimus and ciclosporin are associated with key adverse events such as hypertension or kidney dysfunction; and several metabolic disorders which include glucose intolerance, dyslipidaemia, and diabetes.[93,97-99] Tacrolimus has even been shown to have a direct deleterious effect on pancreatic islets.[100] Current CNIs are further limited by their narrow therapeutic windows (i.e. the level of drug exposure required for efficacy is close to that of toxicity), so regular drug monitoring is needed in the form of blood tests during clinician visits.[93,101,102]

Corticosteroids and cyclophosphamide are also associated with toxicity and adverse outcomes, of which organ damage is a particular concern.[12,103,104] Within the UK, a 21-year prospective study of patients with SLE (n=382) found each treatment to be associated with the development of organ damage (HR 3.4 [95% CI: 2.0–5.7] and HR 2.5 [95% CI: 1.5–4.0], respectively).[105] Corticosteroids and cyclophosphamide also have a unique profile of potentially serious adverse effects. Specifically, corticosteroids may cause an increase of cardiovascular risk factors, osteoporosis, cataracts, and serious infection.[103,106] On the other hand, cyclophosphamide is associated with significantly higher frequencies of infections, leukopenia, hair loss, death, and hospital admission compared to MMF.[107] Safety concerns mean that corticosteroid-use is generally minimised where possible, and MMF may be preferred to cyclophosphamide as a first-choice treatment.[12,13,27,43]

Beyond MMF, cyclophosphamide and CNIs; rituximab is another off-label alternative that can be used as monotherapy or as an add-on therapy (with MMF or cyclophosphamide for patients

with active LN).[43] However, EULAR/ERA-EDTA do not currently recommend it's use in the initial treatment setting, and rituximab failed to demonstrate a superior overall response rate (primary endpoint) to placebo in a Phase 3 trial of patients with active LN treated concomitantly with MMF/corticosteroids.[88]

In conclusion, the SoC for LN has remained largely unchanged over the past 10 years in the form of off-label immunosuppressant therapy with MMF, cyclophosphamide and corticosteroids.[27,108] Despite these treatments, patients remain at high risk of progressing to ESRD due to sub-optimal/slow clinical response, and safety concerns which limit the use of corticosteroids and cyclophosphamide.[27,108] Off-label treatment with CNIs has since shown promising efficacy; however, they are linked with additional safety limitations and are dependent on regular drug monitoring which places undue burden on patients and healthcare professionals.[1,93,97-99,102,109] Therefore, there is a critical need for novel treatments which effectively control disease activity, are more tolerable, and have the potential to minimise cyclophosphamide and/or high-dose corticosteroid use. A novel CNI that has a consistent pharmacokinetic and pharmacodynamic profile which eliminates the need for regular therapeutic drug monitoring, while retaining the efficacy benefits associated with CNI treatments, relative to traditional immunosuppressive therapy.[2]

B.1.3.8 Place of voclosporin in the treatment pathway

Voclosporin is anticipated to be used in accordance with its proposed marketing authorisation; in combination with background immunosuppressive therapies for the treatment of adult patients with active class III, IV or V (including mixed class III/V and IV/V) LN.

All active LN patients (class III, IV or V including mixed class III/V and IV/V) should be considered for treatment with voclosporin, including patients at initial diagnosis of LN, those with newly flaring disease (previously in remission), and those previously diagnosed but inadequately treated for LN.

Voclosporin should be used as a first-line alternative to MMF/MPA and cyclophosphamide-based treatments as an initial treatment of active class III, IV or V (including mixed class III/V and IV/V) LN. As the first CNI to be indicated for the treatment of LN, voclosporin should also be used ahead of other CNI-based treatments due to its improved immunosuppressive potency, tolerable safety profile, and broader therapeutic index which eliminates the need for regular therapeutic drug monitoring.[8,9,11]

B.1.4 Equality considerations

There are no known equality issues relating to the use of voclosporin in patients with LN.

B.2. Clinical effectiveness

B.2.1 Identification and selection of relevant studies

A systematic literature review (SLR) was conducted to identify and summarise the available randomised controlled trial (RCT) evidence for the current and future treatment options for patients with LN. Full details of the SLR are included in Appendix D.

B.2.2 List of relevant clinical effectiveness evidence

The efficacy and safety of voclosporin has been evaluated in the pivotal Phase 3 study (AURORA 1: AUR-VCS-2016-01 [NCT03021499]),[2] as well as a follow-on Phase 3 long-term continuation study (AURORA 2: AUR-VCS-2016-02 [NCT03597464]). In addition, data is provided from a Phase 2b study with post-study long-term outcomes (AURA-LV; AUR-VCS-2012-01 [NCT02141672]),[8] and a pooled analysis of Phase 3 AURORA 1 and Phase 2b AURA-LV.[110] An overview of the clinical effectiveness evidence is presented in Table B.2-1.

Table B.2-1. Clinical effectiveness evidence

Phase 3					
Study	AURORA 1 (AUR-VCS-2016-01; NCT03021499)[2]				
Study design	Phase 3, 52-week, randomised, double-blind, parallel-group, placebo-controlled, two-arm, multicentre study				
Population	Adult patients with diagnosis of SLE according to ACR criteria, kidney biopsy (within 2 years) proven LN class III, IV, or V (alone or in combination with class III or IV)				
Intervention(s)	Voclosporin (23.7 mg BID)				
Comparator(s)	Placebo				
Indicate if trial supports application for marketing authorisation	Yes	X	Indicate if trial used in the economic model	Yes	X
	No			No	
Rationale for use/non-use in the model	Pivotal Phase 3 trial supporting this indication				
Reported outcomes specified in the decision problem	• **Renal response** • **Rate and duration of remission** • **Corticosteroid use** • **HRQoL** • **Adverse effects of treatment**				
All other reported outcomes	• Change in immunology parameters (C3, C4, and dsDNA)				
Phase 3 long-term continuation					
Study	AURORA 2 (AUR-VCS-2016-02; NCT03597464)				
Study design	Phase 3, 24-month extension, randomised, double-blind, parallel-group, placebo-controlled, two-arm, multicentre study				
Population	Adult patients who have completed 52 weeks of treatment (voclosporin or placebo) in the AURORA 1 study				
Intervention(s)	Voclosporin (23.7 mg BID up to 12 months, then patients with controlled UPCR become eligible for a dose reduction to 15.8mg BID for the final 12 months; otherwise dosage remains the same)				
Comparator(s)	Placebo				
Indicate if trial supports application for marketing authorisation	Yes	X	Indicate if trial used in the economic model	Yes	X
	No			No	
Rationale for use/non-use in the model	Pivotal Phase 3 long-term continuation trial supporting this indication				

Reported outcomes specified in the decision problem	• **Renal response** • **Rate and severity of renal-related flares** • **Corticosteroid use** • **HRQoL** • **Adverse effects of treatment**				
All other reported outcomes	• Change in immunology parameters (C3, C4, and dsDNA) • Routine biochemical and haematological assessments				
Phase 2b					
Study	AURA-LV (AUR-VCS-2012-01; NCT02141672)				
Study design	Phase 2b, 48-week, randomised, double-blind placebo-controlled, three-arm, multicentre study				
Population	Adult patients with diagnosis of SLE according to ACR criteria, kidney biopsy proven LN class III, IV, or V (alone or in combination with class III or IV)				
Intervention(s)	Low-dose voclosporin (23.7 mg BID) or high-dose voclosporin (39.55 mg BID)				
Comparator(s)	Placebo				
Indicate if trial supports application for marketing authorisation	Yes	X	Indicate if trial used in the economic model	Yes	
	No			No	X
Rationale for use/non-use in the model	Pivotal Phase 2b trial supporting this indication was not required to populate the economic model due to the availability of Phase 3 and Phase 3 extension data in the same indication				
Reported outcomes specified in the decision problem	• Renal response • Rate and duration of remission • Adverse effects of treatment				
All other reported outcomes	• Change in immunology parameters (C3, C4, and dsDNA), and biomarkers • Active urinary sediment*				

*Defined by >10 RBCs per high powered field with dysmorphic RBC and/or RBC casts on urinalysis of a urine sample which has a minimum volume of 50 ml

Abbreviations: ACR = American College of Rheumatology; BID = twice daily; C3 = complement 3; C4 = complement 4; dsDNA = double-stranded deoxyribonucleic acid; HRQoL = health-related quality of life; LN = lupus nephritis; mg = milligrams; ml = millilitre; RBC = red blood cell; SLE = systemic lupus erythematosus

B.2.3 Summary of methodology of the relevant clinical effectiveness evidence

The efficacy and safety of voclosporin have been evaluated in a comprehensive clinical trial programme. The results of the AURORA 1 Phase 3 and AURORA 2 Phase 3 long-term continuation trials constitute the primary source of clinical evidence for this submission, along with supporting data from the AURA-LV Phase 2 study and an integrated pooled analysis of AURORA 1 and AURA-LV. A summary of methodology for AURORA 1 (Section B.2.3.1), AURORA 2 (Section B.2.4.2) and AURA-LV (Section B.2.3.3) is provided, along with supporting efficacy (Section B.2.6) and safety (Section B.2.10) data for each trial.

Across each trial, the terms “complete remission”, “complete renal remission”, “renal response” and “CRR” have been used interchangeably but share the same definition. Similarly, “partial remission”, “partial response” and “partial renal response (PRR)” have also been used interchangeably but share the same definition. For the purposes of this submission, the outcomes are henceforth referred to as “CRR” and “PRR” for consistency across all three trials.

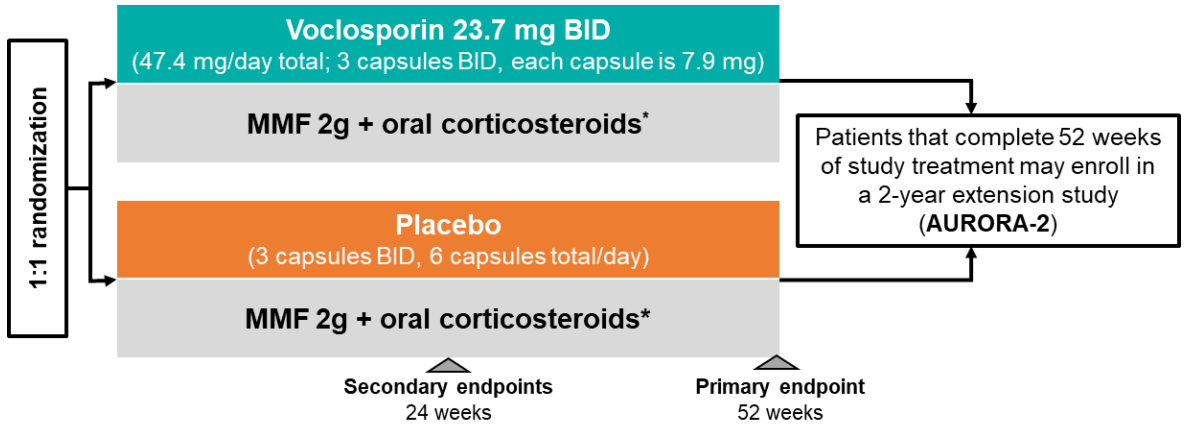
B.2.3.1 AURORA 1 Phase 3 study

B.2.3.1.1 *Study design and objectives: AURORA 1*

AURORA 1 is a Phase 3, multicentre, double-blind, placebo-controlled, randomised trial that compared the efficacy and safety of voclosporin versus placebo, each in combination with MMF and low-dose oral corticosteroids for the treatment of patients with active LN.[2] In each treatment arm, over a period of 52 weeks, the primary objective was to assess efficacy in achieving CRR, while the secondary objective was to assess safety and tolerability of therapy in patients with active LN.[109]

An overview of AURORA 1 trial design is presented in Figure B.2-1, accompanied by a summary of methodology in Table B.2-2.

Figure B.2-1. Trial design: AURORA 1 (AUR-VCS-2016-01; NCT03021499)



*Oral corticosteroids were tapered per protocol
Abbreviations: BID = twice-daily; MMF = mycophenolate mofetil
Source: Rovin et al., 2021[2]

Table B.2-2. Summary of methodology for AURORA 1 (AUR-VCS-2016-01; NCT03021499)

Study name	Aurinia Renal Response in Active Lupus with Voclosporin (AURORA 1)
Identifiers	EudraCT: 2016–004045–81 ClinicalTrials.gov: NCT03021499
Study status	Completed (April 2017 to October 2019)
Study design	Phase 3, 52-week, randomised, double-blind, parallel-group, placebo-controlled, two-arm, multicentre study
Locations	357 patients were randomised across 142 sites in 27 countries: • Europe (40 sites; n=97) o Belarus (2 sites; n=14) o Bulgaria (1 site; n=1) o Croatia (1 site; n=1) o The Netherlands (2 sites; n=4) o Poland (2 sites; n=2) o Russia (14 sites; n=37) o Serbia (4 sites; n=10) o Spain (2 sites; n=4) o Turkey (6 sites; n=7) o Ukraine (6 sites; n=17) • North America (29 sites [US only]; n=52) • Latin America (32 sites; n=97) • South Africa (3 sites; n=7) • Asia (38 sites; n=104)
Study treatments	**Arm 1:** • Voclosporin 23.7 mg BID plus MMF 1g BID and low-dose corticosteroid* (n=179) **Arm 2:** • Placebo BID plus MMF 1g BID and low-dose corticosteroid*(n=178)
Key eligibility criteria	**Inclusion**: • Diagnosis of SLE (per ACR criteria) with active LN(by kidney biopsy), and confirmation of class III, IV, V (alone or in combination with class III or IV) LN† with (UPCR of ≥1.5 mg/mg for class III and IV LN or ≥ 2 mg/mg if pure class V)‡
	Exclusion: • eGFR ≤45 ml/min/1.73 m^2 at screening
Primary outcome	• CRR at Week 52§
Key secondary outcomes	**Key secondary hierarchical endpoints for efficacy (in order) were:** • Time to UPCR of ≤0.5 mg/mg • PRR (≥50% reduction in UPCR from baseline) at Weeks 24 and 52 • Time to 50% reduction in UPCR from baseline • CRR at Week 24
	PROs: HRQoL at Weeks 12, 24, and 52 • SF-36 • LupusPRO
Safety outcomes	• AEs (including SAEs) • Laboratory parameters • Vital signs • 12-lead ECG • Physical examination
Pre-planned subgroups	CRR at Week 52 by: • Age • Gender • Race • Biopsy class

	• Region • MMF use at screening and maximum MMF dose

*IV methylprednisolone (0.5 g/day for patients ≥ 45 kg, or 0.25 g/day for patients < 45 kg) once daily on days 1 and 2; followed by the commencement of oral prednisone (25 mg/day for patients ≥ 45 kg, or 20 mg/day for patients < 45 kg) on day 3. Oral prednisone was then rapidly tapered to a dose of 2.5 mg/day at Week 16, according to a protocol-specified tapering schedule. Any subsequent dose adjustments were made per investigator discretion; †According to kidney biopsy within 2 years of screening; ‡Doubling or greater increase in UPCR in the 6 months before screening was required in patients who had a kidney biopsy > 6 months before screening; §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

Abbreviations: ACR = American College of Rheumatology; AE = adverse event; CRR = complete renal response; ECG = electrocardiogram; eGFR = estimated glomerular filtration rate; g = grams; HRQoL = health-related quality of life; IV = intravenous; LN = lupus nephritis; m^2 = metres squared; mg = milligrams; MMF = mycophenolate mofetil; PROs = patient reported outcomes; PRR = partial renal response; SAE = serious adverse event; SF-36 = 36-Item Short Form Survey; UPCR = urine protein creatinine ratio

B.2.3.1.2 *Eligibility criteria: AURORA 1*

AURORA 1 included patients diagnosed with class III, IV, or V (alone or combination with III or IV) active LN. A summary of inclusion and exclusion criteria is presented in Table B.2-3.

Table B.2-3. Inclusion and exclusion criteria: AURORA 1

Inclusion criteria	• Age 18 to 75 (or legal age of consent if >18 years)
	• Diagnosis of SLE according to ACR 1997 criteria
	• Evidence of active nephritis, defined by:
	  ○ Kidney biopsy indicating Class III, IV-S, IV-G (alone or in combination with Class V), or Class V LN within 2 years prior to screening with a ≥2 times increase of UPCR to a minimum of ≥1.5 mg/mg for Class III/IV or ≥2 mg/mg for Class V within the last 6 months prior to screening. Biopsy results >6 months prior to screening had to be reviewed by a medical monitor to confirm eligibility
	  OR
	  ○ Kidney biopsy indicating Class III, IV-S, or IV-G (alone or in combination with Class V) LN within 6 months prior to screening with a UPCR of ≥1.5 mg/mg at screening.
	  OR
	  ○ Kidney biopsy result within 6 months prior to screening indicating Class V LN and a UPCR of ≥2 mg/mg at screening
	• Patient required high-dose corticosteroids and immunosuppressive therapy
	• Women of childbearing potential were not pregnant, and using effective contraception unless abstinent

Exclusion criteria	• eGFR ≤45 ml/min/1.73 m^2 at screening (according to CKD-EPI) • Patient required renal dialysis at screening or during the study period • Previous or planned kidney transplant during the study treatment period • Patient taking or requiring any medications prohibited in the study protocol • Hypersensitivity or contraindication to MMF, MPA, CsA, corticosteroids, or any components of these drug products • Had a current or medical history of: o Congenital or acquired immunodeficiency o Clinically significant drug or alcohol abuse within 2 years prior to screening o Malignancy within 5 years of screening with exception of BCC and SCC treated by complete excision* o Lymphoproliferative disease or previous total lymphoid irradiation o Severe viral infection (e.g., cytomegalovirus, hepatitis B virus, hepatitis C virus) within 3 months of screening; or known human immunodeficiency virus infection o Active tuberculosis or known history of tuberculosis/evidence of old tuberculosis if not taking prophylaxis with isoniazid • Other known clinically significant active medical conditions† • Overlapping autoimmune condition which may affect study assessments/ outcomes • Vaccines using live organisms, virus, or bacteria during screening or study treatment • Patients who were pregnant, breast feeding or not using adequate contraceptive precautions if of childbearing potential • Participation in another clinical study within 4 weeks prior to screening and/or receipt of investigational drugs within 4 weeks or 5 half-lives prior to screening • Previous treatment with voclosporin in a clinical study

*Patients with cervical dysplasia that was cervical intraepithelial neoplasia 1 but had been treated with conization or loop electrosurgical excision procedure and had a normal repeat Papanicolaou test were Allowed; †Severe cardiovascular disease, liver dysfunction, COPD or asthma requiring steroids, bone marrow insufficiency unrelated to SLE, active bleeding disorders, or infection requiring antibiotics

Abbreviations: ACR = American College of Rheumatology; BCC = basal cell carcinoma; CKD-EPI = Chronic Kidney Disease Epidemiology Collaboration; CsA = ciclosporin; eGFR = estimated glomerular filtration rate; ; LN = lupus nephritis; m^2 = metres squared; mg = milligrams; MMF = mycophenolate mofetil; SCC = squamous cell carcinoma; SLE = systemic lupus erythematosus; UPCR = urine protein creatinine ratio

B.2.3.1.3 ***Study treatments: AURORA 1***

B.2.3.1.3.1 Allocation to treatment

Patients were randomised 1:1 to the voclosporin arm or the placebo arm.[2] Randomisation was stratified by biopsy class (pure class V only vs others), previous MMF use at the time of screening (yes vs no), and region (North America vs Latin America vs Europe and South Africa vs Asia-Pacific).[2]

B.2.3.1.3.2 Treatments administered

Patients received either oral 23.7 mg voclosporin (administered as three 7.9 mg capsules) BID or matching placebo for 52 weeks.[2] In addition to the study drug (voclosporin or placebo), all patients received the following:

IV methylprednisolone (0.5 g/day for patients ≥45 kg, or 0.25 g/day for patients < 45 kg) once daily on days 1 and 2. On day 3, oral prednisone was commenced at 25 mg/day for patients ≥45 kg bodyweight, or 20 mg/day for patients <45 kg. Oral prednisone was then rapidly tapered to a dose of 2.5 mg/day at Week 16. Any subsequent dose adjustments were made per investigator discretion.

Patients who were not taking MMF prior to randomisation received 1 g/day for the first week, increasing to 2 g/day starting from day 8.

B.2.3.1.3.3 Dose modification and treatment discontinuation

Dose modification of study treatment was permitted in the case of decreased renal function, increased blood pressure, or a treatment-emergent abnormal heart rhythm (i.e. increase in QT interval duration corrected for heart rate using method of Fridericia [QTcF]).

- **Decreased renal function:** study treatment was withheld for any patient experiencing >30% decrease in eGFR from baseline to <60 ml/min/1.73m^2 until a confirmation test could be performed (at an unscheduled visit if needed). If eGFR decrease was not confirmed, study treatment was restarted at 2 capsules BID (15.8 mg voclosporin BID) and increased as tolerated with discussion with the Medical Monitor. However, if the decrease was confirmed and not due to other contributing factors, study treatment was stopped and eGFR retested for recovery within 48 hours. eGFR recovery was defined as eGFR >80% of baseline, and patients that recovered were restarted on one capsule BID [7.9mg BID] until reassessment of eGFR within 2 weeks. For patients with a <20%–≤30% reduction in eGFR to <60 mL/min/1.73 m^2 that was not related to other contributing factors, a confirmation test was performed within ~2 weeks (either planned study visit or an unscheduled visit) and patients were managed appropriately in consultation with the Medical Monitor by either a dose reduction (to 1 or 2 capsules BID [7.9–15.8 mg BID]) or a temporary interruption.
- **Increased blood pressure:** study treatment was withheld if systolic or diastolic blood pressure was >165 mmHg or >105 mmHg, respectively, and associated with symptoms of hypertension. Patients were subsequently treated per investigator local practices and best judgement, and the patient continued with all planned study visits. Study treatment could only be reintroduced following discussion with the Medical Monitor.
- **Treatment-emergent increase in QTcF:** any patient with a QTcF value >500 milliseconds (msec), or an increase >60msec from baseline was required to return for an unscheduled visit within 24 hours for confirmation by repeat electrocardiogram (ECG) in triplicate. If confirmed, study treatment was to be permanently discontinued and the patient was followed until the QTcF value returned to baseline (or as appropriate) or until further evaluation was not clinically indicated. If study treatment was discontinued, the patient was to remain in the study and attend all remaining planned study visits.

B.2.3.1.3.4 Concomitant therapies

A summary of permitted and prohibited concomitant therapies is shown in Table B.2-4.

Table B.2-4. Concomitant therapy

Permitted	• Topical steroids (e.g., nose, scalp, skin, inhaled) • Antimalarials when clinically indicated • Herbal supplements (depending on active ingredients) • Treatments of symptomatic minor gastrointestinal AEs • Treatment of neutropenia in presence of major infection (e.g. G-CSF) • Iron supplements for iron deficiency and/or anaemia • Erythropoietin for severe anaemia • Lipid-lowering therapies (e.g. statins) • Acute NSAIDs for ≤7 consecutive days • Cardiovascular treatments (e.g. ACE inhibitors, ARBs, aliskiren and other therapies)* • Diuretic or calcium channel block in case of uncontrolled hypertension • Prophylactic therapy against: o Steroid-induced bone loss (calcium with Vitamin D and/or a bisphosphonate) o Cardiovascular issues (low dose aspirin) o Fungal infection (amphotericin or oral nystatin; low-dose sulfamethoxazole/trimethoprim against *Pneumocystis carinii pneumonia*) o Cytomegalovirus (e.g. with oral valganciclovir)
Prohibited	• MMF dose other than 2g/day or treatment with any other immunosuppressant after randomisation • Antifungal treatment with ketoconazole†, or antibiotic treatment with rifampin • Vaccines using live organisms, viral or bacterial • Oral corticosteroids other than those administered per protocol • IV corticosteroids within 2 weeks PTS† • Any IV Ig within 2 weeks PTS • CYC within 4 weeks PTS • Drugs that may interfere with MMF enterohepatic recirculation within 4 weeks PTS • New treatment with or change in dosage of ARBs and/or ACE inhibitors within 4 weeks PTR • CNIs within 1 month PTS • Immunosuppression biologic agents within 3 months PTS

*If used, patients must be on a stable dose of ACE inhibitors or ARBs for 4 weeks prior to enrolment and dose must remain stable throughout the study; †Unless approved or discussed with the Medical Monitor; ‡Concomitant use of other CYP3A45 inhibitors and inducers to be discussed with Medical Monitor
Abbreviations: ACE = angiotensin-converting enzyme; AE = adverse event; ARB = angiotensin II receptor blocker; CNI = calcineurin inhibitors; CYC = cyclophosphamide; g= gram; G-CSF = granulocyte colony-stimulating factor; Ig = immunoglobulin; IV = intravenous; MMF = mycophenolate mofetil; NSAIDs = non-steroidal anti-inflammatory drug; PTS = prior to screening; PTR = prior to randomisation

B.2.3.1.4 ***Assessments and outcomes: AURORA 1***

B.2.3.1.4.1 Efficacy outcomes

The primary efficacy outcome was CRR at Week 52 assessed by the Clinical Endpoints Committee and defined as a composite of:

- UPCR of ≤ 0.5 mg/mg or less
- eGFR of ≥ 60 mL/min/1.73m^2 or no confirmed eGFR decrease of > 20% from baseline
- No administration of rescue medication
- No more than 10 mg prednisone equivalent per day for 3 or more consecutive days or for 7 or more days in total during weeks 44 through 52, just prior to the primary endpoint assessment

Patients were disqualified from CRR if they failed both eGFR measures (i.e., confirmed eGFR <60 mL/min/1.73 m^2 and confirmed >20% drop from baseline) and had an associated treatment-related or disease-related adverse event (AE) that impacted eGFR. Patients who withdrew from the study prior to the Week 52 assessment and provided insufficient Week 52 data to determine response were defined as non-responders. Patients who discontinued study drug but continued to attend study visits had their data assessed for response.

The following secondary efficacy outcomes were also measured, listed below in terms of key secondary outcomes and other relevant secondary endpoints.

- Key secondary hierarchical endpoints for efficacy were analysed in order using the Hochberg step-up sequential testing procedure were (see section B.2.4.1 for more detail):[2]
  - Time to UPCR of ≤0.5 mg/mg
  - PRR (defined as ≥50% reduction from baseline UPCR) at Weeks 24 and 52
  - Time to 50% reduction in UPCR from baseline
  - CRR at Week 24 (based on primary endpoint definition with corticosteroid dosing assessed from Weeks 16 to 24)
- Other relevant secondary outcomes:[2]
  - Duration of UPCR ≤0.5 mg /mg
  - Proportion of patients with >30% decrease in eGFR by time point
  - Change from baseline in UPCR by time point
  - Change from baseline in serum creatinine, urine protein, and eGFR by time point
  - RR with low-dose steroids at Weeks 24 and 52
  - Change from baseline in immunology parameters (complement 3 (C3), C4, and anti-ds DNA) at weeks 24 and 52
  - Change from baseline in the safety of oestrogens in Safety of Estrogens in Lupus
  - Erythematosus National Assessment-Systemic Lupus Erythematosus Disease Activity Index (SELENA-SLEDAI) score at Weeks 24 and 52
  - Change from baseline in HRQoL at Weeks 12, 24, and 52
  - Healthcare resource utilisation at Week 24 and 52

B.2.3.1.4.2 Efficacy assessment

Blood and urine samples contributing to efficacy and safety assessments were analysed at central laboratories using standard validated methods. Analyses included hematology, blood chemistry, coagulation, lupus markers (immunology parameters), urinalysis and eGFR.

In terms of the study primary outcome, efficacy was assessed according to the ability of study treatment to reduce the level of proteinuria (as measured by UPCR) and improve renal function (as measured by eGFR).[109,111] Urine and blood samples were collected at all study visits except Day 2 (Visit 3 of 16), for measurement of UPCR and eGFR, respectively.

The UPCR was calculated by urinalysis primarily from the first morning void (FMV), although UPCR could also be calculated from 24-hour urinalysis for the purposes of efficacy endpoints (performed at baseline, Week 24, and Week 52) should FMV samples be unavailable or invalid.

eGFR was calculated from serum creatinine results using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation. Patients had a minimum of two pre-study treatment eGFR measurements taken prior to dosing at baseline, and the lowest of the pre-dose measurements was used as a marker of baseline renal function.

Disease activity was assessed using the SELENA-SLEDAI scoring system, which requires a series of tests including includes urinalysis, blood analysis, and physical examination to assess disease activity according to 24 different disease descriptors. Patients were assessed using SELENA-SLEDAI at baseline, Week 24 and Week 52.

B.2.3.1.4.3 Patient-reported outcomes

Patient-reported outcomes (PROs) were measured as secondary endpoints and included SF-36 and the LupusPRO (v1.7) scores, specifically exploring the change in score from baseline at Weeks 2, 4, 8, 12, 16, 24 and 52.

B.2.3.1.4.4 Patient-reported outcome assessment

PROs were collected using the SF-36 and LupusPro (v1.7) questionnaires. SF-36 is a 36-question survey designed to measure general HRQoL, while LupusPro (1.7) is a 43-question HRQoL survey specific for lupus. Patients completed surveys at the baseline visit, then at subsequent pre-planned visits at Weeks 2,4,8, 12, 24, and 52.

B.2.3.1.4.5 Safety outcomes

Safety outcomes included the collection of AE data, laboratory parameters (clinical chemistry, haematology, urinalysis), vital signs, and ECGs from baseline to week 56 (safety follow-up).

B.2.3.1.4.6 Safety assessment

Safety assessments included AEs (throughout the study), vital signs (at screening, baseline, Day 2, and Weeks 2,4,8,12,16), laboratory parameters (at screening, baseline, and Weeks 2,4,8,12,16,20,24,30,48,52, 56), 12-lead ECGs (at screening and Weeks 2,4,8,12,16,24 and 52) and physical examinations (at screening, baseline, and Weeks 24 and 52).

AEs and serious adverse events (SAEs) were defined according to International Council for Harmonisation (ICH) definitions. AEs were reported from time of patient study consent to the Safety Follow-up Visit at Week 56, while SAEs were reported from patient study consent until the final study visit, or 30 days after last study treatment administration in patients who withdrew from the study. A treatment-emergent adverse event (TEAE) was defined as any AE with onset on or after the first dose of voclosporin or placebo up to and including 30 days after the last dose of voclosporin or placebo. Patients who discontinued treatment were encouraged to attend all planned study visits up to the final Safety Follow-up Visit at Week 56, and any AEs that occurred >30 days after the last dose of voclosporin or placebo up to the Safety Follow-up were defined as post-treatment AEs.

AE intensity was assessed by the Investigator, and adjudged to be mild if the AE was easily tolerated and did not interfere with usual activity, moderate if the AE interfered with daily activity but the patient was still able to function, or severe if the AE was incapacitating and the patient was unable to work or complete usual activity.

B.2.3.1.5 *Study population: AURORA 1*

B.2.3.1.5.1 Patient disposition

Among the intention-to-treat (ITT) population (voclosporin, n=179; placebo, n=178), one patient randomised to voclosporin did not start treatment due to an AE.[2] Overall, 86.6% of all randomised patients completed the study up to Week 52 (n=162 in voclosporin arm, n=147 in placebo arm). Among patients who received at least one dose of study drug, 15 (8.4%) of 178 patients in the voclosporin group and 31 (17.4%) of 178 patients in the placebo group withdrew from the study. The most common reason for permanent study withdrawal (n ≥ 5 patients) was withdrawal of consent (voclosporin arm: n=7; placebo arm, n=14) followed by death (voclosporin arm: n=1; placebo arm: n=5) and physician decision (voclosporin arm: n=2; placebo arm: n=3).

Patients discontinuing study treatment were encouraged to remain in the study and attend all scheduled follow-up visits, up to and including the safety follow-up assessment at Week 56. Fewer patients discontinued treatment with voclosporin (33.1%) than with placebo (24.0%). The most common reason for treatment discontinuation was intolerable AEs (13.5% vs 12.8%, respectively). Patient disposition for AURORA 1 is summarised in terms of overall study withdrawals (n=30) and drug discontinuations in Table B.2-5.

Table B.2-5. AURORA 1 patient disposition

	Parameters	Voclosporin (n=179)	Placebo (n=178)	Overall (N=357)
Study withdrawals	Completed Week 24	167 (93.3)	162 (91.0)	329 (92.2)
	Completed Week 52	162 (90.5)	147 (82.6)	309 (86.6)
	Study withdrawals, n (%)	16 (8.9)	31 (17.4)	47 (13.2)
	Intolerable AE	2 (1.1)	0 (0.0)	2 (0.6)
	Death	1 (0.6)	5 (2.8)	6 (1.7)
	Lost to follow-up	1 (0.6)	3 (1.7)	4 (1.1)
	Physician decision	2 (1.1)	3 (1.7)	5 (1.4)
	Prohibited medication required	1 (0.6)	0 (0.0)	1 (0.3)
	Pregnancy	1 (0.6)	0 (0.0)	1 (0.3)
	Protocol non-compliance	1 (0.6)	1 (0.6)	2 (0.6)
	Withdrawal of consent	7 (3.9)	14 (7.9)	21 (5.9)
	Lack of efficacy	0 (0.0)	1 (0.6)	1 (0.3)
	Other	0 (0.0)	4 (2.2)	4 (1.1)
Treatment discontinuations	Treatment discontinuation, n (%)	43 (24.0)	59 (33.1)	102 (28.6)
	Intolerable AE	23 (12.8)	24 (13.5)	47 (13.2)
	Death	0 (0.0)	3 (1.7)	3 (0.8)
	Lost to follow-up	1 (0.6)	2 (1.1)	3 (0.8)
	Physician decision	2 (1.1)	2 (1.1)	4 (1.1)
	Prohibited medication required	2 (1.1)	0 (0.0)	2 (0.6)
	Pregnancy	1 (0.6)	1 (0.6)	2 (0.6)
	Protocol non-compliance	2 (1.1)	0 (0.0)	2 (0.6)
	Withdrawal of consent	5 (2.8)	9 (5.1)	14 (3.9)
	Lack of efficacy	4 (2.2)	11 (6.2)	15 (4.2)
	Other	3 (1.7)	7 (3.9)	10 (2.8)

Abbreviations: AE = adverse event
Source: Otsuka 2020[109]

B.2.3.1.5.2 Analysis sets

The primary and hierarchical secondary efficacy analyses were completed in the ITT population, which included 179 patients randomly assigned to voclosporin and 178 patients to placebo.[2]

The safety analysis population included all patients who received at least 1 dose of study treatment.[2] One patient in the voclosporin group did not start treatment due to an AE; thus, the safety analysis population included 178 patients in the voclosporin treatment group and 178 in the placebo group.

B.2.3.1.5.3 Demographics and baseline characteristics

Baseline characteristics were similar between treatment groups.[2] Most patients (~88%) were female and the most common kidney biopsy class was pure class IV (voclosporin, 51%; placebo, 43%). The average time since initial LN diagnosis was over 4 years. A summary of demographics and baseline characteristics is shown in Table B.2-6.

Table B.2-6. AURORA 1: Baseline Demographic and Clinical Characteristics (ITT Population)

Baseline characteristic	All patients (N=357)	
	Voclosporin n=179	Placebo n=178
Age, median (range), years	31 (18–62)	32 (18–72)
Female, n (%)	161 (90)	152 (85)
Weight, mean (SD), kg	66.49 (17.07)	66.55 (16.11)
Region, n (%)		
Asia Pacific	52 (29)	52 (29)
Europe and South Africa	52 (29)	52 (29)
Latin America	49 (27)	48 (27)
North America	26 (15)	26 (15)
Race[*], n (%)		
White	68 (38)	61 (34)
Black	26 (15)	19 (11)
Asian	53 (30)	56 (31)
Other[†]	32 (18)	42 (24)
Ethnicity[*], n (%)		
Hispanic or Latino	57 (32)	59 (33)
Non-Hispanic or non-Latino	122 (68)	118 (66)
Unknown	0	1 (1)
Time since initial LN diagnosis, mean (SD), years	4.6 (5.1)	4.7 (4.9)
Time since SLE diagnosis, mean (SD), years	6.6 (6.4)	6.9 (6.1)[‡]

Biopsy class, n (%)		
Pure class III	20 (11)	29 (16)
Pure class IV	91 (51)	77 (43)
Pure class V	25 (14)	25 (14)
Class II and V only	0	1 (<1)
Class III and V only	24 (13)	20 (11)
Class IV and V only	19 (11)	26 (15)
Baseline eGFR		
Mean (SD), mL/min/1.73 m²	92.1 (30.6)	90.4 (29.0)
High (≥60 mL/min/1.73 m²), n (%)	146 (82)	144 (81)
Mean (SD) baseline UPCR, mg/mg	4.14 (2.71)	3.87 (2.36)
Complement 3		
Mean (SD), mg/dL	81.6 (34.73)	86.9 (36.42)
Low (<90 mg/dL), n (%)	105 (59)	99 (55)
Complement 3		
Mean (SD), mg/dL	16.6 (11.5)	16.8 (9.7)
Low (<10 mg/dL), n (%)	50 (28)	45 (25)
Anti-dsDNA		
Mean (SD), IU/mL	105.2 (127.7)	94.7 (124.4)
High (>10 IU/mL), n (%)	133 (74)	118 (66)
SELENA-SLEDAI, mean (SD); n	13.2 (6.5); n=177	11.8 (6.1); n=177
MMF use at screening, n (%)		
Yes	100 (56)	96 (54)
No	79 (44)	82 (46)

*Analyses for race and ethnicity were post hoc; †Other include American Indian, Alaska Native, Native Hawaiian, Pacific Islander, and other or mixed races except mixed Black race; ‡Data missing for 1 patient.
Percentages might not add up to 100% because of rounding.
Abbreviations: anti-dsDNA = anti-double-stranded DNA; dL = decilitre; eGFR = estimated glomerular filtration rate; ITT = intention-to-treat; mL = millilitre; MMF = mycophenolate mofetil; SELENA-SLEDAI = Safety of Estrogens in Systemic Lupus Erythematosus National Assessment-Systemic Lupus Erythematosus Disease Activity Index; UPCR = urine protein creatinine ratio.
Source: Rovin et al., 2021[2]

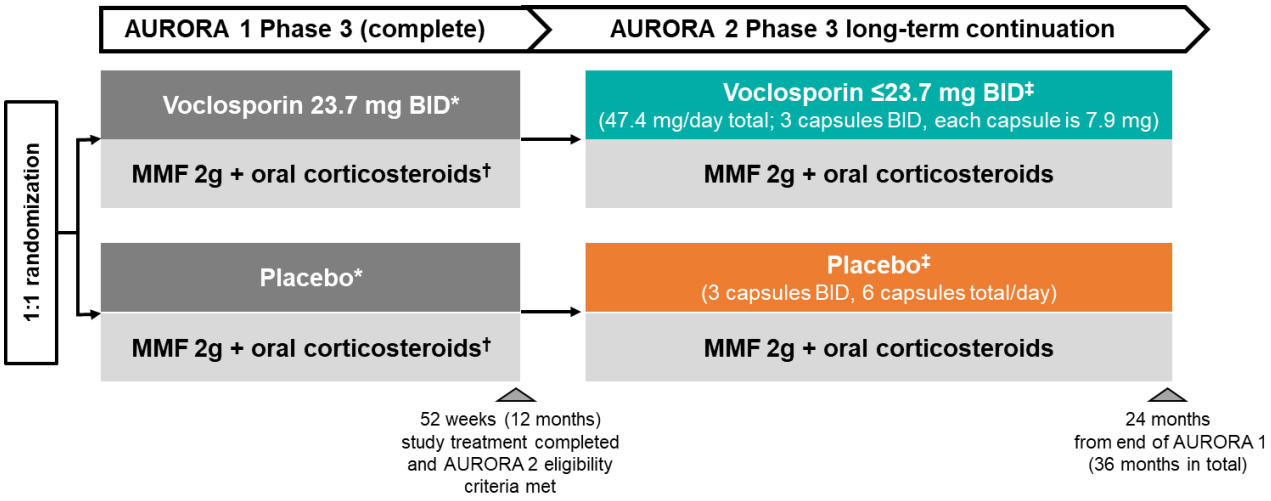
B.2.3.2 AURORA 2 Phase 3 long-term continuation study

B.2.3.2.1 *Study design and objectives: AURORA 2*

AURORA 2 is a Phase 3, multicentre, double-blind, placebo-controlled, randomised, 24-month long-term continuation study to the AURORA 1 study. Patients who completed 52 weeks of study drug treatment in the AURORA 1 study and met eligibility criteria (Section B.2.3.2.2) were allowed to continue long-term treatment as part of the AURORA 2 study.

The primary objective of AURORA 2 was to assess the long-term safety and tolerability of voclosporin compared to placebo for up to an additional 24 months following completion of treatment in the AURORA 1 study in patients with LN. All patients will continue to receive background therapy of MMF and oral corticosteroids, if applicable, starting at the same dose as at the end of the AURORA 1 study. The secondary objective was to assess the long-term efficacy of voclosporin compared to placebo for up to an additional 24 months following completion of treatment in the AURORA 1 study in patients with LN.

Figure B.2-2. Trial design: AURORA 2



*Patients in the voclosporin arm were randomised to receive 47.4 mg/day total; 3 capsules BID (each capsule is 7.9 mg), while patients in the placebo arm received 3 placebo capsules BID (i.e. 6 capsules total per day); †Oral corticosteroids were tapered per protocol; ‡Target doses are presented; however, patients enrolled onto AURORA 2 are initiated on the same dose of study treatment, MMF, and oral corticosteroids as received at the end of the AURORA 1 study

Abbreviations: BID = twice-daily; MMF = mycophenolate mofetil

Source: Otsuka et al., 2018;[112] Rovin et al., 2021[2,112]

Table B.2-7. Summary of methodology for AURORA 2 (AUR-VCS-2016-02; NCT03597464)

Study name	Aurinia Renal Response in Lupus with Voclosporin (AURORA 2)
Identifiers	EudraCT: 2016-004046-28 ClinicalTrials.gov: NCT03597464
Study status	Completed (June 2018 to Oct 2021)
Study design	Phase 3 long-term continuation, multicentre, double-blind, placebo-controlled, randomised trial
Locations	216 patients were randomised across 100 sites in 24 countries: • Europe (30 sites; n=69) • North America (19 sites [US only]; n=24) • Latin America (23 sites; n=61) • South Africa (3 sites; n=6) • Asia (25 sites; n=56)
Study treatments	Patients entering AURORA 2 were initiated on the same dose of study treatment as at the end of the AURORA 1 study Target treatment doses remained at: **Arm 1:** • Oral voclosporin 23.7 mg BID plus MMF 1g BID and low-dose corticosteroid (oral prednisone 2.5 mg/day) (n=116) **Arm 2:** Oral placebo BID plus MMF 1g BID and low-dose corticosteroid* (oral prednisone 2.5 mg/day) (n=100)
Key eligibility criteria	**Inclusion**: • Completed 52 weeks of treatment with study drug in AURORA 1, including patients who had a temporary interruption and successfully restarted study drug during AURORA 1
	Exclusion: • Patient requires or expected to require renal dialysis or kidney transplant during study period

Primary outcome	• AEs and routine biochemical and haematological assessments
Key secondary outcomes	**Efficacy**: • CRR at Week 24 • PRR • Renal and extra-renal flares • SELENA-SLEDAI score change from AURORA 1 baseline • UPCR, eGFR, urine protein, and serum creatinine change from AURORA 1 baseline
	PROs: • HRQoL (SF-36) change from AURORA 1 baseline

Abbreviations: AE = adverse event; CRR = complete renal response; eGFR = estimated glomerular filtration rate; g = grams; HRQoL = health-related quality of life; IV = intravenous; mg = milligrams; MMF = mycophenolate mofetil; PROs = patient reported outcomes; PRR = partial renal response; SELENA-SLEDAI = Safety of Estrogens in Lupus Erythematosus National Assessment - Systemic Lupus Erythematosus Disease Activity Index; SF-36 = 36-Item Short Form Survey; UPCR = urine protein creatinine ratio

B.2.3.2.2 *Eligibility criteria: AURORA 2*

A summary of inclusion and exclusion criteria is presented in Table B.2-8.

Table B.2-8. Inclusion and exclusion criteria: AURORA 2

Inclusion criteria	• Completed 52 weeks of treatment with study drug in the AURORA 1 study* • Continued immunosuppressive therapy was required • Women of childbearing potential were using effective contraception unless abstinent
Exclusion criteria	• Patient taking or requiring any medications prohibited in the study protocol • Patients required renal dialysis (haemodialysis or peritoneal dialysis) or was expected to require dialysis during study period • Planned kidney transplant within study treatment period • Any medical condition which may be associated with increased risk to the patient or may interfere with study assessments or outcomes • Pregnant, breast feeding or, if of childbearing potential, not using adequate contraceptive precautions • Vaccines using live organisms, virus or bacterial during study treatment

*Patients who had a temporary interruption and successfully restarted study drug during the AURORA 1 study were allowed to enrol into AURORA 2 with Medical Monitor approval

B.2.3.2.3 *Study treatments: AURORA 2*

B.2.3.2.3.1 Allocation to treatment

At completion of study treatment within the AURORA 1 study (Week 52), patients meeting the required eligibility criteria continued to receive either oral voclosporin or matching placebo, as randomised in the AURORA 1 study.

B.2.3.2.3.2 Treatments administered

Patients received a maximum of either 3 capsules of voclosporin (23.7 mg BID) or matching placebo BID, as randomised into AURORA 1. Voclosporin and placebo was administered in combination with MMF and oral corticosteroids, if applicable. On enrolment into AURORA 2, treatment was commenced at the same doses given at the time of completion of the AURORA 1 study.

B.2.3.2.3.3 Dose modification and treatment discontinuation

After 12 months treatment in the AURORA 2 continuation study (i.e. 24 months treatment in total), patients taking the full dose of voclosporin (23.7 mg BID [3 capsules]) were permitted to reduce the dose to 15.8 mg BID (2 capsules) at the discretion of the Investigator and after consultation with the Medical Monitor, if it was deemed that UPCR was controlled (UPCR <1.5 mg/mg).

Dose modification of study treatment was also permitted if safety concerns arose during the AURORA 2 treatment period, such as an abnormal deviation in blood pressure, a deterioration in renal function (relative to AURORA 1 baseline; see Section B.2.3.1.3.3), and gastrointestinal issues or other disturbances associated with study treatment. These risks were managed by dose reduction and temporary interruption of study treatment.

Patients were permanently discontinued from study treatment if they required treatment with IV methylprednisolone or any rescue medication other than that permitted in the protocol or experienced an unacceptable AE. Rescue medications included cyclophosphamide, rituximab, abatacept, azathioprine, eculizumab, methotrexate, and tacrolimus. If possible, patients that discontinued study treatment were expected to continue in the study and attend all study visits and assessments up to and including the final visit (Month 36 of treatment) or the early termination visit.

B.2.3.2.3.4 Concomitant therapies

Permitted and prohibited concomitant medications aligned with those specified for AURORA 1. A summary of permitted and prohibited concomitant therapies is shown in Table B.2-9.

Table B.2-9. Concomitant therapy

Permitted	• Topical steroids (e.g., nose, scalp, skin, inhaled) • Antimalarials when clinically indicated • Herbal supplements (depending on active ingredients) • Treatments of symptomatic minor gastrointestinal AEs • Treatment of neutropenia in presence of major infection (e.g. G-CSF) • Iron supplements for iron deficiency and/or anaemia • Erythropoietin for severe anaemia • Lipid-lowering therapies (e.g. statins) • Acute NSAIDs for ≤7 consecutive days • Cardiovascular treatments (e.g. ACE inhibitors or ARBs)* • Diuretic or calcium channel block in case of uncontrolled hypertension • Prophylactic therapy against: o Steroid-induced bone loss o Cardiovascular issues o Fungal infection o Pneumocystis carinii pneumonia o Cytomegalovirus
Prohibited	• MMF dose other than 2g/day or treatment with any other immunosuppressant • Antifungal treatment with ketoconazole, or antibiotic treatment with rifampin • Vaccines using live organisms, viral or bacterial • Oral corticosteroids other than those administered per protocol • IV corticosteroids • Any IV Ig • CYC • Drugs that may interfere with MMF enterohepatic recirculation • New treatment with or change in dosage of ARBs and/or ACE inhibitors • CNIs • Immunosuppression biologic agents

*if used, patients must be on a stable dose of ACE inhibitors or ARBs for 4 weeks prior to enrolment and dose must remain stable throughout the study

Abbreviations: ACE = Angiotensin-converting enzyme; ARB = angiotensin II receptor blocker; CNI = calcineurin inhibitors; CYC = cyclophosphamide; g = gram; G-CSF = granulocyte colony-stimulating factor; Ig = immunoglobulin; IV = intravenous; MMF = mycophenolate mofetil; NSAIDs = non-steroidal anti-inflammatory drug

B.2.3.2.4 ***Assessments and outcomes: AURORA 2***

B.2.3.2.4.1 Efficacy outcomes

The primary outcome of AURORA 2 was to evaluate the safety of study treatment (detailed in Section B.2.3.2.4.5).

The following secondary efficacy outcomes were also measured, listed below in terms of key secondary outcomes and other relevant secondary endpoints:

- Key secondary outcomes
  - Proportion of patients in CRR that met the following criteria:
    - UPCR of ≤0.5 mg/mg
    - eGFR ≥60 mL/min/1.73 m^2 or no confirmed decrease from baseline in eGFR of >20%
    - Received no rescue medication for LN
    - Did not receive more than 10 mg prednisone for ≥3 consecutive days or for ≥7 days in total during the 8 weeks prior to the CRR assessment
  - PRR (defined as a ≥50% reduction from baseline in UPCR)

- Renal flare as adjudicated by the Clinical Endpoints Committee (CEC)
- Extra-renal flare as adjudicated by the CEC
- Change in SELENA-SLEDAI scores from AURORA 1 baseline
- Change in UPCR, eGFR, urine protein, and serum creatinine from AURORA 1 baseline

- Other relevant secondary outcomes:
  - Change in immunology parameters (C3, C4, and anti dsDNA) from AURORA 1 baseline
  - Change in HRQoL (SF-36) from AURORA 1 baseline
  - Healthcare resource utilisation

As an additional exploratory endpoint, kidney biopsies were performed to evaluate renal change in immune markers, histology, and transcriptomics, from the pre-study biopsy in AURORA 1, comparing it to a repeat biopsy conducted within approximately 6 months of starting treatment in this study.

B.2.3.2.4.2 Efficacy assessment

In line with AURORA 1, blood and urine samples contributing to efficacy and safety assessments were analysed at central laboratories using standard validated methods. Analyses included haematology, blood chemistry, coagulation, lupus markers (immunology parameters), urinalysis and eGFR.

CRR (according to eGFR and UPCR levels) was assessed every 3 months (Month 12, 15, 18, 21, 24, 27, 30, 33, 36) at all visits up to and including an additional Safety Follow-up visit at month 37 following completion of study treatment. eGFR and UPCR was assessed in accordance with AURORA 1 methodology (Section B.2.3.1.4.2).

Disease activity was also measured using SELENA-SLEDAI, with assessments conducted at Month 12, 18, 24, and 36 of the study.

B.2.3.2.4.3 Patient-reported outcomes

PROs were measured as a secondary endpoint, whereby SF-36 scores were recorded as a change from AURORA 1 baseline.

B.2.3.2.4.4 Patient reported outcome assessment

PROs using SF-36 were collected at study visits occurring every 6 months at Month 12, 18, 24, 30, and 36.

B.2.3.2.4.5 Safety outcomes

The primary outcome of AURORA 2 was to assess the AE profile and routine biochemical and haematological assessments for up to 36 months of study treatment (i.e. 12 months within AURORA 1 and 24 additional months within AURORA 2).

B.2.3.2.4.6 Safety assessment

Safety assessments included AEs (throughout the study), vital signs and laboratory parameters (at Months 12, 15, 18, 21, 24, 27, 30, 33, 36, 37), 12-lead ECGs (at Months 12, 18, 24, 36) and physical examinations (at Months 12 and 36).

AEs and SAEs were reported in accordance with AURORA 1 methodology (i.e. using ICH definitions; see Section B.2.3.1.4.6), with AEs reporting occurring from time of patient study consent until the final Safety Follow-up visit at Month 37 while SAEs were reported from patient

study consent until 30 days following final Safety Follow-up visit or 30 days after last study treatment administration in patients who withdrew or discontinued prior to study completion.

B.2.3.2.5 ***Study population: AURORA 2***

B.2.3.2.5.1 Patient disposition

Of the 357 patients enrolled in AURORA 1, a total of 216 patients (60.5%) continued to receive blinded treatment in AURORA 2: including 116 of 179 (64.8%) patients from the voclosporin arm and 100 of 178 (56.2%) patients from the placebo arm.

Of the remaining 141 patients that enrolled in AURORA 1 but did not enroll in AURORA 2; [redacted] patients had withdrawn from AURORA 1 prematurely ([redacted] voclosporin-treated and [redacted] placebo-treated), [redacted] patients ([redacted] in each arm) who completed AURORA 1 had permanently discontinued study treatment,[redacted] patients did not enter AURORA 2 for administrative reasons (such as health authority approval not received in time or a decision for a site/country to not participate), and [redacted] patients did not give consent due to planned pregnancy or moving home. Reasons for non-participation were not captured for the remaining [redacted] patients who were potentially eligible but did not enter AURORA 2. The [redacted] patients who did not enroll in AURORA 2 were not followed beyond the previous AURORA 1 safety follow-up visit at Week [redacted].

Among the [redacted] patients that enrolled in AURORA 2, [redacted] completed the study ([redacted]%), with slightly more patients in the voclosporin arm ([redacted] patients, [[redacted]%]) than the placebo arm ([redacted] patients [[redacted]%]) reaching the end of the study at Month 36. All patients received at least one dose of study treatment. Therefore, a total of [redacted] patients withdrew prematurely from the study ([redacted] patients in the voclosporin arm [[redacted]%] and [redacted] patients in the placebo arm [[redacted]%]). In both arms, the most common reason for early permanent study withdrawal was withdrawal of consent ([redacted] patients [[redacted]%]) in the voclosporin arm and [redacted] [[redacted]%]) patients in the placebo arm). Notably, only patients in the placebo arm permanently withdrew from the study early due to death ([redacted] patients, [[redacted]%]) or intolerable AEs ([redacted] patients, [[redacted]%]).

Patients discontinuing study treatment were encouraged to remain in the study and attend all scheduled follow-up visits, up to and including the safety follow-up assessment at Month 37. Fewer patients discontinued treatment with voclosporin ([redacted]%) than with placebo ([redacted]%). The most common reason for treatment discontinuation was intolerable AEs, which was recorded more often in the placebo arm than the voclosporin arm ([redacted]% versus [redacted]%, respectively). Patient disposition for AURORA 2 is summarised in terms of overall study withdrawals (n=[redacted]) and drug discontinuations in Table B.2-10.

Table B.2-10. AURORA 2 patient disposition

	Parameters	Voclosporin (n=116)	Placebo (n=100)	Overall (N=216)
Study withdrawals	Study withdrawals, n (%)	[redacted]	[redacted]	[redacted]
	Intolerable AE	[redacted]	[redacted]	[redacted]
	Death	[redacted]	[redacted]	[redacted]
	Lost to follow-up	[redacted]	[redacted]	[redacted]
	Physician decision	[redacted]	[redacted]	[redacted]
	Pregnancy	[redacted]	[redacted]	[redacted]
	Protocol non-compliance	[redacted]	[redacted]	[redacted]
	Withdrawal of consent	[redacted]	[redacted]	[redacted]
	Lack of efficacy	[redacted]	[redacted]	[redacted]
Treatment discontinuations	Treatment discontinuation, n (%)	[redacted]	[redacted]	[redacted]
	Intolerable AE	[redacted]	[redacted]	[redacted]
	Death	[redacted]	[redacted]	[redacted]
	Lost to follow-up	[redacted]	[redacted]	[redacted]
	Physician decision	[redacted]	[redacted]	[redacted]
	Prohibited medication required	[redacted]	[redacted]	[redacted]
	Pregnancy	[redacted]	[redacted]	[redacted]
	Protocol non-compliance	[redacted]	[redacted]	[redacted]
	Withdrawal of consent	[redacted]	[redacted]	[redacted]
	Lack of efficacy	[redacted]	[redacted]	[redacted]
	Other	[redacted]	[redacted]	[redacted]

Abbreviations: AE = adverse event
Source: Otsuka 2022[113]

B.2.3.2.5.2 Analysis sets

Of the 216 enrolled patients to the AURORA 2 study, all patients were included in both the ITT and safety analyses.

B.2.3.2.5.3 Demographics and baseline characteristics

Baseline characteristics of the patients enrolled in AURORA 2 were well balanced across the two treatment arms and were consistent with the AURORA 1 population (see Table B.2-11). The median age was [redacted] years and most patients ([redacted]%) were female. The majority of patients were White ([redacted]%) or Asian ([redacted]%) and there were more Black patients in the voclosporin arm ([redacted]%) than the placebo arm ([redacted]%).

Table B.2-11. AURORA 2: Baseline Demographic and Clinical Characteristics

Baseline characteristic	Voclosporin (n=116)	Placebo (n=100)	Overall (N=216)
Age, median (range), years	[redacted]	[redacted]	[redacted]
Female. n (%)	[redacted]	[redacted]	[redacted]
Weight, mean (SD), kg	[redacted]	[redacted]	[redacted]
Region, n (%)			
Asia Pacific	NR	NR	[redacted]
Europe and South Africa	NR	NR	[redacted]
Latin America	NR	NR	[redacted]
North America	NR	NR	[redacted]
Race, n (%)			
White	[redacted]	[redacted]	[redacted]
Black (including Mixed Black)	[redacted]	[redacted]	[redacted]
Asian*	[redacted]	[redacted]	[redacted]
Other	[redacted]	[redacted]	[redacted]
Ethnicity, n (%)			
Hispanic or Latino	[redacted]	[redacted]	[redacted]
Not Hispanic or Latino	[redacted]	[redacted]	[redacted]
Biopsy class, n (%)			
Pure class III	[redacted]	[redacted]	[redacted]
Pure class IV	[redacted]	[redacted]	[redacted]
Pure class V	[redacted]	[redacted]	[redacted]
Class III and V only	[redacted]	[redacted]	[redacted]
Class IV and V only	[redacted]	[redacted]	[redacted]
Baseline eGFR			
Mean (SD), mL/min/1.73 m²	[redacted]	[redacted]	[redacted]
Baseline UPCR			
Mean (SD), mg/mg	[redacted]	[redacted]	[redacted]

*Asian race includes Asian Indian, Chinese, Filipino, Japanese, Korean, Vietnamese and Other Asian.
Abbreviations: eGFR = estimated glomerular filtration rate; mg = milligram; mL = millilitre; NR = not reported; SD = standard deviation; UPCR = urine protein creatinine ratio
Source: Otsuka 2022[113]

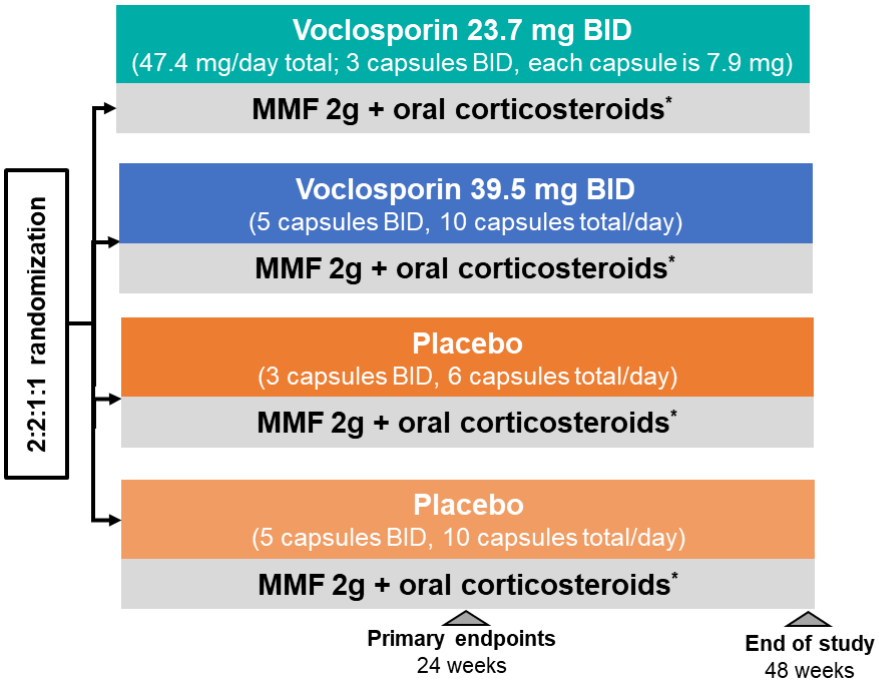
B.2.3.3 AURA-LV Phase 2 study

B.2.3.3.1 *Study design and objectives: AURA-LV*

AURA-LV is a Phase 2, multicentre, double-blind, placebo-controlled, randomised trial of 2 doses of voclosporin versus placebo added to MMF and rapidly tapered low-dose oral corticosteroids for the treatment of patients with active LN.[8] The primary objective of AURA-LV was to evaluate whether voclosporin added to background therapy was more effective in inducing CRR at 24 weeks compared to background therapy alone in patients with active LN. Secondary objectives were to evaluate the efficacy, safety, and tolerability of voclosporin compared with placebo after 48 weeks of treatment.

An overview of AURA-LV trial design is presented in Figure B.2-3, accompanied by a summary of methodology in Table B.2-12.

Figure B.2-3. AURA-LV: Trial Design (AUR-VCS-2012-01; NCT02141672)



*Oral corticosteroids were tapered per protocol.
Abbreviations: BID = twice daily; MMF = mycophenolate mofetil
Source: Rovin et al., 2019[8]

Table B.2-12. Summary of methodology for AURA-LV (AUR-VCS-2012-01; NCT02141672)

Study name	Aurinia Urinary Protein Reduction Active – Lupus with Voclosporin (AURA-LV)
Identifiers	EudraCT: 2012-003364-51 ClinicalTrials.gov: NCT02141672
Study status	Completed (June 2014 to January 2017)
Study design	Phase 2, multicentre, double-blind, placebo-controlled, randomised trial
Locations	265 patients were randomised across 79 sites in 20 countries (sites by region not available): • Americas (n=51) • Europe (n=84) • Asia (n=130)
Study Treatments	• **Arm 1:** voclosporin 23.7 mg BID (low-dose) (n=89) • **Arm 2:** voclosporin 39.5 mg BID (high-dose) (n=88) • **Arm 3:** matched low-dose placebo (n=44) • **Arm 4:** matched high-dose placebo (n=44)
Primary outcome	• CRR at Week 24*
Key secondary outcomes	• CRR at 48 weeks • Median time to CRR • PRR (≥50% decrease in UPCR from baseline) at Week 24 and Week 48 • Median time to PRR
Safety outcomes	• AEs (including SAEs) • Laboratory parameters • Vital signs

*CRR defined as a composite of a decrease in UPCR to ≤0.5 mg/mg, and eGFR of ≥60 mL/min/1.73 m^2 or no eGFR decrease of ≥20% from baseline
Abbreviations: BID = twice daily; CRR = complete renal response; IV = intravenous; LN = lupus nephritis; MMF = mycophenolate mofetil; PRR = partial renal response; UPCR = urine protein creatinine ratio
Source: Rovin et al., 2019;[8] Otsuka et al., 2018[114]

B.2.3.3.2 *Eligibility criteria: AURA-LV*

A summary of inclusion and exclusion criteria of AURA-LV is presented in Table B.2-13.

Table B.2-13. Inclusion and exclusion criteria: AURA-LV

Inclusion criteria	• Age 18 to 75 years • Diagnosis of SLE according to the ACR 1997 criteria • Histologic diagnosis of LN (ISN/RPS 2003 classification of LN) Classes III, IV-S or IV-G, (A) or (A/C); or Class V, alone or in combination with Class III or IV by kidney biopsy within 6 months prior to screening. • Patients with laboratory evidence of active nephritis at screening, defined as follows: o Class III, Class IV-S or Class IV-G: Confirmed proteinuria ≥1,500 mg/24 hours when assessed by 24-hour urine collection, and defined by a UPCR of ≥1.5 mg/mg assessed in a FMV urine specimen (2 samples) o Class V (alone or in combination with Class III or IV): Confirmed proteinuria ≥2,000 mg/24 hours when assessed by 24-hour urine collection, and defined by a UPCR of ≥2 mg/mg assessed in an FMV urine specimen (2 samples) • Patient required high dose corticosteroids and immunosuppressive therapy
Exclusion criteria	• eGFR ≤45 ml/min/1.73 m^2 at screening (according to CKD-EPI) • Patient taking or requiring any medications prohibited in the study protocol • Serum potassium >5.5 mmol/L at screening, confirmed before randomisation • Required renal dialysis (haemodialysis or peritoneal dialysis) or was expected to require dialysis during the study period • Previous or planned kidney transplant during the study treatment period • Did not require long-term immunosuppressive treatment (plus corticosteroids) • Hypersensitivity or contraindication to MMF, MPA, CsA, corticosteroids, or any components of these drug products • Had current or medical history of: o Pancreatitis or gastrointestinal haemorrhage within 6 months prior to screening o Active unhealed peptic ulcer within 3 months prior to screening (unless healed and patient was on adequate therapy) o Congenital or acquired immunodeficiency o Clinically significant drug or alcohol abuse 2 years prior to screening o Malignancy within 5 years of screening, with the exception of BCC and SCC treated by complete excision* o Lymphoproliferative disease or previous total lymphoid irradiation o Severe viral infection within 3 months of screening; or known human immunodeficiency virus infection o Active tuberculosis, or known history of tuberculosis/evidence of old tuberculosis if not taking prophylaxis with isoniazid o Other major physical or psychiatric illness or major traumatic injury within 6 months prior to screening o Other known clinically significant active medical conditions† • Overlapping autoimmune condition which may affect study assessments/ outcomes • Any other medical condition which may have been associated with increased risk to the patient or may have interfered with study assessments or outcomes • Patients who were pregnant, breast feeding or not using adequate contraceptive precautions if of childbearing potential • Participation in another clinical study within 4 weeks prior to screening and/or receipt of investigational drugs within 4 weeks or 5 half-lives prior to screening

* Patients with cervical dysplasia that was cervical intraepithelial neoplasia 1 but had been treated with conization or loop electrosurgical excision procedure and had a normal repeat Papanicolaou test were Allowed; †Severe cardiovascular disease, liver dysfunction, COPD or asthma requiring steroids, bone marrow insufficiency unrelated to SLE, active bleeding disorders, or infection requiring antibiotics

Abbreviations: ACR = American College of Rheumatology; BCC = basal cell carcinoma; CKD-EPI = Chronic Kidney Disease Epidemiology Collaboration; CsA = ciclosporin; eGFR = estimated glomerular filtration rate; FMV = first morning void; LN = lupus nephritis; m^2 = metres squared; mg = milligrams; MMF = mycophenolate

mofetil; MPA = mycophenolic acid; SCC = squamous cell carcinoma; SLE = systemic lupus erythematosus; UPCR = urine protein creatinine ratio

B.2.3.3.3 *Study treatments: AURA-LV*

B.2.3.3.3.1 Allocation to treatment

Patients were randomised 2:2:1:1 to low-dose voclosporin (23.7 mg BID), high-dose voclosporin (39.5 mg BID), low-dose matched placebo, and high-dose matched placebo, respectively.[8] Randomisation was stratified by biopsy class (Class V vs others) and by MMF use at screening.

B.2.3.3.3.2 Treatments administered

Patients received either twice-daily low-dose voclosporin (23.7 mg [3 capsules] BID) or high-dose voclosporin (39.5 mg [5 capsules]), or a low- or high-dose matched placebo for up to 48 weeks.[8]

In addition to the study drug (voclosporin or placebo), all patients received the following:[8]

- An initial treatment with 0.5 g IV methylprednisolone, followed by a reducing taper of oral corticosteroid (prednisone) to a target of 2.5 mg/day by Week 16.
- Background therapy with MMF at a target dose of 2 g/day

B.2.3.3.3.3 Dose modification and treatment discontinuation

Dose-modification instructions were included in the protocol for cases of deterioration in renal function, increased blood pressure, or increase in QTcF.

- **Decreased renal function:** During the treatment period, any patient with a >10-20% reduction in eGFR compared to baseline had potential contributing factors ruled out and appropriate corrective action taken. Any patient with a confirmed >20-30% reduction in eGFR compared to baseline not due to potential contributing factors had the dose of study drug reduced by 1 capsule BID (15.8 mg/day). A repeat eGFR was performed within 2 weeks (at planned study visit if any or an unscheduled visit). If the eGFR remained >20-30% below the baseline value, then the dose was reduced by a further 1 capsule BID (15.8 mg/day). A maximum of two dose reductions were permitted in total throughout the study. If the patient's eGFR did not return to within 20% of the baseline value after two dose reductions, Investigators were instructed to discontinue the patient's voclosporin treatment permanently. Any patient that experienced a >30% decrease in eGFR from baseline, not within normal range, had study drug withheld until a repeat test could be performed (unscheduled visit to be completed). If the decrease was confirmed and not due to potential contributing factors, the case was discussed with the Medical Monitor and study drug was discontinued permanently. If the decrease in eGFR >20% was confirmed and considered due to potential contributing factors, corrective action was taken and the patient reassessed within 2 weeks.
- **Increased blood pressure:** If on any study day, systolic blood pressure was >165 mmHg or diastolic blood pressure was >105 mmHg and was associated with symptoms of hypertension, the study drug was discontinued, and the patient treated as per Investigator local practices and best judgment.
- **Treatment-emergent increase in QTcF:** In the event that a patient had a QTcF value exceeding 500 msec or an increase of >60 msec from baseline, the Medical Monitor was

to be informed. The patient was required to return for an unscheduled visit to have the ECG repeated. If any of the repeat measurements of QTcF were >500 msec or increased >60 msec from baseline, the study drug was to be permanently discontinued and the patient followed until the QTcF value either returned to baseline or until, in the judgment of the Investigator, further evaluation was not clinically indicated.

B.2.3.3.3.4 Concomitant therapies

A summary of permitted and prohibited concomitant therapies is shown in Table B.2-14.

Table B.2-14. Concomitant therapy: AURA-LV

Permitted	• Topical steroids (e.g., nose, scalp, skin, inhaled). • Antimalarials (could be prescribed when clinically indicated) • Herbal supplements (used with caution and depending on active ingredients) • Treatments of symptomatic minor gastrointestinal AEs • Acute NSAIDs for ≤5 consecutive days • Lipid-lowering therapies (e.g. statins) • Cardiovascular treatments (e.g. ACE inhibitors, ARBs and aliskerin)* • Diuretic or calcium channel block in case of uncontrolled hypertension • Prophylactic therapy against: o Steroid-induced bone loss o Cardiovascular issues o Fungal infection o Pneumocystis carinii pneumonia o Cytomegalovirus
Prohibited	• IV corticosteroids within 2 weeks PTS, unless approved by Medical Monitor • IV immunoglobulin treatment within 2 weeks PTS • CYC within 4 weeks PTS • Cholestyramine or other drugs that may interfere with enterohepatic recirculation of MMF within 4 weeks PTS • Initiation of new treatment or change in dosage of ARBs and/or ACE inhibitors within 4 weeks PTS • CNIs (e.g., CsA and TAC) within 12 months of screening • Biologic agents (such as abatacept, belimumab, infliximab, adalimumab etanercept or RTX) within 3 months PTS • MMF dose >2 g/day without prior discussion with the Medical Monitor. • Concomitant therapy with other immunosuppressants after randomisation, other than MMF administered per protocol • Enteric-coated oral corticosteroids during the study were not allowed. • Patients were allowed to be on azathioprine or mycophenolate sodium during screening but were required to switch to MMF at randomisation • Current or planned use of ketoconazole or rifampin • Previous exposure to voclosporin • Concomitant use of other CYP3A4/5 inhibitors and inducers were to be discussed with the Medical Monitor

*if used, patients must be on a stable dose of ACE inhibitors or ARBs for 4 weeks prior to enrolment and dose must remain stable throughout the study; †Unless approved or discussed with the Medical Monitor; ‡concomitant use of other CYP3A45 inhibitors and inducers to be discussed with Medical Monitor
Abbreviations: ACE = Angiotensin-converting enzyme; ARB = angiotensin II receptor blocker; CNI = calcineurin inhibitors; CsA = ciclosporin A; CYC = cyclophosphamide, IV = intravenous; MMF = mycophenolate mofetil; PTS = prior to screening; RTX = rituximab; TAC = tacrolimus

B.2.3.3.4 *Assessments and outcomes: AURA-LV*

B.2.3.3.4.1 Efficacy outcomes

The primary outcome was the number of patients showing CRR at Week 24 in the full analysis set, defined as follows:

- Confirmed decrease in proteinuria as defined by a UPCR of ≤0.5 mg/mg, and;
- Normal or stable renal function defined as no confirmed eGFR <60 mL/min/1.73 m^2 or no confirmed decrease from baseline in eGFR of ≥20%.

Patients were not defined as achieving CRR if they received rescue medication for LN or >10 mg prednisone for >3 consecutive days or >7 days total from 56 days prior to response assessment until the time of the remission assessment. The use of rescue medications was adjudicated prior to unblinding of the study. Patients who withdrew early from the study were excluded from being defined as achieving CRR; however, patients who discontinued study drug but continued study visits were considered for CRR.

The following secondary efficacy outcomes were also measured, listed below in terms of key secondary outcomes and other relevant secondary endpoints:

- Key secondary outcomes
  - CRR at Week 24 and Week 48 using 24-hour urine measurements (instead of FMV)
  - CRR in the presence of low dose steroids at Week 24 (i.e. ≤5 mg prednisone for ≥8 weeks) and Week 48 (in which no UPCR confirmation was required and patients received ≤5 mg prednisone for ≥12 weeks)
  - Time to CRR
  - Time to sustained CRR (defined as the first occurrence of CRR that was sustained through Week 48)
  - Time to (and proportion achieving) sustained early CRR (defined as CRR that occurred on or before Week 24 and was sustained through Week 48)
  - Duration of CRR (in months)
  - PRR at Week 24 and Week 48
  - Time to PRR
  - Time to sustained PRR (defined as the first occurrence of PRR that was sustained through Week 48)
  - Time to (and proportion achieving) sustained early PRR (defined as partial remission that occurred on or before Week 24 and was sustained through Week 48)

- Other relevant secondary outcomes:
  - Change from baseline in UPCR at Week 24 and Week 48
  - Change from baseline in eGFR, serum albumin, urine protein, and serum creatinine at each time point
  - Proportion of patients with active urinary sediment (defined by >10 red blood cells (RBC)/high-powered field with dysmorphic RBC and/or RBC casts on urinalysis of a urine sample which had a minimum volume of 50 mL) at each visit
  - Change from baseline in the SELENA-SLEDAI score at Week 24 and Week 48
  - Change from screening in immunology parameters (C3, C4, and anti-double-stranded DNA (anti-dsDNA)) and biomarkers (cardiolipin antibodies) at Weeks 12, 24, and 48

B.2.3.3.4.2 Efficacy assessment

Blood and urine samples contributing to efficacy and safety assessments were analysed at central laboratories using standard validated methods

Confirmed decreases in proteinuria and eGFR were defined as those where the measurement met the specified criterion at two consecutive measurements at least 3 days apart, one of which being the windowed Week 24 assessment. eGFR was assessed at all screening and all other visits except baseline up to Week 50.

UPCR values were determined using FMV urinalysis samples. In the event that the Investigator determined that the screening, Week 24, or Week 48 FMV urinalysis sample was invalid, the UPCR values from the 24-hour urinalysis at the corresponding visit were used instead of the FMV urinalysis in the calculation of efficacy endpoints. FMV analysis results were still used for all other timepoints.

B.2.3.3.4.3 Safety outcomes

The safety and tolerability of two doses of voclosporin was assessed as a secondary objective over 48 weeks compared to placebo in patients with active LN. Safety outcomes included the collection of AE data, laboratory parameters (clinical chemistry, haematology, urinalysis), physical examinations, vital signs, and blood pressure management and cardiovascular safety.

B.2.3.3.4.4 Safety assessment

Safety outcomes included the collection of AE data, laboratory parameters (clinical chemistry, haematology, urinalysis), physical examinations, vital signs, and blood pressure management and cardiovascular safety.

A summary of MMF exposure, including mean daily dose and incidence of non-protocol specified dose modifications were reported. Safety analyses were based on TEAEs, defined as AEs that occurred or increased in intensity after the first dose of study drug, up to 14 days after study completion/withdrawal.

Symptomatic increased blood pressure was identified in the study protocol as a medically important event and was required to be reported as an SAE. All patients identified were assessed for the seriousness of their symptoms, their relationship to study drug treatment, and association of symptoms related to increased blood pressure. Additional AEs of special interest considered in this study included reduced renal function, QTcF prolongation, and malignancies.

A retrospective high-level safety follow-up of the LN disease status of patients was performed approximately six to nine months following either their last study visit or last dose of study drug was also conducted.

B.2.3.3.5 ***Study population: AURA-LV***

B.2.3.3.5.1 Patient disposition

Among the ITT population, 73 (82%) patients randomised to low-dose voclosporin and 80 (90.9%) patients randomised to high-dose voclosporin completed 48 weeks of treatment compared to 70 (79.5%) patients randomised to placebo.[8]

Reasons for discontinuation were generally similar across treatment groups except for discontinuation due to death.[8] A higher proportion of patients in the low-dose voclosporin group (n=10, 11.2%) died during the study compared with the high-dose voclosporin (n=2, 2.3%) or placebo groups (n=1, 1.1%). Nine of the 13 deaths occurred in the first 2 months of study enrolment, and more than half of deaths (n=7 of 13) were among patients at 2 sites in Bangladesh. Two-fold more patients were randomised to low-dose voclosporin than placebo at these 2 sites, which may possibly be relevant to the imbalance of deaths.

B.2.3.3.5.2 Analysis sets

The ITT population included 89 patients randomised to low-dose voclosporin, 88 to high-dose voclosporin, and 88 patients to placebo (44 each to low-dose and high-dose matched placebo).[8]

B.2.3.3.5.3 Demographics and baseline characteristics

Treatment groups were generally similar with respect to demographics and clinical characteristics, though there were some numeric differences between treatment groups (Table B.2-15).[8] A higher proportion of women (92.0%) were randomised to high-dose voclosporin than to low-dose voclosporin (85.4%) or placebo (83.0%). There was also a higher proportion of patients with Class III + V or IV + V LN randomised to low-dose voclosporin (23.6%) than to the high-dose voclosporin (12.5%) or placebo groups (18.2%). The placebo group included a higher proportion of White patients (47.7%) compared with the voclosporin groups (low-dose 33.7%; high-dose 40.9%). These differences did not appear related to the study outcomes.

Table B.2-15. AURA-LV: Baseline Demographic and Clinical Characteristics (ITT Population)

Baseline characteristic	All patients (N=265)		
	Voclosporin, low-dose n=89	Voclosporin, high-dose n=88	Placebo n=88
Age, mean (SD), years	31.4 (11.8)	30.6 (9.6)	33.1 (10.0)
Female, n (%)	76 (85.4)	81 (92.0)	73 (83.0)
Weight, mean (SD), kg	62.5 (16.7)	66.3 (19.2)	65.0 (16.3)
Region, n (%)			
Asia	52 (58.4)	43 (48.9)	35 (39.8)
Europe	25 (28.1)	25 (28.4)	34 (38.6)
Americas	12 (13.5)	20 (22.7)	19 (21.6)
Race, n (%)			
White	30 (33.7)	36 (40.9)	42 (47.7)
Black	3 (3.4)	6 (6.8)	5 (5.7)
Asian—Indian subcontinent*	22 (24.7)	20 (22.7)	18 (20.5)
Asian—other*	30 (33.7)	24 (27.3)	18 (20.5)
Other	4 (4.5)	2 (2.3)	5 (5.7)
Ethnicity*, n (%)			
Hispanic	9 (10.1)	13 (14.8)	13 (14.8)
Non-Hispanic	80 (89.9)	75 (85.2)	75 (85.2)
Time since initial LN diagnosis, mean (SD), years	4.2 (5.1)	3.2 (4.4)	3.5 (4.0)

Biopsy class, n (%)			
Pure Class V	12 (13.5)	14 (15.9)	13 (14.8)
Class III/V	56 (62.9)	63 (71.6)	59 (67.0)
Class III+V or IV+V	21 (23.6)	11 (12.5)	16 (18.2)
Mean (SD) eGFR, mL/min/ 1.73 m^2	95.3 (28.4)	104.0 (27.3)	100.2 (27.1)
Mean (SD) UPCR, mg/mg	5.16 (4.2)	4.48 (3.0)	4.43 (3.6)†
MMF use at screening, n (%)			
Yes	31 (34.8)	29 (33.0)	32 (36.4)
No	58 (65.2)	59 (67.0)	56 (63.6)
MMF dose at screening, mean (SD), g/d	1.2 (0.4)	1.3 (0.5)	1.2 (0.5)

*Bangladesh, Sri Lanka (Asian-Indian Subcontinent) + Hong Kong, Korea, Philippines, Singapore, Taiwan, Thailand (Asian—other); †Number evaluated was 87

Abbreviations: eGFR = estimated glomerular filtration rate; ITT = intention-to-treat; LN = lupus nephritis; MMF = mycophenolate mofetil; SD = standard deviation; UPCR = urine protein to creatinine ratio

Source: Otsuka 2018;[114] Rovin et al., 2019[8]

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

B.2.4.1 AURORA 1

B.2.4.1.1 *Determination of sample size*

AURORA 1 sample size was estimated to ensure that a two-group continuity corrected Chi square test (two-sided p=0.05) will have 80% power to detect the difference between a CRR rate of 20.0% in the placebo arm, and 34.4% in the voclosporin arm (OR: ~2.1), indicative of a clinically relevant treatment effect.[111]

On this basis, a sample size of 324 patients (162 patients per treatment arm) was determined for enrolment.

B.2.4.1.2 *Study group definitions*

Three analysis populations were defined for AURORA 1:[109,111]

- *Intent-to-Treat (ITT) population* comprised all patients who were randomised to treatment. All efficacy analyses were performed on the ITT population.
- *Per-Protocol (PP) population* comprised all patients from the ITT population who did not have any major protocol violations (i.e., deviations considered to have a serious impact on the efficacy results). Supplementary analyses were performed on the PP population to assess the impact of protocol deviations on CRR.
- *Safety population* comprised all randomised patients who took at least one dose of study treatment. Patients who received treatment from more than one arm were to be assigned to the voclosporin arm. Safety analyses were performed on the safety population.

B.2.4.1.3 *Efficacy analyses*

An overall type 1 (false-positive) error rate of 5% was maintained so that no statistical significance for the key secondary efficacy endpoints was claimed unless the primary efficacy endpoint (CRR at Week 52) was statistically significant at the 5% level (i.e. p<0.05). Key

secondary efficacy endpoints were tested using the Hochberg step-up procedure to adjust for multiple comparisons amongst key secondary endpoints and maintain the overall type 1 (false-positive) error rate of 5%.[109,115]

B.2.4.1.3.1 Renal response

Logistic regression models were used to conduct the primary efficacy analysis (CRR at Week 52) and secondary efficacy analyses of CRR at Week 24, PRR at Week 24/52, and CRR with low-dose steroids at Week 24/52. Logistic regression models incorporated baseline variables within the model as appropriate.[109]

B.2.4.1.3.2 Time to event endpoints

Time to event endpoints for time to UPCR <0.5 mg/mg, 50% reduction in UPCR and duration of UPCR <0.5 mg/mg were measured from baseline as the number of weeks from day of randomisation to the day of the event. Patients who did not experience an event were censored on the day of their last assessment of UPCR. Time-to-event was estimated using Kaplan-Meier methodology and analysed by comparing the survivor function between treatment arms. A Cox's proportional hazards model was performed to assess the significance of the differences between treatment arms, incorporating terms for treatment, baseline UPCR, biopsy class, and MMF use at baseline.[109]

B.2.4.1.3.3 Change from baseline endpoints

Change from baseline endpoints (UPCR, serum creatinine, urine protein, HRQoL [SF-36 and LupusPRO], and SELENA-SLEDAI score) were analysed using a mixed effect model repeated measures (MMRM) analysis with treatment arm, visit, treatment by visit interaction, biopsy class, MMF use at baseline, region, and baseline UPCR included as covariates in the model.[109]

A patient recording a clinically significant >30% decrease in eGFR from baseline at any two consecutive time points was considered a confirmed eGFR drop patient at the earlier time point. The proportion of patients with a confirmed eGFR drop at each visit was compared using the Chi Square test.[109]

B.2.4.1.4 ***Safety analyses***

Descriptive statistics of safety were collected using MedDRA Version 20.0, and medications were categorised using the World Health Organisation Anatomical Therapeutic Chemical (WHO ATC) system. All TEAEs (including drug-related), SAEs and drug-related SAEs were tabulated by System Organ Class and preferred term (PT).

B.2.4.2 AURORA 2

B.2.4.2.1 ***Determination of sample size***

Patients from AURORA 1 entered AURORA 2 to provide the opportunity of an additional 24 months of treatment (a total of 36 months of treatment); therefore, no sample size calculation was required.[112]

B.2.4.2.2 ***Study group definitions***

Two analysis populations were defined for AURORA 2:[109,111]

- *Intent-to-Treat (ITT) population* comprised all patients who consented to AURORA 2 treatment. Patients were analysed based on the treatment they were randomised to in AURORA 1. All efficacy analyses were performed on the ITT population.
- *Safety population* comprised all randomised patients who took at least one dose of study treatment. Patients who received treatment from more than one arm were to be assigned to the voclosporin arm. Safety analyses were performed on the safety population.

B.2.4.2.3 ***Efficacy analyses***

B.2.4.2.3.1 Renal response and renal/extra-renal flares

Logistic regression models were used to conduct the secondary efficacy analysis (RR and PRR at Months 12, 18, 24, 30, 36). Logistic regression models incorporated baseline variables within the model as appropriate (terms for treatment group, baseline UPCR, biopsy class, and MMF use at baseline).[109] The proportion of patients with renal and extra-renal flares (as adjudicated by the CEC) were analysed in a similar manner.[109]

B.2.4.2.3.2 Change from baseline endpoints

Change from AURORA 1 baseline endpoints (UPCR, serum creatinine, urine protein); and AURORA 2 change in HRQoL (SF-36) and SELENA-SLEDAI were analysed using a MMRM analysis with treatment arm, visit, treatment by visit interaction, biopsy class, MMF use at baseline, region, and baseline UPCR included as covariates in the model.[109]

B.2.4.2.4 ***Safety analyses***

Descriptive statistics of safety were collected using MedDRA Version 20.0, and all TEAEs (including drug-related), SAEs and drug-related SAEs were tabulated by System Organ Class and PT.

B.2.4.3 AURA-LV

B.2.4.3.1 ***Determination of sample size***

AURA-LV sample size was estimated using a two-sided alpha level of 0.05. Assuming a CRR of 20% in the placebo arm and 41% in the either of the two voclosporin arms, a sample size of 86 patients per arm was (n=258) determined to provide 81% power to detect clinically relevant significant difference between treatment arms (OR = 2.78). 86 patients per arm was also deemed sufficient to estimate the rates of AEs to an acceptable level of precision (i.e. an event with an incidence of 15% would have a 95% CI of 8.3–24.5%, and an event with an incidence of 6% would have a 95% CI of 1.9 –13.0%).[114] On this basis, a sample size of 258 patients were determined for enrolment.

B.2.4.3.2 ***Study group definitions***

Four analysis populations were defined for AURA-LV:[114]

- *Full analysis set (FAS)* comprised all patients who were randomised to treatment, received at least one dose of study drug, and had at least one post-baseline assessment. The primary population for efficacy analyses was the FAS.

- *Per-Protocol Set (PPS) population* comprised all patients from the FAS population who did not have any major protocol violations (e.g. lack of compliance to protocol-specified steroid tapering schedule, failure to meet inclusion/exclusion criteria, and use of prohibited concomitant medication). Key efficacy analyses were repeated for the PPS as supportive analyses.
- *Modified Intent-to-Treat (mITT)* comprised all randomised patients who took at least one dose of study treatment. Patients who received treatment from more than one arm were to be assigned to the voclosporin arm. Safety analyses were performed on the safety population. Key efficacy analyses were repeated for the mITT as supportive analyses.
- *Safety Set (SS)* comprised all randomised patients who took at least one dose of study treatment. Safety analyses were performed on the safety population.

B.2.4.3.3 ***Efficacy analyses***

All statistical tests were two-sided with no adjustments for multiple comparisons (level of significance $p<0.05$).[114]

B.2.4.3.3.1 Renal response

Logistic regression models were used to conduct the primary efficacy analysis (CRR at Week 24) and secondary efficacy analyses of CRR at Week 48. PRR at Week 24/48, and CRR with low-dose steroids at Week 24/48. Logistic regression models incorporated baseline variables within the model as appropriate.[114]

B.2.4.3.3.2 Time to event endpoints

Time to CRR (UPCR <0.5 mg/mg) and PRR was measured from baseline as the number of days from randomisation to the day of the event. Time to sustained CRR/PRR and sustained early CRR/PRR (beginning ≤Week 24 assessment window) was measured from baseline to CRR/PRR that was sustained through the Week 48 visit. Each time to event endpoint was estimated using Kaplan-Meier methodology and Cox's proportion hazards model. A two-sided log-rank test was performed to assess the significance of differences between the two treatment groups.[114]

B.2.4.3.3.3 Change from baseline endpoints

Change from baseline endpoints (UPCR, eGFR, serum albumin, urine protein, and SELENA-SLEDAI score) were analysed using analysis of covariance (ANCOVA) models adjusted as appropriate.[114]

B.2.4.3.4 ***Safety analyses***

Safety data were summarised for the SS, with the exception of eGFR data which was analysed for the FAS and included as part of efficacy and safety analyses.

Descriptive statistics of safety were collected using Medical Dictionary for Regulatory Activities (MedDRA) Version 17.0, and all TEAEs (including drug-related), SAEs and drug-related SAEs were tabulated by SOC and PT.[114]

B.2.5 Critical appraisal of the relevant clinical effectiveness evidence

Table B.2-16. Quality assessment of AURORA 1

Was randomisation carried out appropriately?	Yes. A total of 357 eligible patients were randomised in 1:1 ratio to treatment with voclosporin, or matching placebo starting on Day 1.
Was the concealment of treatment allocation adequate	Yes. This was a blinded study with all study personnel and patients unaware of the study medication administered. Voclosporin and placebo were identical in taste, smell, and appearance. The dosing schedule in the placebo group was the same as that of the active treatment group. The randomisation schedule was not available at the study centre, or to the study monitors, study statisticians, the project team at Aurinia or the CRO.
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes. The randomisation was stratified by biopsy class and by prior MMF use at the time of screening. To help ensure balance, a centralized randomisation was utilized where region (North America, Latin America, Europe + South Africa and Asia Pacific) was employed as a blocking factor.
Were the care providers, participants and outcome assessors blind to treatment allocation?	Yes. The study was double-blind in nature. The randomisation schedule was not available at the study centre, or to the study monitors, study statisticians, the project team at Aurinia or the CRO.
Were there any unexpected imbalances in drop-outs between groups?	No. A similar proportion of patients in each arm experienced TEAE and had their study treatment discontinued as a result (11.2% and 14.6%, respectively).
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No. All primary and secondary endpoints described in the protocol are reported in the CSR.
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes. The efficacy analysis was based on the ITT principles and consisted of all randomised patients. The impact of withdrawals on the primary endpoint was investigated in a tipping point analysis, where patients whose response assessment was assumed due to missing data had their assessment re-assigned in a series of analyses that were progressively more in favour of placebo.

Abbreviations: CSR = clinical study report; CRO = contract research organisation; ITT, intention-to-treat; MMF = mycophenolate mofetil; TEAE = treatment-emergent adverse event;
Sources: Otsuka 2020[109]

Table B.2-17. Quality assessment of AURORA 2

Was randomisation carried out appropriately?	Yes. Patients who completed 52 weeks of treatment with study drug and participation in the AURORA 1 study continue to receive the same treatment as assigned by randomisation in the AURORA 1 52-week study (either voclosporin or matching placebo).
Was the concealment of treatment allocation adequate	Yes. Study drug treatment in the continuation study remained blinded. All study personnel and patients were blind to the study treatment administered during the study. Voclosporin and placebo were identical in taste, smell, and appearance. The site staff, monitors, and study patients were blind until the end of the study.
Were the groups similar at the outset of the study	Yes. Using an IRT system, eligible patients began dosing with either oral voclosporin or matching placebo, as randomised into AURORA 1, at the same dose as was given at the time of completion of the

in terms of prognostic factors?	AURORA 1 study, using the same patient number, for up to 24 additional months
Were the care providers, participants and outcome assessors blind to treatment allocation?	Yes. The site staff, monitors, and study patients were blind until the end of the study.
Were there any unexpected imbalances in drop-outs between groups?	No. A similar proportion of patients in the voclosporin and placebo arms withdrew from the study prematurely (15.0% and 12.9%, respectively).
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No. All primary and secondary endpoints described in the protocol are reported in the CSR.
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes. The ITT set was based on ITT principles and consisted of all patients who consented to treatment. This group was analysed based on the treatment to which the patient was randomised in the AURORA 1 study.

Abbreviations: CSR = clinical study report; IRT = Interactive Response Technologies; ITT = intention-to-treat
Sources: Otsuka 2018[112]

Table B.2-18. Quality assessment of AURA-LV

Was randomisation carried out appropriately?	Yes. A total of 265 patients were randomised in 2:2:1:1 ratio to receive either low-dose voclosporin (23.7 mg (3 capsules) twice daily) or high-dose voclosporin (39.5 mg (5 capsules) twice daily) or matched placebo (low-/high-dose) for up to 48 weeks. Randomisation was stratified by biopsy class (Class V only (pure and mixed) versus Others), and by MMF use at time of screening.
Was the concealment of treatment allocation adequate	Yes. In order to preserve the double-blind design, patients randomised to the placebo group were matched to the active dosage groups. One-half (n=43) of the patients in the placebo group was randomised to receive a total of 6 capsules per day, and one-half was randomised to receive a total of 10 capsules per day. The dosing schedule in the placebo group was the same as that of the active treatment groups. However, it was not intended to blind dose level (high versus low). Voclosporin and placebo capsules were identical in taste, smell, and appearance.
Were the groups similar at the outset of the study in terms of prognostic factors?	Baseline characteristics were generally well balanced, although when considered together, the higher mean UPCR and lower mean eGFR in the low-dose voclosporin group compared to the high-dose voclosporin group and placebo group suggest that the disease severity was greater for the low-dose voclosporin group. Patients in the low dose voclosporin group also had a longer time since initial LN diagnosis and time since first significant proteinuria compared to the high-dose voclosporin and placebo groups. While randomisation globally was balanced, purely by chance, there was an imbalance in randomisation in the 103 patients randomised in these three low-GDP Asian countries: Bangladesh, Sri Lanka, and the Philippines. Almost half (47.2%) of the low-dose voclosporin group was randomised from these low-GDP countries compared to approximately a third in the high-dose voclosporin (37.5%) and placebo (31.8%) groups.
Were the care providers, participants and outcome assessors	Yes. All study personnel and patients were blind to the study drug administered.

blind to treatment allocation?	
Were there any unexpected imbalances in drop-outs between groups?	Yes. TEAEs and treatment-related TEAEs leading to study drug discontinuation were more frequent in the two voclosporin groups, but did not show a dose-dependent trend. Treatment-related TEAEs leading to study drug discontinuation were reported for 2.3% of patients in the placebo group compared to 12.4% and 9.1% of patients in the low-dose and high-dose voclosporin groups, respectively. When patients who died were excluded, a dose-dependent trend was observed for TEAEs leading to study drug discontinuation, reported for 9.2%, 13.9%, and 15.1% of patients in the placebo, low-dose voclosporin and high-dose voclosporin groups, respectively.
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No. All primary and secondary endpoints described in the protocol are reported in the CSR.
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	The primary populations for analyses of efficacy and safety were the FAS and SS, respectively. Key efficacy analyses were repeated for the mITT and PPS as supportive analyses. The mITT set was derived from the FAS; however, patients who were randomised to high-dose voclosporin but were prescribed this dose level for <14 days were analysed in the low-dose voclosporin group.

Abbreviations: CSR = clinical study report; FAS = full analysis set; GDP = gross domestic product; mITT = modified intent-to-treat; MMF = mycophenolate mofetil; SS = safety set; TEAE = treatment-emergent adverse event

Sources: Otsuka 2018[114]

B.2.6 Clinical effectiveness results of the relevant trials

B.2.6.1 AURORA 1 Phase 3 study

AURORA 1 assessed the efficacy and safety of voclosporin compared with placebo in achieving renal response after 52 weeks of therapy in patients with active LN. A total of 357 eligible patients were randomised into two groups with well-balanced demographic characteristics: 178 to the placebo arm and 179 to the voclosporin arm.

The study met its primary objective, demonstrating that treatment with voclosporin results in a clinically meaningful and statistically significant higher renal response rate compared to placebo.

B.2.6.1.1 *Complete Renal Response at Week 52 (primary endpoint)*

In AURORA 1, significantly more patients treated with voclosporin than with placebo achieved a CRR at Week 52 (73 [40.8%] vs 40 [22.5%] patients; OR 2.65; [95% CI 1.6, 4.3]; p<0.0001).[2] The absolute difference between groups for achieving a CRR was 18% in favour of voclosporin; therefore, the number-needed-to-treat (NNT) with voclosporin is 6 individuals with active LN.[2]

All composite measures of CRR occurred more frequently in patients treated with voclosporin than with placebo, but only UPCR ≤ 0.5 mg/mg was significantly different (Table B.2-19).

Table B.2-19. AURORA 1: Summary of CRR (primary endpoint) and composites of CRR

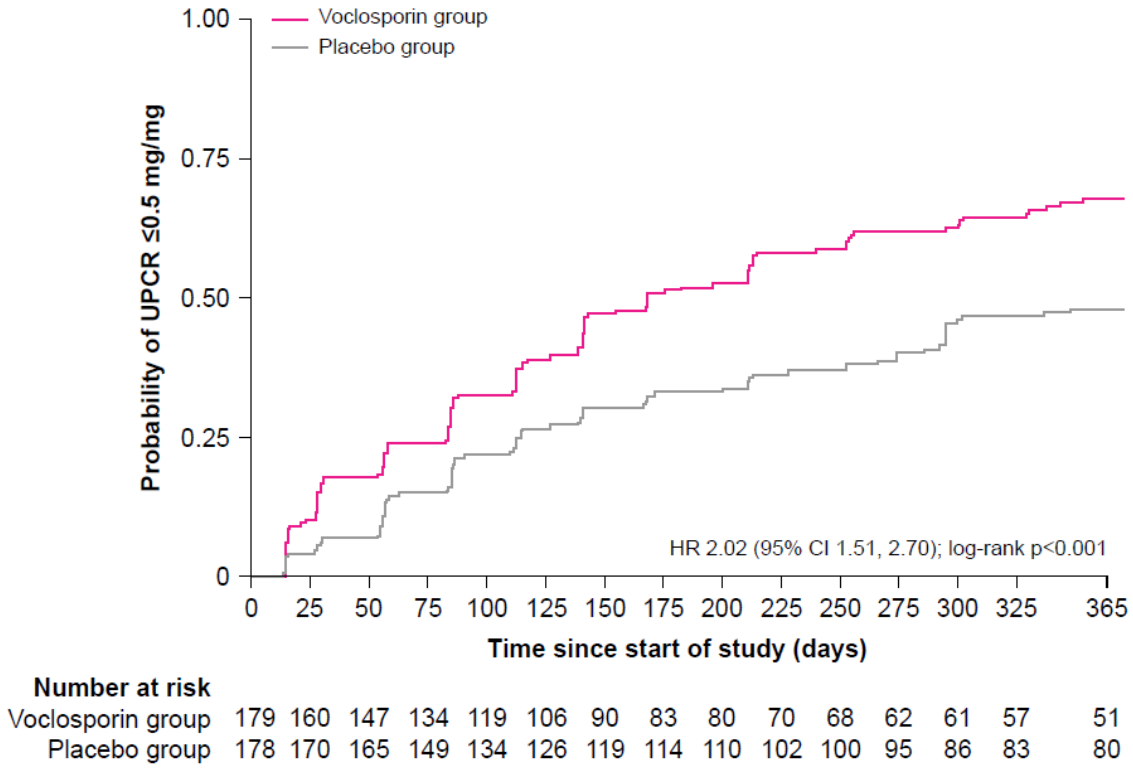
	Patients, n (%)		OR (95% CI)	p value
	Voclosporin n=179	Placebo n=178		
Primary endpoint: CRR at 52 weeks	73 (40.8)	40 (22.5)	2.65 (1.6, 4.3)	<0.0001
Composites of CRR				
UPCR ≤ 0.5 mg/mg	81 (45.2)	41 (23.0)	3.11 (1.9, 5.0)	<0.0001
eGFR ≥ 60, eGFR < 60 with no confirmed decrease of > 20%, or eGFR < 60 with confirmed decrease of > 20% but with no disease-related or treatment-related eGFR associated AE present at time of assessment	147 (82.1)	135 (75.8)	1.50 (0.9, 2.5)	0.129
Received no rescue medication for LN	163 (91.1)	154 (86.5)	1.62 (0.8, 3.2)	0.164
Did not receive > 10 mg/day prednisone for ≥ 3 consecutive days or for ≥ 7 days in total during Weeks 44 through 52	156 (87.2)	152 (85.4)	1.26 (0.7, 2.3)	0.465

Abbreviations: AE = adverse event; CI = confidence interval; CRR = complete renal response; eGFR = estimated glomerular filtration rate; LN = lupus nephritis; OR = odds ratio; UPCR = urine protein creatinine ratio
Source: Otsuka 2020;[109] Rovin et al., 2021[2]

B.2.6.1.2 *Time to UPCR of ≤0.5 mg/mg (secondary endpoint)*

More patients in the voclosporin arm achieved UPCR ≤0.5 mg/mg versus the placebo arm, (64.8% vs 43.8%) and the time to UPCR ≤0.5 mg/mg was also significantly shorter with voclosporin (median time: 169 days vs 372 days; HR 2.0; [95% CI: 1.5, 2.7]; p<0.001; Figure B.2-4).[2]

Figure B.2-4. AURORA 1: Probability of UPCR of ≤0.5 mg/mg



Abbreviation: CI = confidence interval; HR = hazard ratio; UPCR = urine protein creatinine ratio
Percentiles are Kaplan-Meier estimates. The HRs are from a Cox's proportional hazards model with covariates for treatment group, baseline UPCR, biopsy class, mycophenolate mofetil use at baseline, and region.
Source: Rovin et al., 2021[2]

B.2.6.1.3 *Complete Renal Response at Week 24 (secondary endpoint)*

The numbers of patients achieving renal response at Week 24 per CEC adjudication were lower than the numbers achieving response at Week 52. Consistent with the primary endpoint, the proportion of patients achieving an adjudicated renal response at Week 24 was significantly higher in the voclosporin arm than the placebo arm (32.4% vs 19.7%; OR 2.23; [95% CI: 1.3, 3.7]; p=0.002).[2]

B.2.6.1.4 *Partial Renal Response at Weeks 24 and 52 (secondary endpoint)*

Consistent with the results for renal response, more patients in the voclosporin arm achieved a PRR (defined as a 50% reduction from baseline in UPCR) at Week 24 and Week 52 (Table B.2-20). In both arms, PRR was achieved by Week 24 in the majority of patients who responded. The response rate of approximately 50% in the placebo arm demonstrates that the MMF and steroid regimen used in the study is effective in reducing UPCR; however, a greater number of patients responded in the voclosporin arm.

Table B.2-20. PRR at Weeks 24 and 52

	Voclosporin n=179	Placebo n=178	OR (95% CI)	p-value
PRR at 24 weeks, n (%)	126 (70)	89 (50)	2.43 (1.56, 3.79)	< 0.001
PRR at 52 weeks, n (%)	125 (70)	92 (52)	2.26 (1.45, 3.51)	< 0.001

Abbreviations: CI = confidence interval; OR = odds ratio; PRR = partial renal response

Source: Rovin et al., 2021[2]

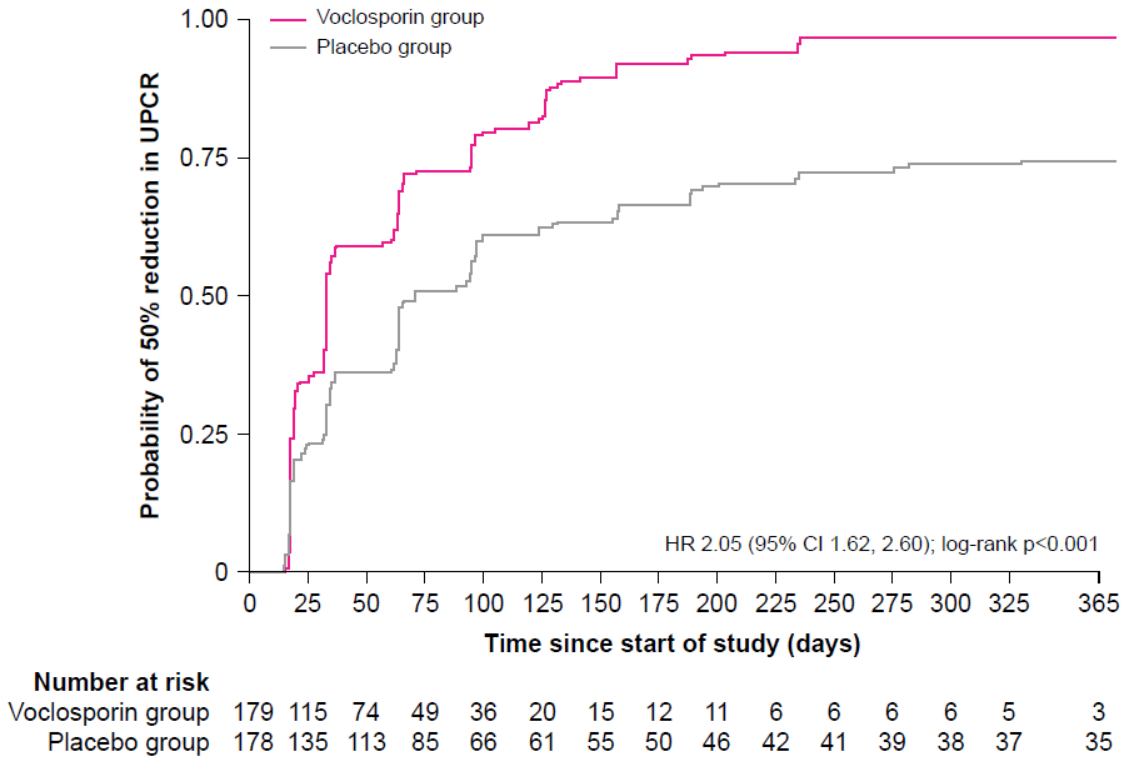
B.2.6.1.5 *Time to 50% Reduction in UPCR (secondary endpoint)*

A 50% reduction in UPCR from baseline at any time during the study was achieved by 96.6% of patients treated with voclosporin compared with 75.8% of patients receiving placebo. The time taken to reach a 50% reduction in UPCR was significantly shorter for the voclosporin arm than the placebo arm (HR 2.05; 95% CI: 1.6, 2.6; p<0.001). Median time to 50% reduction in UPCR was 29 days for voclosporin versus 63 days for placebo. Similar results were seen when using the lowest available pre-dose UPCR measurement as baseline.[2]

Consistent with the time to UPCR ≤0.5 mg/mg, the difference between the two treatment arms in the time to 50% reduction in UPCR was apparent within the first month of treatment and was sustained throughout the study (Figure B.2-5). The Kaplan-Meier curve shows that a small number of patients in the placebo arm achieved a 50% reduction in UPCR late on the study (beyond Day 350). However, most patients in the voclosporin arm achieved this response earlier; 6 and 38 patients were classed as still “at risk” beyond Day 300 in the voclosporin arm and the placebo arm, respectively.

Significantly greater reductions from baseline in UPCR were achieved in the voclosporin arm compared with the placebo arm at every time point.

Figure B.2-5. AURORA 1: Probability of ≥ 50% Reduction from Baseline in UPCR



Abbreviation: HR = hazard ratio; UPCR = urine protein creatinine ratio.
Percentiles are Kaplan-Meier estimates. The HRs are from a Cox’s proportional hazards model with covariates for treatment group, baseline UPCR, biopsy class, mycophenolate mofetil use at baseline, and region
Source: Rovin et al., 2021[2]

B.2.6.1.6 *Disease activity (secondary endpoint)*

Changes from baseline in disease activity were measured using the SELENA-SLEDAI instrument.[109] The SELENA-SLEDAI instrument objectively measures disease activity within the past 10 days by scoring 24 different disease activity descriptors.[116] Higher scores indicate a greater degree of disease activity, and the maximum theoretical score is 105 (all predictors are present). Improvements (i.e., decreases from baseline) in mean SELENA-SLEDAI index scores were observed in both treatment groups. Although numerically greater decreases from baseline were seen with voclosporin, there was no statistically significant difference between voclosporin and placebo (Table B.2-21).

Table B.2-21. AURORA 1: Change in SELENA-SLEDAI Index Score from baseline

Visit (n/n)	Mean difference (95% CI)		Mean difference vs placebo (95% CI)	p-value
	Voclosporin n=179	Placebo n=178		
Week 24 (167/172)	-4.5 (-5.4, -3.7)	-4.1 (-5.0, -3.2)	-0.5 (-1.6, 0.6)	0.375
Week 52 (150/160)	-6.0 (-6.7, -5.2)	-5.5 (-6.3, -4.7)	-0.5 (-1.4, 0.4)	0.277

Abbreviations: CI = confidence interval; SELENA-SLEDAI = Safety of Estrogens in Lupus Erythematosus National Assessment – Systemic Lupus Erythematosus Disease Activity Index
Source: Otsuka 2020[109]

B.2.6.1.7 *Patient-reported outcomes*

Improvements (i.e., increases) in mean scores from baseline were seen in both the voclosporin and the placebo arm for the HRQoL assessments SF-36 and for the health-related domains of the LupusPRO assessment.[109] Smaller changes were seen in both arms for the non-health-related domains of the LupusPRO assessment. There was no significant difference in the degree of improvement between the two treatments.

B.2.6.2 AURORA 2 Phase 3 long-term continuation study

AURORA 2 assessed the long-term safety, tolerability and efficacy of voclosporin compared with placebo for an additional 24 months following completion of treatment in the AURORA 1 study. A total of 216 eligible patients were analysed according to the treatment they were randomised to in the AURORA 1 study (n=100 in the placebo arm; n=116 in the voclosporin arm).[113]

AURORA 2 results reflected similar findings to AURORA 1, demonstrating favourable efficacy of voclosporin compared with placebo and a tolerable safety profile. [113]

B.2.6.2.1 *Complete renal response (secondary endpoint)*

At months 18, 24, 30 and 36 during AURORA 2, the proportion of patients achieving CRR was higher in the voclosporin arm compared with the placebo arm (Table B.2-22).[113] Despite the study not being powered to measure statistical significance, a significant and clinically meaningful difference ($p<0.05$) from placebo was observed at every time point except the 36 month assessment ($p=0.051$).[113] In particular, voclosporin demonstrated significantly greater CRR than placebo at month 18 ([redacted]% vs [redacted]%; OR [redacted] [95% CI [redacted]]; p=[redacted]), month 24 ([redacted]% vs [redacted]%; OR [redacted] [95% CI [redacted]]; p=0.035), and month 30 ([redacted]% vs [redacted]%; OR [redacted] [95% CI [redacted]]; p=[redacted]).[113]

Table B.2-22. CRR at months 18 to 36

	Patients, n (%)		OR (95% CI)	p-value
	Voclosporin n=116	Placebo n=100		
CRR at 18 months	[redacted]	[redacted]	[redacted]	[redacted]
CRR at 24 months	[redacted]	[redacted]	[redacted]	[redacted]
CRR at 30 months	[redacted]	[redacted]	[redacted]	[redacted]
CRR at 36 months	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CI = confidence interval; CRR = complete renal response; OR = odds ratio
Source: AURORA 2 CSR[113]

B.2.6.2.2 *Partial renal response (secondary endpoint)*

A greater proportion of patients in the voclosporin arm also experienced PRR compared with patients in the placebo arm across all time points (defined as a 50% reduction from baseline in UPCR) (Table B.2-23).[113] As observed in AURORA 1, the high response rate in the placebo arm demonstrates that the MMF and steroid regimen used in the study is effective in reducing UPCR.[113] Despite this, voclosporin demonstrated significantly greater PRR than placebo at month 18 ([redacted]% vs [redacted]%; OR [redacted] [95% CI [redacted]]; p=[redacted]), month 24 ([redacted]% vs [redacted]%; OR [redacted] [95% CI [redacted]]; p=[redacted]), and month 30 ([redacted]% vs [redacted]%; OR [redacted] [95% CI [redacted]]; p=[redacted]).[113]

Table B.2-23. PRR at months 18 to 36

	Voclosporin n=116	Placebo n=100	OR (95% CI)	p value
PRR at 18 months, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
PRR at 24 months, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
PRR at 30 months, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
PRR at 36 months, n (%)	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CI = confidence interval; OR = odds ratio; PRR = partial renal response
Source: AURORA 2 CSR[113]

B.2.6.2.3 *Renal flares (secondary endpoint)*

In order to be considered to have experienced a renal flare, patients must first achieve an adequate renal response.[113] Over the three-year course of the study, a greater proportion of patients in the voclosporin arm were considered to have an adequate renal response than those in the placebo arm ([redacted]% versus [redacted]%, respectively).[113] Among these patients, a slightly lower proportion of patients experienced a renal flare in the voclosporin arm compared to the placebo arm ([redacted]% vs [redacted]%, respectively) (Table B.2-24). Although a statistically significant difference could not be demonstrated between treatment arms, this may in part be due to the fact that AURORA 2 was not powered to demonstrate a significant difference in renal flare rates and few renal flare events were observed in either arm over the three year treatment period.[113]

When analysed on a year-by-year basis throughout the study period, the greatest difference in renal flare rate was observed during the first year of treatment; with fewer patients experiencing renal flares in the voclosporin arm compared with the placebo arm ([redacted]% vs [redacted]%, respectively; OR [redacted] [95% CI [redacted]]; p=[redacted]).[113] In years two and three of

treatment, renal flares were similar between the voclosporin and placebo arms (Table B.2-24).[113]

Table B.2-24. Patients with adequate response and renal flares over the three year AURORA 1 and AURORA 2 study period

		Voclosporin n (%) n=116	Placebo n (%) n=100	OR (95% CI)	p value
Overall (AURORA 1 baseline [Month 0] to Month 36)	Patients with adequate response*	[redacted]	[redacted]	[redacted]	[redacted]
	Patients with renal flares	[redacted]	[redacted]		
Year 1 (Months 0–12)	Patients with adequate response	[redacted]	[redacted]	[redacted]	[redacted]
	Patients with renal flares	[redacted]	[redacted]		
Year 2 (Months 12–24)	Patients with adequate response	[redacted]	[redacted]	[redacted]	[redacted]
	Patients with renal flares	[redacted]	[redacted]		
Year 3 (Months 24–36)	Patients with adequate response	[redacted]	[redacted]	[redacted]	[redacted]
	Patients with renal flares	[redacted]	[redacted]		

*A CEC adjudicated the response status of each patient, percentages for patients who responded are based on AURORA 2 population; percentages for patients with renal flares are based on the number of patients who responded prior to visit.

Abbreviations: CEC = Clinical Endpoints Committee; CI = confidence interval; OR = odds ratio

Source: AURORA 2 CSR[113]

Due to the low number of patients with renal flares, a further analysis was conducted to assess and identify patients with sustained 'good renal outcomes' (i.e. those who achieved adequate response and did not experience renal flare). Significantly more patients in the voclosporin arm benefited from a good renal outcome than those in the placebo arm ([redacted]% vs [redacted]%; OR [redacted] [95% CI [redacted]; p=[redacted]), demonstrating a clear-long-term renal benefit of voclosporin treatment (Table B.2-25).[113]

Table B.2-25. Patients with good renal outcomes* over the three-year AURORA 1 and AURORA 2 study period

	Voclosporin n (%) n=116	Placebo n (%) n=100	OR (95% CI)	p value
Overall (AURORA 1 baseline [Month 0] to Month 36)	[redacted]	[redacted]	[redacted]	[redacted]
Year 1 (Months 0–12)	[redacted]	[redacted]	[redacted]	[redacted]
Year 2 (Months 12–24)	[redacted]	[redacted]	[redacted]	[redacted]
Year 3 (Months 24–36)	[redacted]	[redacted]	[redacted]	[redacted]

*Good renal outcome is defined as adequate response and without flare.
Abbreviations: CI = confidence interval; OR = odds ratio
Source: AURORA 2 CSR[113]

B.2.6.2.4 *Extra-renal flares (secondary endpoint)*

Independent of renal response status, patients could experience non-renal ("extra-renal") flares at any point during the AURORA trials.[113] During the three-year study period, [redacted]% of patients in the placebo arm and [redacted]% of patients in the voclosporin arm were considered to have extra-renal flares (OR [redacted] [95% CI [redacted]–[redacted]; p=[redacted]) (Table B.2-26). As with other efficacy endpoints, AURORA 2 was not powered to demonstrate a significant difference in extra-renal flares and there were notably few occurrences of extra-renal flare in the AURORA 2 study population (as is typically the case in patients with LN).[113]

Table B.2-26. Patients with extra-renal flares over the three-year AURORA 1 and AURORA 2 study period

	Voclosporin n (%) n=116	Placebo n (%) n=100	OR (95% CI)	p value
Overall (AURORA 1 baseline [Month 0] to Month 36)	[redacted]	[redacted]	[redacted]	[redacted]
Year 1 (Months 0–12)	[redacted]	[redacted]	[redacted]	[redacted]
Year 2 (Months 12–24)	[redacted]	[redacted]	[redacted]	[redacted]
Year 3 (Months 24–36)	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CI = confidence interval; OR = odds ratio
Source: AURORA 2 CSR[113]

B.2.6.2.5 *Disease activity (secondary endpoint)*

Disease activity, as measured via the SELENA-SLEDAI score (see Section B.2.6.1.6), was higher in the voclosporin arm (mean: [redacted], median: [redacted]) than the placebo arm (mean: [redacted], median: [redacted]).[113] Improvements from AURORA 1 baseline were seen in both arms during AURORA 2, demonstrating improvements in SLE symptoms. The greatest improvements were observed during the first year of treatment, however there was no significant difference between the treatment arms.[113]

B.2.6.2.6 *Change in UPCR from baseline*

At the start of AURORA 1, baseline mean UPCR levels were balanced between the two treatment arms ([redacted] mg/mg in the placebo arm and [redacted] mg/mg in the voclosporin arm).[113] At the end of AURORA 1 (Month 12), mean UPCR was [redacted] in the voclosporin arm compared with [redacted] in the placebo arm. At the follow-up visit, UPCR in the voclosporin arm showed a decrease of [redacted] from baseline compared with a decrease of [redacted] in the placebo arm.[113]

The MMRM analysis confirmed that statistically significantly greater reductions from baseline in UPCR were achieved in the voclosporin arm compared with the placebo arm at Months 18, 24 and 30 but not Month 36.[113]

During AURORA 2 (from Month 12) there was little change in UPCR in either treatment arm. Mean UPCR values at Month 12 were lower in the voclosporin arm ([redacted] mg/mg) than in the placebo arm ([redacted] mg/mg) as a result of benefit derived from 12 months of treatment with voclosporin.[113] There was no demonstrable difference between the two arms in the change from Month 12 at visits through to Month 36, showing that the difference observed at Month 12 is sustained for a further 2 years with continued treatment with voclosporin.[113]

B.2.6.2.7 *Change in urine protein, serum creatinine and eGFR from baseline*

Urine protein decreased across the 3 years of observation during the AURORA 1 and AURORA 2 studies.[113] There was a greater decrease in mean urine protein observed in patients receiving voclosporin compared with placebo, which was consistent with UPCR findings.[113] The MMRM analysis confirmed a statistically significantly greater mean decrease for voclosporin treatment compared to placebo at most time points.[113]

Mean serum creatinine levels at baseline prior to the start of treatment in AURORA 1 were within normal range and similar in both treatment arms (placebo: [redacted] mg/dL, voclosporin: [redacted] mg/dL).[113] Over the first 15 months of treatment, small increases (i.e. within normal range) in mean levels were observed in the voclosporin arm while levels in the placebo arm decreased slightly.[113] This resulted in statistically significant differences between the treatment arms up to Month 15 in the MMRM analysis but not from Month 18 onwards.[113] During AURORA 2, mean corrected eGFR values were similar in both arms prior to the start of study treatment in AURORA 1 ([redacted] mL/min/1.73m^2 in the voclosporin arm and [redacted] mL/min/1.73m^2 in the placebo arm).[113] Over the first 3 months of treatment, the mean corrected eGFR were stable in the voclosporin arm while the mean value in the placebo arm showed a small increase. The [redacted] between the arms remained through to Month 27, after which the mean eGFR value increased slightly in the voclosporin arm and started to decline in the placebo arm.[113]

B.2.6.2.8 *Patient reported outcomes*

Improvements (i.e. increases) in mean scores from baseline were seen in both the voclosporin and the placebo arm for all domains of the SF-36 assessment, with no significant difference in the total mean scores observed between the two treatments.[113]

B.2.6.3 AURA-LV Phase 2 study

AURA-LV was a Phase 2, 48-week, randomised, double-blind, parallel-group, placebo-controlled, three-arm, multicentre study designed to compare the efficacy and safety of two doses (high- and low-dose) of voclosporin and placebo in patients with LN.

The study met its primary objective, demonstrating a higher proportion of patients achieved CRR after 24 weeks in the voclosporin groups than in the placebo group.

B.2.6.3.1 *Complete Renal Response at Week 24 (primary endpoint)*

At Week 24, CRR was achieved by a higher proportion of patients in both the low-dose (32.6%) and high-dose (27.3%) voclosporin groups compared to the placebo group (19.3%). CRR at Week 24 was significantly improved in patients treated with low-dose voclosporin compared to patients in the placebo group (OR=2.03; [95% CI: 1.01, 4.05]; p=0.045).[8]

B.2.6.3.2 *Complete Renal Response at Week 48 (secondary endpoint)*

At Week 48, CRR was achieved by a higher proportion of patients in both the low-dose (49.4%) and high-dose (39.8%) voclosporin groups compared to the placebo group (23.9%), with an increased separation between the treatment and control arms compared to Week 24. CRR was increased in both the voclosporin groups compared to the placebo: i.e., patients treated with low-dose voclosporin had triple the odds of achieving CRR at Week 48 compared to patients in the placebo group (OR=3.21; [95% CI: 1.68, 6.13]; p<0.001), and patients treated with high-dose voclosporin had double the odds of achieving CRR compared to patients in the placebo group (OR=2.10; [95% CI: 1.09, 4.02]; p=0.026).[8]

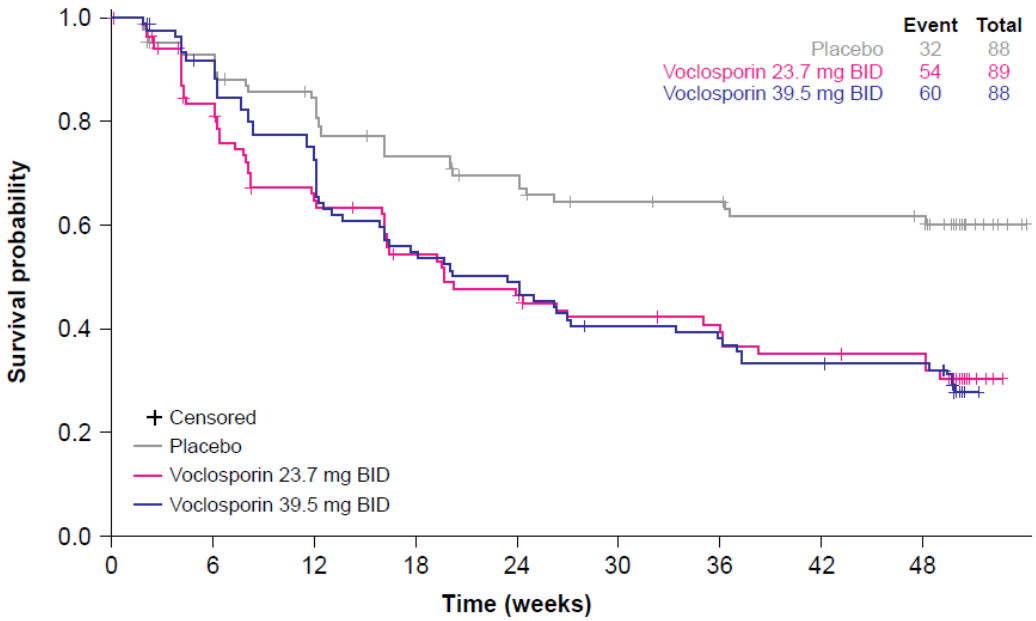
B.2.6.3.3 *Partial renal response at Week 24 and Week 48 (secondary endpoint)*

At Week 24, partial renal response was achieved by a higher proportion of patients in both the low-dose (69.7%) and high-dose (65.9%) voclosporin groups compared to the placebo group (49.4%).[114] Low-dose or high-dose voclosporin had double the odds of achieving partial renal response at Week 24 compared to patients in the placebo group (OR 2.33; p=0.007 and OR=2.03; p=0.024, respectively). Results were similar at Week 48, with even higher odds demonstrated for the high-dose voclosporin group versus placebo (OR 2.68; p=0.002).[114]

B.2.6.3.4 *Time to Complete Renal Response (secondary endpoint)*

CRR occurred statistically significantly earlier in patients treated with either low-dose or high-dose voclosporin compared to placebo (HR 2.26 and 2.25, respectively). The median time to CRR was 19.7 weeks in the low-dose voclosporin group and 23.4 weeks in the high-dose voclosporin group. Median time to CRR could not be determined for the placebo group (Figure B.2-6).[114]

Figure B.2-6: AURA-LV: Analysis of Time to CRR



Source: Otsuka 2018[114]

B.2.6.3.5 *Time to Partial Renal Response, Sustained Partial Renal Response and Sustained Early Partial Renal Response (secondary endpoint)*

Partial renal response occurred significantly earlier in patients treated with either low-dose or high-dose voclosporin compared to placebo (HR 1.63 (p=0.005) and HR 1.74 (p=0.002), respectively). The median time to partial renal response was 4.3 and 4.4 weeks in the low-dose and high-dose voclosporin groups, respectively, compared to 6.6 weeks in the placebo group.[8,114]

Compared to placebo, sustained partial renal response occurred significantly earlier in patients treated with either low-dose voclosporin (HR=2.03; p<0.001) or high-dose voclosporin (HR=1.81; p=0.004).[114] The median time to sustained partial renal response was 26.9 weeks in the placebo group, compared to 6.3 weeks in the low-dose voclosporin group and 8.1 weeks in the high-dose voclosporin group.[114]

Sustained early partial renal response was achieved by a higher proportion of patients in both the low-dose (67.4%) and high-dose (65.9%) voclosporin groups compared to the placebo group (41.4%).[114] Both voclosporin dose groups demonstrated that significantly increased odds of achieving sustained early partial renal response compared to patients in the placebo group. The patients treated with low-dose voclosporin had an OR of 2.93 compared to those treated with placebo (p<0.001) and the patients treated with high-dose voclosporin had an OR of 2.74 compared to those treated with placebo (p=0.021).[114]

Compared to placebo, time to sustained early partial renal response occurred significantly earlier in patients treated with either low-dose voclosporin (HR=2.21; p<0.001) or high-dose voclosporin (HR=1.87; p=0.004).[114] The median time to sustained early partial renal response was 6.3 weeks in the low-dose voclosporin group and 8.1 weeks in the high-dose voclosporin group. Median time to CRR could not be determined for the placebo group.[114]

B.2.6.3.6 *Disease activity*

Mean SELENA-SLEDAI scores improved (i.e., decreased) in all 3 treatment groups. Changes from baseline in mean SELENA-SLEDAI scores were significantly greater for both the low-dose and high-dose voclosporin groups compared with placebo at Week 24 (p=0.003 for both comparisons) and at Week 48 (p<0.001 for both comparisons; Table B.2-27).[114]

Table B.2-27. AURA-LV: Mean Change from Baseline in SELENA-SLEDAI Scores at Week 24 and Week 48

	Voclosporin (low-dose)* *n=74 at Week 24* *n=77 at Week 48*	**Voclosporin (high-dose)†** *n=82 at Week 24* *n=82 at Week 48*	**Placebo** *n=76 at Week 24* *n=79 at Week 48*
Week 24	-6.3‡	-7.1‡	-4.5
Week 48	-7.9‡	-8.3‡	-5.3

*23.7 mg BID; †39.5 mg BID; ‡Significant difference compared with placebo (p<0.05) in ANCOVA for the change from baseline

Abbreviations: ANCOVA = analysis of covariance; CI = confidence interval; SELENA-SLEDAI = Safety of Estrogens in Lupus Erythematosus National Assessment - Systemic Lupus Erythematosus Disease Activity IndexNote: a decrease in SELENA-SLEDAI score indicates improvement

Source: Otsuka 2018[114]

B.2.7 Subgroup analysis

B.2.7.1 AURORA 1 Phase 3 study

B.2.7.1.1 *Methodology and statistical analysis*

The primary endpoint of CRR at Week 52 was analysed for the following pre-specified subgroups:[109]

- Age (≤30 vs >30 years)
- Gender (male, female)
- Race (White, Asian, other)
- Biopsy class (class V, other)
- Region (Asia-Pacific, Europe and South Africa, Latin America, North America)
- MMF use at screening (yes, no)
- Maximum MMF dose (≤2 g vs >2 g)

Prespecified covariate analyses were done using a logistic regression model. An interaction between the subgroup and treatment group was added to the model, and a p value for the main effect of the covariate in question along with the p-value for the interaction between treatment and covariate were reported.[109]

B.2.7.1.2 *Results of subgroup analyses*

Results of the subgroup analyses are presented in Appendix E. The treatment benefit of voclosporin was seen in all pre-specified subgroups.[109] Although the study was not powered to detect a significant difference between the two treatments in the individual subgroups, statistically significant results were observed for many subgroups, confirming the positive effect of voclosporin in achieving renal response. Where the results were not statistically significant (White, pure Class V, Europe + South Africa, North America, no MMF at screening and maximum MMF dose >2 g), the odds ratios still favoured voclosporin over placebo.[109]

B.2.7.2 AURORA 2 Phase 3 long-term continuation study

Subgroup analyses were not planned for the AURORA 2 study, nor have any post-hoc analyses been conducted at the time of this submission.

B.2.7.3 AURA-LV Phase 2 study

B.2.7.3.1 *Methodology and statistical analysis*

No subgroup analyses were stipulated in the Statistical Analysis Plan (SAP). However, post-hoc subgroup analyses were conducted for CRR at Weeks 24 and 48 to explore the impact of the imbalance in randomisation of low gross domestic product (GDP) patients (i.e. low-GDP and non-low GDP) and biopsy class (i.e. class III, III/V, IV, IV/V, and V). TEAEs and serious TEAEs were analysed according to GDP subgroups.[114]

Covariate analyses were also conducted for CRR at Week 24 and 48 including the following covariates:[114]

- Age (≤30 vs >30 years)
- Gender (male, female)
- Race (White, Asian, other)
- Biopsy class (class V, other)
- Region (Asia-Pacific, Europe and South Africa, Latin America, North America)
- MMF use at screening (yes, no)
- Maximum MMF dose (≤2 g vs >2 g)

B.2.7.3.2 *Results of subgroup analyses*

Results of the subgroup and covariate analyses are presented in Appendix E.[114]

B.2.7.3.2.1 Subgroup analysis: CRR and TEAES/serious TEAEs in GDP subgroups

At Week 24, the CRR rate was notably lower for both voclosporin dose groups within the low-GDP subgroup, particularly for those treated with high-dose voclosporin (low GDP: 12.1% vs non-low GDP: 36.4%). The impact was less pronounced at Week 48, with little difference in CRR between the overall population or GDP subgroups.[114] Across both voclosporin dose groups, CRR rates at Week 24 increased when low-GDP patients were excluded (i.e. from 32.6% to 38.3% in the low-dose group and from 27.3% to 36.4% in the high-dose group).[114]

When low-GDP patients were excluded, the overall incidence of TEAEs was also reduced, especially in the two voclosporin groups. In addition, a similar incidence of serious TEAEs and TEAEs leading to death was observed in patients in non-low GDP countries among all three treatment groups.[114]

B.2.7.3.2.2 Subgroup analysis: CRR in biopsy subgroups

At both Week 24 and Week 48, a trend favouring low-dose voclosporin over placebo was maintained across all biopsy classes apart from pure class V. The results for an “all but pure class V” subgroup were consistent with the results for the overall population.[114]

B.2.7.3.2.3 Covariate analyses

Low-dose voclosporin had a beneficial effect in terms of CRR at Week 24 across most covariates compared to placebo. The treatment benefit was not statistically significant for the majority of strata; however, this was likely due to the small sample size (e.g. male gender (n=28) and "other" race (n=17)).[114] ORs in favour of low-dose voclosporin were statistically significant for female gender; "other" biopsy class (i.e. not Class V); no MMF use at screening; White race; the region of Europe; and age >30 years. Odds ratios favoured placebo for male gender (OR 0.30) and Class V biopsy class (OR 0.19), although the results were not statistically significant (p=0.206 and p=0.075, respectively). Overall, similar trends were seen in the covariate analysis for the comparison of high-dose voclosporin versus placebo.[114]

B.2.8 Meta-analysis/pooled analysis

An integrated analysis of AURORA 1 and AURA-LV has been completed to provide more information on the treatment effect for voclosporin. A pooled LN population was defined to comprise patients exposed to voclosporin (23.7 mg twice daily; n=268) or placebo (n=266), each in combination with MMF and low-dose corticosteroids per AURORA 1 and AURA-LV dosing regimens for up to one year.[110]

Within the pooled dataset, key demographics and baseline characteristics were comparable between treatment arms (median age: 30 vs 32; proportion of Hispanic or Latino: 25% vs 27%; median eGFR: 92 vs 98 ml/min/1.73 m^2; median UPCR: 3.5 vs 3.1 mg/mg; median time since LN diagnosis: 2.2 vs 2.2 years for voclosporin and placebo arms, respectively), including an identical proportion of patients with class III or IV± V (38%) or pure class V (14%) LN.[110]

CRR was analysed using a logistic regression model that included terms for study, treatment group, baseline UPCR, biopsy class, MMF use at screening, and region with adjudicated renal response outcomes at one year as the response variable.[117] Time to UPCR ≤0.5mg/mg and time to ≥50% reduction in UPCR were estimated using Kaplan-Meier methodology, with a Cox proportional hazards model fitted using terms for study, baseline UPCR, biopsy class, MMF use at screening, and region.[117] Change from baseline in UPCR was also analysed using a MMRM analysis with study, treatment arm, visit, treatment by visit interaction, treatment by study interaction, biopsy class, MMF use at screening, region, and baseline parameter (UPCR/serum creatinine/eGFR) included as covariates in the model.[117]

In summary, CRR rates were significantly greater in the voclosporin arm compared to the placebo arm at both six months (31.7% vs 20.3%, respectively; OR: 2.01, p=0.008) and one year (43.7% vs 23.3%, respectively; OR: 2.76, p<0.0001).[110] Similarly, a significantly greater proportion of patients achieved PRR in the voclosporin arm at both six months (70.1% vs 49.8%; OR: 2.42; p=<0.0001) and one year (69.4% vs 50.6%; OR: 2.26; p<0.0001) compared to placebo.[117] A ≥50% UPCR reduction was also achieved in 93.7% of patients in the voclosporin arm, and 75.2% of patients in the control arm; and the median time to ≥50% UPCR reduction was significantly shorter for voclosporin relative to placebo (29 days vs 58 days, respectively; HR: 1.96, p<0.0001).[110] Decreases in mean UPCR were observed at Week 4 and sustained over a 52 week period for both treatment arms, with a significantly greater reduction from baseline observed in the voclosporin arm compared to the placebo arm at Week 52 (mean UPCR -1.1 mg/mg; p<0.0001).[117]

Apart from a head-to-head data for voclosporin versus MMF provided by AURORA 1, AURA-LV, and AURORA 2, other head-to-head evidence is not available to compare voclosporin to

alternative comparators (i.e. rituximab, cyclophosphamide, tacrolimus, tacrolimus+MMF and azathioprine). Therefore, a network meta-analysis (NMA) was performed to estimate the relative efficacy of voclosporin versus all relevant comparators (Section B.2.9).

B.2.9 Indirect and mixed treatment comparisons

In the absence of head-to-head data, an NMA was conducted to compare the efficacy of voclosporin to all relevant comparators using published evidence identified from the clinical SLR. NMA efficacy outcomes of interest were pre-defined as CRR and PRR, and NMA results were used to inform comparator short-term efficacy in the cost-effectiveness model (Section B.3). As CRR and PRR are mutually exclusive health states by definition, the PRR network only included patients who achieved a PRR, independent of CRR. Therefore, trials were removed from the NMA if they did not report PRR independently of CRR.

B.2.9.1 Search strategy and study selection for the network meta-analysis

A full overview of the SLR methods undertaken for this submission are provided in Appendix D. Systematic searches were conducted on 1st June 2021, and later repeated on 24 January 2022 to identify RCTs that evaluated the efficacy and safety of active treatments in patients with active LN. A total of 57 publications reporting on 44 unique trials were identified from the databases. To present and describe the key evidence relevant to the final scope, networks that were dependent on the outcomes of interest were constructed by selecting only those RCTs that evaluated voclosporin and the comparators of interest for the treatment of patients with active LN. For a full overview of the trials included and excluded from the NMA, refer to Appendix D.

Criteria for study inclusion/exclusion to define the NMA evidence base are described in Table B.2-28.

Table B.2-28. Criteria for study inclusion/exclusion used in selection for the NMA evidence base

	Inclusion criteria	Exclusion criteria
Population	Adult patients with active lupus nephritis	Studies of patients not in AD e.g., patients in maintenance or patients with refractory disease.
Intervention	Voclosporin 23.7mg BID	Studies that do not include a treatment arm with any of the selected comparators of interest
Comparators	• MMF plus corticosteroids • CYC plus corticosteroids • AZA plus corticosteroids • RTX • CNI plus MMF and corticosteroids	
Outcomes	The number of patients who achieve: • A CRR • A PRR	Studies that do not report on these outcomes of interest
Study Design	RCTs	Studies that are not randomised, reviews, commentaries.

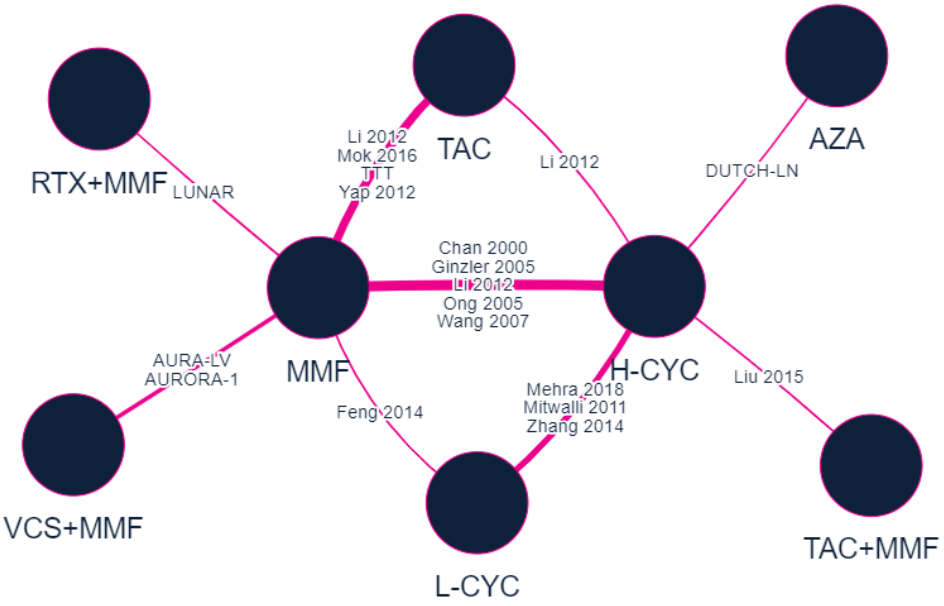
Abbreviations: AD = active disease; AZA = azathioprine; BID = twice daily; CNI = calcineurin inhibitor; CRR = complete renal response; CYC = cyclophosphamide; MMF = mycophenolate mofetil; PRR = partial renal response; RCTs = randomised controlled trials; RTX = rituximab

B.2.9.2 Summary of trials included in the NMA

A summary of RCTs included in the base case NMA and in the scenario analyses are described in Appendix D for the pre-defined outcomes of CRR and PRR, respectively. In addition, Appendix D contains an overview of CRR and PRR outcomes for studies included in the networks for each comparator, with outcomes presented at ≤6 month and ≥12 month follow-up where possible.

The base case treatment network for the CRR outcome is presented in Figure B.2-7, and includes a total of 17 RCTs reporting on 8 treatments in an overall patient population. Scenario analysis networks are also presented in Appendix D, to include trials that are non-essential (i.e. those that contribute additional evidence to the network but do not provide essential links), to exclude trials with a substantially different outcome definition of CRR or those with a 100% Asian patient population, and to assess response at different lengths of follow-up.

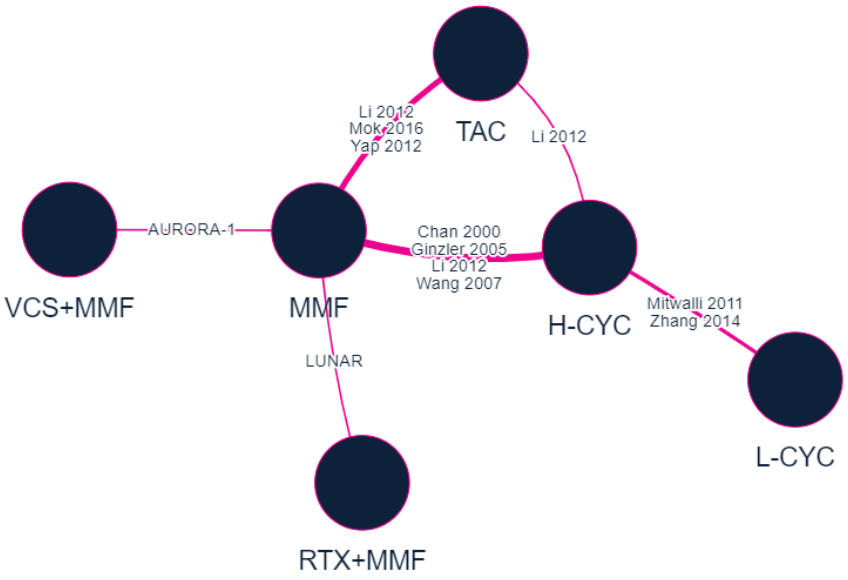
Figure B.2-7. Treatment network for studies contributing to evidence for CRR in the overall population



Abbreviations: AZA = azathioprine; H-CYC = high-dose cyclophosphamide; L-CYC = low-dose cyclophosphamide; MMF = mycophenolate mofetil; RTX = rituximab; TAC = tacrolimus; VCS = voclosporin

The base case treatment network for PRR outcome is presented in Figure B.2-8, and includes a total of 10 RCTs reporting on 6 treatments in an overall patient population. Although Zhang 2020 reported on PRR for tacrolimus + MMF, it could not be connected to the PRR network as no other trials in this network included tacrolimus + MMF or MMF + cyclophosphamide as comparators. Scenario analyses consisted of the same scenarios as performed for CRR, the networks for each scenario are presented in Appendix D.

Figure B.2-8. Treatment network for studies contributing to evidence for PRR in the overall population



Abbreviations: H-CYC = high-dose cyclophosphamide; L-CYC = low-dose cyclophosphamide; MMF = mycophenolate mofetil; RTX = rituximab; TAC = tacrolimus; VCS = voclosporin

B.2.9.3 Heterogeneity assessment of trials included

Study similarity was assessed for heterogeneity according to the population, intervention, comparator, outcome, study design (PICOS) framework detailed in Table B.2-29. Tables with baseline patient characteristics, summary of outcome definitions and background corticosteroid use are provided in Appendix D.

Table B.2-29. PICOS items for heterogeneity assessment

PICOS item	Evaluated information
Patient characteristics	• Age • Sex • Biopsy class (%) • Prior MMF use • Race • Region • Prior treatment
Intervention	• Treatment dose and regimen • Background corticosteroid use
Comparator	
Outcome definition	• Definition of CRR & PRR • Timepoint of renal response
Study characteristics	• Study phase • Number of patients • Study aim • Study design • Follow-up duration

Abbreviations: CRR = complete renal response; MMF = mycophenolate mofetil; PRR = partial renal response

Trial designs and patient population across included studies were generally comparable (Appendix D), although the following key differences were observed:

- Doria 1994 (included in scenario analyses) assessed the efficacy and safety of azathioprine combined with corticosteroids, whereas other studies reported corticosteroid use as background therapy
- Most included studies did not report the study phase, with only the AURORA 1 and LUNAR trials listed as Phase 3. Other studies tended to include a smaller sample size
- The dosage of MMF (the NMA reference treatment) varied between included studies, while AURORA-1 and AURA-LV used a dosage which was lower than in some studies (1 mg)
- Trial length of follow-up varied between studies, with most reporting outcomes at six months only
- Outcome definitions for CRR and PRR varied across studies. Some studies required patients to fulfil many criteria to achieve renal response, while others included less stringent criteria
- Yap 2012 and Doria 1994 were randomised controlled pilot studies. Therefore, few patients were assigned to treatment (<10 patients per treatment arm in each study). Wang 2007 was also a small sample study (phase not reported), and included only 20 patients across two treatment arms
- Six of the included trials were restricted to the Asian-Pacific region and consisted of Asian patients only (Feng 2014, Kamanamol, Li 2012, Liu 2015, Mok 2016, and Yap 2012)

B.2.9.4 Statistical methods for the network meta-analysis

The NMA was conducted in a Bayesian framework using Monte Carlo Markov Chain (MCMC) and implemented using models developed in the probabilistic modelling language of Stan (Version 2.21.0).[118] A generalised linear model for dichotomous outcomes was applied, as presented within the NICE Decision Support Unit (DSU) Technical Support Document (TSD) 2.[119] Treatment effects were synthesised using the observed number of events from the known number of patients in the respective treatment arms. The data was assumed to come from a binomial likelihood. Therefore, the binomial model with a logit link was used to model the log odds of the outcome on a given treatment, in a specified trial via an effect (fixed or random). As recommended, a non-informative prior was assigned for the treatment effect, in both fixed and random effects models, $N(0, 100^2)$. A more informative prior, half~N(0, 5), was applied for the parameter representing the between study variation in the random effects model.

In the Monte Carlo simulation, 4 simulation chains with a minimum of 10,000 iterations (including 5,000 burn-in) were used to summarise the posterior distribution. The number of samples was deemed appropriate for model convergence. Convergence was then assessed in accordance with NICE DUS TSD 2; by examining diagnostic autocorrelation, trace, and density plots as well as the recommended statistics such as the Gelman-Ruben Rhat, and whether the Monte Carlo standard errors are ≤5% of the posterior deviation of the parameters of interest.[119]

Evidence networks were also assessed for inconsistency between the direct and indirect evidence, by comparison of the standard consistency model and with an inconsistency model, as proposed in the NICE DSU TSD 4.[120] Deviance contributions from each fitted point were assessed along with the effective number of parameters, and deviance information criterion (DIC) were compared to assess model fit and validity of the consistency assumption.

Detailed results and plots for the consistency checks are provided in Appendix D for the outcomes of CRR and PRR. Potential inconsistency was discovered in the CRR network, arising from the Feng 2014 study. A careful review of the evidence was undertaken, and no data extraction errors were identified. A comparison between the unrestricted means (UME) inconsistency model and the standard consistency model, for the fixed effects NMA presented, returned no significant differences between model fit and DIC (Appendix D). Comparisons for the UME model and consistency model for the PRR demonstrated equivalence between the models in terms of the deviance contributions and the consistency model is deemed appropriate.

Full details of the statistical methods adopted for the NMA are provided in Appendix D.

B.2.9.5 Results of the network meta-analysis

NMA results of relevance to the decision problem are summarised in Table B.2-30 for CRR and Table B.2-32 for PRR. For indirect comparisons, MMF was selected as the reference treatment for which all other treatments are compared to, as MMF was the most common comparator across trials. Pairwise ORs of all treatment comparisons are provided in Table B.2-31 and Table B.2-33 for CRR and PRR, respectively. Results of additional scenario analyses not of relevance to the decision problem have been reported in Appendix D.

For the CRR outcome, the NMA estimated a high probability (≥95%) for voclosporin + MMF to be more efficacious than MMF in the overall population, thereby reiterating the results of the AURA-LV and AURORA-1 clinical trials for voclosporin + MMF (median OR [redacted] [95% credible interval (CrI): [redacted]]; Figure B.2-9). No further treatments demonstrated a greater efficacy than MMF in terms of CRR, and both the high-dose (H-CYC) and low-dose (L-CYC) regimens for cyclophosphamide were inferior to MMF in terms of achieving a CRR (median OR [redacted] [95% CrI: [redacted]] and [redacted] [95% CrI: [redacted]], respectively).

Surface under the cumulative ranking curve (SUCRA) values are provided for the ranking of treatments in Table B.2-30 and Table B.2-32 for CRR and PRR, respectively. The SUCRA shows that voclosporin + MMF is highly likely to be the preferred treatment option with a value of [redacted]%, followed by the combination therapy of tacrolimus + MMF ([redacted]%) and the reference MMF ([redacted]%).

Table B.2-30. Primary analysis, fixed-effects network meta-analysis for CRR

Treatment	Median OR (vs. MMF)	CrI 2.5%	CrI 97.5%	SUCRA
MMF	Ref	Ref	Ref	[redacted]
VCS+MMF	[redacted]	[redacted]	[redacted]	[redacted]
AZA	[redacted]	[redacted]	[redacted]	[redacted]
H-CYC	[redacted]	[redacted]	[redacted]	[redacted]
L-CYC	[redacted]	[redacted]	[redacted]	[redacted]
RTX+MMF	[redacted]	[redacted]	[redacted]	[redacted]
TAC	[redacted]	[redacted]	[redacted]	[redacted]
TAC+MMF	[redacted]	[redacted]	[redacted]	[redacted]
Model selections statistics: DIC = 66.09, pD = 24.34, Residual deviance = 41.75				

Notes: Values underlined demonstrate a high probability (≥95%) of being more efficacious than MMF

Abbreviations: AZA = azathioprine; CrI = credible interval; CRR = complete renal response; DIC = deviance information criterion; H-CYC = high dose cyclophosphamide; L-CYC = low-dose cyclophosphamide; MMF = mycophenolate mofetil; OR = odds ratio; pD = parameters; RTX = rituximab; SUCRA = surface under the cumulative ranking curve; TAC = tacrolimus; VCS = voclosporin

Figure B.2-9. Forest plot for posterior median ORs and 95% CrI, for CRR

Abbreviations: AZA = azathioprine; CrI = credible interval; CRR = complete renal response; H-CYC = high-dose cyclophosphamide; L-CYC = low-dose cyclophosphamide; MMF = mycophenolate mofetil; OR = odds ratio; RTX = rituximab; TAC = tacrolimus; VCS = voclosporin

Table B.2-31. Pairwise odds ratios for CRR, OR (95% CrI)

	MMF	VCS+MMF	AZA	H-CYC	L-CYC	RTX+MMF	TAC	TAC+MMF
MMF vs								
VCS+MMF vs								
AZA vs								
H-CYC vs								
L-CYC vs								
RTX+MMF vs								
TAC vs								
TAC+MMF vs								

Abbreviations: AZA = azathioprine; CrI = credible Interval; CRR = complete renal response; H-CYC = high-dose cyclophosphamide; L-CYC = low-dose cyclophosphamide; MPR = methylprednisolone; MMF = mycophenolate mofetil; OR = odds ratio; PR = prednisolone; RTX = rituximab; TAC = tacrolimus; VCS = voclosporin

For the PRR outcome, the NMA indicated that voclosporin + MMF and rituximab + MMF have a high probability (≥95%) of being more efficacious than MMF in the overall population based on studies that reported partial responders independently from those who achieved a CRR (median OR [redacted] [95% CrI: [redacted]] and [redacted] [95% CrI: [redacted]], respectively; Figure B.2-10). On the other hand, neither cyclophosphamide regimens nor tacrolimus were significantly different to MMF in achieving PRR. Furthermore, the SUCRA demonstrated that voclosporin + MMF was the second most likely regimen to be the preferred treatment option when considering an independent PRR (SUCRA: [redacted]%), behind rituximab + MMF ([redacted]%) but ahead of tacrolimus ([redacted]%), and the reference MMF ([redacted]%).

Table B.2-32. Primary analysis: fixed-effects network meta-analysis for PRR

Treatment	Median OR (vs. MMF)	CrI 2.5%	CrI 97.5%	SUCRA
MMF	Ref	Ref	Ref	[redacted]%
VCS+MMF	[redacted]	[redacted]	[redacted]	[redacted]%
H-CYC	[redacted]	[redacted]	[redacted]	[redacted]%
L-CYC	[redacted]	[redacted]	[redacted]	[redacted]%
RTX+MMF	[redacted]	[redacted]	[redacted]	[redacted]%
TAC	[redacted]	[redacted]	[redacted]	[redacted]%
Model selections statistics: DIC = 32.30, pD = 15.20., Residual deviance = 17.10				

Notes: Values underlined demonstrate a high probability (≥95%) of being more efficacious than MMF
Abbreviations: CrI = credible interval; DIC = deviance information criterion; H-CYC = high-dose cyclophosphamide; L-CYC = low-dose cyclophosphamide; MMF = mycophenolate mofetil; OR = odds ratio; pD = parameters; PRR = partial renal response; RTX = rituximab; SUCRA = surface under the cumulative ranking curve; TAC = tacrolimus; VCS = voclosporin

Figure B.2-10. Forest plot for posterior median ORs and 95% CrI, for PRR

Abbreviations: AZA = azathioprine; CrI = credible interval; CRR = complete renal response; H-CYC = high-dose cyclophosphamide; L-CYC = low-dose cyclophosphamide; MMF = mycophenolate mofetil; OR = odds ratio; RTX = rituximab; TAC = tacrolimus; VCS = voclosporin

Table B.2-33. Pairwise odds ratios for PRR, OR (95% CrI)

	MMF	VCS+MMF	H-CYC	L-CYC	RTX+MMF	TAC
MMF vs						
VCS+MMF vs						
H-CYC vs						
L-CYC vs						
RTX+MMF vs						
TAC vs						

Abbreviations: AZA = azathioprine; CrI = credible Interval; CRR = complete renal response; H-CYC = high-dose cyclophosphamide; L-CYC = low-dose cyclophosphamide; MMF = mycophenolate mofetil; OR = odds ratio; PR = prednisolone; RTX = rituximab; TAC = tacrolimus; VCS = voclosporin

B.2.9.6 Uncertainties in the indirect and mixed treatment comparisons

While a NMA allows for the indirect comparison of voclosporin + MMF versus the comparators relevant to the decision problem, some uncertainties exist within the approach taken.

The binomial approach considered does present some limitations, as the included trials do not all have the same follow-up time. The logit model assumes either that all patients who reach

the endpoint, do so by a specific follow-up time, and further follow-up makes no difference; or that the proportional odds assumption holds.[119] However, scenario analyses at different time points indicated that the ORs changed at the 6-month analysis to that of the >1 year analysis (the base case used the longest-follow up available up to a maximum of 2-years). The length of follow-up available was also identified as a contributor for heterogeneity of the studies included, as many only reported on outcomes for 6-months.

A further limitation was the heterogeneity observed between the studies included. This was present for several factors and one that would considerably affect the number of events was the definition of response across trials. For example, the AURORA 1 and AURA-LV trials required a more stringent definition of CRR as patients were required to achieve an additional eGFR component, whereas in other trials, CRR was determined if the proteinuria or UPCR condition was met. In addition, there was some imbalance in patient characteristics across trials, mainly in terms of patient race. Although a scenario analysis was conducted to remove studies with a 100% Asian patient population, this inadvertently led to the removal of all evidence for the comparator of tacrolimus alone. Thus, the only evidence that contributed for tacrolimus was from trials that only contained Asian patients. Further to this, there was a lack of reporting on subgroups; with few trials reporting outcomes for subgroups of interest (i.e. those presented in the AURA-LV and AURORA-1 studies), so networks were unable to be constructed for analysis.

Finally, the differences between the studies included are likely due to largely off-label treatments being used in the treatment of LN so, historically, there has been a lack of high-quality pivotal studies designed and developed for regulatory HTA purposes. A resulting outcome of this is that many of the trials included were relatively small in sample size, mostly with less than 50 patients in the entire study, and therefore contributes to the uncertainty of the estimates from the NMA.

B.2.9.7 Conclusions

In summary, the results of the NMA indicate that treatment of active LN with voclosporin + MMF is superior to current standard of care immunosuppressant treatments for inducing a CRR (OR [redacted] [95% CrI: [redacted]]) and highly likely to be ranked the best treatment in terms of SUCRA. The primary analysis also showed voclosporin + MMF to be similar to current treatments in inducing a PRR; although this is likely due to the large number of patients in AURORA 1 and AURA-LV achieving a CRR over a PRR.

B.2.10 Adverse reactions

B.2.10.1.1***Safety population***

This submission is supported by safety data from a Phase 3 study (AURORA 1), a long-term Phase 3 continuation study (AURORA 2), and the Phase 2 study (AURA-LV). A summary of patients evaluable for safety and toxicity in each study is presented in Table B.2-34.

Table B.2-34. Safety populations

Study	Study treatment, n		
	Voclosporin 23.7mg BID*	Voclosporin 39.5 mg BID*	Placebo*
AURORA 1 (n=356)	178	N/A	178
AURORA 2 (n=216)	116	N/A	100
AURA-LV (n=265)	89	88	88

*In addition to oral corticosteroid and MMF

Abbreviations: BID = twice daily; MMF = mycophenolate mofetil; N/n = number of patients evaluable; N/A = not applicable

Sources: Otsuka 2018, 2020 and 2022[109,113,114]

B.2.10.1.2 *Extent of exposure*

The extent of exposure to voclosporin for each study (AURORA 1, AURORA 2, and AURA-LV) is presented in Table B.2-35.

Table B.2-35. Extent of exposure to voclosporin

	AURORA 1	AURORA 2	AURA-LV	
	Voclosporin (n=178)*	Voclosporin (n=116)*	Voclosporin 23.7mg BID (n=178)*	Voclosporin 39.5 mg BID (n=178)*
Median duration (range) of exposure, days	359.5 (18.0, 381.0)	1084.5 (361.0, 1123.0)	NR	NR
Median (range) dose intensity				
Voclosporin, mg/day	47.1 (5.98, 47.40)	46.4 (14.8, 47.4)	39.5 (0.0, 47.0)	51.7 (1.0, 78.0)
Median (range) overall compliance, %	99.1 (27, 183)	99.1 (68, 116)	99.3 (21, 145)	98.9 (25, 224)

**In addition to oral corticosteroid and MMF

Abbreviations: mg = milligram; MMF = mycophenolate mofetil; n = number of patients evaluable; NR = not reported

Source: Otsuka 2018, 2020 and 2022[109,113,114]

B.2.10.2 AURORA 1 Phase 3 study

B.2.10.2.1 *Adverse events*

Overall and serious AEs occurred at similar frequencies in both treatment groups, and most AEs were of mild or moderate intensity (Table B.2-36).[2] The most frequent type of AE in both groups was infections and infestations, which is expected in this immunocompromised patient population.[109]

Table B.2-36 AURORA 1: summary of AEs

	TEAEs		Treatment-related TEAEs	
	Voclosporin (n=178)	Placebo (n=178)	Voclosporin (n=178)	Placebo (n=178)
AEs, n (%)	162 (91.0)	158 (88.8)	80 (44.9)	45 (25.3)
Serious	37 (20.8)	38 (21.3)	8 (4.5)	8 (4.5)
Leading to discontinuation	20 (11.2)	26 (14.6)	NR	NR
Leading to death	0	3 (1.7)	0	0

Abbreviations: AE = adverse event; n = number of patients; NR = not reported; TEAE = treatment-emergent adverse event

Source: Otsuka 2020[109]

B.2.10.2.2 *Commonly reported adverse events*

Approximately 90% of patients in both arms experienced at least one TEAE (voclosporin arm: 162 [91.0%]; placebo arm: 158 [88.8%]. The most common TEAEs in both groups were Infections and Infestations, reported by 64.6% of patients in the voclosporin arm and 56.7% of patients in the placebo arm (Table B.2-37). The most frequent infections in both arms were upper respiratory tract infections (URTIs) and urinary tract infections (UTIs). The majority of infections were of mild or moderate intensity; severe infections (predominantly pneumonia), were recorded in 10 patients (5.6%) in the voclosporin arm and 7 patients (3.9%) in the placebo arm.[109]

Known side effects of MMF use include diarrhoea, nausea, vomiting and dyspepsia. Gastrointestinal Disorders were the second most common TEAEs. More gastrointestinal events were recorded in patients in the voclosporin arm than the placebo arm (46.6% vs 34.3%), particularly diarrhoea and abdominal pain/upper abdominal pain.[109]

Known adverse effects of CNIs, such as diabetes, kidney dysfunction and hypertension, were also of particular interest in this study.[2,109] New onset diabetes did not occur in any voclosporin-treated patients and in 1 placebo-treated patient,[2] the incidence of investigator-reported serious renal dysfunction was low and similar between treatment groups (voclosporin, 3%; placebo, 2%),[2] and overall, there was no significant difference in mean blood pressure between the treatment groups.[2]

Table B.2-37. AURORA 1: Most common TEAEs (occurring in ≥ 4% of patients in any group)

System organ class (Preferred term)	Voclosporin, n=178	Placebo, n=178
Any TEAE, n (%)	162 (91.0)	158 (88.8)
Infections and infestations	115 (64.6)	101 (56.7)
Upper respiratory tract infection	31 (17.4)	26 (14.6)
Viral upper respiratory tract infection	20 (11.2)	18 (10.1)
Urinary tract infection	19 (10.7)	13 (7.3)
Herpes zoster	14 (7.9)	9 (5.1)
Influenza	12 (6.7)	10 (5.6)
Gastroenteritis	9 (5.1)	10 (5.6)
Pneumonia	9 (5.1)	11 (6.2)
Bronchitis	3 (1.7)	10 (5.6)
Pharyngitis	3 (1.7)	9 (5.1)
Gastrointestinal disorders	83 (46.6)	61 (34.3)
Diarrhoea	34 (19.1)	22 (12.4)
Abdominal pain upper	13 (7.3)	1 (0.6)
Abdominal pain	10 (5.6)	2 (1.1)
Nausea	10 (5.6)	17 (9.6)

Dyspepsia	10 (5.6)	3 (1.7)
Vomiting	5 (2.8)	12 (6.7)
Investigations and infestations	60 (33.7)	31 (17.4)
GFR decreased	43 (24.2)	15 (8.4)
Nervous system disorders	47 (26.4)	27 (15.2)
Headache	30 (16.9)	11 (6.2)
Skin and subcutaneous tissue disorders	42 (23.6)	31 (17.4)
Alopecia	10 (5.6)	5 (2.8)
Musculoskeletal and connective tissue disorders	40 (22.5)	46 (25.8)
Systemic lupus erythematosus	8 (4.5)	10 (5.6)
Arthralgia	8 (4.5)	17 (9.6)
Vascular disorders	38 (21.3)	23 (12.9)
Hypertension	36 (20.2)	15 (8.4)
General disorders and administration site conditions	36 (20.2)	32 (18.0)
Oedema peripheral	11 (6.2)	11 (6.2)
Blood and lymphatic system disorders	35 (19.7)	29 (16.3)
Anaemia	21 (11.8)	10 (5.6)
Neutropenia	8 (4.5)	6 (3.4)
Leukopenia	7 (3.9)	10 (5.6)
Respiratory, thoracic, and mediastinal disorders	26 (14.6)	17 (9.6)
Cough	13 (7.3)	3 (1.7)
Renal and urinary disorders	26 (14.6)	37 (20.8)
Renal impairment	13 (7.3)	6 (3.4)
Lupus nephritis	2 (1.1)	12 (6.7)
Proteinuria	0 (0.0)	8 (4.5)
Metabolism and nutritional disorders	25 (14.0)	37 (20.8)
Hypokalaemia	3 (1.7)	10 (5.6)

Abbreviations: TEAE = treatment-emergent adverse event
Source: Otsuka 2020;[109] Rovin et al., 2021[2]

Treatment-related TEAEs were reported in 44.9% and 25.3% of patients in the voclosporin and placebo arms, respectively. The majority of treatment-related TEAEs were of mild or moderate intensity, with severe events recorded in 12 patients (6.7%) in the voclosporin arm and two patients (1.1%) in the placebo arm. The most common treatment-related TEAE was GFR decreased (18.0% vs 2.8%, respectively).[109] Hemodynamically mediated decreases in GFR are known to be associated with CNIs and so this outcome was not unexpected. Vascular disorders (predominantly hypertension) and renal and urinary disorders were also considered treatment-related in a greater proportion of patients in the voclosporin arm than the placebo arm (hypertension: 7.3% vs 1.7%, respectively; renal and urinary disorders: 4.4% vs 1.7%, respectively).[109]

B.2.10.2.3 ***Serious adverse events***

A similar proportion of patients in each arm experienced serious TEAEs (voclosporin arm: 37 [20.8%]; placebo arm: 38 [21.3%]).[2,109] The most common serious TEAEs (reported in ≥2 patients in any treatment group) are summarised in Table B.2-38.

Table B.2-38. AURORA 1: Most common serious TEAEs (in ≥2 patients in any group)

System organ class (Preferred term)	Voclosporin n=178	Placebo n=178
Any serious TEAE, n (%)	37 (20.8)	38 (21.3)
Infections and infestations	18 (10.1)	20 (11.2)
Pneumonia	7 (3.9)	8 (4.5)
Gastroenteritis	3 (1.7)	0 (0.0)
Urinary tract infection	2 (1.1)	1 (0.6)
Pyelonephritis acute	1 (0.6)	1 (0.6)
Upper respiratory tract infection	1 (0.6)	1 (0.6)
Bronchitis	0 (0.0	3 (1.7)
Renal and urinary disorders	8 (4.5)	8 (4.5)
Acute kidney injury	4 (2.2)	2 (1.1)
Renal impairment	2 (1.1)	1 (0.6)
Lupus nephritis	1 (0.6)	4 (2.2)
Renal failure	1 (0.6)	1 (0.6)
Blood and lymphatic system disorders	4 (2.2)	0 (0.0)
Anaemia	3 (1.7)	0 (0.0)
Vascular disorders	4 (2.2)	3 (1.7)
Hypertension	3 (1.7)	1 (0.6)
Hypertensive crisis	1 (0.6)	2 (1.1)
Musculoskeletal and connective tissue disorders	3 (1.7)	4 (2.2)
Systemic lupus erythematosus	3 (1.7)	3 (1.7)
Investigations	2 (1.1)	1 (0.6)
Glomerular filtration rate decreased	1 (0.6)	1 (0.6)
Respiratory, thoracic, and mediastinal disorders	1 (0.6)	2 (1.1)
Pleural effusion	1 (0.6)	1 (0.6)
General disorders and administration site conditions	1 (0.6)	1 (0.6)
Generalised oedema	1 (0.6)	1 (0.6)

Abbreviations: TEAE = treatment-emergent adverse event
Source: Otsuka 2020[109]

Serious treatment-related TEAEs were observed in the same number of patients in each treatment group (voclosporin arm: 8 [4.5%]; placebo arm: 8 [4.5%]).[109] Serious treatment-related TEAEs are summarised in Table B.2-39.

Table B.2-39. AURORA 1: Serious treatment-related TEAEs

System organ class (Preferred term)	Voclosporin n=178	Placebo n=178
Any serious treatment-related TEAE, n (%)	8 (4.5)	8 (4.5)
Infections and infestations	4 (2.2)	6 (3.4)
Pneumonia	1 (0.6)	2 (1.2)
Upper respiratory tract infection	1 (0.6)	1 (0.6)
Acute sinusitis	0 (0.0)	1 (0.6)
Lung abscess	0 (0.0)	1 (0.6)
Pyeloneprhritis acute	0 (0.0)	1 (0.6)
Bronchitis	1 (0.6)	0 (0.0)
Herpes zoster disseminated	1 (0.6)	0 (0.0)
Pyelonephritis	1 (0.6)	0 (0.0)
Renal and urinary disorders	2 (1.2)	1 (0.6)
Renal impairment	1 (0.6)	1 (0.6)
Acute kidney injury	1 (0.6)	0 (0.0)
Vascular disorders	2 (1.2)	0 (0.0)
Hypertension	2 (1.2)	0 (0.0)
Blood and lymphatic system disorders	1 (0.6)	0 (0.0)
Anaemia	1 (0.6)	0 (0.0)

Neoplasms benign, malignant and unspecified*	1 (0.6)	0 (0.0)
Schwannoma	1 (0.6)	0 (0.0)

*including cysts and polyps
Abbreviations: TEAE = treatment-emergent adverse event
Source: Otsuka 2020[109]

B.2.10.2.4 *Deaths*

Mortality was lower in the voclosporin group of this study (Table B.2-36). Three placebo-treated patients died as a result of TEAEs (pneumonia; pneumonia and septic shock; LN). An additional two patients in the placebo group and one patient in the voclosporin group died due to AEs that started more than 30 days after the last dose of study drug. None of the events leading to death were considered by the investigators to be related to study treatment.[109]

B.2.10.2.5 *Adverse events leading to treatment discontinuation*

A similar proportion of patients in the voclosporin and placebo arm had their study treatment discontinued as a result of a TEAE; 20 patients (11.2%) in the voclosporin arm and 26 patients (14.6%) in the placebo arm had their study drug discontinued as a result of a TEAE, most commonly this was due to Renal and Urinary Disorders.[109] A summary of most common TEAEs leading to treatment discontinuation is presented in Table B.2-40.

Table B.2-40. AURORA 1: Most common TEAEs leading to treatment discontinuation (in ≥2% of patients in any group)

System organ class (Preferred term)	Voclosporin n=178	Placebo n=178
Any TEAE leading to permanent study drug discontinuation, n (%)	20 (11.2)	26 (14.6)
Renal and urinary disorders	8 (4.5)	15 (8.4)
Renal impairment	4 (2.2)	4 (2.2)
Lupus nephritis	2 (1.1)	5 (2.8)
Proteinuria	0 (0.0)	4 (2.2)
Investigations	4 (2.2)	4 (2.2)
Glomerular filtration rate decreased	3 (1.7)	4 (2.2
Infections and infestations	3 (1.7)	4 (2.2)
Pneumonia	1 (0.6)	2 (1.1)
Vascular disorders	2 (1.1)	0 (0.0)
Hypertension	2 (1.1)	0 (0.0)
Musculoskeletal and connective tissue disorders	1 (0.6)	2 (1.1)
Systemic lupus erythematosus	1 (0.6)	2 (1.1)

Abbreviations: TEAE = treatment-emergent adverse event
Source: Otsuka 2020[109]

B.2.10.2.6 ***Adverse events leading to dose interruption or modification***

More patients in the voclosporin arm (80 patients [44.9%]) than the placebo arm (47 patients [26.4%]) had their dose of study drug modified as a result of a TEAE.[109]

As expected for a CNI, the most common TEAE leading to dose modification was GFR decreased (reported for 40 patients [22.5%] in the voclosporin arm and 11 patients [6.2%] in the placebo arm.[109] However, only 3 patients in the voclosporin arm and 4 in the placebo arm had their treatment permanently discontinued as a result of decreased GFR (Table B.2-40). Serious TEAEs resulting in study drug dose modifications were reported for 19 patients (10.7%) in the voclosporin arm and 15 patients (8.4%) in the placebo arm; these were predominantly infections (in 11 voclosporin patients [6.2%] and 10 placebo patients [5.6%]). A summary of most common TEAEs leading to dose modification are summarised in Table B.2-41.

Table B.2-41. AURORA 1: Most common TEAEs leading to dose modification (in ≥2% of patients in any group)

System organ class (Preferred term)	Voclosporin n=178	Placebo n=178
Any TEAE leading to dose modification, n (%)	80 (44.9)	47 (26.4)
Investigations	43 (24.2)	11 (6.2)
Glomerular filtration rate decreased	40 (22.5)	11 (6.2)
Infections and infestations	23 (12.9)	24 (13.5)
Gastroenteritis	5 (2.8)	2 (1.1)
Herpes zoster	5 (2.8)	1 (0.6)
Upper respiratory tract infection	4 (2.2)	3 (1.7)
Pneumonia	4 (2.2)	5 (2.8)
Bacterial diarrhoea	2 (1.1)	1 (0.6)
Viral upper respiratory tract infection	1 (0.6)	2 (1.1)
Bronchitis	0 (0.0)	3 (1.7)
Influenza	0 (0.0)	2 (1.1)
Gastrointestinal disorders	10 (5.6)	7 (3.9)
Diarrhoea	3 (1.7)	2 (1.1)
Nausea	3 (1.7)	1 (0.6)
Gastritis	2 (1.1)	0 (0.0)
Renal and urinary disorders	9 (5.1)	3 (1.7)
Renal impairment	7 (3.9)	1 (0.6)
Blood and lymphatic system disorders	5 (2.8)	1 (0.6)
Leukopenia	2 (1.1)	1 (0.6)
Anaemia	2 (1.1)	0 (0.0)
Neutropenia	2 (1.1)	0 (0.0)
Nervous system disorders	5 (2.8)	1 (0.6)
Headache	2 (1.1)	0 (0.0)
Migraine	2 (1.1)	0 (0.0)
Vascular disorders	4 (2.2)	0 (0.0)
Hypertension	3 (1.7)	0 (0.0)
Musculoskeletal and connective tissue disorders	2 (1.1)	2 (1.1)
Systemic lupus erythematosus	2 (1.1)	2 (1.1)

Abbreviations: TEAE = treatment-emergent adverse event
Source: Otsuka 2020[109]

B.2.10.2.7 *Adverse events of special interest*

Known adverse effects of the CNIs ciclosporin and tacrolimus include kidney dysfunction, hypertension, electrolyte disturbances, tremor, and diabetes. Therefore, these events were of particular interest in this study.[109]

Hypertension occurred at a higher incidence in the voclosporin arm (20.2% vs 8.4% for placebo).[109] Consistent with the protocol guidance to maintain normal blood pressure through the use of antihypertensives, more patients in the voclosporin arm than the placebo arm were prescribed calcium channel blockers (33% vs 21%) and beta blockers (18% vs 11%) during the study; a similar proportion of patients in each arm (32% and 30%, respectively) were treated with diuretics. The majority of hypertension events were mild or moderate. Overall, there was no significant difference in mean blood pressure between the treatment groups.

No voclosporin-treated patients recorded TEAEs of diabetes or hyperglycemia (vs one of each event in the placebo arm).[2] A total of 18 (10%) patients in each treatment group had a confirmed eGFR decrease (prespecified as a > 30% decrease from baseline) at any time throughout the study. Only 2% of patients in each treatment group discontinued study drug due to eGFR decrease, which suggests that the eGFR decreases were largely reversible in both treatment groups.[2] Incidence of investigator-reported serious renal dysfunction was low and similar between treatment groups (voclosporin, 3%; placebo, 2%). Mean systolic blood pressure increased by 3.9 mmHg in the voclosporin group at week 2 and returned to baseline levels by week 8.

B.2.10.2.8 *AURORA 1 safety conclusions*

Voclosporin was well tolerated in the AURORA 1 study with no new or unexpected safety signals observed.[109] Three placebo patients died as a result of TEAEs. An additional two patients in the placebo group and one patient in the voclosporin group died due to AEs which started more than 30 days after the last dose of study drug. A similar proportion of patients in each arm experienced serious TEAEs (20.8% in the voclosporin arm and 21.3% in the placebo arm) or had their study treatment discontinued as a result of a TEAE (11.2% and 14.6%, respectively).

The safety profile of voclosporin was comparable with that of the placebo on a background of MMF and low-dose steroids in this 52-week trial. The AEs observed in both treatment groups were as expected for the population and treatment regimen.[2]

B.2.10.3 AURORA 2 Phase 3 long-term continuation study

B.2.10.3.1 *Adverse events*

The primary objective of the AURORA 2 study was to evaluate the long-term safety and tolerability of continued treatment with voclosporin for up to three years.[113] Throughout the study, voclosporin was well tolerated with no new or unexpected safety signals observed. The overall profile of adverse events seen in the second and third years of treatment was similar to that seen in the first year (AURORA 1), although the frequency of AEs reduced each year. A summary of TEAEs reported during AURORA 2 is in Table B.2-42.[113]

Table B.2-42. Summary of TEAEs reported in AURORA 2

	Voclosporin (n=116)		Placebo (n=100)	
	Patients n (%)	Events n	Patients n (%)	Events n
Any TEAE	[redacted]	[redacted]	[redacted]	[redacted]
Treatment-Related TEAE	[redacted]	[redacted]	[redacted]	[redacted]
Serious TEAE	[redacted]	[redacted]	[redacted]	[redacted]
Treatment-Related Serious TEAE	[redacted]	[redacted]	[redacted]	[redacted]
TEAE Leading to Voclosporin/Placebo Discontinuation	[redacted]	[redacted]	[redacted]	[redacted]
TEAE Leading to Death	[redacted]	[redacted]	[redacted]	[redacted]
Treatment-Related TEAE Leading to Death	[redacted]	[redacted]	[redacted]	[redacted]
Disease-Related TEAE	[redacted]	[redacted]	[redacted]	[redacted]
Disease-Related Serious TEAE	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: TEAE = treatment-emergent adverse event
Source: AURORA 2 CSR[113]

B.2.10.3.2 *Commonly reported adverse events*

The most commonly reported AEs in AURORA 2 were infections and was consistent with findings from the AURORA 1 study.[113] Infections were reported by [redacted]% of patients in the voclosporin arm and [redacted]% of patients in the placebo arm (see Table B.2-43). Given the study population was immunosuppressed, an expected wide variety of infections were reported; with most frequent infections in the voclosporin arm being UTIs, URTIs, and viral URTIs. Coronavirus infections and herpes zoster were more common in the placebo arm.[113] Most infections were of mild or moderate intensity, with only three patients in each study arm recording severe infections (viral URTI, coronavirus and breast abscess in the voclosporin arm; three events of coronavirus in the placebo arm).[113]

Table B.2-43. Summary of TEAEs reported by ≥3% of patients in either arm (AURORA 2)

	Voclosporin n=116		Placebo n=100	
System Organ Class **Preferred term**	**Patients n (%)**	**Events n**	**Patients n (%)**	**Events n**
Any TEAE	[redacted]	[redacted]	[redacted]	[redacted]
Infections and infestations Urinary tract infection Upper respiratory tract infection Viral upper respiratory tract infection Coronavirus infection Gastroenteritis Bronchitis Gingivitis Herpes zoster	[redacted]	[redacted]	[redacted]	[redacted]
Gastrointestinal disorders Diarrhoea Nausea	[redacted]	[redacted]	[redacted]	[redacted]
Musculoskeletal and connective tissue disorders Arthralgia Systemic lupus erythematosus Arthritis Osteonecrosis	[redacted]	[redacted]	[redacted]	[redacted]
Investigations Glomerular filtration rate decreased Neutrophil count decreased	[redacted]	[redacted]	[redacted]	[redacted]
Skin and subcutaneous tissue disorders Alopecia Dermatitis	[redacted]	[redacted]	[redacted]	[redacted]
Renal and urinary disorders Lupus nephritis Proteinuria Renal impairment	[redacted]	[redacted]	[redacted]	[redacted]

	Voclosporin n=116		Placebo n=100	
System Organ Class **Preferred term**	**Patients n (%)**	**Events n**	**Patients n (%)**	**Events n**
Blood and lymphatic system disorders Anaemia Neutropenia	[redacted]	[redacted]	[redacted]	[redacted]
Injury, poisoning and procedural complications Ligament sprain Tooth fracture	[redacted]	[redacted]	[redacted]	[redacted]
General disorders and administration site Oedema peripheral	[redacted]	[redacted]	[redacted]	[redacted]
Nervous system disorders Headache	[redacted]	[redacted]	[redacted]	[redacted]
Metabolism and nutrition disorders	[redacted]	[redacted]	[redacted]	[redacted]
Vascular disorders Hypertension	[redacted]	[redacted]	[redacted]	[redacted]
Respiratory, thoracic and mediastinal disorders Cough	[redacted]	[redacted]	[redacted]	[redacted]
Eye disorders Dry eye	[redacted]	[redacted]	[redacted]	[redacted]
Psychiatric disorders	[redacted]	[redacted]	[redacted]	[redacted]
Reproductive system and breast disorders	[redacted]	[redacted]	[redacted]	[redacted]
Cardiac disorders	[redacted]	[redacted]	[redacted]	[redacted]
Hepatobiliary disorders	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: TEAE = treatment-emergent adverse event
Source: AURORA 2 CSR[113]

B.2.10.3.3 *Serious adverse events*

There were more SAEs in the placebo arm than the voclosporin arm during AURORA 2 ([redacted] patients [[redacted]%] versus [redacted] patients [[redacted]%]).[113] Infections were the most frequently reported SAE, with the predominant cause being coronavirus infections; reported by five patients in the placebo arm ([redacted]%) and two patients ([redacted]%) in the voclosporin arm (see Table B.2-44). [113]

The AURORA 2 investigators considered only three SAEs to be related to study treatment, namely disseminated tuberculosis and hypertension in placebo-treated patients and URTI in a voclosporin-treated patient. [113] More patients in the placebo arm than the voclosporin arm experienced SAEs that were considered to be related to their disease, most commonly worsening LN ([redacted]% versus [redacted]% respectively), SLE flare ([redacted]% versus [redacted]%) and osteonecrosis ([redacted]% versus [redacted]%). One patient in the voclosporin arm recorded an SAE of decreased GFR.[113]

Table B.2-44. Summary of serious TEAEs occurring in >1% of patients in either treatment arm (AURORA 2)

	Voclosporin n=116		Placebo n=100	
System Organ Class Preferred term	**Patients n (%)**	**Events n**	**Patients n (%)**	**Events n**
Any serious TEAE	[redacted]	[redacted]	[redacted]	[redacted]
Infections and infestations Coronavirus infection Urinary tract infection Pneumonia viral Disseminated tuberculosis	[redacted]	[redacted]	[redacted]	[redacted]
Renal and Urinary Disorders Lupus nephritis	[redacted]	[redacted]	[redacted]	[redacted]
Musculoskeletal and connective tissue disorders Systemic lupus erythematosus Osteonecrosis	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: TEAE = treatment-emergent adverse event
Source: AURORA 2 CSR[113]

B.2.10.3.4 *Deaths*

[redacted] patients died during the study, all of whom were in the placebo arm and three of which were due to SARS-CoV-2 coronavirus infection.[113] [redacted] was due to a pulmonary embolism. [redacted] events were treatment-emergent and none of the events were considered by the study investigators to be related to study treatment. In the case of the pulmonary embolism, the investigator considered it to be related to LN disease. [113]

B.2.10.3.5 *Adverse events leading to treatment discontinuation*

More patients in the placebo arm than the voclosporin arm ([redacted] [[redacted]%] versus [redacted] [[redacted]%], respectively) had their study treatment discontinued permanently as a consequence of an AE (see Table B.2-45).[113] The most common AEs leading to treatment discontinuation were worsening LN ([redacted]% versus [redacted]%), decreased GFR ([redacted]% versus [redacted]%), SLE flare ([redacted]% versus [redacted]%) and renal impairment ([redacted]% versus [redacted]%) in the placebo and voclosporin arms,

respectively. Infections causes [redacted] patients in the placebo arm to stop treatment and [redacted] patient in the voclosporin arm.[113]

Table B.2-45. TEAEs leading to discontinuation of voclosporin or placebo

	Voclosporin (n=116)		Placebo (n=100)	
System Organ Class Preferred term	**Patients n (%)**	**Events n**	**Patients n (%)**	**Events n**
Any TEAE Leading to Permanent Voclosporin/Placebo Discontinuation	[redacted]	[redacted]	[redacted]	[redacted]
Renal and urinary disorders	[redacted]	[redacted]	[redacted]	[redacted]
Lupus nephritis	[redacted]	[redacted]	[redacted]	[redacted]
Renal impairment	[redacted]	[redacted]	[redacted]	[redacted]
Nephrotic syndrome	[redacted]	[redacted]	[redacted]	[redacted]
Infections and infestations	[redacted]	[redacted]	[redacted]	[redacted]
Lymph node tuberculosis	[redacted]	[redacted]	[redacted]	[redacted]
Coronavirus infection	[redacted]	[redacted]	[redacted]	[redacted]
Disseminated tuberculosis	[redacted]	[redacted]	[redacted]	[redacted]
Pulmonary tuberculosis	[redacted]	[redacted]	[redacted]	[redacted]
Sinobronchitis	[redacted]	[redacted]	[redacted]	[redacted]
Investigation	[redacted]	[redacted]	[redacted]	[redacted]
Glomerular filtration rate decreased	[redacted]	[redacted]	[redacted]	[redacted]
Electrocardiogram QT prolonged	[redacted]	[redacted]	[redacted]	[redacted]
Musculoskeletal and connective tissue disorders	[redacted]	[redacted]	[redacted]	[redacted]
Systemic lupus erythematosus	[redacted]	[redacted]	[redacted]	[redacted]
Vascular disorders	[redacted]	[redacted]	[redacted]	[redacted]
Hypertension	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: TEAE = treatment-emergent adverse event
Source: AURORA 2 CSR[113]

B.2.10.3.6 *Adverse events leading to dose interruption or modification*

More doses of study drug were modified in the voclosporin arm than the placebo arm (this includes increases, decreases or interruptions) due to an AE.[113] The most frequently reported type of TEAE leading to these dose modifications was infections, reported in [redacted]% of placebo-treated patients and [redacted]% of voclosporin-treated patients (see Table B.2-46).[113]

Specifically in voclosporin-treated patients, the most common AE leading to dose modification was decreases in eGFR ([redacted] patients [[redacted]%] in the voclosporin arm versus 2 patients [[redacted]%] in the placebo arm).[113]

Table B.2-46. TEAEs leading to dose modification of voclosporin or placebo

	Voclosporin (n=116)		Placebo (n=100)	
System Organ Class Preferred Term	**Patients n (%)**	**Events n**	**Patients n (%)**	**Events n**
Any TEAE Leading to Dose Modification	[redacted]	[redacted]	[redacted]	[redacted]
Infections and infestations	[redacted]	[redacted]	[redacted]	[redacted]
Coronavirus infection	[redacted]	[redacted]	[redacted]	[redacted]
Urinary tract infection	[redacted]	[redacted]	[redacted]	[redacted]
Herpes zoster	[redacted]	[redacted]	[redacted]	[redacted]
Upper respiratory tract infection	[redacted]	[redacted]	[redacted]	[redacted]
Investigations	[redacted]	[redacted]	[redacted]	[redacted]
Decreased GFR	[redacted]	[redacted]	[redacted]	[redacted]
Renal and urinary disorders	[redacted]	[redacted]	[redacted]	[redacted]
Renal impairment	[redacted]	[redacted]	[redacted]	[redacted]
Urinary tract infection	[redacted]	[redacted]	[redacted]	[redacted]
Blood and lymphatic system disorders	[redacted]	[redacted]	[redacted]	[redacted]
Gastrointestinal disorders	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: TEAE = treatment-emergent adverse event
Source: AURORA 2 CSR[113]

B.2.10.3.7 *Adverse events of special interest*

As mentioned in Section B.2.10.2.7, AEs of particular interest in the AURORA studies were hypertension, kidney dysfunction, electrolyte disturbances, tremor and diabetes.[113]

Similar to AURORA 1, during AURORA 2 hypertension occurred at a higher incidence in the voclosporin arm ([redacted]%) compared with the placebo arm ([redacted]%).[113] As per the protocol guidance to maintain normal blood pressure through the use of antihypertensives, more patients in the voclosporin arm than the placebo arm were prescribed calcium channel blockers ([redacted]% versus [redacted]%, respectively) during AURORA 2.[113] More patients in the placebo arm than the voclosporin arm were prescribed beta blockers ([redacted]% versus [redacted]%, respectively). More patients in the placebo arm were treated with diuretics than the voclosporin arm ([redacted]% versus [redacted]%, respectively). The majority of hypertension events were mild or moderate – only one case of severe hypertension was reported in a placebo-treated patient.[113]

Various renal disorders were reported during AURORA 2, consistently more frequently in the voclosporin arm compared with the placebo arm. LN was reported in [redacted]% versus [redacted]% (voclosporin versus placebo, respectively); proteinuria was reported in [redacted]% versus [redacted]% (voclosporin versus placebo, respectively); and renal impairments were reported in [redacted]% and [redacted]% of voclosporin- and placebo-treated patients, respectively.[113]

No electrolyte imbalances, tremors or diabetes were reported in AURORA 2.[113]

B.2.10.4 Safety conclusions

Across three years of follow-up, the addition of voclosporin to MMF and low dose corticosteroids demonstrated acceptable safety and tolerability with sustained efficacy. The resulting risk/benefit profile is favourable for the patients with LN.[113]

The profile of AEs reported in AURORA 2 was consistent with AURORA 1; however incidence reduced with each year of continued treatment with voclosporin, further demonstrating tolerability in this population.[113]

In contrast to known safety risks with other CNIs, there was no evidence suggestive of renal toxicity, neurotoxicity or malignancy with long-term treatment with voclosporin.[113]

B.2.10.5 AURA-LV Phase 2 study

B.2.10.5.1 *Adverse events*

TEAEs and treatment-related TEAEs were more common in the voclosporin groups (low-dose and high-dose) compared with placebo (TEAEs: 92.1%, 96.6%, and 85.2%, respectively; treatment-related TEAEs: 50.6%, 62.5%, and 17.0%, respectively).[8] The frequency of patients with TEAEs and treatment-related TEAEs is summarised in Table B.2-47.

Table B.2-47 AURA-LV: summary of AEs

	TEAEs			Treatment-related TEAEs		
	Voclosporin Low-dose* (n=89)	Voclosporin High-dose† (n=88)	Placebo (n=88)	Voclosporin Low-dose* (n=89)	Voclosporin High-dose† (n=88)	Placebo (n=88)
AEs, n (%)	82 (92.1)	85 (96.6)	75 (85.2)	45 (50.6)	55 (62.5)	15 (17.0)
Grade ≥3	-	-	-	-	-	-
Serious	25 (28.1)	22 (25.0)	14 (15.9)	4 (4.5)	7 (8.0)	1 (1.1)
Leading to discontinuation	16 (18.0)	14 (15.9)	9 (10.2)	11 (12.4)	8 (9.1)	2 (2.3)
Leading to death	10 (11.2)	2 (2.3)	1 (1.1)	0 (0.0)	0 (0.0)	0 (0.0)

*23.7 mg BID; †39.5 mg BID

Abbreviations: AE = adverse event; BID = twice daily; n = number of patients; TEAE = treatment-emergent adverse event

Source: Otsuka 2018[114]

B.2.10.5.2 *Commonly reported adverse events*

The most common TEAEs are summarised in Table B.2-48. The incidence of TEAEs was >10% more frequent in both voclosporin groups compared to placebo (primarily attributable to GFR decrease) and the General Disorders and Administration Site Conditions.[114]

Infections and gastrointestinal disorders were the most frequent AEs across the 3 groups; low-dose voclosporin, high-dose voclosporin and placebo (Table B.2-48). The next most frequent AE across all three treatment groups was Gastrointestinal Disorders (placebo: 37.5%; low-dose voclosporin: 42.7%; and high-dose voclosporin: 52.3%). Diarrhoea, nausea, and vomiting were common occurrences in the two voclosporin groups, as was diarrhoea and vomiting in the placebo group. The incidence of Infections and Infestations and Gastrointestinal Disorders appeared to increase in a dose-dependent manner.[114]

Respiratory, Thoracic and Mediastinal Disorders were reported for 31.5% of patients in the low-dose voclosporin group compared to only 9.1% and 12.5% of patients in the placebo and high-dose voclosporin groups, respectively. Renal and Urinary Disorders occurred at a slightly higher frequency in the placebo group (13.6%) compared to both the low-dose (10.1%) and high-dose voclosporin groups (11.4%).[114]

Table B.2-48. AURA-LV: Most common TEAEs (in ≥ 5% of patients in any group)

System organ class (Preferred term)	Voclosporin Low-dose* (n=89)	Voclosporin High-dose† (n=88)	Placebo (n=88)
Any TEAE, n (%)	82 (92.1)	85 (96.6)	75 (85.2)

Glomerular filtration rate decreased	27 (30.3)	27 (30.7)	12 (13.6)
Diarrhoea	16 (18.0)	14 (15.9)	14 (15.9)
Nausea	16 (18.0)	11 (12.5)	7 (8.0)
Cough	16 (18.0)	5 (5.7)	3 (3.4)
Hypertension	15 (16.9)	16 (18.2)	8 (9.1)
Vomiting	15 (16.9)	9 (10.2)	10 (11.4)
Anaemia	13 (14.6)	14 (15.9)	7 (8.0)
Upper respiratory tract infection	12 (13.5)	18 (20.5)	14 (15.9)
Hypokalaemia	12 (13.5)	12 (13.6)	9 (10.2)
Headache	10 (11.2)	15 (17.0)	11 (12.5)
Oedema peripheral	9 (10.1)	7 (8.0)	8 (9.1)
Arthralgia	9 (10.1)	7 (8.0)	7 (8.0)
Urinary tract infection	8 (9.0)	6 (6.8)	5 (5.7)
Back pain	8 (9.0)	5 (5.7)	3 (3.4)
Pneumonia	7 (7.9)	7 (8.0)	2 (2.3)
Decreased appetite	7 (7.9)	5 (5.7)	2 (2.3)
Alopecia	7 (7.9)	4 (4.5)	2 (2.3)
Pyrexia	6 (6.7)	10 (11.4)	1 (1.1)
Dyslipidaemia	6 (6.7)	7 (8.0)	6 (6.8)
Dyspepsia	6 (6.7)	6 (6.8)	4 (4.5)
Gastroenteritis	6 (6.7)	4 (4.5)	2 (2.3)
Renal failure acute	5 (5.6)	8 (9.1)	0 (0.0)
Herpes zoster	5 (5.6)	7 (8.0)	5 (5.7)
Abdominal pain upper	5 (5.6)	7 (8.0)	5 (5.7)
Nasopharyngitis	5 (5.6)	4 (4.5)	3 (3.4)
Muscle spasms	5 (5.6)	2 (2.3)	3 (3.4)
Dizziness	5 (5.6)	2 (2.3)	1 (1.1)
Iron deficiency anaemia	5 (5.6)	0 (0.0)	0 (0.0)
Insomnia	4 (4.5)	5 (5.7)	4 (4.5)
Hypertrichosis	3 (3.4)	7 (8.0)	0 (0.0)
Gingival hypertrophy	3 (3.4)	6 (6.8)	0 (0.0)
Blood pressure increased	3 (3.4)	5 (5.7)	1 (1.1)
Bronchitis	2 (2.2)	6 (6.8)	3 (3.4)
Tachycardia	2 (2.2)	5 (5.7)	1 (1.1)
Oedema	2 (2.2)	5 (5.7)	1 (1.1)
Gastritis	2 (2.2)	4 (4.5)	5 (5.7)
Oral candidiasis	2 (2.2)	5 (5.7)	0 (0.0)
Leukopenia	1 (1.1)	3 (3.4)	6 (6.8)

*23.7 mg BID; †39.5 mg BID
Abbreviations: BID = twice daily; mg = milligram; TEAE = treatment-emergent adverse event
Source: Rovin et al., 2019;[8] Otsuka 2018[114]

B.2.10.5.3 *Serious adverse events*

Serious TEAEs were reported more frequently in patients treated with voclosporin (low-dose: 28.1%; high-dose: 25.0%) compared to placebo (15.9%), but the incidence did not increase with increasing dose of voclosporin (
Table B.2-49).[114]

When low-GDP countries were excluded, the incidence of TEAEs was reduced overall, especially in the two voclosporin groups; the incidence of serious TEAEs (including serious TEAEs were similar among all three treatment groups in the remaining population.[114]

Table B.2-49. AURA-LV: Most common serious TEAEs (in ≥2 patients in any group)

System organ class (Preferred term)	Voclosporin Low-dose* (n=89)	Voclosporin High-dose† (n=88)	Placebo (n=88)
Any serious TEAE	25 (28.1)	22 (25.0)	14 (15.9%)
Infections and infestations	11 (12.4)	12 (13.6)	7 (8.0)
Pneumonia	5 (5.6)	3 (3.4)	2 (2.3)
Urinary tract infection	2 (2.2)	1 (1.1)	0 (0.0)
Gastroenteritis	1 (1.1)	2 (2.3)	1 (1.1)
Sepsis	1 (1.1)	2 (2.3)	0 (0.0)
Renal and urinary disorders	5 (5.6)	1 (1.1)	1 (1.1)
Renal failure acute	4 (4.5)	1 (1.1)	0 (0.0)
Respiratory, thoracic, and mediastinal disorders	5 (5.6)	1 (1.1)	0 (0.0)
Pulmonary embolism	2 (2.2)	1 (1.1)	0 (0.0)
Acute respiratory distress syndrome	2 (2.2)	0 (0.0)	0 (0.0)
Nervous system disorders	4 (4.5)	3 (3.4)	1 (1.1)
Posterior reversible encephalopathy syndrome	2 (2.2)	2 (2.3)	0 (0.0)
Gastrointestinal disorders	2 (2.2)	2 (2.3)	1 (1.1)
Vascular disorders	2 (2.2)	2 (2.3)	0 (0.0)
Hypertension	2 (2.2)	2 (2.3)	0 (0.0)
Cardiac disorders	2 (2.2)	1 (1.1)	2 (2.3)
Musculoskeletal and connective tissue disorders	1 (1.1)	2 (2.3)	2 (2.3)
Systemic lupus erythematosus	1 (1.1)	2 (2.3)	2 (2.3)
Blood and lymphatic system disorders	1 (1.1)	0 (0.0)	2 (2.3)

*23.7 mg BID; †39.5 mg BID
Abbreviations: TEAE = treatment-emergent adverse event
Source: Rovin et al., 2019;[8] Otsuka 2018[114]

In contrast to serious TEAEs, a dose-dependent increase was observed in the incidence of serious treatment-related TEAEs by the Investigator, although the overall incidence was low even in the high-dose voclosporin group (i.e., placebo: 1.1%; low-dose voclosporin: 4.5%; high-dose voclosporin: 8.0%) (Table B.2-50).[114]

Table B.2-50. AURA-LV: Serious treatment-related TEAEs

System organ class (Preferred term)	Voclosporin Low-dose* (n=89)	Voclosporin High-dose† (n=88)	Placebo (n=88)
Any serious treatment-related TEAE	4 (4.5)	7 (8.0)	1 (1.1)
Hypertension	1 (1.1)	2 (2.3)	0 (0.0)
Pneumonia	1 (1.1)	0 (0.0)	0 (0.0)
Sepsis	1 (1.1)	0 (0.0)	0 (0.0)

Convulsion	1 (1.1)	0 (0.0)	0 (0.0)
Renal failure acute	1 (1.1)	0 (0.0)	0 (0.0)
Bacterial pyelonephritis	0 (0.0)	1 (1.1)	0 (0.0)
Bacterial sepsis	0 (0.0)	1 (1.1)	0 (0.0)
Body tinea	0 (0.0)	1 (1.1)	0 (0.0)
Bronchitis	0 (0.0)	1 (1.1)	0 (0.0)
Cellulitis	0 (0.0)	1 (1.1)	0 (0.0)
Hypersensitivity	0 (0.0)	1 (1.1)	0 (0.0)
Tuberculosis of genitourinary system	0 (0.0)	1 (1.1)	0 (0.0)
Bronchiolitis	0 (0.0)	0 (0.0)	1 (1.1)
Congestive cardiomyopathy	0 (0.0)	0 (0.0)	1 (1.1)

*23.7 mg BID; †39.5 mg BID
Abbreviations: TEAE = treatment-emergent adverse event
Source: Rovin et al., 2019;[8] Otsuka 2018[114]

B.2.10.5.4 *Deaths*

A higher proportion of patients in the low-dose voclosporin group (n=10, 11.2%) died during the study compared with the high-dose voclosporin (n=2, 2.3%) or placebo groups (n=1, 1.1%).[8] None of the 13 deaths were considered related to study drug by the investigators.[114]

Most deaths (9 of 13) occurred in the first 2 months of study enrolment, and more than half of deaths (7 of 13) occurred at 2 study sites. Two-fold more patients were randomised to low-dose voclosporin than placebo at these 2 sites, which may possibly be relevant to the imbalance of deaths. Analysis of the patients who died confirmed that these patients had more severe LN disease at baseline as evidenced by higher mean UPCR and lower mean eGFR compared to the rest of the patients.[114]

B.2.10.5.5 *Adverse events leading to treatment discontinuation*

TEAEs leading to study drug discontinuation were more frequent in the two voclosporin groups but did not show a dose-dependent trend. TEAEs leading to study drug discontinuation were reported for 10.2%, 18.0%, and 15.9% of patients in the placebo, low-dose voclosporin, and high-dose voclosporin groups, respectively (Table B.2-51). In both voclosporin groups, the most frequently occurring TEAEs leading to discontinuation were in the GFR decrease and Infections and Infestations. Permanent discontinuations of study drug due to TEAEs of GFR decrease were reported for 7.9% and 5.7% of patients in the low-dose and high-dose voclosporin groups, respectively, compared to 1.1% in the placebo group.[114] Treatment-related TEAEs leading to study drug discontinuation were reported for 2.3% of patients in the placebo group compared to 12.4% and 9.1% of patients in the low-dose and high-dose voclosporin groups, respectively.[114]

When patients from low-GDP countries were excluded, the dose-response was normalized in the two voclosporin groups and the incidence of TEAEs leading to study drug discontinuation was similar between the placebo (13.3%) and low-dose voclosporin (10.6%) groups.[114]

Furthermore, when patients who died were excluded, a dose-dependent trend was observed for TEAEs leading to study drug discontinuation, reported for 9.2%, 13.9%, and 15.1% of patients in the placebo, low-dose voclosporin and high-dose voclosporin groups, respectively.[114]

Table B.2-51. AURA-LV: Most common TEAEs leading to treatment discontinuation (in ≥2% of patients in any group)

System organ class (Preferred term)	Voclosporin Low-dose* (n=89)	Voclosporin High-dose† (n=88)	Placebo (n=88)
Any TEAE leading to permanent study drug discontinuation, n (%)	16 (18.0)	14 (15.9)	9 (10.2)
Investigations	7 (7.9)	5 (5.7)	2 (2.3)
Glomerular filtration rate decreased	7 (7.9)	5 (5.7)	1 (1.1)
Infections and Infestations	3 (3.4)	4 (4.5)	1 (1.1)
Pneumonia	2 (2.2)	0 (0.0)	0 (0.0)
Nervous System Disorders	3 (3.4)	0 (0.0)	1 (1.1)
Renal and Urinary Disorders	2 (2.2)	0 (0.0)	3 (3.4)
Musculoskeletal and Connective Tissue Disorders	1 (1.1)	1 (1.1)	2 (2.3)
Gastrointestinal Disorders	0 (0.0)	2 (2.3)	2 (2.3)

*23.7 mg BID; †39.5 mg BID
Abbreviations: TEAE = treatment-emergent adverse event
Source: Otsuka 2018[114]

B.2.10.5.6 *Adverse events leading to dose interruption or modification*

TEAEs leading to dose modification were reported in 53.9% of patients in the low-dose voclosporin group, 58.0% of patients in the high-dose voclosporin group, and 31.8% of patients in the placebo group.[114] As expected for a CNI, the most common TEAE leading to dose modification was GFR decrease (reported for 29.2% and 31.8% of patients in the low-dose and high-dose voclosporin groups, respectively, compared to 9.1% in the placebo group).[114] A summary of TEAEs leading to dose modification in the AURA-LV study is presented in Table B.2-52.

Table B.2-52. AURA-LV: TEAEs leading to dose modification

System organ class (Preferred term)	Voclosporin Low-dose* (n=89)	Voclosporin High-dose† (n=88)	Placebo (n=88)
Any TEAE leading to dose modification, n (%)	48 (53.9)	51 (58.0)	28 (31.8)
Investigations	26 (29.2)	28 (31.8)	9 (10.2)
Glomerular filtration rate decreased	26 (29.2)	25 (28.4)	8 (9.1)
Creatinine renal clearance decreased	0 (0.0)	1 (1.1)	0 (0.0)
Blood creatinine increased	0 (0.0)	1 (1.1)	0 (0.0)
Blood potassium increased	0 (0.0)	1 (1.1)	0 (0.0)
Electrocardiogram QT prolonged	0 (0.0)	1 (1.1)	0 (0.0)
Gamma-glutamyltrasnferase increased	0 (0.0)	1 (1.1)	0 (0.0)
Urine protein/creatinine ratio increased	0 (0.0)	0 (0.0)	1 (1.1)
Infections and infestations	15 (16.9)	15 (17.0)	9 (10.2)

Upper respiratory tract infection	2 (2.2)	3 (3.4)	0 (0.0)
Herpes zoster	3 (3.4)	4 (4.5)	2 (2.3)
Gastroenteritis	2 (2.2)	2 (2.3)	2 (2.3)
Sepsis	0 (0.0)	1 (1.1)	0 (0.0)
Pneumonia	3 (3.4)	1 (1.1)	1 (1.1)
Cellulitis	1 (1.1)	1 (1.1)	1 (1.1)
Gingivitis	1 (1.1)	1 (1.1)	0 (0.0)
Urinary tract infection	1 (1.1)	1 (1.1)	0 (0.0)
Viral infection	0 (0.0)	1 (1.1)	1 (1.1)
Bacterial pyelonephritis	0 (0.0)	1 (1.1)	0 (0.0)
Bacterial sepsis	0 (0.0)	1 (1.1)	0 (0.0)
Body tinea	0 (0.0)	1 (1.1)	0 (0.0)
Tuberculosis of genitourinary system	0 (0.0)	1 (1.1)	0 (0.0)
Pulmonary tuberculosis	3 (3.4)	0 (0.0)	0 (0.0)
Dengue fever	1 (1.1)	0 (0.0)	0 (0.0)
Furuncle	1 (1.1)	0 (0.0)	0 (0.0)
Herpes simplex	1 (1.1)	0 (0.0)	0 (0.0)
Herpes virus infection	1 (1.1)	0 (0.0)	0 (0.0)
Infectious pleural effusion	1 (1.1)	0 (0.0)	0 (0.0)
Nasopharyngitis	1 (1.1)	0 (0.0)	0 (0.0)
Subcutaneous abscess	1 (1.1)	0 (0.0)	0 (0.0)
Bronchiolitis	0 (0.0)	0 (0.0)	1 (1.1)
Carbuncle	0 (0.0)	0 (0.0)	1 (1.1)
Escherichia urinary tract infection	0 (0.0)	0 (0.0)	1 (1.1)
Varicella	0 (0.0)	0 (0.0)	1 (1.1)
Gastrointestinal disorders	5 (5.6)	9 (10.2)	4 (4.5)
Gastritis	1 (1.1)	2 (2.3)	2 (2.3)
Diarrhoea	0 (0.0)	2 (2.3)	1 (1.1)
Gingival hypertrophy	0 (0.0)	2 (2.3)	0 (0.0)
Vomiting	1 (1.1)	1 (1.1)	0 (0.0)
Gastritis erosive	0 (0.0)	1 (1.1)	0 (0.0)
Gastrooesophageal reflux disease	0 (0.0)	1 (1.1)	0 (0.0)
Gingival swelling	0 (0.0)	1 (1.1)	0 (0.0)
Abdominal pain upper	2 (2.2)	0 (0.0)	0 (0.0)
Peptic ulcer	1 (1.1)	0 (0.0)	0 (0.0)
Duodenal ulcer	1 (1.1)	0 (0.0)	0 (0.0)
Dyspepsia	1 (1.1)	0 (0.0)	0 (0.0)
Gastric disorder	1 (1.1)	0 (0.0)	0 (0.0)
Gastrointestinal haemorrhage	1 (1.1)	0 (0.0)	0 (0.0)
Nausea	1 (1.1)	0 (0.0)	0 (0.0)
Constipation	0 (0.0)	0 (0.0)	1 (1.1)
Nervous system disorders	4 (4.5)	5 (5.7)	2 (2.3)
Headache	1 (1.1)	3 (3.4)	0 (0.0)
Posterior reversible encephalopathy syndrome	1 (1.1)	1 (1.1)	0 (0.0)
Post herpetic neuralgia	0 (0.0)	1 (1.1)	1 (1.1)
Migraine	0 (0.0)	1 (1.1)	0 (0.0)
Cerebral haemorrhage	1 (1.1)	0 (0.0)	0 (0.0)
Convulsion	1 (1.1)	0 (0.0)	0 (0.0)
Hypoaesthesia	1 (1.1)	0 (0.0)	0 (0.0)
Cerebrovascular accident	0 (0.0)	0 (0.0)	1 (1.1)
Vascular disorders	3 (3.4)	4 (4.5)	1 (1.1)
Hypertension	3 (3.4)	2 (2.3)	0 (0.0)
Flushing	0 (0.0)	1 (1.1)	0 (0.0)
Malignant hypertension	0 (0.0)	1 (1.1)	0 (0.0)
Hypertensive crisis	0 (0.0)	0 (0.0)	1 (1.1)
Cardiac disorders	1 (1.1)	2 (2.3)	1 (1.1)
Pericardial effusion	0 (0.0)	1 (1.1)	0 (0.0)
Palpitations	0 (0.0)	1 (1.1)	0 (0.0)

Pericarditis	0 (0.0)	1 (1.1)	0 (0.0)
Wolff-Parkinson-White syndrome	1 (1.1)	0 (0.0)	0 (0.0)
Acute coronary syndrome	0 (0.0)	0 (0.0)	1 (1.1)
Renal and urinary disorders	4 (4.5)	3 (3.4)	4 (4.5)
Renal failure acute	2 (2.2)	3 (3.4)	0 (0.0)
Renal impairment	2 (2.2)	0 (0.0)	1 (1.1)
Oliguria	1 (1.1)	0 (0.0)	0 (0.0)
Lupus nephritis	0 (0.0)	0 (0.0)	1 (1.1)
Proteinuria	0 (0.0)	0 (0.0)	1 (1.1)
Strangury	0 (0.0)	0 (0.0)	1 (1.1)
Musculoskeletal and connective tissue disorders	1 (1.1)	2 (2.3)	2 (2.3)
Systemic lupus erythematosus	0 (0.0)	1 (1.1)	1 (1.1)
Myalgia	0 (0.0)	1 (1.1)	0 (0.0)
Back pain	1 (1.1)	0 (0.0)	1 (1.1)
Metabolism and nutrition disorders	1 (1.1)	2 (2.3)	1 (1.1)
Hypokalaemia	0 (0.0)	1 (1.1)	1 (1.1)
Metabolic acidosis	0 (0.0)	1 (1.1)	0 (0.0)
Diabetes mellitus	1 (1.1)	0 (0.0)	0 (0.0)
General disorders and administration site conditions	2 (2.2)	1 (1.1)	0 (0.0)
Pyrexia	0 (0.0)	1 (1.1)	0 (0.0)
Fatigue	1 (1.1)	0 (0.0)	0 (0.0)
Generalised oedema	1 (1.1)	0 (0.0)	0 (0.0)
Blood and lymphatic system disorders	0 (0.0)	1 (1.1)	1 (1.1)
Thrombocytopenia	0 (0.0)	1 (1.1)	0 (0.0)
Leukopenia	0 (0.0)	0 (0.0)	1 (1.1)
Skin and subcutaneous tissue disorders	0 (0.0)	1 (1.1)	1 (1.1)
Hypertrichosis	0 (0.0)	1 (1.1)	0 (0.0)
Rash generalised	0 (0.0)	0 (0.0)	1 (1.1)
Immune system disorders	0 (0.0)	1 (1.1)	0 (0.0)
Hypersensitivity	0 (0.0)	1 (1.1)	0 (0.0)
Respiratory, thoracic, and mediastinal disorders	4 (4.5)	0 (0.0)	0 (0.0)
Acute respiratory distress syndrome	1 (1.1)	0 (0.0)	0 (0.0)
Cough	1 (1.1)	0 (0.0)	0 (0.0)
Dyspnoea	1 (1.1)	0 (0.0)	0 (0.0)
Productive cough	1 (1.1)	0 (0.0)	0 (0.0)
Pulmonary alveolar haemorrhage	1 (1.1)	0 (0.0)	0 (0.0)
Injury, poisoning and procedural complications	1 (1.1)	0 (0.0)	0 (0.0)
Procedural headache	1 (1.1)	0 (0.0)	0 (0.0)

*23.7 mg BID; †39.5 mg BID
Abbreviations: TEAE = treatment-emergent adverse event
Source: Otsuka 2018[114]

B.2.10.5.7 ***Adverse events of special interest***

Known adverse effects of CNIs, such as diabetes, kidney dysfunction, hyperkalaemia, and increased blood pressure, were evaluated in this study.[8] Diabetes was reported in 1 patient each in the low-dose voclosporin and placebo treatment groups. Eight total patients withdrew from the study due to a >30% decrease of eGFR from baseline (placebo, n=2; low-dose voclosporin, n=3; high-dose voclosporin, n=3). No patient withdrew from the study due to hyperkalaemia, and mean blood pressure decreased from baseline and remained lower than baseline for the duration of the study for all treatment groups.

B.2.10.6 Safety conclusions

When compared with the tolerability profile of voclosporin from studies in other therapeutic areas, no new or unexpected safety signals were observed with the use of voclosporin in LN; voclosporin was generally well-tolerated over a 48-week period.[114] The overall safety profile was consistent with the expectations for the class of drug, the patient population, and concomitant therapies. Treatment compliance was high in all groups (≥97.6%), including placebo.

As would be expected in a population with active LN treated for 48 weeks, most patients reported at least one TEAE during the study (i.e., 85.2%, 92.1%, and 96.6%) in the placebo, low-dose voclosporin, and high-dose voclosporin groups, respectively).[114] The majority of TEAEs in all three groups were mild or moderate in severity. Severe TEAEs were more frequent in the low-dose voclosporin (23.6%) group compared to either the placebo (15.9%) or high-dose voclosporin (13.6%) group. As expected for patients with highly disordered immune systems treated with immunosuppressants, the highest incidence of TEAEs in all three treatment groups was Infections and Infestations, reported for 53.4%, 58.4%, and 65.9% of patients in the placebo, low-dose voclosporin, and high-dose voclosporin groups, respectively.

The overall incidence of treatment-related TEAEs increased with increasing dose of voclosporin.[114] The incidence of treatment-related TEAEs and serious TEAEs were higher in both the low-dose and high-dose voclosporin treatment groups compared to the placebo group. TEAEs leading to study drug discontinuation were reported more frequently for voclosporin-treated patients. The majority of TEAEs and serious TEAEs occurred in the first half of the study. In general, the reduction in TEAEs over time may be reflective of improvement/stabilisation in disease status with treatment, reductions in steroid dosing, and early withdrawals of the most severe patients.[114]

The frequency of deaths was higher in the low-dose voclosporin treatment group (10 patients(11.2%) compared to either the high-dose voclosporin (2 patients (2.3%)) or placebo (1 (1.1%) patient) treatment group.[114] Analysis of the patients who died confirmed that these patients had more severe LN disease. Three additional deaths in the placebo group were reported after study completion. When these deaths are included, the overall incidence of deaths is more balanced, with deaths reported for 4 (4.5%) patients in the placebo group compared to an overall death rate of 12 (6.7%) patients in the voclosporin-treated patients.

B.2.11 Ongoing studies

Other than the completed studies, AURORA 1, AURORA 2, and AURA-LV; there are currently no ongoing studies of voclosporin for the treatment of LN.

B.2.12 Interpretation of clinical effectiveness and safety evidence

B.2.12.1 Findings from the clinical evidence

Three double-blind, randomised clinical studies, AURORA 1, AURORA 2, and AURA-LV, support the efficacy and safety of voclosporin, as an effective new treatment option for patients with LN.[109,112,114]

The AURORA 1 Phase 3 study met its primary endpoint, demonstrating treatment with voclosporin resulted in a clinically meaningful and statistically significant higher CRR rate

compared to placebo at Week 52 (40.8% vs 22.5%; OR 2.65; p<0.0001)[109]. In addition, patients in the voclosporin arm experienced a significant improvement in CRR at Week 24 (32% vs 20%; OR 2.23; p=0.002), PRR at Week 24 (70% vs 50%; OR 2.43; p<0.001) and Week 52 (70% vs 52%; OR 2.26; p<0.001); as well as a significant reduction in median time to UPCR ≤ 0.5 mg/mg (169 days vs 372 days; HR 2.02; p<0.001) and median time to 50% reduction in UPCR (29 days vs 63 days; HR 2.05; p<0.001).[2] A significant reduction in UPCR is particularly important, as the level of proteinuria is a well-established prognostic factor for renal flares, ESRD, and death in patients with LN.[121] Furthermore, the efficacy of voclosporin in LN was demonstrated without the need for high-dose corticosteroids, that are otherwise associated with side-effects and morbidity.[2] Voclosporin was well tolerated with no new or unexpected safety signals. TEAE incidence was similar in the voclosporin and placebo arms (91% vs 89%, respectively), while treatment-related TEAEs were reported in 45% and 25% of patients, respectively. In the voclosporin arm, treatment-related TEAEs were mostly mild or moderate arm (85% of all observed treatment-related TEAEs) and the most common treatment-related TEAE, GFR decreased, (18% of patients) was effectively managed through dose modification.[109]

Long-term safety and efficacy of voclosporin has also been demonstrated in the Phase 3 follow-up study, AURORA 2. The primary objective of this study was to assess the long-term safety and tolerability of voclosporin compared with placebo for an additional 24 months following completion of treatment in the AURORA 1 study.[113] The profile of AEs reported in AURORA 2 was consistent with AURORA 1. In the voclosporin and placebo arms, TEAEs were reported in 86% and 80% of patients, respectively, and treatment-related TEAEs were reported in 24% vs 21% of patients, respectively. Furthermore, voclosporin did not lead to an increased incidence of serious TEAEs (18% vs 23%) or treatment-related serious TEAEs (1% vs 2%) relative to placebo.[113] In contrast to known safety risks with other CNIs, there was no evidence suggestive of diabetes, renal toxicity, neurotoxicity or malignancy with long-term treatment with voclosporin.[113] Long-term efficacy was assessed as a secondary objective in AURORA 2. Over three years, voclosporin demonstrated significantly greater renal response rates (complete and partial) and fewer renal/extra-renal flares compared with placebo. Complete renal responses were significantly higher in the voclosporin arm up to Month 30 (59.5% vs 42.0%; OR 2.24 [95% CI 1.28–3.92]; p=0.005). In addition to this, voclosporin demonstrated significantly greater partial renal responses than placebo up to and including month 30 (73.3% vs 61.0%; OR 1.86 [95% CI 1.03–3.34]; p=0.040). Among a greater proportion of patients in the voclosporin arm achieving renal responses, a slightly lower proportion of patients experienced a renal flare in the voclosporin arm compared to the placebo arm (23.8% vs 26.0%, respectively). Extra-renal flares were observed in 14.0% of patients in the placebo arm and 18.1% of patients in the voclosporin arm (OR 1.33 [95% CI 0.63–2.81; p=0.448) during the three year study period. Other efficacy outcomes showed voclosporin to be favourable compared with placebo. Changes in UPCR seen at Month 12 at the end of AURORA 1 were sustained until Month 36 in patients receiving voclosporin. Urine protein was significantly decreased in the voclosporin arm compared with the placebo arm, serum creatinine levels showed a small increase in voclosporin-treated patients but was not cause for concern. Small but stable increases of eGFR were observed in the voclosporin arm throughout the 36 months of treatment.

The results of AURORA 1 are further supported by the AURA-LV Phase 2 study, which demonstrated the superiority of low-dose (23.7 mg BID) voclosporin relative to placebo for

achievement of CRR at Week 24 (32.6% vs 19.3%; OR 2.03; p=0.045), and indicated that voclosporin was generally well-tolerated over a 48-week period.[114]

In conclusion, clinical evidence from AURORA 1, AURORA 2, and AURA-LV demonstrates that voclosporin results in a clinically meaningful and statistically significant higher renal response rate and shorter time to renal response compared to placebo (each in combination with MMF and low-dose corticosteroids).[2,8] The AURORA 2 study demonstrated that voclosporin efficacy observed in AURORA 1 were sustained with treatment for 36 months. Early reduction in proteinuria (a component of response) is associated with improved long-term outcomes including reduced risk of disease flares, ESRD, and death.[2,27] For this reason, voclosporin represents an important new treatment option for a potentially life-threatening disease with substantial risk of advancing to CKD (including ESRD).

B.2.12.1.1 *Strengths and limitations of the clinical evidence base*

Overall, clinical data for voclosporin provide an appropriate evidence base for assessment of its clinical and cost-effectiveness effectiveness for the treatment of LN.

The strengths of the clinical evidence base are:

- AURORA 1 is a robust, multicentre Phase 3 RCT which randomised 357 patients with active LN, including 97 patients from 40 sites across Europe[2,109]
- The efficacy and safety of voclosporin was assessed in combination with, and in comparison to, standard of care treatment (MMF and corticosteroids) plus placebo[2]
- Long-term data is provided by AURORA 2, a robust, multicentre phase 3 long-term continuation study designed to evaluate outcomes in patients with LN after 36 months of treatment (12 months in AURORA 1, and an additional 24 months in AURORA 2)
- The primary and secondary efficacy endpoints of AURORA 1, AURORA 2, and AURA-LV (e.g. CRR, PRR, time to 50% reduction in UPCR, disease activity) are relevant to routine clinical practice
    - Primary efficacy outcomes were met in AURORA 1 (CRR at Week 52) and AURA-LV (CRR at Week 24) and sensitivity analyses of the primary outcome in AURORA 1 were consistent with the primary analysis, demonstrating robustness of the clinical benefit of voclosporin[109]
    - Secondary efficacy outcomes in AURORA 2 demonstrated sustained efficacy of voclosporin over placebo, including significantly greater CRR at months 18, 24, and 30
    - AURORA 1 included assessment of HRQoL - information was collected using the SF-36 and the LupusPRO (v1.7) HRQoL assessment, and long-term HRQoL data collection continued into the AURORA 2 study (SF-36 only)
    - Between all three studies, all outcomes specified in the decision problem (Section B.1) were assessed apart from mortality and the incidence of ESRD

The limitations of the clinical evidence base are:

- AURORA 1 had a duration of only 52 weeks, despite the chronic nature of LN. To circumvent this limitation, AURORA 2 provided long-term efficacy and safety data for an additional 24 months of treatment.[2] Other limitations of AURORA 1 included:
    - AURORA 1 did not assess LN activity and chronicity indices. Although most patients had biopsies within 6 months of screening, activity and chronicity analyses would require all patients to have a biopsy just prior to enrolment[2]

    - AURORA 1 did not collect information on dose of MMF before enrolment, nor did it differentiate response to treatment in patients with new onset compared with relapsed lupus nephritis, or evaluate extra-renal systemic lupus erythematosus activity
- AURORA 2 was powered to assess the long-term safety and tolerability of voclosporin compared with placebo for an additional 24 months following completion of treatment in the AURORA 1 study. Therefore, AURORA 2 was not powered to demonstrate a difference in efficacy between treatment arms
- In accordance with the fluctuating nature of LN, there were discrepancies between CEC members in the adjudication of adequate response and the occurrence/severity of flares in AURORA 2, demonstrating inherent variability between clinicians in assessing patient response. This may have led to inconsistencies in treatment decision-making. For example, some physicians may respond to an apparent flare by altering treatment or increasing steroids sooner, while others may have continued to monitor the patient to see if symptoms are just part of the natural instability of the disease)
- AURA-LV kidney biopsies were read locally and not by a central nephropathologist.

B.3. Cost effectiveness

B.3.1 Published cost-effectiveness studies

A SLR and targeted literature review was conducted to identify economic evaluations of voclosporin and other comparators for the treatment of adult patients with LN.

There are not currently any published NICE technology appraisals for the treatment of patients with LN. However, the SLR identified four published cost-effectiveness models[122-125] and a cumulative cost analysis[17] for LN, which were supplemented by an additional cost-effectiveness model[126] and two other costing models identified within targeted literature searches.[127,128] An overview of the cost-effectiveness models is provided in Table B.3-1, with further details of the economic SLR, targeted searches, and identified economic evaluations detailed in Appendix G. Notably, none of the identified cost-effectiveness models were from a UK NICE reference case perspective.

Markov and mixed decision tree-Markov models were most commonly employed over a lifetime horizon, with largely consistent health states that included AD, CR, PR, ESRD, kidney-transplant, post-kidney transplant and death. Response definitions varied, with one model using eGFR to determine response, and all other models included at least serum creatine levels and UPCR.[18,122-124,126] Prior models did not model LN through LN class progression for two key reasons. First, data on progression is limited due to biopsies not being repeated to confirm LN class. Second, the natural history of LN is not 'sequential' through the LN classes; specifically LN class 5 patients have a different pathophysiology to class 3/4 LN.[18] A number of costing models did focus on modelling the LN patient using eGFR levels only as opposed to combined UPCR and eGFR levels as only registry eGFR data was available to estimate these costs over time. However, eGFR levels can vary over time for multiple reasons which may or may not be related to CR to treatment. Based on clinical guidelines CR is confirmed using multiple biomarkers such as kidney function (confirmed eGFR measures), proteinuria and UPCR level; as was the case in the AURORA trial.

A lifetime horizon was the commonly assumed time horizon. The models commonly adopted an initial six-month cycle followed by a long-term one-year cycle length. Treatment stages such as induction, maintenance and post-maintenance were often modelled; although the time a patient spent on treatment within each of these stages varied. All models included health state specific utilities, while some models included utility increments or decrements to account for differences between treatments.

Table B.3-1. Summary of published cost-effectiveness studies assessing initial and maintenance treatments for LN

Study (year)	Summary of model	Population (age [yrs])	Treatment	QALYs	Costs	ICER
Wilson et al., (2007)[125]	Short-term patient-level simulation model of 6 months (cycle length: 3 months)	Patients with active LN receiving initial treatment with CYC or MMF (mean: NR)	Initial MMF	0.3 QALYs	£1,388	Initial MMF dominant vs CYC
			Initial CYC	0.2 QALYs	£2,994	
Mohara et al., (2014)[124]	Lifetime Markov (cycle length: 6 months in first year; then 12 months)	Patients with LN and "active, severe disease" (mean: 40)	Initial CYC/maint. CYC	9.4 QALYs	3,979,910 baht	Reference
			Initial CYC/maint. AZA	9.7 QALYs	3,966,611 baht	-49,167 baht/QALY gained
			Initial CYC/maint. MMF	9.7 QALYs	4,118,461 baht	+618,014 baht/QALY gained
			Initial MMF/maint. MMF+AZA	9.7QALYs	4,072,513 baht	+349,029 baht/QALY gained
Nee et al., (2015)[123]	Mixed: short-term Markov model of 3 years (cycle length: 6 months) followed by lifetime Markov model (cycle length: 12 months)	Patients with class III/IV LN who responded to initial therapy (range: 20–40)	Maint. AZA	14.2 QALYs	$478,333	Reference
			Maint. MMF	15.1 QALYs	$484,310	+$6,454/QALY gained
Kim et al., (2019)[122]	Mixed: decision tree for induction phase, followed by Markov model for maintenance (cycle length: 3 months)*	Patients with class III/IV LN, ± class V (mean: 18)	Initial TAC/maint. TAC	11.9 QALYs	CN¥180,448	Initial TAC/maint. TAC dominant vs all other comparators
			Initial TAC/maint. AZA	11.4 QALYs	CN¥272,007	
			Initial TAC/maint. MMF	11.5 QALYs	CN¥704,959	
			Initial CYC/maint. TAC	11.9 QALYs	CN¥292,085	
			Initial CYC/maint. AZA	11.3 QALYs	CN¥291,206	
			Initial CYC/maint. MMF	11.5 QALYs	CN¥721,084	
			Initial MMF/maint. TAC	11.8 QALYs	CN¥298,252	
			Initial MMF/maint. AZA	11.3 QALYs	CN¥297,568	
			Initial MMF/maint. MMF	11.4 QALYS	CN¥728,080	
ICER report (2021)[126]	Mixed: short-term Markov model of 3 years and lifetime PSM	SLE patients with class III, IV, or V LN (mean: 35)	Initial placebo + MMF	11.7 QALYs	$784,416	Reference
			Initial VCS + MMF	12.6 QALYs	$928,486	$149,260/QALY gained

*3-month cycle length based on clinical feedback to reflect how often treatment was evaluated

Abbreviations: CN¥ = Chinese Yuan; CYC = cyclophosphamide; ICER = incremental cost-effectiveness ratio; maint. = maintenance; MMF = mycophenolate mofetil; NR = not reported; PSM = partitioned survival model; QALYs = quality-adjusted life years; VCS = voclosporin; yrs = years

B.3.2 Economic analysis

The LN model structures identified in the literature searches were discussed with external key opinion leaders (KOLs), who concluded that the health states (AD, CR, PR, ESRD and Death) included in previous economic models were relevant for modelling LN; with CR and PR response definitions from the AURORA trial considered suitable for assessing response over time in the model.

However, a key limitation of previous economic models for LN is that they did not fully capture the LN disease pathway. Specifically, the cumulative impact of renal flares over time were not captured by modelling LN progression through the advanced CKD stages prior to reaching ESRD. KOL expert feedback indicated that it would be relevant to model advanced CKD stages; as when modelling an LN patient's kidney deterioration there are different costs, outcomes and mortality rates associated with the early (CKD 1-3a) versus advanced (CKD 3b-4) stages prior to reaching CKD 5.

Therefore, with consideration for the limitations of previous cost-effectiveness models in LN and KOL expert feedback, a Markov cohort state transition model was developed to incorporate all stages of CKD and accurately model LN patient progression over a lifetime horizon (detailed in Section B.3.2.2).

B.3.2.1 Patient population

In accordance with the final scope issued by NICE and anticipated marketing authorisation, the cost-effectiveness analysis evaluates the cost-effectiveness of voclosporin in combination with background immunosuppressive therapies for the treatment of adult patients with active class III, IV or V (including mixed class III/V and IV/V) LN. This population reflects the use of voclosporin in the pivotal studies, AURORA 1 (Section B.2.3.1) and AURORA 2 (Section B.2.3.2).

B.3.2.2 Model structure

In the absence of published NICE technology appraisals for the treatment of patients with LN, the cost-effectiveness model structure was based on previously published models identified by SLR and targeted literature review (Section B.3.1), data availability from the AURORA 1 and AURORA 2 trials, and the known clinical pathway of patients with LN supported by KOL expert feedback.

A cohort state transition model with nine health states was developed, encompassing the LN-related stages of CKD (CKD1–4), ESRD (CKD 5), and death (the absorbing health state):

- CR with CKD stages 1-3a (CR CKD 1-3a)
- PR with CKD stages 1-3a (PR CKD 1-3a)
- AD with CKD stages 1-3a (AD CKD 1-3a)
- CR with CKD stages 3b-4 (CR CKD 3b-4)
- PR with CKD stages 3b-4 (PR CKD 3b-4)
- AD with CKD stages 3b-4 (AD CKD 3b-4)
- CKD stage 5, dialysis (CKD 5 dialysis)
- CKD stage 5, after kidney transplant (CKD 5 transplant)
- Death

All patients enter the model in the AD CKD 1-3a health state; and then either:

- Die
- Achieve CR and transition to CR CKD 1-3a
- Achieve PR and transition to PR CKD 1-3a
- Remain in AD CKD 1-3a
- Or have worsening eGFR and transition to AD CKD 3b-4

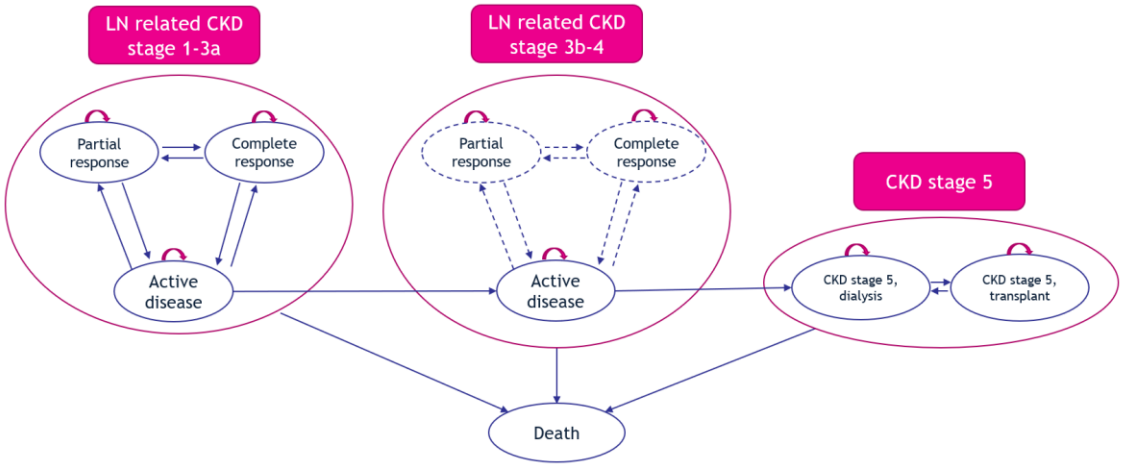
As eGFR levels are sensitive to multiple factors, it was necessary to take account of only the consistent and confirmed eGFR changes over time as a proxy for changes to CR to treatment when using the patient level data from the AURORA trials. Patients who deteriorate to AD CKD 3b-4 may then either:

- Die
- Achieve complete response and transition to CR CKD 3b-4
- Achieve partial response and transition to PR CKD 3b-4
- Remain in AD CKD 3b-4
- Or progress to CKD 5 where they may die, commence kidney dialysis or await transplant.

Although the model includes functionality for patients with AD CKD 3b-4 to transition to PR or CR states, the base case analysis does not use CKD 3b-4 response states due to a lack of available data and in line with KOL feedback that indicated response to be rare in patients that reach CKD 3b-4. Therefore, a conservative approach is taken, and it is assumed that patients can only transition to CKD stage 5 from AD CKD 3b-4 in the base case analysis (i.e. cannot achieve response in CKD 3b-4). Furthermore, it was not possible to estimate transition probabilities for LN patients with more advanced CKD beyond CKD stages 1-3a based on AURORA 2 data (due to limited follow-up in the latest AURORA 2 data cut). Therefore, literature sources and KOL expert feedback were used for the transitions between AD CKD 1-3a and AD CKD 3b-4, and for all transitions in CKD 3b-4 and CKD stage 5.

A summary of the health states and possible state transitions is presented in Figure B.3-1.

Figure B.3-1. Cost-effectiveness analysis model structure



Note: Dotted lines refer to functionality included in the model, but not used in the base case. Transition to death due to LN or background mortality can occur from any state in the model.
Abbreviations: CKD = chronic kidney disease; LN = lupus nephritis

Cost-effectiveness was modelled over a lifetime horizon from the perspective of the UK NHS and Personal Social Services (PSS) perspective, and a six-month cycle length was deemed sufficient to accurately capture the clinical and cost outcomes for patients from the AURORA 1 and AURORA 2 trials. Half cycle correction has been applied to account for events not occurring at the beginning or end of every cycle. Based on NICE guidelines, an adjustable 3.5% discount rate has been applied to the cost and effects.

Table B.3-2. Features of the economic analysis

Factor	Current evaluation	
	Chosen values	Justification
Time horizon	Lifetime, with the option to consider reduced time horizons	Appropriate to reflect the potential long-term outcomes for patients with LN.
Model structure and health states	Nine-state Markov cohort state transition model (seven states utilised in the base case analysis)	Although there are yet to be any published NICE TAs for the treatment of LN, a nine-state Markov model was informed by previous LN cost-effectiveness models identified in the literature and KOL expert feedback. Among the nine health states, the base case analysis excludes CKD 3b-4 PR and CKD 3b-4 CR states due to a lack of available data and in line with KOL feedback which highlighted response to be rare among these patients.
Stopping rule / treatment waning effect	A 36-month stopping rule is applied for voclosporin + MMF and all other treatments apart from TAC-containing regimens (12-month 12 month stopping rule). A treatment waning effect is applied to all treatments following treatment discontinuation and maintained for the outstanding duration of the lifetime horizon. As such, the model assumes that upon discontinuation of VCS + MMF, patient health state transition probabilities wane to an average (i.e. midpoint) of those recorded within the AURORA 2 trial at Months 30 and 36 for the VCS + MMF arm, and those recorded at Months 30 and 36 months for the MMF alone arm. Similarly for all other treatments, long-term health state transition probabilities wane to an average of those derived from ITC data and those recorded at months 30 and 36 months for the MMF alone arm in AURORA 2. Therefore, unlike other treatments, MMF transitions do not change following discontinuation of treatment.	Stopping rule assumptions were applied on the basis that patients received up to 36 months of treatment with voclosporin + MMF and MMF alone across the AURORA 1 and AURORA 2 trials. In particular, 87.1% of all patients enrolled onto AURORA 2 reached Month 36 of treatment with voclosporin + MMF.[113] Other treatments were assumed to have the same initial treatment duration (36 months) apart from CNI-containing comparator regimens of tacrolimus monotherapy and tacrolimus + MMF, which were assumed to have a treatment duration of 12 months based on KOL expert feedback. Therefore, there is some uncertainty in terms of any sustained efficacy benefit for VCS beyond the duration of the trial. However, the loss of treatment effect is unlikely to occur instantaneously so a treatment waning effect was applied.

Source of utilities	AURORA 1 and AURORA 2 trials and literature	Utility estimates provided by pivotal trials (AURORA 1 and AURORA 2) required the post-hoc conversion of SF-36 scores to EQ-5D values to generate health-state specific utilities for CKD 1-3a within the model base case analysis. Beyond CKD 1-3a, data from the AURORA 1/AURORA 2 trials could not be used for other health states. Therefore, health state utility values identified in the literature were used for these health states within the model.
Source of costs	eMIT, BNF, National Schedule of NHS costs (2019–2020), PSSRU unit costs (2020), published literature	Drug acquisition costs obtained from eMIT national database to accurately reflect average price paid for drug products. If prices were unavailable, other sources were consulted (e.g. the BNF). Drug administration costs for intravenous comparator treatments were sourced from a recent publication of NHS reference costs; while general resource use costs (e.g. nurse/specialist visits) were sourced from recently published PSSRU unit costs. If costs could not be obtained from the above national sources, costs were sourced from published literature or assumptions were made based on KOL expert advice.
Perspective	NHS/PSS	As per the NICE reference case.

Abbreviations: BNF = British National Formulary; CKD = chronic kidney disease; eMIT = electronic market information tool; EQ-5D = EuroQol-5 Dimension; ITC = indirect treatment comparison; KOL = key opinion leader; LN = lupus nephritis; NHS = National Health Service; PSS = Personal Social Services; PSSRU = Personal Social Services Research Unit; SoC = standard of care; TA = Technology Appraisal; TAC = tacrolimus

B.3.2.3 Intervention technology and comparators

The intervention relevant to this application and economic analysis is voclosporin (23.7 mg BID) in combination with MMF (1g BID) and low-dose corticosteroid; in line with the pivotal AURORA 1 and AURORA 2 Phase 3 trials (Section B.2.3.1 and Section B.2.3.2), its anticipated marketing authorisation and the final scope.

All comparators specified within the final scope are captured in the analysis and have been implemented in line with their respective marketing authorisations. The comparators include: MMF plus corticosteroids, cyclophosphamide plus corticosteroids, azathioprine plus corticosteroids, rituximab, and the CNI, tacrolimus, plus MMF/corticosteroids.

Among the comparators specified within the final scope, expert KOL feedback indicates that MMF is regarded as the most commonly used initial therapy, with rituximab and tacrolimus often used in more severe patients (Section B.1.3.6.3). It is important to note that azathioprine is not typically used as an initial therapy in UK clinical practice, and typically reserved as a subsequent treatment.

B.3.2.4 Model outcomes

The model allows benefit to be measured in terms of life years (LYs) and quality-adjusted life years (QALYs) over a lifetime horizon. In accordance with the NICE reference case, base case results were generated using QALYs as the measure of benefit and the primary outcome was

the incremental cost-effectiveness ratio (ICER) in terms of incremental cost per QALY. Total costs associated were considered from a NHS and PSS perspective.

B.3.3 Clinical parameters and variables

B.3.3.1 Overview of clinical outcomes

Health state transitions between AD, PR, and CR were estimated based on individual patient-level data from AURORA 1 and AURORA 2 trials for the voclosporin + MMF and MMF alone arms (Section B.2),[129,130] and outputs of the ITC for all other comparators (Section B.2.9 and Section B.3.3.3). Health state occupancy was further informed by patient-level treatment discontinuation rates collected in the AURORA 1 and AURORA 2 trials, which was used to estimate time to treatment discontinuation (TTD). In accordance with the NICE DSU TSD 14,[131] long-term treatment discontinuation and TTD was estimated by fitting parametric models to Kaplan-Meier curves which describe the proportion of patients that discontinued voclosporin + MMF or MMF throughout AURORA 1 and AURORA 2 (Section B.3.3.4).

Given the lack of evidence regarding long term data on LN disease progression, a targeted literature review was conducted to identify relevant observational evidence (e.g. registry-based studies, retrospective analysis, claimed based analysis) CKD, ESRD, and mortality due to renal or cardiovascular events in patients with SLE. Data identified in this review was used to inform long-term clinical assumptions for patients with CKD stage ≥3b (i.e. those who were not otherwise included in the AURORA 1 and AURORA 2 trials).

B.3.3.2 Health state transition probabilities

B.3.3.2.1 *LN patients with CKD stages 1–3a*

AURORA 1 and AURORA 2 trial response data was used to inform the health states included within CKD stages 1–3a for voclosporin + MMF and MMF alone. Patients were defined according to CKD stages using eGFR thresholds reported in KDIGO 2021 guidelines.[43] According to these guidelines, CKD stages correspond to the following eGFR thresholds:

- **CKD 1:** eGFR >90ml/min/1.73m^2
- **CKD 2:** eGFR 60–89ml/min/1.73m^2
- **CKD 3a:** eGFR 45–59ml/min/1.73m^2
- **CKD 3b:** eGFR 30-44ml/min/1.73m^2
- **CKD 4:** eGFR 15–29ml/min/1.73m^2
- **CKD 5:** eGFR <15ml/min/1.73m^2

After screening, a proportion of patients had eGFR levels which fell outside that of CK1-3a thresholds based on single timepoint eGFR measurements. However, KDIGO guidelines have established that changes to eGFR need to be confirmed over time to determine progression of CKD.[43] In AURORA 2, no patients experienced CKD as defined by eGFR < 60 ml/min/1.73m^2 for more than 3 months, irrespective of kidney damage.[113] For the purposes of this economic analysis, the decision problem focuses on modelling CKD progression based on confirmed and irreversible eGFR changes which reflect deterioration in kidney function, rather than reversible changes in eGFR levels. Therefore, patients who had eGFR levels which were transiently outside the thresholds for CKD 1-3a after screening were grouped with

patients who consistently had eGFR levels corresponding to CKD 1-3a, since these patients were eligible for inclusion to the trial at screening.

Transition probabilities were generated by counting the transitions per period (termed the 'count method'). For every six-month period, the transition of each patient to CR, PR or death is recorded in AURORA 1 and AURORA 2. At the commencement of the AURORA 1 trial, all patients are assumed to begin in the CKD 1-3a AD health state, due to average baseline eGFR being in CKD stage 1 for both treatment groups. A transition probability was then generated for each transition within the CKD stages 1-3a by dividing the number of transitions from health state A to health state B by the total number of patients starting in health state A at the beginning of the six-month period. This method resulted in six transition matrices for both voclosporin + MMF and MMF alone (i.e. one for each six-month period in the 36-month period spanning AURORA 1 and AURORA 2). AURORA 1 data is used to inform the transitions between baseline to 6 months and 6 months to 12 months. AURORA 2 data is used to inform the transitions from 12 months onwards. As not every patient that completed AURORA 1 went on to AURORA 2, there is censoring occurring between the second and the third transition period.

A second approach of calculating transition probabilities was also explored by fitting a multinomial logit model per transition per health state. However, the multinomial method provided unrealistic outcomes that did not match the trial data. Therefore, the multinomial method is not incorporated into the model.

As the model includes up to 36 months of count data (AURORA 1 and AURORA 2), a post-follow-up transition matrix was used to estimate long-term post-follow-up transitions whereby the base case applied a weighted average of the transition probabilities from the last two periods (Month 30 and 36) by weighting the event numbers relative to the number of observations. This approach could only be taken for voclosporin + MMF and MMF treatments due to the availability of patient-level data in the AURORA trials. For all other treatments, long-term transitions were generated by applying the NMA CRR and PRR ORs to the transitions of MMF (i.e. transitions from AD to CR or PR were informed by the NMA, whereas all transitions from CR and PR were shared with MMF). Long-term transitions were validated using external data sources[49,132] and KOL expert clinical opinion, as a reliance on count data for long-term extrapolation has the potential to introduce variations based on the choice of the long-term transition matrix.

As there was no additional data beyond 36 months of treatment with voclosporin + MMF, treatment was discontinued in all patients at 36 months apart from the CNI, tacrolimus, which was discontinued at 12 months (Section B.3.3.5). Uncertainty related to any sustained efficacy following treatment discontinuation was therefore accounted for by applying a long-term treatment waning effect to voclosporin + MMF and all comparators (described in Table B.3-2).

B.3.3.2.2 *Transitions between AD CKD 1-3a and AD CKD 3b–4*

Transitions between AD CKD 1-3a to AD CKD 3b-4 were informed by literature searches, external health economists and external KOL experts to reach a plausible estimate for the entire time horizon of the cost-effectiveness model. No external data sources were identified to provide estimates of progression from CKD 1-3a to CKD 3b-4. However, according to KOL clinical experts, an estimated 6% of patients transition from CKD 1-3a to CKD 3b-4 per year (3.05% per 6-month cycle) and 95% of patients transition from CKD 3b-4 to CKD 5 over 10 years, which leads to a transition probability of 13.9% per 6-month cycle. In addition, the

transition probability from AD CKD 1-3a to death could be informed by mortality data collected in the MMF arm in AURORA 1 and AURORA 2 ([redacted]% per 6-month cycle).[129,130]

A summary of transition probabilities estimated for AD CKD 1-3a is presented in Table B.3-3.

Table B.3-3. Transition probabilities in CKD stages 1-3a (all treatments)

Transition	Transition probability	Reference
AD CKD 1-3a → AD CKD 3b-4	3.05%	KOL expert feedback. Probability of 6% transitioning to CKD 3b-4 per year.
AD CKD 1-3a → Death	[redacted]%	AURORA 1 and AURORA 2 patient-level mortality data for the MMF arm.[129,130] 6 deaths recorded over 347 periods of 6 months (6/347 = 1.73%)

Abbreviations: AD = active disease; CKD = chronic kidney disease; KOL = key opinion leader

Transition probabilities suggested by external KOL clinical experts were validated with external data sources (Section B.3.3.2.2.1).

As the AURORA 2 trial did not report any incidence of CKD 3b-4 progression, the model includes a toggle for allowing transitions to CKD 3b-4 in the first three years. In the base case, it is assumed that patients cannot transition into CKD 3b-4 in the first three years.

Since the count data does not include a transition to AD CKD 3b-4 nor a mortality constant over time, the transition probabilities to CR, PR and AD in CKD 1-3a were discounted by the sum of the transition probability to leave the CKD 1-3a state, such that transition probabilities would sum to 100%, and the responses to CR and PR remain proportional to the probability of remaining in AD. Formulaically, given a probability of leaving CKD 1-3a of X%, and a transition probability from the count data to CR, PR or AD of Y%, once can see the discounted transition as Y%*(1-X%).

B.3.3.2.2.1 Validation of transitions between AD CKD 1-3a and AD CKD 3b-4

An iterative process was followed to reach a plausible estimate of transitions between AD CKD 1-3a and AD CKD 3b-4. Firstly, transition probability values were identified in the literature to identify the probability of patients moving from AD CKD 1-3a to AD CKD 3b-4 (Tektonidou et al., 2016)[49] and CKD 3b-4 to CKD5 (Tselios et al., 2020).[133] According to Tektonidou et al., 2016,[49] an estimated 14.5% of patients had to be in CKD stage 5 after 15 years; while Tselios et al., 2020[133] reported 27.8% of patients to transition between CKD 3b-4 and CKD 5 over 10 years and a 1.62% transition probability between CKD 3b-4 and CKD 5 in a 6-month cycle. Using this data, a six-month transition probability of 3.19% was estimated for patients transitioning between AD CKD 1-3a and AD CKD 3b-4.

In accordance with external health economist feedback, a transition to CR and PR states was then included to estimate AD CKD 1-3a to AD CKD 3b-4 transition probability, leading to considerably higher transition probability from CKD 1-3a to CKD 3b-4 that ranged between 12.26% and 20.55% per 6 months. However, two consulted clinicians indicated that these values were too high, likely due to the inclusion of the Tselios et al., 2020[133] study that followed a Canadian cohort with different patient characteristics compared to the UK. UK specific sources were therefore identified in order to validate model outcomes (percentage of patients

in ESRD after 5 and 10 years) using the transition estimates for AD CKD 1-3a to AD CKD 3b-4, and for CKD 3b-4 to CKD 5, that were provided by clinicians.[132]

B.3.3.2.3 *LN patients with CKD stages 3b–4*

Patients transition to AD in CKD stages 3b-4 from the AD state in CKD stages 1-3a. From this point on, patients cannot return to an earlier CKD stage, based on the progressive, irreversible damage to nephrons occurring. Therefore, they can theoretically remain in AD, respond or deteriorate further, reaching CKD stage 5. However, data to support treatment-specific transitions were not identified for LN patients in CKD stage 3b-4. UK-based KOL experts consulted also noted that the proportion of patients achieving response in this progressed stage can be as low as 2.5-5%. Therefore, in the base case, no patients can reach response states in CKD stage 3b-4, and all patients regardless of treatment have the same probability of transitioning to CKD stage 5.

The probability for an LN patient to transition from AD CKD stage 3b-4 to CKD stage 5, dialysis, is informed using the KOL clinical expert-provided probability of 95% over 10 years. Transitions to death are informed using a CKD-specific literature review on transitions reported in CKD, Sugrue et al., 2019,[134] with KOL expert feedback broadly agreeing with the transition probability, but indicating that the true mortality for LN patients may be lower than found in CKD publications, given that CKD usually occurs in an older population. A summary of transition probabilities for CKD 3b-4 is presented in Table B.3-4.

Table B.3-4. Transition probabilities in CKD stages 3b-4 (all treatments)

Transition	Transition probability	Reference
AD → CR	0.0%	Assumption based on lack of data being identified
AD → PR	0.0%	Assumption based on lack of data being identified
AD → CKD stage 5, dialysis	13.91%	KOL expert feedback. Probability of 95% transitioning to dialysis over 10 years
AD → Death	3.92%	Sugrue et al., 2019[134]
AD → AD	82.17%	Remaining probability to stay in this state

Abbreviations: AD = active disease; CKD = chronic kidney disease; CR = complete response; KOL: key opinion leader; PR = partial response

B.3.3.2.4 *CKD stage 5*

A targeted literature search was undertaken and identified no LN-specific data to inform this state. As such, KOL expert feedback was sought to confirm the relevance of CKD-specific data for LN patients. UK-based KOL experts reported that 90% of LN patients who enter ESRD receive a transplant within two years. This is a higher rate than reported in the literature for CKD patients, as the average LN patient is younger and therefore more suitable for receiving a transplant. The KOL experts also stated that LN patients have an additional risk of mortality due to LN-related cardiovascular events. However, no LN-specific sources were identified for mortality risks in CKD stage 5 and as such it was considered an assumption that no LN-related cardiovascular events are included in the model. This assumption is conservative as

voclosporin + MMF results in patients remaining longer in CKD 1-3a stages, and as such it would primarily be comparators which would have been incurring LN-related cardiovascular event costs. A summary of transition probabilities in CKD stage 5 is presented in Table B.3-5.

Table B.3-5. Transition probabilities in CKD stage 5 (all treatments)

Transition	Transition probability	Reference
CKD Stage 5 dialysis → CKD Stage 5 dialysis	48.76%	Remaining probability to stay in this state
CKD Stage 5 dialysis → CKD Stage 5 transplant	43.77%	KOL expert feedback. Probability of 90% transplant over 2 years
CKD Stage 5 dialysis → Death	7.47%	Sugrue et al., 2019[134]
CKD Stage 5 transplant → CKD Stage 5 dialysis	2.96%	Palmer et al., 2004[135]
CKD Stage 5 transplant → CKD Stage 5 transplant	95.65%	Remaining probability to stay in this state
CKD Stage 5 transplant → Death	2.62%	Sugrue et al., 2019[134]

Abbreviations: CKD = chronic kidney disease; KOL = key opinion leader

B.3.3.3 Indirect treatment comparison

Base case outputs of the ITC described in Section B.2.9 informed comparator efficacy outcomes within the cost-effectiveness model in terms of CR and PR.

In the base case network, all available evidence was included, regardless of the length of follow-up. The PR base case network (10 RCTs reporting on 6 treatments) included approximately 40% fewer trials than the CR network (17 RCTs reporting on 8 treatments). Therefore, not all comparators included in the model could be informed by the PR network and it was assumed that the PR of azathioprine and tacrolimus + MMF is equivalent to the MMF arm. The ITC results used in the cost-effectiveness model are presented in Table B.3-6 and Table B.3-7, for CR and PR respectively.

Table B.3-6. ITC CR results included in the cost-effectiveness model

Treatment	Median OR	CrI 2.5%	CrI 97.5%
MMF	Ref	Ref	Ref
VCS+MMF	[redacted]	[redacted]	[redacted]
AZA	[redacted]	[redacted]	[redacted]
H-CYC	[redacted]	[redacted]	[redacted]
L-CYC	[redacted]	[redacted]	[redacted]
RTX+MMF	[redacted]	[redacted]	[redacted]
TAC	[redacted]	[redacted]	[redacted]
TAC+MMF	[redacted]	[redacted]	[redacted]

Abbreviations: AZA = azathioprine; CR = complete response; CrI = credible interval; H-CYC = high-dose cyclophosphamide; L-CYC = low-dose cyclophosphamide; MMF = mycophenolate mofetil; MPR = methylprednisolone; OR = odds ratio; RTX = rituximab; TAC = tacrolimus; VCS = voclosporin

Table B.3-7. ITC PR results included in the cost-effectiveness model

Treatment	Median OR	CrI 2.5%	CrI 97.5%
MMF	Ref	Ref	Ref
VCS+MMF	[redacted]	[redacted]	[redacted]
H-CYC	[redacted]	[redacted]	[redacted]
L-CYC	[redacted]	[redacted]	[redacted]
RTX+MMF	[redacted]	[redacted]	[redacted]
TAC	[redacted]	[redacted]	[redacted]

Abbreviations: CrI = credible interval; H-CYC = high-dose cyclophosphamide; ITC = indirect treatment comparison; L-CYC = low-dose cyclophosphamide; MMF = mycophenolate mofetil; OR = odds ratio; PR = partial response; RTX = rituximab; TAC = tacrolimus; VCS = voclosporin

ITC ORs (vs MMF) were adjusted to estimate the transition probability per treatment. To apply the ITC OR to the transition probabilities of MMF, the following formula is used, where O_X is the odds of treatment X and $OR_{X,Y}$ is the OR of treatment X versus treatment Y:

$$\frac{O_{MMF} * OR_{X,MMF}}{O_{MMF} * OR_{X,MMF} + 1}$$

This simplifies to the transition probability of treatment X, since

$$O_{MMF} * OR_{X,MMF} = O_{MMF} * \left(\frac{O_X}{O_{MMF}}\right) = O_X$$

$$\frac{O_{MMF} * OR_{X,MMF}}{O_{MMF} * OR_{X,MMF} + 1} = \frac{O_X}{O_X + 1}$$

B.3.3.4 Time to event analyses and efficacy outcomes

Patient-level data from the AURORA 1 and 2 trials was used to generate the TTD outcomes for both voclosporin + MMF and MMF. In the base case analysis, parametric models were fitted to the Kaplan-Meier TTD data from AURORA 1 and AURORA 2 trials (Figure B.3-2) in order to estimate treatment discontinuation for patients over the 36-month treatment period.

The model duration of treatment is determined by the TTD curves of the voclosporin + MMF and MMF only treatment arms. In the AURORA trials, patients were discontinued if the following occurred:

- After 12 weeks of treatment, the patient showed a confirmed >30% decrease from baseline value in CKD-EPI eGFR in two successive measurements separated by at least 4 weeks
- After 8 weeks of treatment, the patient showed a confirmed reduction of UPCR of ≤25% assessed by two consecutive measurements at least 2 weeks apart.
- Patient required treatment with IV methylprednisolone or any rescue medication other than that permitted in the protocol
- Patient discontinued voluntarily or at the Investigator's discretion if it was in the patient's best interest

Figure B.3-2. Time to study drug discontinuation (AURORA 1 and AURORA 2)

Abbreviations: BID = twice daily; mg = milligrams
Source: Otsuka 2022[136]

Parametric model fitting for TTD was conducted according to the following steps recommended in the NICE DSU TSD 14:[131]

1. Proportional hazards (PH) assumption was tested between treatment arms (Section B.3.3.4.1), which inferred the choice of fitting independent or dependent models. If the PH assumption could not be rejected, a single dependent model for each survival curve was estimated, with treatment modelled as a single covariate. Otherwise, an independent model was fitted.
2. Following the PH test, parametric survival models were fitted to the survival data of the pivotal trial (Section B.3.3.4.2)
3. An initial selection of extrapolation models was based on visual inspection and statistical fit of the models to the trial data, based on Akaike's Information Criterion (AIC) and the Bayesian Information Criterion (BIC), as well as visual inspection of the survival and hazard curves.

TTD curves for voclosporin + MMF and MMF are used alongside drug acquisition costs to determine treatment cost (Section B.3.5.1.1). However, since no data on TTD was available for non-AURORA regimens, other comparator treatments were assumed to have no discontinuation.

B.3.3.4.1 *Proportional hazards assumption*

The PH assumption was tested to indicate whether it may be preferable to separately fit parametric models to each treatment arm (voclosporin + MMF and MMF alone). The PH assumption was investigated by constructing log-cumulative hazard plots, and performing both a Schoenfeld residuals test, and a Supremum test. None of the analyses provided evidence against the PH assumption, meaning that a single dependent model could be used for each treatment arm.

The log-cumulative plot in Figure B.3-3 demonstrated convergence of the trial arms at several points, particularly during the first 168 days (in agreement with the Kaplan-Meier TTD data in Figure B.3-2). The Schoenfeld residuals plot in Figure B.3-4 also shows two sets of residuals (one per treatment arm), with no consistent trend over time and therefore no evidence against PH. The Kaplan-Meier curve shows a clear distinction between the voclosporin + MMF and MMF alone arms after the initial 168 days, following which the treatment arms are parallel. The treatment by time interaction test estimated a p-value of 0.7808, showing no evidence to reject assumption of PH. Furthermore, these results were confirmed by the Supremum Test for PH with a p-value of 0.6540, showing no evidence to reject the assumption of PH.

Figure B.3-3. TTD log-cumulative hazard plot (AURORA 1 and AURORA 2)

Abbreviations: BID = twice daily; mg = milligrams; TTD = time to treatment discontinuation
Source: Otsuka 2022[136]

Figure B.3-4. TTD Schoenfeld residual plot (AURORA 1 and AURORA 2)

Abbreviations: TTD = time to treatment discontinuation
Source: Otsuka 2022[136]

B.3.3.4.2 *Survival model selection*

Exponential, Weibull, log-normal, log-logistic and gamma parametric distributions were fitted to the trial TTD data and final model selection was based on statistical fit (AIC and BIC) and visual inspection of the extrapolated curves and hazard plots.

The five parametric distributions were fit using a dependent model to the TTD Kaplan-Meier data, whereby treatment and MMF use at screening were additional covariates. Based on the AIC and BIC results (Table B.3-8) and the visual fits, the log-logistic distribution was the best fitting distribution and therefore selected for use in the cost-effectiveness model to extrapolate TTD overtime for the voclosporin + MMF and the MMF arms.

Table B.3-8. AIC and BIC values for TTD extrapolations

Distributions	AIC	BIC
Exponential	901.2	912.8
Weibull	891.9	907.4
Log-logistic	888.2	903.7
Gamma	891.5	910.9
Log-normal	894.6	910.1

Abbreviations: AIC = Akaike's Information Criterion; BIC = Bayesian Information Criterion

B.3.3.5 Treatment duration / stopping rule

Treatment duration assumptions were made to inform both health state transition probabilities and treatment-related costs (Section B.3.5.1). In particular, patients who reached a stopping rule (specified below) transitioned to a long-term health state transition probability phase whereby treatment effect was waned relative to the on-treatment period (Table B.3-2). In addition, treatment-related costs were not applied beyond the pre-defined stopping rule.

As patients received up to 36 months of treatment with voclosporin + MMF and MMF alone across the AURORA 1 and AURORA 2 trials, an initial treatment duration of 36 months was applied to the base case analysis to each of these treatments. Other treatments were assumed to have the same initial treatment duration (36 months) apart from CNI-containing comparator regimens of tacrolimus monotherapy and tacrolimus + MMF, which were assumed to have a treatment duration of 12 months based on KOL expert feedback.

Uncertainty relating to treatment duration was also explored in a scenario analysis which modified all initial treatment durations from 36 months to 18 months (i.e. all treatments but tacrolimus-containing regimens which remained at 12 months). This scenario analysis was designed to reflect clinician feedback collected within a US-based survey of 96 treating physicians, which suggested that clinicians may keep patients on treatment for no longer than 1.5 years.[137]

B.3.4 Measurement and valuation of health effects

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

HRQoL data was collected in the AURORA 1 trial using the LupusPRO and SF-36 PRO questionnaires at baseline, Week 12, Week 24, and Week 52 of the study. Additional HRQoL data was then collected in the AURORA 2 trial using the SF-36 PRO questionnaire every six months until 36 months from AURORA 1 baseline.

Two sets of analyses were performed, to include only patients in AURORA 1 assessed over a 12-month period, or those who entered AURORA 2 for assessment of up to 36 months. While the AURORA 1 population starts with a larger sample size, the combined AURORA 1 and AURORA 2 population has data until 36 months and was therefore used to inform the base case. The cost-effectiveness model also includes an option to choose from either AURORA 1 or the AURORA 2 utility estimates.

However, health state-specific utility values were required to calculate the cost effectiveness of treatments in terms of incremental cost per QALY in accordance with the NICE reference case.

Although there are currently no available conversion methods to generate utility values from LupusPRO, SF-36 data can be used to generate utility values by conversion to EuroQol Five Dimension (EQ-5D) scores (Section B.3.4.2). Although SF-36 data may be mapped to EQ-5D data, it is important to note that the conversion is associated with an overprediction of severe health states and there is a risk that lower EQ-5D scores would be allocated to the ‘active disease’ health state because of the mapping process.[138,139]

Using SF-36-derived EQ-5D utility values, linear mixed effects models (LMMs) were then used to generate health state specific values (Section B.3.4.2). As HRQoL data is typically collected by repeat measurements over time, observations tend to be correlated between time points (i.e. time-dependent). LMMs were chosen to account for the longitudinal nature of the HRQoL data and explore the influence of patient demographics and time from treatment on health state specific EQ-5D values. LMMs represent a robust method to produce unbiased estimates of the impact of risk factors under the ‘missing-at random’ assumption, and are often used to analyse PRO data which is typically both longitudinal and hierarchical in nature (i.e. level 1 = repeated measures; level 2 = patient factors).

B.3.4.2 Mapping

The University of Oxford's Population health group - HERC have conducted a review in Medline (last search in March 2020) to identify various studies which use mapping functions to convert PRO or clinical instruments to EQ-5D.[140] Out of the six sources suggested, regression analysis was commonly used to assess the relationship between EQ-5D values and SF-36, where EQ-5D is the dependent variable. The regression analysis uses the eight SF-36 dimensions scores, the squared dimension scores, and interaction terms are derived by multiplying two-dimension scores.

As patient-level SF-36 data was available from the AURORA 1 and AURORA 2 studies, the Rowen et al., 2009 method[139] was used to convert SF-36 to EQ-5D three level data (EQ-5D-3L). A summary of AURORA 1 and AURORA 2 SF-36 scores are provided in Appendix N, and mapped EQ-5D scores are presented below in Table B.3-9.

Table B.3-9. Summary of mapped EQ-5D scores based on SF-36 data (AURORA 1 and AURORA 2)

Study visit	n	Mean (SD)	Median	Q1/Q3	Min/Max
Baseline	215	0.70 (0.19)	0.73	0.58/0.86	-0.02/0.97
Month 6	215	0.77 (0.17)	0.80	0.66/0.90	-0.00/0.99
Month 12	215	0.80 (0.16)	0.85	0.71/0.92	0.18/0.99
Month 18	206	0.80 (0.16)	0.85	0.72/0.92	0.18/0.99
Month 24	192	0.80 (0.16)	0.85	0.70/0.93	0.07/0.99
Month 30	189	0.80 (0.16)	0.87	0.71/0.92	0.24/0.99
Month 36	188	0.80 (0.17)	0.86	0.74/0.93	0.09/0.99

Abbreviations: EQ-5D = EuroQol 5 Dimension; Max = maximum; Min = minimum; SD = standard deviation; SF-36 = 36-Item Short Form Survey; Q1 = first quartile; Q3 = third quartile

LMMs were then utilised to generate health state specific utility values, using the mapped EQ-5D utility values as a dependent variable. Various regression models were then implemented using forward and backward selection model building methods to identify relevant covariates. The covariates investigated in the models were EQ-5D (baseline), Biopsy Class, MMF Use at Screening, Sex, Treatment Group, Response Category, Response Category at Previous Visit and Age (years.). A 'Visit' covariate was included in every model, and each covariate had an interaction term with Visit. Results showed that Sex, MMF Use at Screening, Biopsy class and Response Category at Previous Visit were not significant covariates and therefore were not included in the final best fitting model.

The results demonstrated that AD is associated with the lowest utility value followed by PR and CR; and a trend in utility was observed values over the first 18 months. A summary of mapped EQ-5D scores by Visit and patient response status is presented in Table B.3-10.

Table B.3-10. Summary of mapped EQ-5D by Visit and response status

Study visit	Response category	n	Mean (SD)
Baseline	AD: Non-Response	215	0.70 (0.19)
Month 6	CR	73	0.77 (0.15)
	PR	86	0.79 (0.17)
	AD: Non-Response	56	0.72 (0.18)
Month 12	CR	95	0.81 (0.15)
	PR	77	0.81 (0.15)
	AD: Non-Response	43	0.74 (0.20)
Month 18	CR	116	0.81 (0.15)
	PR	43	0.85 (0.12)
	AD: Non-Response	46	0.76 (0.16)
Month 24	CR	106	0.83 (0.16)
	PR	37	0.78 (0.16)
	AD: Non-Response	45	0.77 (0.16)
Month 30	CR	111	0.82 (0.15)
	PR	35	0.76 (0.20)
	AD: Non-Response	42	0.79 (0.16)
Month 36	CR	98	0.83 (0.16)
	PR	56	0.80 (0.18)
	AD: Non-Response	33	0.71 (0.19)

Abbreviations: AD = active disease; CR = complete response; EQ-5D = EuroQol 5 Dimension; eGFR = estimated glomerular filtration rate; PR = partial response; SD = standard deviation

B.3.4.3 Health-related quality-of-life studies

A SLR was also conducted to identify relevant HRQoL studies for LN and humanistic outcomes associated with voclosporin and the relevant comparators (see Appendix H). The SLR identified 15 HRQoL studies, although no articles assessing utility values in LN were identified.

Economic models identified by the SLR and an accompanying targeted literature review (Section B.3.1 and Appendix G) included health state specific utilities. Additional targeted literature reviews were also performed to identify recent and relevant CKD specific utility estimates outside of the scope of the SLR.

An overview of all health state specific estimates identified is presented in Table B.3-11.

Table B.3-11. Overview of all identified utility estimates by health state

Health state	Options for utilities	Source
CKD 1–3a		
CR	Option 1: 0.800 (SE: 0.160) EQ-5D, Sweden	Bexelius et al., 2013[141] / Institute for Clinical and Economic Review 2021[126]
	Option 2: 0.820 (SE: 0.180) Time trade off UK SLE population reporting on mild, moderate, severe SLR flares, and severe renal flares	Pollard et al., 2015[142]
	Option 3: 0.750 (SE: 0.180) EQ-5D, US Corresponds to a SLEDAI score < 5	Aggarwal et al., 2009[143]
PR	Decrement: -0.090 (SE: -0.018)	Mohara et al., 2014[124] / Institute for Clinical and Economic Review 2021[126]

AD	Option 1: -0.176 (SE: -0.035)	Mohara et al., 2014[124]
	Option 2: 0.450 (SE: NR)	Pollard et al., 2015[142]
CKD 3b–4*		
	Option 1: -0.055 (SE: NR) EQ-5D, UK Decrement is currently between a population of equal parts CKD 1/2 and CKD3a, and a population of equal parts CKD 3b and CKD 4.	Jesky et al., 2016[144]
	Option 2: -0.052666667 (SE: NR) EQ-5D, Japan Decrement is currently between a population of equal parts CKD 1, 2 and 3, and a population of equal parts CKD 3 and 4.	Tajima et al., 2010[145]
CKD 5, pre-transplant/dialysis		
	Option 1: Peritoneal dialysis: 0.65 (SE: NR) Haemodialysis: 0.46 (SE: NR EQ 5D, Sweden	Sennfalt et al., 2002[146]
	Option 2: Peritoneal dialysis: 0.53 (SE: 0.34) Haemodialysis: 0.44 (SE: 0.36) EQ-5D, Wales	Lee et al., 2005[147]
	Option 3: 0.549 (SE: NR) Decrement as in Mohara, used in the ICER report	Mohara et al., 2014[124]
CKD 5, post-transplant		
	Option 1: 0.86 EQ-5D, Sweden	Sennfalt et al., 2002
	Option 2: 0.71 (SE: 0.27) EQ-5D, Wales	Lee et al., 2005[147]
	Option 3: 0.73 (IQR:0.62–1) EQ-5D, UK CKD stage 5 utility, not specifically post-transplant	Jesky et al., 2016[144]

*Utility values stratified by response status (i.e. CR, PR, AD) were not identified in the CKD 3b–4 population)
Abbreviations: AD = active disease; CKD = chronic kidney disease; EQ-5D = EuroQol 5 Dimension; IQR = interquartile range; NR = not reported; SE = standard error; SLEDAI = Systemic Lupus Erythematosus Disease Activity Index; UK = United Kingdom

B.3.4.4 Adverse reactions

Grade 3/4 TEAEs with an incidence of ≥1% in AURORA 1 are incorporated into the base case of the model (pneumonia, gastroenteritis, headache, hypertension/hypertensive crisis, anaemia, and neutropenia). A summary of AE frequencies is detailed in Section B.3.5.3, alongside costs incurred for the management of each respective AE.

AE disutility values and duration estimates were used to assess the impact of AEs on QALYs, by multiplying an AE disutility value with the AE duration to estimate a QALY decrement which is applied during the first model cycle. AE disutility values and duration of AEs were informed by the SLR (Appendix H) and additional targeted PubMed searches. AE disutilities and assumed AE durations applied within the model are summarised in Table B.3-12.

Table B.3-12. Disutility and mean duration of AEs

Parameter	Disutility	Source	Mean duration (days)	Source
Pneumonia	0.31	Kim et al., 2019[122]	3.50	Assumption, 0.5 weeks
Gastroenteritis	0.01	Kim et al., 2019[122]	8.00	Hudgens et al., 2016,

				assumption, equal to diarrhoea
Headache	0.29	Hudgens et al., 2016[148]	13.00	Hudgens et al., 2016[148]
Hypertension/hypertensive crisis	0.15	Swinburn et al., 2010[149]	8.00	Swinburn et al., 2010[149]
Anaemia	0.12	Swinburn et al., 2010[149]	16.07	Swinburn et al., 2010[149]
Neutropenia	0.09	Kim et al., 2019[122]	15.09	Nafees et al., 2008[150]
Infections and infestations	0.20	Beusterien et al., 2010,[151] assumption, same as pneumonia and infections	3.50	Assumption, 0.5 weeks
Respiratory, thoracic, and mediastinal disorder	0.20	Beusterien et al., 2010,[151] assumption, same as pneumonia and infections	3.50	Assumption, 0.5 weeks
Blood and lymphatic system disorders	0.12	Assumption, same as anaemia	16.07	Assumption, same as anaemia
Herpes Zoster/ Varicella zoster virus	0.01	Assumption, same as gastroenteritis	8.00	Assumption, same as gastroenteritis
Nausea and vomiting	0.05	Nafees et al., 2008[150]	10.50	Assumption, 1.5 weeks
Upper respiratory tract infection	0.20	Beusterien et al., 2010,[151] assumption, same as pneumonia and infections	3.50	Assumption, 0.5 weeks
Epilepsy	0.14	Stavem et al., 2010[152]	10.50	Assumption, average from NICE TA316[153]
Septicaemia / Sepsis	0.20	Tolley et al., 2013[154]	17.85	Assumption, average from NICE TA359[155] and TA370[156]

Abbreviations: AE = adverse event; TA = Technology Appraisal

B.3.4.5 Health-related quality-of-life data used in the cost-effectiveness analysis

Utility estimates derived from AURORA 1 and AURORA 2 trial data were not reflective of utility data identified in published literature (Section B.3.4.2), and did not always present expected relationships with health states over time. For example, the CR health state was estimated to have lower utility values than the PR health state at certain time points.

AURORA 1 and AURORA 2-derived utility estimates were prioritised over literature-based utility estimates as they were collected within pivotal voclosporin clinical trials and represent utilities for LN-related CKD stages 1-3a. LN-specific utilities could not otherwise be sourced from the literature for CKD stages 1-3a; however, literature sources were used to inform health state specific utilities for LN-related CKD stages ≥3b.

The final approach taken for the response-based health states included in the cost-effectiveness model is based on data collected in AURORA 2, with patients matched to their AURORA 1 data to inform the CKD 1-3a health state. It is then assumed that the decrement observed in Jesky et al., 2016[144] between CKD 1-3a and CKD 3b-4 can be applied to the CKD 1-3a CR, PR and AD utilities. CKD literature was used to inform the utility of the two non-response health states due to an absence of LN-specific values. Death has been assumed to have a utility of zero.

A summary of the utility values used in the cost-effectiveness model is presented in Table B.3-13.

Table B.3-13. Summary of utility values for cost-effectiveness analysis

Health state		Utility value: mean (SE)	95% CI*	Reference in submission	Justification
CKD 1–3a	CR	0.830 (0.155)[141]	0.433, 0.997	Section B.3.4.1 and Section B.3.4.2	Utility values derived from pivotal AURORA 1 and AURORA 2 SF-36 trial data
	PR	0.800 (0.181)[124]	0.345, 0.997		
	AD	0.710 (0.192)[124]	0.277, 0.979		
CKD 3b–4	CR	0.775 (0.155**)[144]	0.409, 0.983		In absence of LN-related CKD 3b-4 utility data, a progression-related utility decrement was applied to the CKD 1-3a utility values based on a UK observational study (2016)[144]
	PR	0.745 (0.149**)[144]	0.406, 0.964		
	AD	0.655 (0.131**)[144]	0.380, 0.882		
CKD 5	Dialysis	0.485 (0.33)[147]	0.005, 0.993		Utility values are based on EQ-5D data presented in a UK survey of patients who received dialysis (peritoneal and haemo-dialysis) or renal transplant. It was assumed that there was an equal distribution of patients receiving peritoneal and haemodialysis in the model
	Transplant	0.710 (0.27)[147]	0.100, 0.999)		

*Assuming a beta distribution.

**SE assumed to be 20% of utility value due to no SE reported in publication.

Abbreviations: AD = active disease; CI = confidence interval; CR = complete response; EQ-5D = EuroQol-5 Dimension; HS = health state; PR = partial response; SE = standard error; SF-36 = 36-item Short Form Survey

In accordance with the NICE DSU TSD 12,[157] health state specific utilities included in the model were adjusted for age-related deterioration, with age-adjusted utility implemented using

age-specific utility values collected in a pooled analysis of four consecutive health surveys conducted in the English general population (Ara and Brazier, 2011).[158]

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

Literature searches were conducted to identify published studies reporting cost and healthcare resource use data for patients with LN (full details in Appendix I).

B.3.5.1 Intervention and comparators' costs and resource use

B.3.5.1.1 *Acquisition costs*

Drug acquisition costs for the intervention and comparators are presented in Table B.3-14, in terms of both the initial treatment of AD and second-line follow-up treatments. The cost-effectiveness analysis takes a confidential Patient Access Scheme (PAS) discount of [redacted]% into account for the acquisition of voclosporin (list price: [redacted] per pack), along with the list price of all comparators. Background therapy costs are also incorporated into the model to account for the co-administration of tapered corticosteroids and hydroxychloroquine (Table B.3-15).

Table B.3-14. Drug acquisition costs of intervention and comparators

Regimen	Drug(s)	Dosing*	Cost per package (list price)	Units per package	Stopping rule	Cost per model (6-month) cycle	Source
Initial treatment							
Voclosporin + MMF	Voclosporin	47.4 mg/day, oral	[redacted]	180 x 7.9 mg	36 months (assumption)	[redacted]	Preliminary submitted price, Rovin et al., 2021[2]
	MMF	2000-3000 mg/day, oral	£6.83	50 x 500 mg			eMIT,[159] Rovin et al., 2021[2]
			£9.81	100 x 250 mg			
MMF monotherapy†	MMF	2000-3000 mg/day, oral	£6.83	50 x 500 mg	36 months (assumption)	£124.31	eMIT,[159] Rovin et al., 2021[2]
			£9.81	100 x 250 mg			
CYC monotherapy†	CYC	*Low dose:* 500 mg IV, Q2W (6 cycles) *High dose:* 500-750 mg/m^2 IV, Q4W (6 cycles)	£13.55	1 x 1000 mg	36 months (assumption)	*Low dose:* Model cycle 1: £40.65 Model cycle 2+: £0.00 *High dose:* Model cycle 1: £86.73 Model cycle 2+: £0.00	eMIT,[159] EULAR 2020[27]
			£27.50	1 x 2000 mg			
			£8.23	1 x 500 mg			
Azathioprine monotherapy	Azathioprine	2 mg/kg/day, oral	£1.57	56 x 50mg	36 months (assumption)	£13.58	eMIT,[159] EULAR 2020[27]
Tacrolimus + MMF†	Tacrolimus	4 mg/day, oral	£59.10	30 x 1 mg	12 months (assumption)	£1,483.88	BNF,[160] Liu et al., 2015[92]
			£236.40	30 x 4 mg			
			£44.33	30 x 0.75 mg			
	MMF	1000 mg/day, oral	£6.83	50 x 500 mg			
			£9.81	100 x 250 mg			

Rituximab + MMF	Rituximab	1000 mg IV on days 1, 15, 168, and 182	£314.33	2 x 50 mg	36 months (assumption)	Model cycle 1: £6,470.49 Model cycle 2+: £150.81	BNF,[160] Rovin et al., 2012[88]
			£785.84	1 x 500 mg			
	MMF	2000-3000 mg/day, oral	£6.83	50 x 500 mg			
			£9.81	100 x 250 mg			
Second-line follow-up treatment							
MMF‡	MMF	1000 mg/day, oral	£6.83	50 x 500 mg	48 months (assumption)	£74.58	eMIT,[159] EULAR 2020[27]
			£9.81	100 x 250 mg			
Azathioprine + prednisone§	Azathioprine	2 mg/kg/day, oral	£1.57	56 x 50mg	48 months (assumption)	£13.58	eMIT,[159] BNF,[160] EULAR 2020[27]
	Prednisone	2.5–5 mg/day, oral, when needed to control disease activity	£0.88	28 x 1 mg			
			£1.42	30 x 2.5 mg			
			£0.95	30 x 5 mg			
			£1.90	30 x 10 mg			
			£3.80	30 x 20 mg			
			£40.00	56 x 25 mg			
			£29.12	28 x 30 mg			
Rituximab + MMFǁ	Assumed to be the same as initial treatment						
Tacrolimus + MMF ¶	Assumed to be the same as initial treatment						

*Dose intensities are 100% for all treatments; †plus corticosteroids; ‡used in 20% of patients following any initial treatment regimen; §used in 11% of patients following any initial treatment regimen; ǁused in 23% of patients following any initial treatment regimen apart from rituximab + MMF; ¶used in 11% of patients following any initial treatment regimen apart from tacrolimus +MMF and voclosporin + MMF

Abbreviations: BNF = British National Formulary; CYC = cyclophosphamide; eMIT = electronic market information tool; EULAR = European Alliance of Associations for Rheumatology; IV = intravenous; kg = kilograms; mg = milligrams; MMF = mycophenolate mofetil; mo. = months; Q2W = every 2 weeks; Q4W = every 4 weeks

Table B.3-15. Drug acquisition costs of background therapies

Regimen	Drug(s)	Dosing*	Cost per package	Units per package	Stopping rule	Cost per model (6-month) cycle	Source
Background therapy							
Tapered corticosteroids (AURORA) *used in 99.2% of patients receiving voclosporin + MMF, and MMF monotherapy*	Methylprednisolone	500 mg IV, per day for 2 days	£1.59–£7.60*	1 x 40–1000 mg*	84 months – assumed to cover initial (36 months) and second-line (48 months) treatment duration	Cycle 1: £15.02 Cycle 2+: £2.88	eMIT,[159] BNF,[160] Rovin et al., 2021[2]
	Prednisone	20-25 mg/day on day 3, decreased to 2.5 mg/day at week 16 according to protocol-defined schedule	£0.88–40.00†	28–56 x 1–30 mg†			
Tapered corticosteroids *used in 99.2% of patients receiving CYC, azathioprine and tacrolimus monotherapies, as well as CYC +MMF*	Methylprednisolone	500-2500 mg, IV, total dose	£1.59–£7.60*	1 x 40–1000 mg*	84 months – assumed to match other glucocorticoid regimen	Cycle 1: £27.97 Cycle 2+: £8.65	eMIT,[159] BNF,[160] EULAR 2020[27]
	Prednisone	Starting oral dose of 0.3-0.5 mg/kg/day, tapered to <7.5mg/day after 3-6 months	£0.88–40.00†	28–56 x 1–30 mg†			
Hydroxychloroquine *used in 76.9% of patients receiving any therapy*	Hydroxychloroquine	5 mg/kg/day, oral	£3.82	60 x 200mg	Assumed to match lifetime horizon	£19.27	eMIT,[159] EULAR 2020[27]

*Methylprednisolone: £1.59 (1 x 40 mg), £3.89 (1 x 500 mg), £6.39 (1 x 1000 mg), £7.60 (1 x 125 mg)

†Prednisone: £0.88 (28 x1 mg), £0.95 (30 x 5 mg), £1.42 (30 x 2.5 mg), £1.90 (30 x 10 mg), £3.80 (30 x 20 mg), £29.12 (28 x 30 mg), £40.00 (56 x 25 mg)

Abbreviations: CYC = cyclophosphamide; eMIT = electronic market information tool; EULAR = European Alliance of Associations for Rheumatology; IV = intravenous; kg = kilograms; mg = milligrams; MMF = mycophenolate mofetil

B.3.5.1.2 *Administration costs*

Administration costs are not relevant for the intervention treatment, voclosporin + MMF, since both treatments are administered orally. However, some first line regimens and background corticosteroids are applied intravenously. A summary of administration costs is presented in Table B.3-16.

Table B.3-16. Drug administration costs

	Cost	Source
Initial intravenous administration	£404.89	National Schedule of NHS Cost 2019–20 - SB14Z Deliver Complex Chemotherapy, including Prolonged Infusional Treatment, at First Attendance[161]
Subsequent intravenous administration	£339.75	National Schedule of NHS Cost 2019–20 - SB15Z Deliver Subsequent Elements of a Chemotherapy Cycle[161]
Oral administration*	£0.00	Assumption

*It is assumed that there is no cost for oral administration

Costs have been adjusted for inflation using the NHS cost inflation index[162]

B.3.5.2 Health-state unit costs and resource use

Clinical guidelines and KOL expert feedback were used to inform the resource use categories. General resource use was considered in three categories: LN-related costs, CKD-related costs, and costs specific to CKD stage 5 (Table B.3-17). In addition, the model includes a treatment-specific resource use cost to account for therapeutic drug monitoring tests that are required for the CNI, tacrolimus (Table B.3-17).[102] As previously described in Section B.1.2 and Section B.1.3.7, the improved immunosuppressive potency, tolerable safety profile, and broader therapeutic index eliminates the need for regular therapeutic drug monitoring of voclosporin, and so these costs do not apply to voclosporin.[8,9,11]

Table B.3-17. Resource use costs

	Cost	Reference
General resource unit costs		
Nurse visit	£34.07	PSSRU 2020, KOL expert feedback (40 minutes of nurse time is required per visit)[163]
Specialist visit	£41.09	PSSRU 2020, KOL expert feedback (20 minute of specialist time is required per visit)[163]
Psychologist	£76.00	PSSRU, (average session time of length of 70 minutes)
Kidney biopsy	£902.82	National Schedule of NHS Costs 2019–2020. YL20A – Percutaneous Needle Biopsy of Lesion of Kidney, 19 years and over[161]
Urinalysis (includes eGFR, serum albumin, proteinuria and urinary sediment)	£4.37	Kerr 2012[164]
Complete blood count	£2.54	National Schedule of NHS cost 2019–20. DAPS05 – Haematology[161]
Serum immunoglobulin measurement	£7.42	National Schedule of NHS cost 2019–20. DAPS064 – Immunology[161]
Antibody tests	£7.42	National Schedule of NHS cost 2019–20. DAPS06 – Immunology[161]
Chronic infection screening	£3.55	Assumption. National Schedule of NHS Cost 2019–20. DAPS09 - Other[161]
Cholesterol and lipid monitoring	£3.55	Assumption. National Schedule of NHS Cost 2019–20. DAPS09 - Other[161]
Anti-dsDNA and C3 and C4 level monitoring	£3.55	Assumption. National Schedule of NHS Cost 2019–20. DAPS09 - Other[161]
Dialysis	£27,653.00	NICE 2018 (NG107)[165]
Initial assessment for kidney transplant	£3,205.72	Kerr 2012[164]
Waiting list clinic attendance (pre-transplant)	£3,754.12	Kerr 2012[164]
Kidney transplantation	£14,562.47	National Schedule of NHS Cost 2019–20. Weighted from LA01A, LA02A, LA03A, LA12A, LA13A, LA11Z, LA14Z[161]
Post-kidney transplantation, year 1	£21,090.07	Kerr 2012, with immunosuppressive costs not inflated[164]
Post-kidney transplantation, year 2+	£9,246.94	Kerr 2012[164]
Vitamin D supplements	£23.29	NICE 2014[166]
ESAs and EPO	£2,297.93	BNF[160]
Phosphate binders	£218.05	Bernard 2013[167]
ACEI or ARB	£218.05	Assumption. Equal to phosphate binders.
Anti-hypertensive medication	£166.79	Kerr 2012[164]
Ultrasound	£75.17	National Schedule of NHS Cost 2019–20. DIM007 – Ultrasound (non-obstetric)[161]
Echocardiogram	£87.19	National Schedule of NHS Cost 2019–20. RD51A – Simple Echocardiogram, 19 years and over[161]
Treatment-specific resource unit costs		
Tacrolimus therapeutic drug monitoring	£29.55	Jones-Hughes 2015[102]

Costs have been adjusted for inflation using the NHS cost inflation index.[162] Abbreviations: ACEI =, angiotensin converting enzyme inhibitor; anti-dsDNA = anti-double stranded deoxyribonucleic acid; ARB = angiotensin receptor blocker; BNF = British National Formulary; eGFR = estimated glomerular filtration rate; EPO = erythropoietin; ESA = erythropoiesis-stimulating agents; NHS = National Health Service; PSSRU = Personal Social Services Research Unit

The frequency of each resource use is based on clinical guidelines and KOL expert feedback.[15,27] Since guidelines are not explicit on every resource use category and there was some variation in estimates provided by KOL experts, the following assumptions were made:

- Resource use frequency for patients in the CR health state reflects standard care in the absence of flare or AD; while resource use frequency for patients in the AD health state reflects standard care among patients who are experiencing a flare or AD. Since nothing could be identified for the PR health state, the resource use frequency is an average of CR and active disease
- Urinalysis, complete blood count and anti-dsDNA, C3 and C4 monitoring occur every visit
- Serum immunoglobulin measurement, antibody tests, chronic infection screening and cholesterol and lipid monitoring occur every visit in AD, and every second visit in CR
- Resource use is identical between response states across different CKD stages, except for CKD-specific categories

According to KOL expert feedback, tacrolimus therapeutic drug monitoring tests occur at every regular clinical visit. Therefore, the model assumes that a tacrolimus therapeutic drug monitoring test occurred at every nurse and specialist visit, of which, the frequency varies depending on patient CKD disease stage.

Resource use administration frequency is presented in Table B.3-18.

Table B.3-18. Resource use frequency

Resource	CR CKD 1-3a		PR CKD 1-3a		AD CKD 1-3a		CR CKD 3b-4		PR CKD 3b-4		AD CKD 3b-4		CKD 5 dia.		CKD 5 transp.		
	C1	C2+	C1	C2+	C1	C2+	C1	C2+	C1	2+	C1	C2+	C1	C2+	C1	C2	C3+
Nurse visit	1.00	1.00	3.50	2.00	6.00	3.00	2.00	2.00	4.00	2.50	6.00	3.00					
Specialist visit	1.00	1.00	3.50	2.00	6.00	3.00	2.00	2.00	4.00	2.50	6.00	3.00	6.00	3.00			
Psychologist													6.00	1.50			
Kidney biopsy											1.00						
Urinalysis*	2.00	2.00	7.00	4.00	12.00	6.00	4.00	4.00	8.00	5.00	12.00	6.00					
Complete blood count	2.00	2.00	7.00	4.00	12.00	6.00	4.00	4.00	8.00	5.00	12.00	6.00					
SIM	0.50	0.50	6.25	3.25	12.00	6.00	0.50	0.50	6.25	3.25	12.00	6.00					
Antibody tests	0.50	0.50	6.25	3.25	12.00	6.00	0.50	0.50	6.25	3.25	12.00	6.00					
Chronic infection screening	0.50	0.50	6.25	3.25	12.00	6.00	0.50	0.50	6.25	3.25	12.00	6.00					
Cholesterol and lipid monitoring	0.50	0.50	6.25	3.25	12.00	6.00	0.50	0.50	6.25	3.25	12.00	6.00					
Anti-dsDNA and comp.3/4 level monitoring	2.00	2.00	7.00	4.00	12.00	6.00	4.00	4.00	8.00	5.00	12.00	6.00					
Dialysis													0.50	0.50			
Initial assessment for KT													1.00				
Waiting list clinic attendance†													2.00	2.00			
Kidney transplantation															1.00		
Post-KT, Yr 1															0.50	0.50	
Post-KT, Yr 2+																	0.50
Vitamin D supplements							0.50	0.50	0.50	0.50	0.50	0.50	0.50	0.50	0.50	0.50	0.50
ESAs and EPO							0.50	0.50	0.50	0.50	0.50	0.50	0.50	0.50	0.50	0.50	0.50
Phosphate binders							0.50	0.50	0.50	0.50	0.50	0.50	0.50	0.50	0.50	0.50	0.50
ACEI or ARB	0.50	0.50	0.50	0.50	0.50	0.50	0.50	0.50	0.50	0.50	0.50	0.50	0.50	0.50	0.50	0.50	0.50
Anti-hypertensive medication	0.50	0.50	0.50	0.50	0.50	0.50	0.50	0.50	0.50	0.50	0.50	0.50	0.50	0.50	0.50	0.50	0.50
Ultrasound											1.00						
Echocardiogram	0.50	0.50	0.50	0.50	0.50	0.50	0.50	0.50	0.50	0.50	0.50	0.50	0.50	0.50	0.50	0.50	0.50

*includes GFR, serum albumin, proteinuria and urinary sediment; †pre-transplant

Abbreviations: ACEI = angiotensin converting enzyme inhibitor; anti-dsDNA = anti-double stranded deoxyribonucleic acid; ARB = angiotensin receptor blocker; C1/2+/3+ = cycle 1, cycle 2+ or cycle 3+; comp. = complement; EPO = erythropoietin; ESAs = erythropoiesis-stimulating agents; KT = kidney transplant; SIM = serum immunoglobulin measurement; Yr = year

B.3.5.3 Adverse reaction unit costs and resource use

The cost implications of Grade III/IV TEAEs with an incidence of ≥1% are considered in the base case analysis.

Grade III/IV TEAE frequencies were collected from AURORA 1 for both the voclosporin + MMF and MMF arms. For all other comparators, Grade III/IV TEAE frequencies were sourced from the literature identified by the clinical SLR (Appendix D). However, comparator Grade III/IV TEAE data was not typically reported, with only all-grade TEAE incidence reported in most cases. Therefore, in the absence of Grade III/IV TEAE data, some assumption options had to be introduced to the model:

- Option 1: All treatments that were not included in the AURORA trials have the same incidence as MMF
- Option 2: Treatment-specific TEAE incidences were included where possible for all treatments, and if not available, the treatments were assumed to have the same TEAE incidences as MMF
- Option 3: All treatment regimens which include MMF are assumed to have the same incidence as MMF. All other treatments which do not include MMF are assumed to have no incidence of AEs

In the base case analysis, option 3 was selected as the most conservative assumption, so a large number of treatments receive no costs or disutilities for Grade III/IV TEAEs. TEAE costs were identified from the National Schedule of NHS Costs 2019–2020.

A summary of Grade III/IV TEAE costs and frequencies incorporated into the model is presented in Table B.3-19.

Table B.3-19. Grade III/IV TEAE costs and frequencies

TEAE	Cost (2021)	TEAE frequency									Source
		VCS + MMF[109]	MMF[109]	L-CYC[92]	H-CYC[168]	AZA	RTX + MMF	TAC + MMF[92]	TAC	CYC + MMF[169]	
Pneumonia	£2,701.93	0.02	0.03	0.01	0.05	0.00	0.00	0.04	0.00	0.00	National Schedule of NHS Costs 2019–2020 – DZ11P[161]
Gastroenteritis	£2,490.47	0.01	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.02	National Schedule of NHS Costs 2019–2020 - FD01C [161]
Headache	£562.23	0.02	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	National Schedule of NHS Costs 2019–2020 - AA31E [161]
Hypertension/ hypertensive crisis	£640.41	0.02	0.02	0.00	0.00	0.00	0.00	0.00	0.00	0.00	National Schedule of NHS Costs 2019–2020 - EB04Z [161]
Anaemia	£872.29	0.02	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	National Schedule of NHS Costs 2019–2020 - SA01G-K[161]
Neutropenia	£619.36	0.02	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	National Schedule of NHS Costs 2019–2020 - WJ11Z[161]
Infections and infestations	£1,876.32	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	National Schedule of NHS Costs 2019–2020 - WH07A-G[161]
Respiratory, thoracic, and mediastinal disorder	£1,216.98	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	National Schedule of NHS Costs 2019–2020 - DZ22K-Q[161]
Blood and lymphatic system disorders	£2,489.40	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	National Schedule of NHS Costs 2019–2020 - WH54A-B[161]
Herpes zoster/Varicella zoster virus	£8,868.09	0.00	0.00	0.01	0.00	0.00	0.00	0.01	0.00	0.00	Gauthier et al., 2009[170]
Nausea and vomiting	£3,699.12	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.01	National Schedule of NHS Costs 2019–2020 - FD10F[161]

Upper respiratory tract infection	£1,458.20	0.00	0.00	0.00	0.00	0.00	0.00	0.01	0.00	0.00	National Schedule of NHS Costs 2019–2020 - CA70Z[161]
Epilepsy	£1,472.93	0.00	0.00	0.00	0.00	0.00	0.00	0.01	0.00	0.00	National Schedule of NHS Costs 2019–2020 - AA26C-H[161]
Septicaemia/Sepsis	£2,422.00	0.00	0.00	0.01	0.05	0.00	0.00	0.00	0.00	0.00	National Schedule of NHS Costs 2019–2020 - WJ06A-J[161]

Abbreviations: AZA = azathioprine; CC = clinical coding; H-CYC = high-dose cyclophosphamide; L-CYC = low-dose cyclophosphamide; MMF = mycophenolate mofetil; NHS = National Health Service; RTX = rituximab; TAC = tacrolimus; TEAE = treatment-emergent adverse event; VCS = voclosporin

Source: NHS reference costs 2019/2020[161] Costs have been adjusted for inflation using the NHS cost inflation index[162]

B.3.5.4 Miscellaneous unit costs and resource use

B.3.5.4.1 *End-of-life costs*

All mortality in the model incurred an end-of-life cost. Costs incurred due to background mortality were different to those incurred by those transitioning to the death state, as the latter was assumed to occur due to complications relating to LN. As such, death due to background mortality was costed as a death unrelated to LN, while all others were considered to have an LN-related death and were associated with a hospital care cost due to renal failure. Per cycle, background mortality was applied before transitions between health states occurred. The cost of a background mortality-related death was £9,590, which is the cost of hospital care for any diagnosis from the latest PSSRU report.[163] The cost of an LN-related death was £12,636, based on hospital care costs associated with renal failure.[163]

B.3.6 Severity

The population under consideration does not meet the criteria for a severity weight, and so calculation of QALY shortfall is not provided with this submission.

B.3.7 Uncertainty

Data supporting the efficacy and safety of voclosporin is provided by a Phase 3 trial (AURORA 1), a Phase 3 extension trial (AURORA 2), and a Phase 2 trial (AURA-LV). Therefore, there is sufficient quality of evidence to support the use voclosporin in patients with LN.

However, certain aspects of LN introduce some uncertainties to the economic analysis. Firstly, the rarity of the disease means that there is generally limited published clinical, humanistic, and economic data available for LN and/or SLE. Therefore, there is some uncertainty in terms of long-term transitions to advanced CKD stages. Secondly, the chronic, progressive nature of the disease means that patients typically remain on treatment for a number of years and there is some variation in clinical practice in terms of treatment duration on a treatment-by-treatment basis. Thirdly, there is currently limited knowledge of treatment waning effects in the field of LN.

For the above reasons, substantial KOL expert advice has been sought to inform the cost-effectiveness model presented in this submission, including the population of any key assumptions.

B.3.8 Managed access proposal

Voclosporin is not eligible for the Cancer Drugs Fund or the Innovative Medicines Fund. Therefore, a managed access proposal is not submitted with this application.

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

B.3.9.1 Summary of base-case analysis inputs

A summary of variables applied in the economic model is presented in Appendix O, including base case values, their uncertainty distribution, and sources.

B.3.9.2 Assumptions

An overview of key model assumptions is provided in Table B.3-20.

Table B.3-20. Key model assumptions

Model input	Assumption	Justification
Initial treatment duration	Three year (36 month) stopping rule applied for initial treatments in the base case, apart from a one year (12 month) stopping rule for TAC	Patients received VCS + MMF and MMF for up to three years across the AURORA 1 and AURORA 2 trial. Due to the chronic nature of the disease, patients with LN are known to receive treatment for months to years. However, there is a lack of available guidance to specify precisely how long patients should remain on treatment for. For this reason, other treatments included in the model were also assumed to have a three-year stopping rule apart from TAC-containing regimens, which had a 12-month stopping rule applied based on KOL expert feedback (Section B.3.3.4). Following completion of initial treatment, the costs related to subsequent treatment are then applied.
Long-term treatment effect	Treatment waning effect applied following treatment discontinuation for all treatments	Treatment waning effect applied to account for a partial treatment effect, sustained beyond the treatment period (Table B.3-2)
Transition from CKD 1-3a to CKD 3b-4	It is assumed that patients do not progress from CKD 1-3a to CKD 3b-4 in the first three years	The AURORA 2 study did not report any incidence of progression to CKD 3b-4 over a three-year treatment period[113]
TTD	TTD extrapolations based on combined AURORA 1 and AURORA 2 trial data were used to estimate VCS + MMF and MMF discontinuation over 36-month treatment period	Log-logistic curves were fitted to Kaplan-Meier discontinuation data collected across the 36-month treatment period of AURORA 1 and AURORA 2, to estimate a parametric fit that informs treatment discontinuation over the 36-month treatment period (Section B.3.3.4)
	It is assumed that no other treatments were discontinued in the model	No TTD data was available for treatments which were not investigated within the AURORA trials
Patient response status and utility for CKD 1-3a	It is assumed that patients in the AURORA 1 and AURORA 2 trials are reflective of LN patients with CKD 1-3a	Patient-level response, and TTD data from AURORA 1 and AURORA 2 trials were used to inform transition probabilities in the CKD 1-3a health state. AURORA trial patients were assumed to reflect CKD 1-3a on the basis of confirmed eGFR levels, in line with KDIGO-guideline published eGFR CKD thresholds.
	It is assumed that only consistent and confirmed eGFR changes over time were reflective of patient response status and CKD progression	CKD progression was modelled based on confirmed and irreversible eGFR changes as opposed to transient, reversible changes in eGFR levels in accordance with KDIGO 2021 guidelines which indicate that eGFR changes need to be confirmed over time to determine progression of CKD[43]
Utility for CKD 3b-4	It is assumed that a CKD 1-3a to CKD 3b-4 progression-related utility decrement is reflective of LN-related CKD 3b-4 utility	In absence of published LN-related CKD 3b-4 utility data, a CKD 1-3a to CKD 3b-4 progression-related utility decrement reported in a UK observational study[144] was applied to the CKD 1-3a utility values to inform CKD 3b-4 utility
AE disutility and AE-related costs	It is assumed that only Grade III/IV TEAEs identified in ≥1% patients in the AURORA 1 are associated with disutility and costs	Grade III/IV TEAE frequencies were collected from AURORA 1 for both VCS + MMF and MMF alone. For all other comparators, Grade III/IV TEAE frequencies were sourced from the literature identified by the clinical SLR.

	It is assumed that in the absence of Grade III/IV TEAE data for comparators, they either have the same Grade III/IV incidence as the AURORA 1 MMF (when the treatment regimen includes MMF) or they have no incidence of Grade III/IV TEAEs	Conservative assumption applied to reflect the likelihood of Grade III/IV TEAEs expected in all MMF-containing comparator treatment regimens, or exclude consideration for Grade III/IV TEAEs entirely for comparator regimens that do not contain MMF.
Therapeutic drug monitoring	It is assumed that therapeutic drug monitoring of TAC occurs at every regular nurse and specialist visit.	According to KOL expert feedback, tacrolimus therapeutic drug monitoring tests occur at every regular clinical visit. Therefore, the model assumes that a tacrolimus therapeutic drug monitoring test occurred at every nurse and specialist visit, of which, the frequency varies depending on patient CKD disease stage.
Mortality rates for AD CKD 1-3a	Average taken to match AURORA 1 and AURORA 2 MMF arm	In absence of LN-related CKD specific data, it was assumed that the mortality in AD CKD 1-3a was accurately represented by the average 6-month mortality rate reported in AURORA 1 and AURORA 2 for the MMF arm.

Abbreviations: AE = adverse event; CKD = chronic kidney disease; CNI = calcineurin inhibitor; HRQoL = health-related quality of life; LN = lupus nephritis; MMF = mycophenolate mofetil; TAC = tacrolimus; TEAEs = treatment-emergent adverse event; TTD = time to treatment discontinuation; VCS = voclosporin

B.3.10 Base-case results

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

Base case results for voclosporin + MMF versus other comparators are presented in Table B.3-21 (3.5% discount rate) and Table B.3-22 (undiscounted). All results were inclusive of a confidential [redacted]% PAS discount to the voclosporin list price. Discounted results indicate that voclosporin + MMF generates an additional [redacted] LYs and [redacted] QALYs versus MMF, and an additional [redacted] LYs and [redacted] QALYs versus tacrolimus + MMF. The base case ICERs indicate that voclosporin + MMF is a cost-effective treatment versus all assessed comparators. In particular, a discounted ICER of £20,001/QALY was estimated versus MMF, the current standard of care in the treatment of LN, and £17,864/QALY versus a CNI combination therapy, tacrolimus + MMF.

Estimates of clinical outcomes and disaggregated results from the model are presented in Appendix J, and a summary of net health benefit is presented in Table B.3-23.

Table B.3-21. Base-case results (discounted)

Technologies	Total			Incremental			ICER (£/QALY)*
	Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs	
VCS + MMF	[redacted]	[redacted]	[redacted]	-	-	-	-
MMF	[redacted]	17.93	13.08	[redacted]	[redacted]	[redacted]	£20,001
L-CYC	[redacted]	17.53	12.73	[redacted]	[redacted]	[redacted]	£10,701
H-CYC	[redacted]	17.48	12.69	[redacted]	[redacted]	[redacted]	£10,221
AZA	[redacted]	17.73	12.91	[redacted]	[redacted]	[redacted]	£15,009
RTX + MMF	[redacted]	18.40	13.49	[redacted]	[redacted]	[redacted]	£20,742
TAC + MMF	[redacted]	17.99	13.14	[redacted]	[redacted]	[redacted]	£17,864
TAC	[redacted]	18.04	13.19	[redacted]	[redacted]	[redacted]	£16,737

*ICER for VCS + MMF vs comparator

Abbreviations: AZA = azathioprine; CYC = cyclophosphamide; ICER = incremental cost-effectiveness ratio; L-CYC = low-dose CYC; H-CYC = high-dose CYC; LYG = life years gained; MMF = mycophenolate mofetil; QALYs = quality-adjusted life years; RTX = rituximab; TAC = tacrolimus; VCS = voclosporin

Table B.3-22. Base-case results (undiscounted)

Technologies	Total			Incremental			ICER (£/QALY)*
	Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs	
VCS + MMF	[redacted]	[redacted]	[redacted]	-	-	-	-
MMF	[redacted]	33.48	23.60	[redacted]	[redacted]	[redacted]	£7,697
L-CYC	[redacted]	32.47	22.80	[redacted]	[redacted]	[redacted]	£3,692
H-CYC	[redacted]	32.33	22.70	[redacted]	[redacted]	[redacted]	£3,433
AZA	[redacted]	32.89	23.14	[redacted]	[redacted]	[redacted]	£5,098
RTX + MMF	[redacted]	34.84	24.64	[redacted]	[redacted]	[redacted]	£10,174
TAC + MMF	[redacted]	33.66	23.74	[redacted]	[redacted]	[redacted]	£7,249
TAC	[redacted]	33.83	23.87	[redacted]	[redacted]	[redacted]	£6,583

*ICER for VCS + MMF vs comparator

Abbreviations: AZA = azathioprine; ICER = incremental cost-effectiveness ratio; L-CYC = low-dose cyclophosphamide; H-CYC = high-dose cyclophosphamide; LYG = life years gained; MMF = mycophenolate mofetil; QALYs = quality-adjusted life years; RTX = rituximab; TAC = tacrolimus; VS = voclosporin

Table B.3-23. Net health benefit

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	NHB at £20,000	NHB at £30,000
VCS + MMF	[redacted]	[redacted]	-	-	10.354	11.586
MMF	[redacted]	13.08	[redacted]	[redacted]	10.354	11.264
L-CYC	[redacted]	12.73	[redacted]	[redacted]	9.742	10.738
H-CYC	[redacted]	12.69	[redacted]	[redacted]	9.692	10.692
AZA	[redacted]	12.91	[redacted]	[redacted]	10.071	11.018
RTX + MMF	[redacted]	13.49	[redacted]	[redacted]	10.375	11.414
TAC + MMF	[redacted]	13.14	[redacted]	[redacted]	10.258	11.220
TAC	[redacted]	13.19	[redacted]	[redacted]	10.214	11.205

Abbreviations: ICER = incremental cost-effectiveness ratio; LYG = life years gained; QALYs = quality-adjusted life years; NHB = net health benefit

B.3.11 Exploring Uncertainty

B.3.11.1 Probabilistic sensitivity analysis

A probabilistic sensitivity analysis (PSA) was conducted to further explore uncertainty around model inputs by varying all model parameters simultaneously within their respective bounds of uncertainty across 1,000 simulations. PSA scatterplots showing the probabilistic results for voclosporin + MMF versus all relevant comparators are presented in Figure B.3-5 and Figure B.3-6, along with the mean results of the PSA in Table B.3-24. A multi-way cost-effectiveness acceptability curve is also presented in Figure B.3-7.

Table B.3-24. Mean results of PSA (1000 simulations) and comparison with base-case results

Technologies	Total costs (£)		Total QALYs		ICER (£/QALY)*	
	Base case	PSA	Base case	PSA	Base case	PSA
VCS + MMF	[redacted]	[redacted]	[redacted]	[redacted]	-	-
MMF	[redacted]	[redacted]	13.08	[redacted]	£20,001	£20,609
L-CYC	[redacted]	[redacted]	12.73	[redacted]	£10,701	£10,830
H-CYC	[redacted]	[redacted]	12.69	[redacted]	£10,221	£10,394
AZA	[redacted]	[redacted]	12.91	[redacted]	£15,009	£15,556
RTX + MMF	[redacted]	[redacted]	13.49	[redacted]	£20,742	£22,395
TAC + MMF	[redacted]	[redacted]	13.14	[redacted]	£17,864	£17,526
TAC	[redacted]	[redacted]	13.19	[redacted]	£16,737	£16,779

*ICER for VCS + MMF vs comparator

Abbreviations: AZA = azathioprine; CYC = cyclophosphamide; ICER = incremental cost-effectiveness ratio; L-CYC = low-dose cyclophosphamide; H-CYC = high-dose cyclophosphamide; MMF = mycophenolate mofetil; PSA = probabilistic sensitivity analysis; QALY = quality-adjusted life year; RTX = rituximab; TAC = tacrolimus; VCS = voclosporin

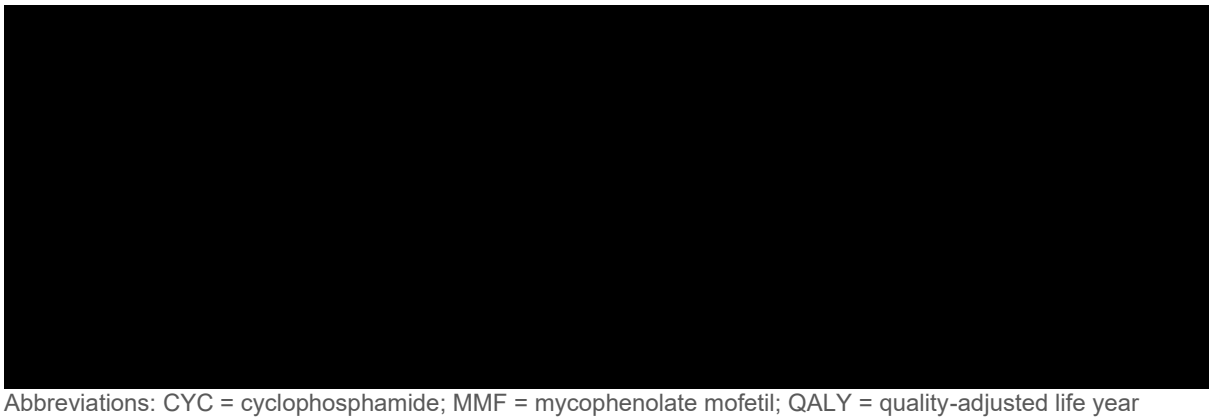
Figure B.3-5. Scatter plot of PSA results for total discounted costs and QALYs

Abbreviations: L-CYC = low-dose cyclophosphamide; H-CYC = high-dose cyclophosphamide; MMF = mycophenolate mofetil; PSA = probabilistic sensitivity analysis; QALY = quality-adjusted life year

Figure B.3-6. Scatter plot of PSA results for incremental discounted costs and QALYs (voclosporin + MMF vs comparators)

Abbreviations: L-CYC = low-dose cyclophosphamide; H-CYC = high-dose cyclophosphamide; MMF = mycophenolate mofetil; PSA = probabilistic sensitivity analysis; QALY = quality-adjusted life year

Figure B.3-7. Cost-effectiveness acceptability curve



Abbreviations: CYC = cyclophosphamide; MMF = mycophenolate mofetil; QALY = quality-adjusted life year

B.3.11.2 Deterministic sensitivity analysis

Deterministic one-way sensitivity analysis (DSA) was conducted to account for input parameter uncertainty in the deterministic base-case model results. All parameters were varied once at a time to the lower and upper bounds of their respective CIs and model results were recorded.

The ten most influential parameters whose uncertainty has the largest impact on the incremental cost, incremental QALY, and ICER estimates for voclosporin + MMF vs MMF are presented in Figure B.3-8 and Figure B.3-9, Figure B.3-10. The key drivers of the model-estimated ICERs included utility in patients in the CKD 1-3a health states, patient age, and transition from AD CKD 1-3a to death and AD CKD 3b-4. DSA results for other comparators are presented in Appendix P.

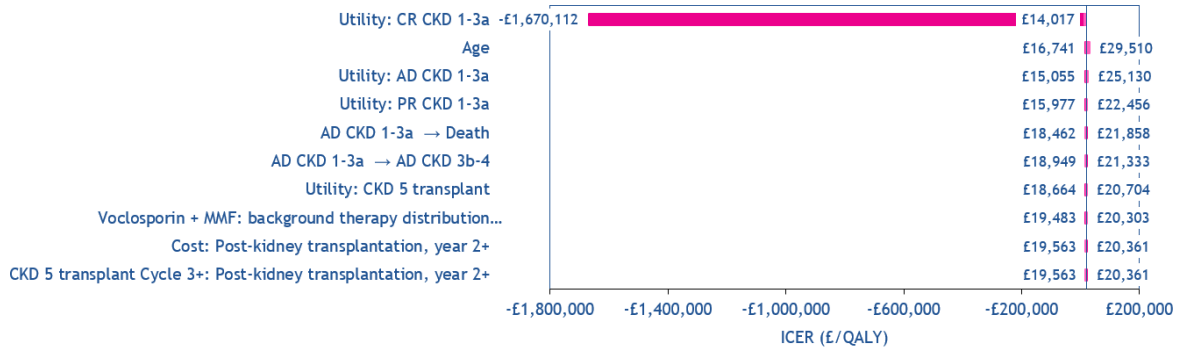
Figure B.3-8. DSA tornado diagram - incremental costs for voclosporin + MMF vs MMF

Abbreviations: AD = active disease; CKD = chronic kidney disease; CR = complete response; DSA = deterministic sensitivity analysis; LN = lupus nephritis; MMF = mycophenolate mofetil

Figure B.3-9. DSA tornado diagram - incremental QALYs for voclosporin + MMF vs MMF

Abbreviations: AD = active disease; CKD = chronic kidney disease; CR = complete response; DSA = deterministic sensitivity analysis; MMF = mycophenolate mofetil; PR = partial response; QALY = quality-adjusted life year

Figure B.3-10. DSA tornado diagram – ICER (£/QALY) for voclosporin + MMF vs MMF*



*The negative value of £-1,670,112 for 'utility: CR CKD 1-3a' is due to voclosporin + MMF having positive incremental cost but an incremental QALY of -0.012, leading to the ICER being negative and highly inflated
Abbreviations: AD = active disease; CKD = chronic kidney disease; DSA = deterministic sensitivity analysis; MMF = mycophenolate mofetil; PR = partial response; QALY = quality-adjusted life year

B.3.11.3 Scenario analysis

Scenario analyses were performed to assess the robustness of economic analysis results by investigating the impact of key methodological, parameter, and structural assumptions/inputs which are associated with some uncertainty. A summary of scenario analyses conducted for voclosporin + MMF compared to MMF only is presented in Table B.3-25.

Table B.3-25. Scenario analyses (voclosporin + MMF versus MMF)

Scenario		VCS + MMF		MMF		ICER (£/QALY)
		Total costs (£)*	Total QALYs*	Total costs (£)*	Total QALYs*	
#	Base case	[redacted]	[redacted]	[redacted]	13.08	£20,001
1 a)	Time horizon: 60 years				13.07	£20,063
1 b)	Time horizon: 40 years				12.49	£22,742
2 a)	Discounting for costs and effects: 0%				23.60	£7,697
2 b)	Discounting for costs and effects: 5%				10.82	£26,950
3 a)	Stopping rule and efficacy: 18 months				12.37	£7,627
3 b)	Stopping rule: 36 months for all treatments**				13.08	£19,479
4 a)	Utilities: CKD 1-3a based on literature				12.04	£19,107
4 b)	Utilities: no age adjustment				13.90	£18,203
5	TTD extrapolation: using AURORA 1 only				13.08	£18,019
6	Wastage: include vial wastage				13.08	£20,001

*Discounted costs and QALYs **Including tacrolimus, which is a subsequent treatment option following MMF
Abbreviations: CKD = chronic kidney disease; ICER = incremental cost-effectiveness ratio; MMF = mycophenolate mofetil; QALY = quality-adjusted life year; TTD = time to treatment discontinuation; VCS = voclosporin

The ICER was found to decrease in all scenarios, apart from when the time horizon and discounting were adjusted, reflecting the conservative assumptions used in the base case.

The largest fluctuations occurred in the scenarios related to discounting, and when the stopping rule and efficacy of all treatments was limited to the first 18 months of AURORA data.

When the discount rate was reduced to 0% for costs and effects, the additional QALY gains made by voclosporin + MMF over a lifetime horizon were not discounted, resulting in higher incremental QALYs and therefore a lower ICER. Similarly, when the QALY gains made by voclosporin + MMF later in life were discounted more heavily, the incremental QALYs decreased, leading to a higher ICER.

Among the scenario analyses, it was considered to be particularly important to explore the impact of shortening the duration of initial treatments from 36 months to 18 months (apart from tacrolimus-containing regimens which remained at 12 months). This was to account for clinician feedback collected within a US-based survey, which suggested that clinicians may keep patients on treatment for no longer than 1.5 years.[137] Results for this scenario analysis are presented in Table B.3-26 and Table B.3-27.

Table B.3-26. Scenario analysis results following adjustment of treatment duration from 36 months to 18 months (apart from TAC-containing regimens)

Technologies	Total costs (£)		Total QALYs		ICER (£/QALY)*	
	Base case	Scenario	Base case	Scenario	Base case	Scenario
VCS + MMF	[redacted]	[redacted]	[redacted]	[redacted]	-	-
MMF	[redacted]	[redacted]	13.08	12.37	£20,001	£7,627
L-CYC	[redacted]	[redacted]	12.73	12.06	£10,701	£594
H-CYC	[redacted]	[redacted]	12.69	12.03	£10,221	£104
AZA	[redacted]	[redacted]	12.91	12.21	£15,009	£3,673
RTX + MMF	[redacted]	[redacted]	13.49	12.74	£20,742	£6,091
TAC + MMF	[redacted]	[redacted]	13.14	12.42	£17,864	£3,505
TAC	[redacted]	[redacted]	13.19	12.46	£16,737	£1,781

*ICER for VCS + MMF vs comparator

Abbreviations: AZA = azathioprine; CYC = cyclophosphamide; ICER = incremental cost-effectiveness ratio; L-CYC = low-dose cyclophosphamide; H-CYC = high-dose cyclophosphamide; MMF = mycophenolate mofetil; PSA = probabilistic sensitivity analysis; QALY = quality-adjusted life year; RTX = rituximab; TAC = tacrolimus; VCS = voclosporin

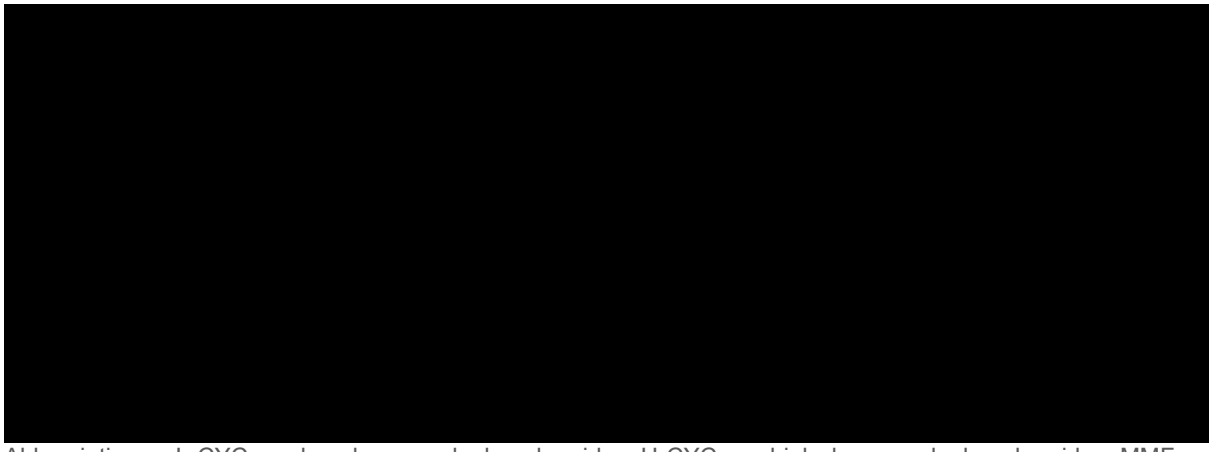
Table B.3-27. Mean results of PSA (1000 simulations) for scenario and comparison with deterministic scenario results

Technologies	Total costs (£)		Total QALYs		ICER (£/QALY)*	
	Scenario	PSA	Scenario	PSA	Scenario	PSA
VCS + MMF	[redacted]	[redacted]	[redacted]	[redacted]	-	-
MMF	[redacted]	[redacted]	12.37	12.31	£7,627	£6,446
L-CYC	[redacted]	[redacted]	12.06	12.02	£594	Dominant
H-CYC	[redacted]	[redacted]	12.03	11.98	£104	Dominant
AZA	[redacted]	[redacted]	12.21	12.16	£3,673	£2,742
RTX + MMF	[redacted]	[redacted]	12.74	12.68	£6,091	£5,583
TAC + MMF	[redacted]	[redacted]	12.42	12.36	£3,505	£1,311
TAC	[redacted]	[redacted]	12.46	12.40	£1,781	Dominant

*ICER for VCS + MMF vs comparator

Abbreviations: AZA = azathioprine; CYC = cyclophosphamide; ICER = incremental cost-effectiveness ratio; L-CYC = low-dose cyclophosphamide; H-CYC = high-dose cyclophosphamide; MMF = mycophenolate mofetil; PSA = probabilistic sensitivity analysis; QALY = quality-adjusted life year; RTX = rituximab; TAC = tacrolimus; VCS = voclosporin

Figure B.3-11. Scenario – Scatter plot of PSA results for total discounted costs and QALYs



Abbreviations: L-CYC = low-dose cyclophosphamide; H-CYC = high-dose cyclophosphamide; MMF = mycophenolate mofetil; PSA = probabilistic sensitivity analysis; QALY = quality-adjusted life year

Figure B.3-12. Scenario - Scatter plot of PSA results for incremental discounted costs and QALYs (voclosporin + MMF vs comparators)

Abbreviations: L-CYC = low-dose cyclophosphamide; H-CYC = high-dose cyclophosphamide; MMF = mycophenolate mofetil; PSA = probabilistic sensitivity analysis; QALY = quality-adjusted life year

Figure B.3-13. Scenario – Cost-effectiveness acceptability curve

Abbreviations: CYC = cyclophosphamide; MMF = mycophenolate mofetil; QALY = quality-adjusted life year

B.3.12 Subgroup analysis

No subgroups were modelled for this economic evaluation.

B.3.13 Benefits not captured in the QALY calculation

There are additional benefits in introducing voclosporin as a treatment option for patients with active LN, which may not have been captured in the QALY calculation:

- Voclosporin's novel molecular structure and mechanism of action eliminate the need for regular therapeutic drug monitoring required with currently available CNIs.[2] Voclosporin therefore has the potential to alleviate the monitoring burden on patients and healthcare professionals.
- Voclosporin is administered orally, whereas some other treatment options for LN (e.g. rituximab) are administered intravenously. There may be potential benefits associated with oral therapy vs therapy delivered intravenously, including a reduced need for hospital visits. The NICE COVID-19 rapid guideline for rheumatological autoimmune, inflammatory and metabolic bone disorders advises on delaying or deferring regular rituximab infusions if possible, and maximising use of home care administration to reduce exposure to COVID-19 and make best use of available hospital resources.[171]

B.3.14 Validation

B.3.14.1 Validation of cost-effectiveness analysis

The cost-effectiveness analysis was subject to an internal quality control check prior to submission. An internal validation comparing the AURORA 1 Phase 3 trial data[109] to the model outcomes in terms of CR and PR rates for voclosporin + MMF and MMF alone was conducted. Model-estimated 12-month CR and PR rates were generally consistent with the raw count data of AURORA 1 (

Table B.3-28).

Table B.3-28. Internal validation of model outputs at 12 months

Treatment	Health state	AURORA 1 data	Model output data
VCS + MMF	CR	40.78%	43.64%
	PR	34.08%	36.50%
MMF	CR	22.47%	25.57%
	PR	29.21%	34.57%

Abbreviations: CR = complete response; MMF = mycophenolate mofetil; PR = partial response; VCS = voclosporin

The model was also reviewed by an external health economist who was not involved in the development of the submission, with feedback incorporated into the model prior to submission.

B.3.15 Interpretation and conclusions of economic evidence

A model was developed to assess the cost-effectiveness of voclosporin in combination with MMF as a treatment of adult patients with active class III, IV, or V (including mixed class III/V and IV/V) LN compared to MMF, cyclophosphamide (with and without MMF), azathioprine, rituximab + MMF, and tacrolimus (with and without MMF). While all comparators specified in the final scope are covered within this submission, MMF is considered to be the most

commonly used first-line initial treatment of LN in UK clinical practice; with rituximab and tacrolimus often used in more severe patients and azathioprine typically limited to maintenance therapy.

As of the date of submission, no other NICE technology appraisals have been completed for the indication of LN. Therefore, a de novo model was developed based on insights collected from published cost-effectiveness models in LN and KOL expert feedback. In line with feedback from KOL experts, the model accounted for all stages of LN-related CKD over a lifetime horizon to account for differing costs, outcomes, and mortality associated with LN patients with CKD stages 1-3a, CKD stages 3b-4, and CKD stage 5 (i.e. ESRD). Health state transitions between AD, PR, and CR were informed by patient-level Phase 3 response data collected across AURORA 1 and AURORA 2 trials for voclosporin + MMF and MMF alone arms (Section B.2), while all other comparators were informed by response outputs of an ITC (Section B.2.9 and Section B.3.3.3). Health state occupancy was further informed by patient-level treatment discontinuation rates collected in the AURORA 1 and AURORA 2 trials for voclosporin + MMF and MMF regimens, although other comparator regimens were assumed to have no discontinuation due to a lack of available TTD data.

In the absence of previous NICE Technology Appraisals for the indication of LN, it is important to note that this expert-informed economic evaluation of LN is both novel and innovative in its approach, and accounts for key limitations of other published LN models (Section B.3.1) by considering both a patient's response to LN treatment and the long-term ramifications of kidney deterioration by modelling progression through CKD. Data limitations are expected for a novel model framework. However, there is a strong rationale for the approach taken over other published cost-effectiveness models which do not accurately reflect patient's transition through CKD health states.

Other key strengths of the model include the fact that CKD 1-3a health state transition probabilities were directly informed by patient-level response and TTD data collected across robust one-year Phase 3 (AURORA 1) and two-year Phase 3 extension (AURORA 2) studies which directly assessed voclosporin + MMF against the current standard of care LN treatment in the UK, MMF. In the absence of other head-to-head data, all other comparator transition probabilities needed to be informed by ITC response data. As well as health state transition probabilities, LN-related CKD 1-3a utility values were also informed by HRQoL data collected directly within AURORA 1 and AURORA 2 using the SF-36 patient questionnaire. Although neither AURORA 1 nor AURORA 2 included UK-based patients, the studies were conducted internationally across Europe, North America, Latin America, South Africa, and Asia and deemed to applicable to UK clinical practice by KOL clinical experts. In accordance with the NICE reference case, the evaluation was also conducted from an NHS and PSS perspective, and can therefore be considered relevant to all patients with class III, IV, or V (including mixed class III/V and IV/V) in the UK.

In the model base-case analysis, voclosporin + MMF was shown to be a cost-effective use of NHS resources relative to all assessed comparators (inclusive of a simple PAS discount of [redacted]% applied to the list price of voclosporin). Parameter uncertainty was explored by PSA, with mean PSA results indicating that voclosporin + MMF remains cost-effective versus all treatments; showing the highest probability of being cost-effective across 1,000 simulations. According to DSA, utility inputs for the CKD 1-3a state was a key driver of model ICER outputs vs MMF; however, utility inputs were informed by SF-36 PRO data collected within the AURORA 1 and AURORA 2 trials mapped to EQ-5D. Furthermore, DSA revealed that

voclosporin + MMF remained cost-effective vs the current standard of care, MMF, when accounting for uncertainty associated with out of the top ten drivers of cost-effectiveness, excluding patient age and utility in the CR CKD 1-3a health.

In conclusion, the clinical and economic evaluations presented within this submission demonstrates that voclosporin (in combination with background immunosuppressive therapies) is a next generation CNI that offers both a clinically effective, and cost-effective treatment option for all patients with active class III, IV or V (including mixed class III/V and IV/V) LN.

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B.5. Appendices

Appendix C. Summary of product characteristics (SmPC) and UK public assessment report (UKPAR)

Appendix D. Identification, selection and synthesis of clinical evidence

Appendix E. Subgroup analysis

Appendix F. Adverse reactions

Appendix G. Published cost-effectiveness studies

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

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

Appendix J. Clinical outcomes and disaggregated results from the model

Appendix K. Price details of treatments included in the submission

Appendix L. Checklist of confidential information

Appendix M. Clinical effectiveness – supplementary information

Appendix N. SF-36 results

Appendix O. Summary of base-case analysis inputs

Appendix P. DSA tornado diagrams

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

Voclosporin with immunosuppressive therapies for treating lupus nephritis [ID3962]

Clarification questions

June 2022

File name	Version	Contains confidential information	Date
ID3962 voclosporin clarification questions	1	Yes	20/06/2022

Notes for company

Highlighting in the template

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

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

Section A: Clarification on effectiveness data

Literature searching

A1. Appendix D Table B.5-1. Were Medline and Embase both searched together in Proquest at the same time or have they just been presented in that way in the table?

Medline and Embase were both searched together at the same time and search results were presented in Appendix D, Table B.5-1.

A2. Appendix D Table B.5-1. Which RCT filter have you have used for the Medline and Embase searches?

Current randomised controlled trial (RCT) filters were based on both Scottish Intercollegiate Guidelines Network (SIGN) and Canada's Drug and Health Technology Agency (CADTH) filters. We combined the relevant search strings from both (SIGN and CADTH) filters to develop current search strategy for RCTs.

A3. Appendix D.1.1.1 Were any clinical trials registers searched? Please provide details of any such searches.

Clinical trial registers were not searched in the company submission (CS).

A4. Appendix D.1.1.3 p35. Please provide the Excel spreadsheet of excluded studies as a separate document, the embedded link does not work.

Excel spreadsheet of excluded studies is attached along with response document.

A5. Adverse events. Submission section B.3.4.4. reports "AE disutility values and duration of AEs were informed by the SLR (Appendix H) and *additional targeted PubMed searches*." Please provide further details of these searches and the search strategies used.

Clinical systematic literature review (SLR) search strategy was not restricted by efficacy or safety outcomes. AE disutility values for pneumonia and gastroenteritis were collected from Kim et al., 2019, a study identified within the economic SLR.[1] All other studies that reported relevant AE disutility values and duration of AEs were identified within previous NICE Technology Appraisals. Additional PubMed searches did not uncover any addition adverse event (AE)-related information. Therefore, assumptions were used to fill any remaining data gaps where necessary.

Clinical effectiveness

A6. Can you please clarify whether there was a reason that centres in the UK did not participate in the included trials?

Although the United Kingdom (UK) did form part of the feasibility process for AURA-LV and AURORA 1, UK sites were not ultimately approached for inclusion due to the general understanding that interest/uptake would be greater elsewhere in Europe.

A7. For AURORA 2 and AURA-LV, can you please provide data for the individual outcomes that make up the composite CRR outcome?

A summary of AURORA 2 and AURA-LV composite complete renal response (CRR) outcomes data is presented in Table 1 and

Table 2, respectively.

Table 1. AURORA 2: Summary of CRR at Week 48 and composites of CRR

	Patients, n (%)		OR (95% CI)	p value
	Voclosporin n=116	Placebo n=100		
CRR at Month 18	74 (63.8)	46 (46.0)	2.19 (1.3, 3.8)	0.006
Composites of CRR				
UPCR ≤ 0.5 mg/mg	[redacted]	[redacted]	[redacted]	[redacted]
eGFR success*	[redacted]	[redacted]	[redacted]	[redacted]
Received no rescue medication for LN	[redacted]	[redacted]	[redacted]	[redacted]
No withdrawal	[redacted]	[redacted]	[redacted]	[redacted]
Did not receive > 10 mg/day prednisone for ≥ 3 consecutive days or for ≥ 7 days	[redacted]	[redacted]	[redacted]	[redacted]
CRR at Month 24	65 (56.0)	43 (43.0)	1.81 (1.0, 3.2)	0.035
Composites of CRR				
UPCR ≤ 0.5 mg/mg	[redacted]	[redacted]	[redacted]	[redacted]
eGFR success*	[redacted]	[redacted]	[redacted]	[redacted]
Received no rescue medication for LN	[redacted]	[redacted]	[redacted]	[redacted]
No withdrawal	[redacted]	[redacted]	[redacted]	[redacted]
Did not receive > 10 mg/day prednisone for ≥ 3 consecutive days or for ≥ 7 days	[redacted]	[redacted]	[redacted]	[redacted]
CRR at Month 30	69 (59.5)	42 (42.0)	2.24 (1.3, 3.9)	0.005
Composites of CRR				
UPCR ≤ 0.5 mg/mg	[redacted]	[redacted]	[redacted]	[redacted]
eGFR success*	[redacted]	[redacted]	[redacted]	[redacted]
Received no rescue medication for LN	[redacted]	[redacted]	[redacted]	[redacted]
No withdrawal	[redacted]	[redacted]	[redacted]	[redacted]
Did not receive > 10 mg/day prednisone for ≥ 3 consecutive days or for ≥ 7 days	[redacted]	[redacted]	[redacted]	[redacted]
CRR at Month 36	59 (50.9)	39 (39.0)	1.74 (1.0, 3.0)	0.051
Composites of CRR				
UPCR ≤ 0.5 mg/mg	[redacted]	[redacted]	[redacted]	[redacted]
eGFR success*	[redacted]	[redacted]	[redacted]	[redacted]
Received no rescue medication for LN	[redacted]	[redacted]	[redacted]	[redacted]
No withdrawal	[redacted]	[redacted]	[redacted]	[redacted]
Did not receive > 10 mg/day prednisone for ≥ 3 consecutive days or for ≥ 7 days	[redacted]	[redacted]	[redacted]	[redacted]

*eGFR ≥ 60, eGFR < 60 with no confirmed decrease of > 20% from baseline, eGFR < 60 with confirmed decrease of > 20% but with no disease-related or treatment-related eGFR associated AE present at time of assessment

Abbreviations: AE = adverse event; CI = confidence interval; CRR = complete renal response; eGFR = estimated glomerular filtration rate; LN = lupus nephritis; mg = milligram; OR = odds ratio; UPCR = urine protein creatinine ratio

Source: Otsuka 20222

Table 2. AURA-LV: Summary of CRR at Week 48 and composites of CRR

	Patients, n (%)		OR (95% CI)	p value
	Voclosporin 23.7mg BID n=89	Placebo n=88		
CRR at Week 48	44 (49.4)	21 (23.9)	3.21 (1.7, 6.1)	<0.001
Composites of CRR				
UPCR ≤ 0.5 mg/mg	[redacted]	[redacted]	[redacted]	[redacted]
eGFR success*	[redacted]	[redacted]	[redacted]	[redacted]
Received no rescue medication for LN	[redacted]	[redacted]	[redacted]	[redacted]
No withdrawal	[redacted]	[redacted]	[redacted]	[redacted]
Did not receive > 10 mg/day prednisone for ≥ 3 consecutive days or for ≥ 7 days	[redacted]	[redacted]	[redacted]	[redacted]

*eGFR ≥ 60 or eGFR < 60 with no confirmed decrease of > 20% from baseline

Abbreviations: AE = adverse event; BID = twice daily; CI = confidence interval; CRR = complete renal response; eGFR = estimated glomerular filtration rate; LN = lupus nephritis; mg = milligram; OR = odds ratio; UPCR = urine protein creatinine ratio

Source: Otsuka 2020 and 20223,4

A8: For each trial, can you please provide the numbers of patients who did not experience a ≥20% decrease in eGFR?

A summary of the number of patients who did not experience a confirmed >20% decrease in estimated glomerular filtration rate (eGFR) from baseline at any time is presented for each trial in Table 3.

Table 3. Logistic regression of confirmed decrease from baseline in eGFR (>20%)

	AURORA 1		AURORA 2		AURA-LV	
	VCS (n=179)	PbO (n=178)	VCS	PbO	VCS 23.7 mg BID	PbO
Patients who did not experience >20% decrease in eGFR, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: BID = twice daily; eGFR = estimated glomerular filtration rate; mg = milligrams; OR = odds ratio; PbO = placebo; VCS = voclosporin

Source: Otsuka 2022[5]

A9. Please can you confirm that rates of PRR reported for the three trials include those participants that went on to achieve a CRR, and that the rates of PRR included in the NMA are those participants who achieved a PRR without ever achieving a CRR? If this is the case, can you please report the number of participants who achieved a PRR without a CRR for AURORA 2 and AURA-LV?

Yes, it can be confirmed for AURORA-1 and the base case NMA. The inputs included in the base case network meta-analysis (NMA; used to inform the economic model) represents patients who independently achieved partial renal response (PRR) without achieving CRR at 12-months follow-up. For the scenario analysis at 6-months, the number of partial responders is likely to include several patients who then went on to achieve CRR during the 6-12-month period. The number of participants who achieved PRR without achieving CRR values was calculated using the IPD, the table below includes the values calculated from the IPD analyses. PRR data was calculated from the larger Phase 3 trial, AURORA-1, rather than the Phase 2 study, AURA-LV.

Table 4. Partial responders calculated from AURORA-1 via count data from the IPD

	Voclosporin + MMF (n=179)	Placebo + MMF (n=178)
Month 6 status	[redacted]	[redacted]
Month 12 status	[redacted]	[redacted]

Abbreviations: IPD = individual patient data; n = Number
Source: Otsuka 2021[6]

As mentioned in Appendix D section D.1.1.4, AURORA-2 was excluded from the NMA due to the difference in follow-up times between AURORA-2 and the comparator trials included in the network. AURORA-2 had a longer follow-up time than all other included trials. Therefore, its inclusion would bias the comparison.

In response to this question, it was noticed that a mistake was made in the base case and scenario analysis networks for PRR. This mistake refers to the PRR numbers for both arms from the AURORA-1 study, the 12-month values and the 6-month values were in fact the wrong way around. A reanalysis has been performed for both the base case NMA and scenario analysis NMAs. As the base case NMA

was incorrect this has also affected the base case of the cost-effectiveness analysis. The re-analysis of the cost effectiveness provided in section C now contains the input data from the NMA with the correct number of partial responders.

For the PRR re-analysis, the NMA indicated that [redacted] has a high probability (≥95%) of being more efficacious than MMF in the overall population based on studies that reported partial responders independently from those who achieved a CRR (median OR [redacted] [95% CrI: [redacted]]. On the other hand, neither [redacted] were significantly different to MMF in achieving PRR. Furthermore, the surface under the cumulative ranking curve (SUCRA) demonstrated that voclosporin + MMF was the third most likely regimen to be the preferred treatment option when considering an independent PRR (SUCRA: [redacted]%), behind rituximab + MMF ([redacted]%) and tacrolimus ([redacted]%).

Table 5 Results of the base case PRR NMA

Treatment	Median OR (vs. MMF)	CrI 2.5%	CrI 97.5%	SUCRA
MMF	Ref	Ref	Ref	[redacted]
VCS+MMF	[redacted]	[redacted]	[redacted]	[redacted]
H-CYC	[redacted]	[redacted]	[redacted]	[redacted]
L-CYC	[redacted]	[redacted]	[redacted]	[redacted]
RTX+MMF	[redacted]	[redacted]	[redacted]	[redacted]
TAC	[redacted]	[redacted]	[redacted]	[redacted]
Model selections statistics: DIC = 32.26, pD = 15.18, Residual deviance = 17.90				

Abbreviations: CrI = credible interval; DIC = deviance information criterion; H-CYC = high-dose cyclophosphamide; L-CYC = low-dose cyclophosphamide; MMF = mycophenolate mofetil; OR = odds ratio; RTX = rituximab; SUCRA = surface under the cumulative ranking curve; TAC = tacrolimus; VCS = voclosporin

Figure 1. Forest plot for posterior median ORs and 95% CrI, for PRR base case

Abbreviations: CrI = credible interval; CRR = complete renal response; H-CYC = high-dose cyclophosphamide; L-CYC = low-dose cyclophosphamide; MMF = mycophenolate mofetil; OR = odds ratio; RTX = rituximab; TAC = tacrolimus; VCS = voclosporin

Table 6. Pairwise odds ratios for PRR, OR (95% CrI)

	MMF	VCS+MMF	H-CYC	L-CYC	RTX+MMF	TAC
MMF vs						
VCS+MMF vs						
H-CYC vs						
L-CYC vs						
RTX+MMF vs						
TAC vs						

Abbreviations: CrI = credible interval; CRR = complete renal response; H-CYC = high-dose cyclophosphamide; L-CYC = low-dose cyclophosphamide; MMF = mycophenolate mofetil; OR = odds ratio; RTX = rituximab; TAC = tacrolimus; VCS = voclosporin

Table 7. Results of scenario analyses: restricting follow-up to at least 6-months

	Fixed effects				Random effects			
Treatment	Median OR (vs. MMF)	CrI 2.5%	CrI 97.5%	SUCRA	Median OR (vs. MMF)	CrI 2.5%	CrI 97.5%	SUCRA
MMF	Ref	Ref	Ref	[redacted]	Ref	Ref	Ref	[redacted]
VCS+MMF	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
H-CYC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
L-CYC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
RTX+MMF	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TAC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Tau	NA				0.62			
Model selection statistics FE: DIC = 24.88, pD = 12.15, Residual deviance = 12.73 RE: DIC = 26.74., pD = 13.26, Residual deviance = 13.48								

Abbreviations: CrI = credible interval; DIC = deviance information criterion; FE = fixed effects; H-CYC = high-dose cyclophosphamide; L-CYC = low-dose cyclophosphamide; MMF = mycophenolate mofetil; NA = not applicable; OR = odds ratio; RE = random effects; RTX = rituximab; SUCRA = surface under the cumulative ranking curve; TAC = tacrolimus; VCS = voclosporin

Table 8. Results of scenario analyses: restricting follow-up to at least 12-months

Treatment	Median OR (vs. MMF)	CrI 2.5%	CrI 97.5%	SUCRA
MMF	Ref	Ref	Ref	[redacted]
VCS+MMF	[redacted]	[redacted]	[redacted]	[redacted]
H-CYC	[redacted]	[redacted]	[redacted]	[redacted]
L-CYC	[redacted]	[redacted]	[redacted]	[redacted]
RTX+MMF	[redacted]	[redacted]	[redacted]	[redacted]
TAC	[redacted]	[redacted]	[redacted]	[redacted]
Model selection statistics FE: DIC = 20.77, pD = 10.39, Residual deviance = 10.39				

Abbreviations: CrI = credible interval; DIC = deviance information criterion; FE = fixed effects; H-CYC = high-dose cyclophosphamide; L-CYC = low-dose cyclophosphamide; MMF = mycophenolate mofetil; NA = not applicable; OR = odds ratio; RE = random effects; RTX = rituximab; SUCRA = surface under the cumulative ranking curve; TAC = tacrolimus; VCS = voclosporin

Table 9. Results of scenario analyses: excluding trials with a significantly different outcome definition

Treatment	Median OR (vs. MMF)	CrI 2.5%	CrI 97.5%	SUCRA
MMF	Ref	Ref	Ref	[redacted]
VCS+MMF	[redacted]	[redacted]	[redacted]	[redacted]
H-CYC	[redacted]	[redacted]	[redacted]	[redacted]
L-CYC	[redacted]	[redacted]	[redacted]	[redacted]
RTX+MMF	[redacted]	[redacted]	[redacted]	[redacted]
TAC	[redacted]	[redacted]	[redacted]	[redacted]
Model selections statistics: DIC = 29.98, pD = 14.26, Residual deviance = 15.72				

Abbreviations: Cr =, credible interval; DIC = deviance information criterion; H-CYC = high-dose cyclophosphamide; L-CYC = low-dose cyclophosphamide; MMF = mycophenolate mofetil; O =, odds ratio; RTX = rituximab; SUCRA = surface under the cumulative ranking curve; TAC = tacrolimus; VCS = voclosporin

Table 10. Results of scenario analyses: excluding trials with a 100% Asian patient population

Treatment	Median OR (vs. MMF)	CrI 2.5%	CrI 97.5%	SUCRA
MMF	Ref	Ref	Ref	[redacted]
VCS+MMF	[redacted]	[redacted]	[redacted]	[redacted]
H-CYC	[redacted]	[redacted]	[redacted]	[redacted]
L-CYC	[redacted]	[redacted]	[redacted]	[redacted]
RTX+MMF	[redacted]	[redacted]	[redacted]	[redacted]
Model selections statistics: DIC = 22.65, pD = 11.16, Residual deviance = 11.49				

Abbreviations: CrI = credible interval; DIC = deviance information criterion; H-CYC = high-dose cyclophosphamide; L-CYC = low-dose cyclophosphamide; MMF = mycophenolate mofetil; OR = odds ratio; RTX = rituximab; SUCRA = surface under the cumulative ranking curve; TAC = tacrolimus; VCS = voclosporin

A10. Please provide reasons for permanent treatment discontinuation for the patients who completed AURORA 1 but did not enrol in AURORA 2 (with numbers separated by study arm). In particular, we are interested in the numbers of patients in each arm who discontinued due to: response; lack of response; and AEs. Please can you also comment on whether there were baseline differences between those who did and did not enter AURORA 2?

Reasons for permanent treatment discontinuation for patients who completed AURORA 1 but did not enrol in AURORA 2 are summarised in Table 11.

Table 11. Reasons for permanent treatment discontinuation among patients who completed AURORA 1, but did not enrol in AURORA 2

Reason for discontinuation, n (%)	AURORA 1	
	VCS (n=27)*	PbO (n=28)
AE	[redacted]	[redacted]
Protocol non-compliance	[redacted]	[redacted]
Pregnancy	[redacted]	[redacted]
Physician decision	[redacted]	[redacted]
Prohibited medication required	[redacted]	[redacted]
Lack of efficacy	[redacted]	[redacted]
Other	[redacted]	[redacted]

*Please note that the AURORA 2 clinical study report incorrectly reported that 56 patients (28 in each arm) in AURORA 1 permanently discontinued study treatment but went on to complete the AURORA 1 study, yet did not enrol in AURORA 2. Instead, among the 141 patients that enrolled in AURORA 1 but did not enrol in AURORA 2, 55 patients (27 in voclosporin arm and 28 in placebo arm) who completed AURORA 1 (i.e. did not withdraw from the study) had permanently discontinued study treatment during AURORA 1.
Abbreviations: AE = adverse event; PbO = placebo; VCS = voclosporin
Source: Otsuka 2022[5]

A11. For inclusion in the analysis for renal flares, was an adequate renal response defined as either CRR or PRR?

In AURORA 2, patients were considered to have an adequate renal response by the Clinical Endpoints Committee if they achieved urine protein to creatinine ratio (UPCR) ≤0.7 milligram (mg)/mg.[2]

A12. For clarity, was the analysis of 'patients with good renal outcomes' a post hoc analysis?

The endpoint of 'good renal outcome' (defined as adequate renal response [UPCR ≤0.7 mg/mg] and no renal flare) was a post-hoc analysis, although the renal flare component of 'good renal outcome' was a pre-specified analysis for AURORA 2.[7]

A13. Please provide missing variance data for outcomes of AURA-LV where these are not reported in the CS, including covariate analyses

Where relevant, variance data has been added to excerpts from Document B that describe outcomes for AURA-LV (presented below). Additional variance data has been underlined to aid review.

AURA-LV: Partial renal response at Week 24 and 48 (secondary endpoint)

At Week 24, partial renal response was achieved by a higher proportion of patients in both the low-dose (69.7%) and high-dose (65.9%) voclosporin groups compared to the placebo group (49.4%).[3] Low-dose or high-dose voclosporin had double the odds of achieving partial renal response at Week 24 compared to patients in the placebo group (odds ratio [OR] 2.33; [95% confidence interval (CI): 1.26, 4.33]; p=0.007 and OR=2.03; [95% CI: 1.10, 3.76]; p=0.024, respectively).[3] Results were similar at Week 48, with even higher odds demonstrated for the high-dose voclosporin group versus placebo (OR 2.68; [95% CI: 1.43, 5.02]; p=0.002).[3]

AURA-LV: Time to complete renal response (secondary endpoint)

CRR occurred statistically significantly earlier in patients treated with either low-dose or high-dose voclosporin compared to placebo (hazard ratio [HR] 2.26; [95% CI: 1.45, 3.51]; p<0.001, and HR 2.25; [95% CI: 1.46, 3.47]; p<0.001, respectively).[3] The median time to CRR was 19.7 weeks (95% CI: 16.1, 36.1) in the low-dose voclosporin group and 23.4 weeks (95% CI: 13.7, 33.4) in the high-dose voclosporin group.[3]

AURA-LV: Time to partial renal response, sustained partial renal response, and sustained early partial renal response (secondary endpoint)

Partial renal response occurred significantly earlier in patients treated with either low-dose or high-dose voclosporin compared to placebo (HR 1.63; [95% CI: 1.16, 2.27]; p=0.005, and HR 1.74; [95% CI: 1.25, 2.43]; p=0.002, respectively). The median time

to partial renal response was 4.3 (95% CI: 2.6, 5.9) and 4.4 (95% CI: 4.1, 6.1) weeks in the low-dose and high-dose voclosporin groups, respectively, compared to 6.6 weeks (95% CI: 4.6, 8.6) in the placebo group.[3,8]

Compared to placebo, sustained partial renal response occurred significantly earlier in patients treated with either low-dose voclosporin (HR=2.03; [95% CI: 1.36, 3.03]; p<0.001) or high-dose voclosporin (HR=1.81; [95% CI: 1.22, 2.69]; p=0.004).[3] The median time to sustained partial renal response was 26.9 weeks (95% CI: 16.1, not reached) in the placebo group, compared to 6.3 weeks (95% CI: 4.0, 11.9) in the low-dose voclosporin group and 8.1 weeks (95% CI: 6.1, 16.6) in the high-dose voclosporin group.[3]

Sustained early partial renal response was achieved by a higher proportion of patients in both the low-dose (67.4%) and high-dose (65.9%) voclosporin groups compared to the placebo group (41.4%).[3] Both voclosporin dose groups demonstrated that significantly increased odds of achieving sustained early partial renal response compared to patients in the placebo group.[3] The patients treated with low-dose voclosporin had an OR of 2.93 (95% CI: 1.58, 5.43) compared to those treated with placebo (p<0.001) and the patients treated with high-dose voclosporin had an OR of 2.74 (95% CI: 1.48, 5.07) compared to those treated with placebo (p=0.021).[3]

Compared to placebo, time to sustained early partial renal response occurred significantly earlier in patients treated with either low-dose voclosporin (HR=2.21; [95% CI: 1.45, 3.36]; p<0.001) or high-dose voclosporin (HR=1.87; [95% CI: 1.23, 2.84]; p=0.004).[3] The median time to sustained early partial renal response was 6.3 weeks (95% CI: 4.0, 11.9) in the low-dose voclosporin group and 8.1 weeks (95% CI: 6.1, 16.6) in the high-dose voclosporin group. Median time to CRR could not be determined for the placebo group.[3]

AURA-LV: Disease activity

Mean Systemic Lupus Erythematosus Disease Activity Index (SELENA-SLEDAI)scores improved (i.e., decreased) in all 3 treatment groups. Changes from baseline in mean SELENA-SLEDAI scores were significantly greater for both the low-dose

and high-dose voclosporin groups compared with placebo at Week 24 (p=0.003 for both comparisons) and at Week 48 (p<0.001 for both comparisons; Table 12).[3]

Table 12. AURA-LV: Mean Change from Baseline in SELENA-SLEDAI Scores at Week 24 and Week 48

	Voclosporin (low-dose)* *n=74 at Week 24 n=77 at Week 48*	**Voclosporin (high-dose)†** *n=82 at Week 24 n=82 at Week 48*	**Placebo** *n=76 at Week 24 n=79 at Week 48*
Week 24, change in score (SD; min, max)	-6.3 (5.86; -25, 6)‡	-7.1 (7.41; -26, 10)‡	-4.5 (7.09; -26,12)
Week 48, change in score (SD)	-7.9 (6.39; -25, 8)‡	-8.3 (6.93; -26, 6)‡	-5.3 (6.85; -28, 8)

*23.7 mg BID; †39.5 mg BID; ‡Significant difference compared with placebo (p<0.05) in ANCOVA for the change from baseline

Abbreviations: ANCOVA = analysis of covariance; CI = confidence interval; SD = standard deviation; SELENA-SLEDAI = Safety of Estrogens in Lupus Erythematosus National Assessment - Systemic Lupus Erythematosus Disease Activity IndexNote: a decrease in SELENA-SLEDAI score indicates improvement

Source: Otsuka 2018[3]

A14. The results of the AURORA 1 subgroup analyses are reported in the cost effectiveness chapter of the CS, and cross-references to the results of the subgroup analyses are incorrect. We also seem to be missing the results of covariate analyses in either the CS or the appendices. For completeness, can you please provide the full results of all subgroup and covariate analyses in your response?

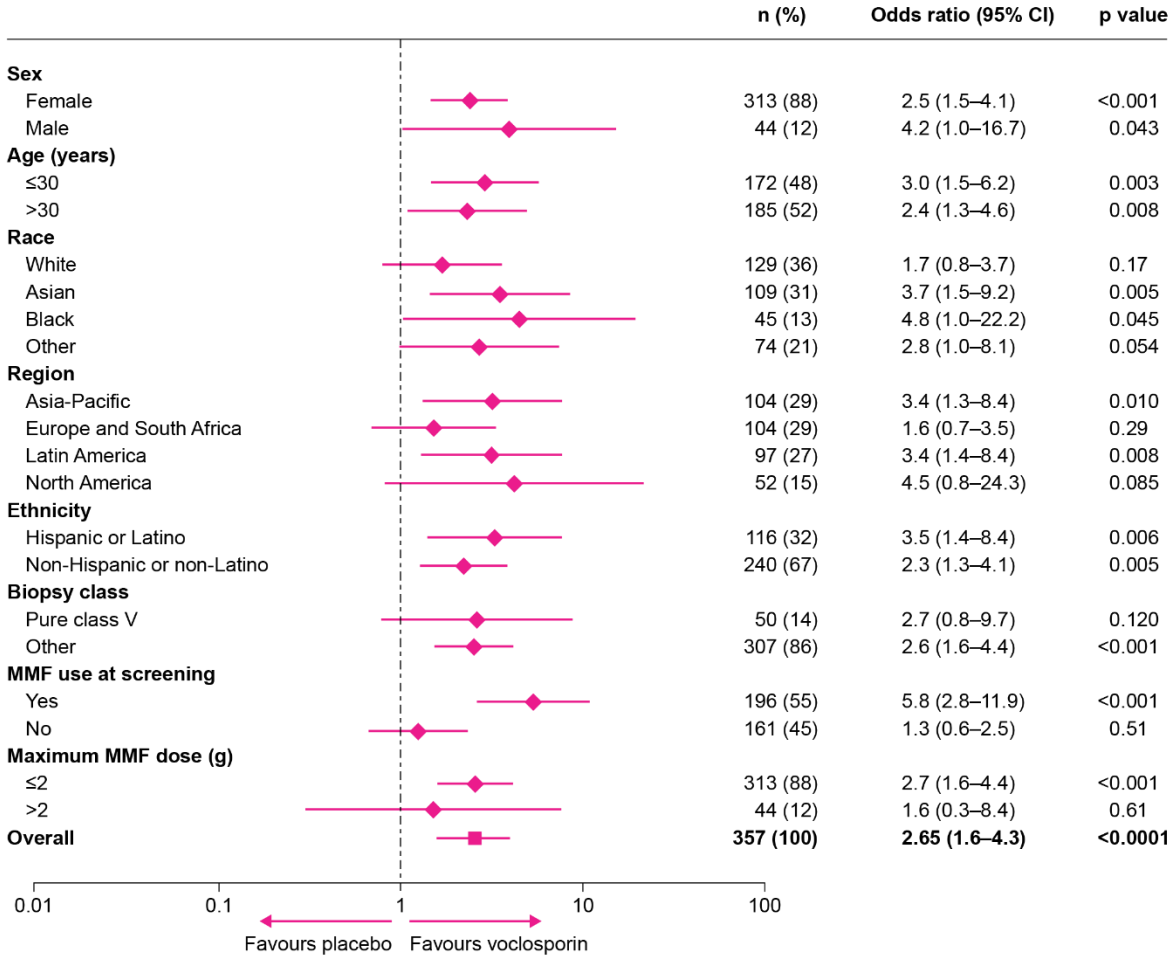
In AURORA 1, covariate analyses were performed for the primary endpoint of CRR at Week 52 for the pre-specified subgroups of:

- Age (≤30 vs >30 years)
- Gender (male, female)
- Race (White, Asian, other)
- Biopsy class (class V, other)
- Region (Asia-Pacific, Europe and South Africa, Latin America, North America)
- MMF use at screening (yes, no)
- Maximum MMF dose (≤2 g vs >2 g)

These analyses indicated that voclosporin was consistently associated with a higher CRR at Week 52 across all subgroups (

Figure 2).[9]

Figure 2. AURORA 1: Subgroup analyses of CRR at Week 52



Abbreviations: CI = confidence interval; CRR = complete renal response; g = gram; MMF = mycophenolate mofetil; n = number of patients in category

Analysis uses a logistic regression model with covariates for study, treatment group, subgroup, and treatment by subgroup interaction. Race and ethnicity analyses were post hoc. MMF use at screening was determined by nominal yes or no question at screening visit. Maximum MMF dose reflects the maximum daily dose of MMF received during the study.

Source: Rovin et al. 2021[9]

A15. Based on the subgroup analysis for CRR from the AURORA 1 trial, there appears to be a different response to treatment with voclosporin depending on whether patients were receiving MMF at baseline. This pattern is not replicated in the AURA-LV trial. Can you please comment on the following, providing supplementary data as required:

- **Can you please advise the duration of MMF treatment participants were receiving at baseline of each trial?**
- **For each trial, please advise were participants receiving MMF at baseline as treatment for lupus nephritis, or for SLE? If receiving the treatment for lupus nephritis, please confirm that these participants could be considered as not responsive to MMF at the time of entry to the trial.**
- **For each trial, please provide some demographic information about those receiving and not receiving MMF at baseline; for example, disease severity indicators or other prognostic markers**
- **While we understand that additional subgroup analyses were not planned and are not powered in these studies, we would be interested to view other subgroup analyses exploring whether the effect of voclosporin on PRR varies according to MMF use at baseline.**

In each trial, patients receiving MMF at screening were receiving MMF as a treatment for lupus nephritis. MMF at screening was defined as the subject being prescribed MMF at the screening visit, i.e. within 30 days prior to the start of study treatment. However, the specific duration of MMF was not recorded, meaning that we cannot determine how long a patient had been treated with MMF prior to the screening visit. As we cannot determine the duration of MMF prior to screening, it is not possible to confirm that patients on MMF at screening were non-responsive to treatment. Demographic information by MMF at screening has also not been reported for either AURORA 1 or AURA-LV.

In AURORA 1, 55.9% (n/N=100/179) and 53.9% (n/N = 96/178) of patients were receiving MMF at screening in the voclosporin and placebo arms, respectively.[9] In AURA-LV, the proportion of patients that were receiving MMF at screening was

lower in each arm (32.6% [n/N = 29/89] and 35.2% n/N=31/88] for voclosporin and placebo arms, respectively).[8] CRR rates at 1-year for subjects treated with voclosporin were broadly similar for subjects with or without MMF at screening in both AURORA 1 and AURA-LV, with a logistic regression analysis demonstrating a trend in favour of voclosporin (vs placebo) both in patients that received MMF at screening, and those who did not receive MMF at screening (Table 13). Random variation alone will result in subgroups with response rates that are higher or lower than those for the whole population. Beyond this random variation, there is no other obvious explanation for the differences seen.

Table 13. CRR at 1 Year (controlling for MMF at screening)

	AURORA 1		AURA-LV	
	VCS*	PbO	VCS*	PbO
MMF at screening				
n	100	96	29	31
CRR, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
No CRR, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
OR (vs PbO)	[redacted]		[redacted]	
95% CI	[redacted]		[redacted]	
p-value	[redacted]		[redacted]	
No MMF at screening				
n	79	82	60	57
CRR, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
No CRR, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
OR (vs PbO)	[redacted]		[redacted]	
95% CI	[redacted]		[redacted]	
p-value	[redacted]		[redacted]	

*23.7 mg BID

Abbreviations: BID = twice daily; CI = confidence interval; CRR = complete renal response; mg = milligrams; OR = odds ratio; PbO = placebo; VCS = voclosporin

Source: Otsuka 2022[10]

In accordance with the trial protocols, subgroup analyses to explore the effect of voclosporin on PRR according to MMF use at baseline have not been conducted to date for AURORA 1. However, a subgroup analysis has been conducted for the pooled population across both AURORA 1 and AURA-LV trials for PRR at 1 Year according to MMF use at screening.[11] A significant treatment benefit was observed in the voclosporin arm relative to the placebo arm for both patients receiving MMF at

screening (n/N= [redacted]; OR = [redacted] [95% CI: [redacted]]; p=[redacted]) and those who were not receiving MMF at screening (n/N= [redacted]; OR = [redacted] [95% CI: [redacted]]; p=[redacted]).[11]

A16. While we appreciate few centres in AURORA 1 grouped with Europe were based in South Africa, can you please provide a subgroup analysis for CRR limited to centres in Europe?

AURORA 1 was not powered to identify a significant difference between the limited number of European patients in each treatment arm.[12] Despite this, subgroup analysis of CRR rates recorded in European centres indicates a trend in favour of voclosporin (Table 14). In line with the very small sample size, the potentially favourable treatment effect was not significant in this select population of patients.

Table 14. AURORA 1: Logistic regression of CRR at Week 52 (1-year) in European subjects only

	AURORA 1	
	VCS n = 46	PbO n = 51
CRR, n (%)	[redacted]	[redacted]
OR	[redacted]	
p-value	[redacted]	

*Extent of exposure is presented across both AURORA 1 and AURORA 2 trials
Abbreviations: CRR = complete renal response; OR = odds ratio; PbO = placebo; VCS = voclosporin
Source: Otsuka 2022[12]

A17. Please provide 95% CIs for the outcomes of the pooled pairwise meta-analyses

Where appropriate, 95% CIs for the outcomes of the pooled pairwise meta-analysis (B.2.8 of Document B) have been added to an excerpt below and underlined.

As part of the pooled pairwise meta-analysis, CRR rates were significantly greater in the voclosporin arm compared to the placebo arm at both six months (31.7% vs 20.3%, respectively; OR: 2.01 [redacted], p=0.008) and one year (43.7% vs 23.3%, respectively; OR: 2.76 [redacted], p<0.0001).[11,13] Similarly, a significantly greater proportion of patients achieved PRR in the voclosporin arm at both six months (70.1% vs 49.8%; OR: 2.42 [redacted]; p=<0.0001) and one year (69.4% vs 50.6%; OR: 2.26 [redacted]; p<0.0001) compared to placebo.[11]

A ≥50% UPCR reduction was also achieved in 93.7% of patients in the voclosporin arm, and 75.2% of patients in the control arm; and the median time to ≥50% UPCR reduction was significantly shorter for voclosporin relative to placebo (29 days vs 58 days, respectively; HR: 1.96 [redacted], p<0.0001).[11,13]

A18. Please provide exposure data (duration and dose intensity) for MMF and corticosteroids in the treatment and placebo arms of the trials

Extent of exposure to MMF and corticosteroids is presented in Table 15 and

Table 16, respectively, for each of the trials.

Table 15. Extent of exposure to MMF

	AURORA 1		AURORA 2*		AURA-LV		
	VCS	PbO	VCS	PbO	VCS 23.7 mg BID	VCS 39.5 mg BID	PbO
n	[redacted]	[redacted]	[redacted]	[redacted]	-	-	-
Median duration of exposure, days (range)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median exposure, g/day (range)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

*Extent of exposure is presented across both AURORA 1 and AURORA 2 trials

Abbreviations: g = gram; MMF = mycophenolate mofetil; n = number of patients in category; NR = not reported; PbO = placebo; VCS = voclosporin

Source: Otsuka 2018, 2020 and 2022[2,3,14]

Table 16. Extent of exposure to corticosteroids

	AURORA 1		AURORA 2*		AURA-LV		
	VCS	PbO	VCS	PbO	VCS 23.7 mg BID	VCS 39.5 mg BID	PbO
IV methylprednisolone							
n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median duration of exposure, days (range)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median total exposure, g (range)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Oral corticosteroids, prednisone equivalent							
n	[redacted]						
Median duration of exposure, days (range)	[redacted]						
Median exposure, mg/day (range)	[redacted]						

*Extent of exposure is presented across both AURORA 1 and AURORA 2 trials

Abbreviations: BID = twice daily; g = gram; kg = kilogram; mg = milligram; MMF = mycophenolate mofetil; n = number of patients in category; PbO = placebo; VCS = voclosporin

Source: Otsuka 2018, 2020 and 2022[2,3,14]

In AURORA 1, patients were scheduled to receive intravenous (IV) methylprednisolone over Days 1 and 2 (subjects <45 kilogram [kg]: 0.25 gram [g]/day and ≥45kg: 0.5 g/day), before commencing oral prednisone (subjects <45kg: 20 mg/day and ≥45kg: 25 mg/day) which was then tapered to 2.5 mg/day over a period of 16 weeks. A summary of median oral prednisone dose over the AURORA 1 trial period is presented in

Table 17, with patients continuing on the tapered oral corticosteroid dose for the duration of AURORA 2 (Table 18).

Similarly in AURA-LV, patients were scheduled to receive IV methylprednisolone on Days 1 and 2 (subjects <45kg: 0.25 g/day and ≥45kg: 0.5 g/day), before commencing before commencing oral prednisone (subjects <45kg: 20 mg/day and ≥45kg: 25 mg/day) which was then tapered to 2.5 mg/day over a period of 16 weeks. Medial oral prednisone dose over the AURA-LV trial period was not reported by visit. However, a summary of Week 16 dose level is presented in

Table 19.

Table 17. AURORA 1: summary of oral corticosteroid taper

	AURORA 1	
	VCS	PbO
Median oral corticosteroid dose, mg (range)		
n	[redacted]	[redacted]
Study Day 3	[redacted]	[redacted]
n	[redacted]	[redacted]
Study Day 28 (Week 4)	[redacted]	[redacted]
n	[redacted]	[redacted]
Study Day 56 (Week 8)	[redacted]	[redacted]
n	[redacted]	[redacted]
Study Day 84 (Week 12)	[redacted]	[redacted]
n	[redacted]	[redacted]
Study Day 118 (Week 16)*	[redacted]	[redacted]
n	[redacted]	[redacted]
Study Day 168 (Week 24)	[redacted]	[redacted]
n	[redacted]	[redacted]
Study Day 364 (Week 52)	[redacted]	[redacted]

*Study Day 118 was the last possible day for the Week 16 visit

Abbreviations: mg = milligram; n = number of patients in category; PbO = placebo; VCS = voclosporin

Source: Otsuka 2020[14]

Table 18. AURORA 2: summary of oral corticosteroid exposure by visit

	AURORA 2	
	VCS	PbO
Median oral corticosteroid dose, mg (range)		
n	[redacted]	[redacted]
Study Day 118 (Week 16)*	[redacted]	[redacted]
n	[redacted]	[redacted]
Study Visit 15 (Month 12)	[redacted]	[redacted]
n	[redacted]	[redacted]
Study Visit 16 (Month 15)	[redacted]	[redacted]
n	[redacted]	[redacted]
Study Visit 17 (Month 18)	[redacted]	[redacted]
n	[redacted]	[redacted]
Study Visit 18 (Month 21)	[redacted]	[redacted]
n	[redacted]	[redacted]
Study Visit 19 (Month 24)	[redacted]	[redacted]
n	[redacted]	[redacted]
Study Visit 20 (Month 27)	[redacted]	[redacted]
n	[redacted]	[redacted]
Study Visit 21 (Month 30)	[redacted]	[redacted]
n	[redacted]	[redacted]
Study Visit 22 (Month 33)	[redacted]	[redacted]

n	[redacted]	[redacted]
Study Visit 23 (Month 36)	[redacted]	[redacted]

*Study Day 118 was the last possible day for the Week 16 visit

Abbreviations: mg = milligram; n = number of patients in category; PbO = placebo; VCS = voclosporin

Source: Otsuka 2022[2]

Table 19. AURA-LV: summary of oral corticosteroid exposure at Week 16

	AURA-LV		
	VCS 23.7 mg BID	VCS 39.5 mg BID	PbO
Week 16 dose level, n (%)			
n	[redacted]	[redacted]	[redacted]
≤2.5 mg/day	[redacted]	[redacted]	[redacted]
>2.5 mg/day	[redacted]	[redacted]	[redacted]
Withdrawn prior to Week 16	[redacted]	[redacted]	[redacted]

Abbreviations: BID = twice daily; kg = kilogram; mg = milligram; n = number of patients in category; PbO = placebo; VCS = voclosporin

Source: Otsuka 2018[3]

A19. While the EAG accepts that the identification of non-randomised studies was considered beyond the scope of the clinical SLR undertaken to inform the CS, please can the company comment on whether it is aware of any non-randomised, comparative studies of tacrolimus for LN?

As stated in clarification question A19, non-randomised studies were beyond the scope of the clinical SLR. However, a targeted search of PubMed for "non-randomized tacrolimus lupus nephritis" has yielded a single result; a non-randomised, single centre, Chinese, prospective cohort study that compared the efficacy and safety of tacrolimus to cyclophosphamide in patients with lupus nephritis (N=40).[15]

A20. In Appendix D, the company describes differences between CRR definitions:

- **Please clarify if you had recourse to any clinical guidelines or standards in judging the similarity of CRR outcome definitions.**

- **Please clarify if a similar process was undertaken for PRR and provide a similar table of PRR outcomes included.**

Clinical experts were consulted when comparing the similarity of CRR definitions between trials. A clinician confirmed that the UPCR < 0.5 mg/day and proteinuria < 0.5 mg/day thresholds could be used interchangeably and therefore can be considered as the same. This also applies to other UPCR and proteinuria thresholds. A clinician also determined that trials with different levels of UPCR or proteinuria i.e., those that determined CRR by a proteinuria of < 0.3 mg/day could be considered more stringent, as this threshold was harder to achieve than that of a proteinuria of < 0.5 mg/day, equating to differences in the outcome definition for CRR. UPCR or proteinuria was the most common component of CRR across trials. Therefore, those that did not report on achieving CRR through this component were determined to be unsimilar to that of those who defined CRR with UPCR or proteinuria.

A similar process was undertaken for PRR, however, due to the PRR network including fewer trials than that of CRR, the trials included were similar in determining PRR by a proteinuria or UPCR component and no major outliers were identified. Table 20 shows the definitions of PRR per trial as presented for CRR.

Table 20. Overview of PRR outcome definitions and background corticosteroid steroid use for trials included in the

Trial name/study	Treatment	PRR outcome definition	Background steroid use
AURORA-1	VCS + MMF	Partial renal response, defined by 50% reduction from baseline UPCR at Weeks 24 and 52	Steroid use: Yes Treatment: Methylprednisolone Tapering: Yes
	PbO + MMF		
Chan 2000	H-CYC	Partial remission, defined as a value for urinary protein excretion that was between 0.3 and 2.9 g per 24 hours, with a serum albumin concentration of at least 3.0 g per deciliter and stable renal function	Steroid use: Yes Treatment: Prednisolone Tapering: Yes
	MMF		
Ginzler 2005	MMF	Partial remission, defined as improvement of 50 percent in all abnormal renal measurements, without worsening (within 10 percent) of any measurement	Steroid use: Yes Treatment: Prednisolone Tapering: Yes
	H-CYC		
Li 2012	H-CYC	Partial remission, defined as urinary protein excretion between 0.3 and 2.9 g/24 h, having decreased by at least 50% from baseline values, with a serum albumin concentration of at least 30 g/L and relative stabilization (+/-30%) in serum creatinine	Steroid use: Yes Treatment: Prednisolone Tapering: Yes
	MMF		
	TAC		
Mitwali 2011	H-CYC	Partial remission, defined as an improvement of >50% from baseline protienuria, serum albumin levels of at least 30 g/L, and serum creatinine level of ≥25% from baseline or stable serum creatinine level within 25% of the baseline	Steroid use: Yes Treatment: Prednisolone Tapering: Yes
	L-CYC		
Mok 2016	MMF	Stabilisation (within 25%) or improvement in serum creatine with persistent reduction of proteinuria (if nephrotic range at baseline, a ≥50% decrease in proteinuria but <3g/day (or uP/Cr <3.0); if non-nephrotic at baseline, a decrease to ≤50% of the pre-treatment value but >1g/day [or UPCR >1.0] and improvement in urinary sediment abnormalities (≥50% reduction in haematuria and urine red blood cells [RBC] <10/HPF)	Steroid use: Yes Treatment: Prednisolone Tapering: Yes
	TAC		

LUNAR	PbO+MMF RTX+MMF	Serum creatinine level ≤115% of baseline; RBCs/hpf ≤50% above baseline and no RBC casts; and at least a 50% decrease in the UPC ratio to <1.0 (if the baseline UPCR ratio was ≤3.0) or to ≤3.0 (if the baseline UPC ratio was >3.0)	Steroid use: Yes Treatment: Methylprednisolone and prednisolone Tapering: Yes
Wang 2007	H-CYC MMF	Partial remission defined as a decrease in urinary protein excretion level of at least 50% and <2 g/24 h; a decrease in haematuria and serum creatinine levels of at least 50% or by a stable serum creatinine; and a serum albumin concentration of at least 30 g/L	Steroid use: Yes Treatment: Methylprednisolone and prednisolone Tapering: Yes
Yap 2012	MMF TAC CYC	Partial response was defined as reduction of baseline proteinuria by 50% or more, non-nephrotic range proteinuria, serum albumin ≥30 g/L and creatinine level not higher than 15% above baseline	Steroid use: Yes Treatment: Prednisolone Tapering: Yes
Zhang 2014	H-CYC L-CYC	A partial remission was defined as a value for urinary protein excretion that was 0.3–2.9 g per 24 h, with an albumin concentration of at least 3.0 g/dL and stable renal function	Steroid use: Yes Treatment: Prednisolone Tapering: Yes

Abbreviations: AZA = azathioprine; CYC = cyclophosphamide; ECLAM = European Consensus Lupus Activity Measurement; L = low-dose; H = high-dose; MMF = mycophenolate mofetil; MPR = methylprednisolone; NR = not reported; PbO = placebo; RBC = red blood cell; RTX = rituximab; TAC = tacrolimus; VCS = voclosporin; UPCR = urine protein/creatine ratio

A21. In Appendix D, the company states that the longest follow-up was used in base case NMAs. Please undertake a meta-analysis grouping all available follow-up times up to and including six months, beyond six months and up to 12 months, and beyond 12 months.

The 6-month time point selection for sensitivity analyses was selected based on the availability of follow-up. The majority of the trials in the NMA reported outcomes at 6-months and then if they included longer follow-up, this was usually at one year. Therefore, these timeframes seemed most appropriate given the availability of follow-up from the studies included.

To clarify, the base case NMA included all trials with follow-up data available and was used to inform the economic model. Among studies reporting CRR at various timepoints, a large proportion of patients had already achieved CRR by the 6-month timepoint in the majority of studies. Under scenario analyses, a network was therefore constructed for trials that report CRR at follow-up of up to and including 24 weeks/6 months and another network that consists of trials that report CRR at ≥ 1 year. Tables B.5-7 and B.5-8 in Appendix D contains efficacy input data used for both scenarios in the NMA. We grouped the follow-up times due to the sparsity of data, especially with the, up to and including, 1-year/12-month analyses eliciting highly unstable results, reflected by unrealistic ORs (tacrolimus specifically) and the uncertainty in the point estimates shown in the 95% credible intervals.

A meta-analysis is already provided for the grouping of trials up to and including six months in Appendix D. Please refer to Document B, Table B.5-13 and Table B.5-18 for the outcomes of CRR and PRR, respectively. A meta-analysis is also provided for the grouping of trials that had follow-up of 12 months, please refer to Table B.5-14 and Table B.5-19. Uncertainty is associated with both 12-month PRR and CRR networks; however, the PRR is particularly unstable due to the lack of trials and smaller sample sizes.

For the suggested timepoint of “beyond 12 months”, this comparison cannot be performed as the evidence provided for voclosporin + MMF (AURA-LV and AURORA 1) has a maximum follow-up of 12-months. AURORA 2 (maximum follow-up of 36

months) was excluded from the NMA on the basis that a comparison with other studies with much shorter follow-ups (i.e. comparing 36-month with 6-month studies) would lead to a biased comparison. This decision was made due to the availability of follow-up, with the majority of trials reporting outcomes at 6-months only. LUNAR did report on outcomes beyond 12-months; however, patients were allowed to switch to a maintenance therapy and therefore this cannot be considered for comparison.

A22. Please justify the use of the between-studies variance parameter prior distribution and clarify if other empirical alternatives were considered.

A relatively weakly informative prior has been used for the between-study heterogeneity parameter on all NMA models. This parameter is represented by a half-normal distribution with a mean of 0 and standard deviation of 5. This prior has been selected due to the absence of several trials per treatment comparison in the networks. According to Dias et al. (2018),[16] the posterior distribution of σ may be poorly identified and include values which are implausible high or low when considering a vague prior for the between-study heterogeneity parameter - Gelman 2006[17] has suggested ~4-5 trials as a minimum. The half-normal was chosen as per the Beta blocker example of the binomial model with a logit link from the multinma package, based on that of program 1 from the NICE Technical Support Document (TSD) 02.[18,19]

The use of informative priors for the random effects model has not been considered. Attempts have been made to increase the probability of convergence in the random effects model. This includes increasing the number of iterations and reducing the step size of the No-U-Turn sampler, making the sampler slower but more robust, (as suggested in the Stan manual).[20] However, this did not resolve the convergence issues in our NMA, most likely due to the low number of studies per treatment comparison.

While the TSD3 presents a solution to the posteriors which allow for unrealistically high levels of heterogeneity, these would require expert opinion or available meta-epidemiological data for the indication and outcomes of interest.[21,22]

A23. Please justify the decision to undertake separate meta-analyses for CRR and PRR instead of an ordinal model using a probit link, as recommended in NICE TSD 02.

As per the NICE TSD 02,[18] it is stated that the ordinal model using a probit link models a conditional binomial likelihood, i.e., the likelihood that you have a specified outcome (CRR) given that you have achieved something else (PRR). Therefore, the patients in CRR are required to be a subset of the patients qualifying for PRR. This depends on the definition of both PRR and CRR, from the trials included it is not entirely clear that these are specifically subsets of one another. Further to this point, as indicated as part of the heterogeneity assessment, there was significant variation in the criterion for what qualifies for a PRR and CRR between studies in the network, thus adding to the difficulty of aligning the definitions required to perform a multinomial model. Moreover, AURORA 1 was the only study included that counted the patients who went on to achieve CRR within the number of patients who achieved PRR, other trials reported on patients achieving either a PRR or CRR independent from one another. The continuity of the outcome measure is not as clear as something such as stated in the NICE TSD 02,[18] i.e., the Psoriasis and Severity Index (PASI) score for psoriasis. Therefore, due to this uncertainty in the continuity of the PRR and CRR outcomes, the decision was taken to perform two separate meta-analyses, resulting in fewer assumptions. It is further important to clarify that 7 of the 17 studies included in the CRR network did not report on PRR as an outcome of interest.

A24. Please provide all meta-analysis code and data input files exactly as run.

Relevant meta-analysis code and data input files are provided with this clarification questions response document. All analyses were performed on R, using the packages *rstan* (the R interface to Stan) and *multinma* (the package that implements NMA with models estimated in a Bayesian framework using Stan). *Multinma* has been described in the core CS. The below code provides the key functions that were used to run the analysis for the NMA. Input files are attached as RData files along with an R script containing the below code (titled NICE NMA Code), the example shows the base case model for CRR.

```
load("Base_Case_CRR.RData")
```

```
  intervention <- "VCS+MMF"

  intervention_d <- "d[VCS+MMF]"

  reference <- "MMF"

  tx_order <- c("MMF", "VCS+MMF")

  iterations <- 10000

  n_warmup <- iterations/2

  net <- set_agd_arm(x, study = Study,

                     trt = Treatment, n = n, r = r,

                     trt_ref = reference)

  fit <- list(

    FE = nma(net, seed = 1, link = "logit",trt_effects = "fixed",

             iter = iterations, prior_trt = normal(scale = 100),

             warmup = n_warmup),

    RE = nma(net, seed = 2, link = "logit", trt_effects = "random",

             iter = iterations, prior_trt = normal(scale = 100),

             prior_het = half_normal(scale = 5), warmup = n_warmup, adapt_delta =
0.999, control = list(max_treedepth = 15))

  )

  analysis <- list(data = x)

  launch_shinystan(fit$FE$stanfit)

  launch_shinystan(fit$RE$stanfit)
```

```
  analysis$dic <- lapply(fit, dic)

  analysis$dic$FE <- as_tibble(print(analysis$dic$FE[1:3], digits = 4), .name_repair =
~ c("DIC", "pD", "Resdev"))

  analysis$dic$RE <- as_tibble(print(analysis$dic$RE[1:3], digits = 4), .name_repair =
~ c("DIC", "pD", "Resdev"))

  analysis$Log_ORs <- map(fit, ~ .x

                          %>% summary() %>% as_tibble())

  analysis$ORs$FE <- analysis$Log_ORs$FE %>% mutate(mean =
round(exp(mean),4), sd = round(exp(sd),4), `2.5%` = round(exp(`2.5%`),4),`25%` =
round(exp(`25%`),4), `50%` = round(exp(`50%`),5),`75%` = round(exp(`75%`),5),
`97.5%` = round(exp(`97.5%`),5))

  analysis$ORs$FE <- analysis$ORs$FE %>% select(parameter, `50%`, sd, `2.5%`,
`97.5%`, Rhat)

  analysis$ORs$RE <- analysis$Log_ORs$RE %>% mutate(mean =
round(exp(mean),4), sd = round(exp(sd),4), `2.5%` = round(exp(`2.5%`),4),`25%` =
round(exp(`25%`),4), `50%` = round(exp(`50%`),5),`75%` = round(exp(`75%`),5),
`97.5%` = round(exp(`97.5%`),5))

  analysis$ORs$RE <- analysis$ORs$RE %>% select(parameter, `50%`, sd, `2.5%`,
`97.5%`, Rhat)

  analysis$pairwise <- lapply(fit, relative_effects, all_contrasts = TRUE)

  analysis$pairwise$FE <- as.array(analysis$pairwise$FE)

  analysis$pairwise$FE <- exp(analysis$pairwise$FE)

  analysis$pairwise$FE <- summary(analysis$pairwise$FE)

  analysis$pairwise$RE <- as.array(analysis$pairwise$RE)

  analysis$pairwise$RE <- exp(analysis$pairwise$RE)
```

```
  analysis$pairwise$RE <- summary(analysis$pairwise$RE)

  analysis$treatment_ranks <- lapply(fit, posterior_ranks, lower_better = FALSE)

  analysis$rank_probs <- lapply(fit, posterior_rank_probs, lower_better = FALSE)

  analysis$sucra <- lapply(fit, posterior_rank_probs, lower_better = FALSE, sucra =
TRUE)

  coda <- lapply(fit, function(x) x |> relative_effects(trt_ref = reference) |> as.matrix()
|> exp())

  coda_logOR <- lapply(fit, function(x) x |> relative_effects(trt_ref = reference) |>
as.matrix())


  openxlsx::write.xlsx(file = "Coda.xlsx", overwrite = TRUE, x = list(

    "CODA FE"               = coda$FE,

    "Log CODA FE"           = coda_logOR$FE,

    "CODA RE"               = coda$RE,

    "Log CODA RE"           = coda_logOR$RE

  ))


  openxlsx::write.xlsx(file = "outcomes.xlsx", overwrite = TRUE, x = list(

    "Log Results FE"      = analysis$Log_ORs$FE,

    "Results FE"          = analysis$ORs$FE,

    "Fit statistics FE"   = analysis$dic$FE,

    "Ranks FE"            = analysis$treatment_ranks$FE$summary,

    "Rank probs FE"       = analysis$rank_probs$FE$summary,
```

```
  "SUCRA FE"           = analysis$sucra$FE,
  "pairwise FE"        = analysis$pairwise$FE,


  "Log Results RE"     = analysis$Log_ORs$RE,
  "Results RE"         = analysis$ORs$RE,
  "Fit statistics RE"  = analysis$dic$RE,
  "Ranks RE"           = analysis$treatment_ranks$RE$summary,
  "Rank probs RE"      = analysis$rank_probs$RE$summary,
  "SUCRA RE"           = analysis$sucra$RE,
  "pairwise RE"        = analysis$pairwise$RE
))
```

A25. Please can you clarify if additional rules of thumb were used to select outcome data for the NMAs from included trials?

No additional rules of thumb were used to select outcome data for the NMA other than the one stated in the main CS for PRR. This refers to the condition that PRR must have been reported independently to the outcome of CRR so that separate meta-analyses could be undertaken. For AURORA-1, this data was calculated form the IPD (as described in in clarification question A9). In addition, some evidence was provided by curve digitization, however, this has been stated in the main CS the only evidence this refers to is the outcome data derived from the LUNAR and DUTCH-LN studies and was only used as part of the up to and including 6-month follow-up scenario analysis.

A26. Please share with us the AURA-LV Mortality Analysis Report cited in the CSR for AURA-LV. The link in the trial CSR does not work for us.

The AURA-LV Mortality Analysis Report is provided with this response document.

Section B: Clarification on cost-effectiveness data

Literature searches

B1. Priority question: Appendix G p78. Please provide the full search strategy/strategies for the cost effectiveness and utilities searches

The full search strategy of economic SLR including the filters for the cost-effectiveness, cost and resource use, and utilities are presented in Table 21.

Table 21. Economic SLR search terms used in Embase, Medline (In-Process), APA Psychinfo, and EconLit (using ProQuest)

Topic	#	Terms	# Results	
			1 June 2021	4 February 2022
Population	S1	(TI,AB((lupus OR lupoid) AND (nephritis OR glomerulonephritis OR kidney OR nephropathy)))	36703	38272*
	S2	(EMB.EXACT("lupus erythematosus nephritis"))	18505	19490*
	S3	(MESH.EXACT("Lupus Nephritis"))	6780	7180*
	S4	S3 OR S2 OR S1	41946	43818*
Cost-effectiveness	S5	(EMB.EXACT("Cost effectiveness analysis"))	164978	170955*
	S6	(MESH.EXACT("Cost-benefit analysis"))	89979	93614*
	S7	MESH.EXACT("Economics")	460469	467135*
	S8	(AB(cost NEAR/1 effectiveness) AND AB(costs or cost))	154119	162002*
	S9	(TI(cost NEAR/1 effectiveness))	61128	64014*
	S10	(EMB.EXACT("Cost benefit analysis"))	90435	92733*
	S11	(EMB.EXACT("Economic aspect"))	127211	129227*
	S12	EMB.EXACT("Socioeconomics")	155936	160948*
	S13	(MESH.EXACT("Economics, pharmaceutical"))	3140	3048°
	S14	(EMB.EXACT("Health economics"))	40953	41493*
	S15	(MESH.EXACT("Costs and cost analysis"))	51434	52228*
	S16	(MESH.EXACT("Value of life"))	6245	6281*
	S17	(TI,AB(Economic* OR pharmacoeconomic* OR price* OR pricing))	1386671	1456204*
	S18	(TI,AB,IF(monte carlo))	137610	143879*
	S19	EMB.EXACT("Probability")	131006	138488*
	S20	(MESH.EXACT("Decision Theory" OR "Decision Trees"))	13154	13507*

Topic	#	Terms	# Results	
			1 June 2021	4 February 2022
	S21	(EMB.EXACT("Decision Tree"))	15904	17591*
	S22	(MESH.EXACT("Markov chains"))	15750	16349*
	S23	(EMB.EXACT("Statistical Model"))	197301	200852*
	S24	(MESH.EXACT("Monte carlo method"))	30415	31747*
	S25	(EMB.EXACT("Decision Theory"))	2829	2835°
	S26	(EMB.EXACT("Monte carlo method"))	44737	46959*
	S27	TI,AB,IF(markov)	75864	79984*
	S28	(AB,IF(cost* NEAR/2 (effective* or utilit* or benefit* or minimi* or analy* or outcome or outcomes)))	688956	718388*
	S29	(TI,AB,IF(value NEAR/2 (money or monetary)))	10231	10697*
	S30	(TI,AB,IF(Decision* NEAr/2 (tree* or analy* or model*)))	121721	130953*
	S31	(TI,IF(economic* or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic* or pharmaco-economic* or expenditure or expenditures or expense or expenses or financial or finance or finances or financed))	2623373	2705221*
	S32	(MESH.EXACT.EXPLODE("Costs and cost analysis"))	261864	256814*
	S33	EMB.EXACT("Economics")	249698	251704*
	S34	EMB.EXACT("Cost")	64072	65093*
	S35	(AB,IF(economic model*))	244644	259709*
	S36	(MESH.EXACT("Models, economic"))	11359	11704*
	S37	(EMB.EXACT("Cost utility analysis"))	10981	11480*
	S38	(TI,AB(cost NEAR/2 effectiveness))	170834	179149*
	S39	(TI,AB(cost NEAR/2 utility))	19351	20558*
	S40	(TI,AB(cost NEAR/2 benefit))	79308	82249*
	S41	S40 OR S39 OR S38 OR S37 OR S36 OR S35 OR S34 OR S33 OR S32 OR S31 OR S30 OR S29 OR S28 OR S27 OR S26 OR S25 OR S24 OR S23 OR S22 OR S21 OR S20 OR S19 OR S18 OR S17 OR S16 OR S15 OR S14 OR S13 OR S12 OR S11 OR S10 OR S9 OR S8 OR S7 OR S6 OR S5	4360092	4521945*
	S42	S41 AND S4	630	569°
Costs/ resource use	S43	MESH.EXACT("Economics")	460469	467135*
	S44	(EMB.EXACT("Economic aspect"))	127212	129227*
	S45	EMB.EXACT("Socioeconomics")	155936	160948*
	S46	(MESH.EXACT("Economics, pharmaceutical"))	3140	3048°
	S47	(EMB.EXACT("Health economics"))	40953	41493*

Topic	#	Terms	# Results	
			1 June 2021	4 February 2022
	S48	(MESH.EXACT("Costs and cost analysis"))	51434	52228*
	S49	(MESH.EXACT("Value of life"))	6245	6281*
	S50	(TI,AB(Economic* OR pharmacoeconomic* OR price* OR pricing))	1386673	1456204*
	S51	(MESH.EXACT("Hospital costs"))	11742	12009*
	S52	(MESH.EXACT("Employer health costs"))	1155	1097°
	S53	(MESH.EXACT("Cost savings"))	12657	12942*
	S54	(MESH.EXACT("Direct service costs"))	1275	1214°
	S55	(EMB.EXACT("Financial management"))	123651	125321*
	S56	(EMB.EXACT("Health care financing"))	13976	14124*
	S57	MESH.EXACT.EXPLODE("Budgets")	14151	14258*
	S58	(MESH.EXACT.EXPLODE("Economics, medical"))	14564	14495*
	S59	(TI,AB(Low NEAR/1 cost))	220013	236979*
	S60	(MESH.EXACT("Drug costs"))	17376	17822*
	S61	(MESH.EXACT("Deductibles and Coinsurance"))	1863	1812°
	S62	(EMB.EXACT("Health care cost"))	204072	211256*
	S63	(MESH.EXACT("Health expenditures"))	22860	24015*
	S64	(TI,AB(Cost NEAR/1 variable))	4834	5040*
	S65	(EMB.EXACT("Cost of illness"))	20537	21074*
	S66	(MESH.EXACT("Capital expenditures"))	2012	1998°
	S67	(MESH.EXACT("Cost allocation"))	2073	2022°
	S68	(EMB.EXACT("Hospital cost"))	23815	24617*
	S69	(MESH.EXACT("Cost control"))	22307	22359*
	S70	(MESH.EXACT.EXPLODE("Economics, hospital"))	25549	25600*
	S71	(MESH.EXACT("Cost sharing"))	2801	2652°
	S72	(MESH.EXACT("Cost of illness"))	34043	35576*
	S73	(TI,AB((Healthcare OR health*care) NEAR/1 cost*))	41806	45121*
	S74	(TI,AB(Fiscal OR funding OR financial OR finance))	666028	712442*
	S75	(MESH.EXACT.EXPLODE("Fees and charges"))	34194	33840*
	S76	(EMB.EXACT("Cost minimization analysis"))	3786	3879°
	S77	(TI,AB(Cost NEAR/1 estimate*))	46867	49191*
	S78	(MESH.EXACT("Health care costs"))	44491	46035*
	S79	(MESH.EXACT("Economics, Nursing"))	4033	3982°
	S80	(MESH.EXACT("Medical savings accounts"))	554	542°

Topic	#	Terms	# Results	
			1 June 2021	4 February 2022
	S81	(EMB.EXACT("Cost control"))	74713	76355*
	S82	(TI,AB(High NEAR/1 cost))	125915	134484*
	S83	(TI,AB(Unit NEAR/1 cost*))	12867	13430*
	S84	(TI,IF(Economic* or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic* or pharmaco-economic* or expenditure or expenditures or expense or expenses or financial or finance or finances or financed))	2623375	2705221*
	S85	(MESH.EXACT.EXPLODE("Costs and cost analysis"))	261864	256814*
	S86	EMB.EXACT("Economics")	249698	251704*
	S87	EMB.EXACT("Cost")	64072	65093*
	S88	(AB,IF(economic model*))	244644	259709*
	S89	(MESH.EXACT("Models, economic"))	11359	11704*
	S90	(MESH.EXACT("Economics, Dental"))	1919	1896°
	S91	EMB.EXACT("Budget")	35987	36703*
	S92	TI,AB,IF(budget*)	141472	146601*
	S93	S43 OR S44 OR S45 OR S46 OR S47 OR S48 OR S49 OR S50 OR S51 OR S52 OR S53 OR S54 OR S55 OR S56 OR S57 OR S58 OR S59 OR S60 OR S61 OR S62 OR S63 OR S64 OR S65 OR S66 OR S67 OR S68 OR S69 OR S70 OR S71 OR S72 OR S73 OR S74 OR S75 OR S76 OR S77 OR S78 OR S79 OR S80 OR S81 OR S82 OR S83 OR S84 OR S85 OR S86 OR S87 OR S88 OR S89 OR S90 OR S91 OR S92	4195476	4369468*
	S94	S4 AND S93	534	466°
Utilities	S95	(MESH.EXACT("Quality-Adjusted Life Years") OR EMB.EXACT("quality adjusted life year"))	44755	47616*
	S96	(TI,AB,IF(quality adjusted OR adjusted life year*))	151835	163157*
	S97	(TI,AB,IF(qaly* OR qald* OR qale* OR qtime*))	35828	38199*
	S98	(TI,AB,IF(illness state[*1] OR health state[*1]))	1534390	1496044*
	S99	(TI,AB,IF(hui OR hui1 OR hui2 OR hui3))	7260	7695*
	S100	(TI,AB,IF(multiattribute* OR multi attribute*))	17098	18560*
	S101	(TI,AB,IF(utility NEAR/3 (score[*1] OR valu* or health* OR cost* OR measur* OR disease* OR mean OR gain or gains OR index*)))	77166	81398*

Topic	#	Terms	# Results	
			1 June 2021	4 February 2022
	S102	TI,AB,IF(utilities)	651690	685895*
	S103	(TI,AB,IF(eq-5d OR eq5d OR eq-5 OR eq5 OR euro qual OR euroqual OR euro qual5d OR euroqual5d OR euro qol OR euroqol OR euro qol5d OR euroqol5d OR euro quol OR euroquol OR euro quol5d OR euroquol5d OR eur qol OR eurqol OR eur qol5d OR eur qol5d OR eur?qul OR eur?qul5d OR euro* quality of life OR european qol))	41561	45492*
	S104	(TI,AB,IF(euro* NEAR/3 (5*d OR 5d OR 5*dimension* OR 5dimension* OR 5*domain* OR 5domain*)))	33505	36557*
	S105	(TI,AB(sf6 OR sf 6 OR sf6d OR sf 6d OR sf six OR sfsix OR sf8 OR sf 8 OR sf eight OR sfeight))	7829	8195*
	S106	(TI,AB(sf12 OR sf 12 OR sf twelve OR sftwelve))	15226	16123*
	S107	(TI,AB(15D OR 15-D OR 15 dimension))	12121	12534*
	S108	(TI,AB(sf16 OR sf 16 OR sf sixteen OR sfsixteen))	87	61°
	S109	(TI,AB(sf20 OR sf 20 OR sf twenty OR sftwenty))	733	475°
	S110	(TI,AB,IF(sf36* OR sf 36* OR sf thirtysix OR sf thirty six))	68925	71638*
	S111	(TI,AB(standard gamble* OR sg))	30609	32437*
	S112	(TI,AB,IF(time trade off[*1] OR time tradeoff[*1] OR tto OR timetradeoff[*1]))	5718	6007*
	S113	(TI,AB(rating scal*))	292369	306249*
	S114	(TI,AB(linear scal*))	115131	123946*
	S115	((TI,AB(linear analog*)))	27390	28420*
	S116	(TI,AB(visual analog* OR "VAS"))	235018	247660*
	S117	TI,AB(LupusPRO)	128	105°
	S118	(TI,AB(SLE Symptom Checklist OR "SCC"))	56208	58695*
	S119	(TI,AB(Kidney Disease Quality of Life OR "KDQoL"))	12777	13889*
	S120	(TI,AB(Kidney Symptom Questionnaire OR "KSQ"))	2286	1641°
	S121	((MESH.EXACT("Quality of Life") OR EMB.EXACT("quality of life")) AND TI,AB,IF(quality of life OR qol NEAR/3 (score[*1] or measure[*1])))	782930	836679*
	S122	((MESH.EXACT("Quality of Life") OR EMB.EXACT("quality of life")) AND TI,AB,IF(health NEAR/3 status))	71031	73906*
	S123	(TI,AB,IF(quality of life OR qol) AND (MESH.EXACT("Cost-Benefit Analysis")	22222	23901*

Topic	#	Terms	# Results	
			1 June 2021	4 February 2022
		OR EMB.EXACT("cost benefit analysis")))		
	S124	S95 OR S96 OR S97 OR S98 OR S99 OR S100 OR S101 OR S102 OR S103 OR S104 OR S105 OR S106 OR S107 OR S108 OR S109 OR S110 OR S111 OR S112 OR S113 OR S114 OR S115 OR S116 OR S117 OR S118 OR S119 OR S120 OR S121 OR S122 OR S123	3689221	3777814*
	S125	S4 AND S124	1194	1258°
	S126	S42 OR S94 OR S125	**1487°**	1592°
	S127	**(S126) and (pd(>20210531))**		**97°**
	S128	(EMB.EXACT.EXPLODE("systemic lupus erythematosus") OR MESH.EXACT.EXPLODE("Lupus Erythematosus, Systemic")) AND (TI,AB("renal damage" OR "renal activity"))	Nil	619°
	S129	S128 OR S3 OR S2 OR S1	Nil	44116*
	S130	S129 AND (S124 OR S93 OR S41)	Nil	1613°
	S131	**S130 NOT S126**	**Nil**	**27°**

Parent search date: 1 June 2021

Fist update search date: 4 February 2022

*Duplicates are removed from the search but included in the result count.

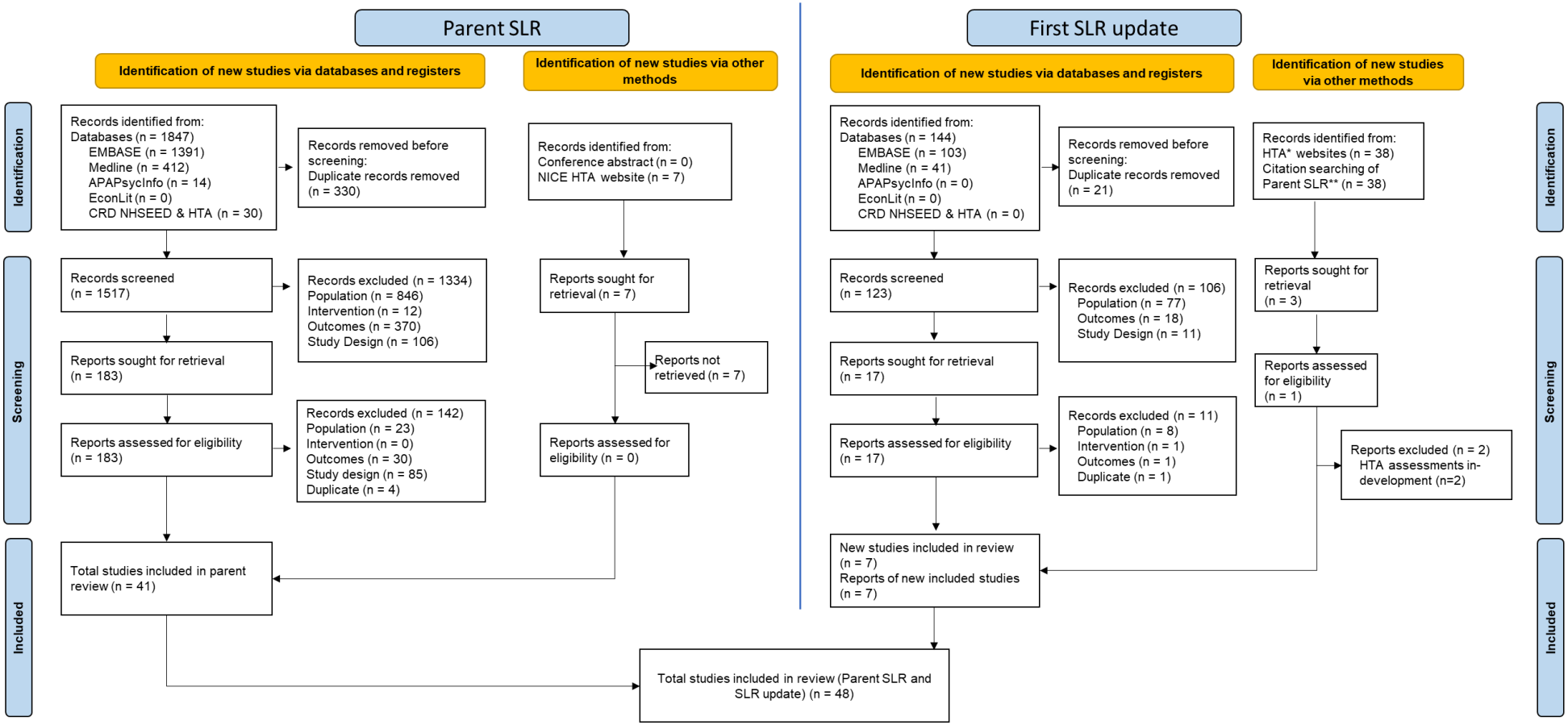
° Duplicates are removed from the search and from the result count.

Note: records obtain at S127 and S131 level were combined in EndNote. Duplicates were removed using EndNote and DistillerSR tools. **Total 123 unique record identified**.

B2. Appendix G. Figure B.521. The PRISMA diagram does not appear to add up, number screened should be 1,630? In G.1.1.21 total reports excluded is 153 with 31 excluded on population (not 150 as reported in the PRISMA). Please provide a corrected version.

A revised Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) diagram (combining original SLR and first SLR update) is presented in Figure 3.

Figure 3. Economic SLR: PRISMA for parent and SLR update searches



Model structure

B3. Priority question: In the CS, a description of previous models of both initial and maintenance treatments for LN is provided (see Section B.3.1). Referring to these previous models, please can the company explain the key decisions it made with respect to determining the final structure used to inform this appraisal, such that the EAG can understand how these previous models informed the final structure? More specifically, please can the company:

- ***Clarify the main reason(s) why specific models were not re-constructed per their original design to inform this appraisal?***
- ***Provide justification for differences in modelling approach compared with the ICER (2021) report (given that this was the only study identified which included a comparison of VCS + MMF versus placebo + MMF)?***

From the SLR, four cost-effectiveness models[1,23-25] and one cumulative cost analysis[26] were identified in lupus nephritis. The commonalities within these models informed the health states and the decision to build a Markov model. All models relied on a response-based structure, even though response definitions varied. A cycle length of six months was informed using Nee et al., 2015[23] and Mohara et al., 2014.[24]

Additionally, all models with a lifetime horizon allowed for patients to transition to chronic kidney disease (CKD) stage 5 (i.e., ESRD). According to Hanly et al., 2016, most costs are incurred during the CKD 5 state,[27] indicating that CKD 5 is a key driver of costs and should also be included in the model structure. Further distinctions between entering CKD 5 and receiving a kidney transplant also encouraged the division within this model, as did clinical opinion that costs and some transitions are similar between LN patients in CKD 5 and other patients with CKD 5.

However, the existing model structures had the potential for improvement from two perspectives. First, key opinion leader (KOL) expert feedback indicated that the division between induction and maintenance therapy was diminishing in clinical practice, and therefore a distinction between the two phases was not required. As such, rather than building a model with distinct induction and maintenance treatment

phases, the initial treatments can be given until a stopping rule, after which subsequent therapy can occur. This is different to the models by Kim et al., 2019,[1] Nee et al., 2015,[23] and Mohara et al., 2014.[24] Secondly, further KOL expert feedback indicated that kidney damage is not sufficiently captured in the disease states seen in other models. Later CKD stages (3b-4) have differing costs and effects than earlier CKD stages. While this data is sparse for LN, the Barber et al., 2018 study shows that as eGFR decreases, costs increase before reaching ESRD (i.e., CKD stage 5).[26] Rationally, LN patients kidney function worsens progressively during periods of AD. Allowing for patients to transition to CKD 5 every cycle simplifies this process and does not capture the different costs and effects associated with worsening kidney function during the natural progression of LN.

The model structure for the Institute for Clinical and Economic Review (ICER) report was seriously considered to inform the modelling approach for voclosporin. However, ICER report's approach was considered incomplete due to both the lack of consideration for CKD stages, as well as the inclusion of an additional assumption that patients must remain in the same health state that they are in at the end of the trials for the duration of the three years. Therefore, the ICER report's approach would not capture renal flares and model disease progression. Furthermore, ICER would have preferred modelling based on proteinuria, which would have defined "stages of LN progression using criteria identical to those in chronic kidney disease (CKD)".[28] However, due to data paucity, we built a response-based model instead. This informed company discussions with KOL experts regarding the use of CKD stages to model progression in LN, and was another reason that distinction was included between CKD states for active disease (AD), partial response (PR) and complete response (CR).

B4. Priority question: The CS states that a key limitation of previous models is that the cumulative impact of renal flares was not adequately captured (see Section B.3.2). For the avoidance of doubt, please can the company confirm precisely how renal flares are captured within the model? Furthermore, please can the company confirm why CKD stages were combined rather than separated (as it is the EAG's understanding that theoretically, the cumulative impact of renal flares *may* have been more accurately captured if the model structure included separate CKD stage health states, particularly considering CKD stages 3b and 4)?

Renal flares are partly captured in the model by both AD states, as whenever a patient returns to AD after having been in a response state, they are experiencing a renal flare. While the model is Markovian and therefore cannot track how often one or multiple patients have experienced renal flares, the cumulative impact of renal flares is captured by allowing patients to progress through CKD stages. In particular, a patient cannot experience a worsening of kidney function (as captured by CKD stage) without having spent a cycle in an AD state.

CKD stages were modelled in two groups, CKD stages 1-3a and CKD stages 3b-4, for multiple reasons. The first is that clinical opinion indicated that, after an eGFR $\leq$ 45 (i.e. CKD stage 3b or worse), that further deterioration of kidney function is inevitable, and nearly all patients will progress to CKD 5 within ten years; this groups CKD 3b with CKD 4. These patients also have distinctly different mortality, utilities and costs, with additional resources required to manage disease as a patient progresses through CKD stages. The second is that there is very little data for LN patients with CKD, either within or transitioning between CKD stages. As far as we know, there has been no study which reports the transitions of LN patients between CKD stages in a stage-by-stage manner; and modelling of individual CKD stages would therefore introduce much greater uncertainty to the model.

Furthermore, any available non-LN-related CKD data is also not necessarily generalisable to the LN population, as CKD patients tend to have different population characteristics to LN patients. The AURORA 1 trial also only considered patients in CKD stage 1-3a at baseline and AURORA 2 found that no patients experienced chronic kidney disease, defined as an "eGFR <60 mL/min/1.73 m^2 for ≥3 months,

with or without kidney damage," during the study.[2,14] Therefore, the individual patient data reflected CKD 1-3a, and it was logical to robustly inform the transitions for this one CKD health state.

Transitions and efficacy

B5. Priority question: Please can the company confirm how censored observations were handled within the 'count method' used to obtain transition probabilities? The EAG's current understanding is that censored observations appear to be assumed as non-informative (i.e., they are removed from both the numerator and denominator, and all other probabilities are re-scaled accordingly). Please can the company provide two alternative scenarios in which censored patients are (i) allocated to a health state based on last observation carried forward (LOCF) and (ii) allocated to the AD state?

Censored observations were indeed removed from both the numerator and denominator, leading to rescaled probabilities. The two scenarios requested are provided below, with the understanding that the only difference between (i) and (ii) is that censored patients are allocated to different states. Additionally, a table showing the distribution of censoring across health states at the end of AURORA 2 is provided in Table 22.

Table 22. Censoring across health states at the end of AURORA 2

Health state	MMF	VCS+MMF
CR	[redacted]	[redacted]
PR	[redacted]	[redacted]
AD	[redacted]	[redacted]

Abbreviations: AD = active disease; CR = complete response; MMF = mycophenolate mofetil; PR = partial response; VCS = voclosporin

The company stresses that these scenarios are considered entirely exploratory. While we understand that changing the transitions of censored patients allows for exploration of the model, the assumption that censored observations are non-informative underlies all results. Changes which affect the treatment arms in an imbalanced way will have significant effects on outcomes over a lifetime horizon. As transitions are only known for the AURORA trials, the relationship between VCS + MMF and MMF informs all comparators, with comparators anchored to the transitions for MMF alone using NMA results. This comparison would be fair if trial

data was known for comparators and the same censoring rules could be applied, but this is not the case. Therefore, the scenario has been provided, with the understanding that analysis does not reflect the outcomes seen in the trial, nor would it be reflective of expected outcomes in clinical practice.

Table 23 shows the results of scenario (i), while Table 24 shows the results of scenario (ii). The results deviate from the base case as expected, given the censoring information provided in Table 22. Since more censoring occurred in the response health states for voclosporin + MMF than MMF, scenario (i) is beneficial to voclosporin + MMF, as the transition probability to remain in a response health state increases. Furthermore, by 8 additional patients remaining in AD for MMF, the response transition decreases, further improving the comparison for voclosporin + MMF. Meanwhile, scenario (ii) shows that when all censored patients move to AD and remain there, the likelihood of remaining in AD is inflated compared to the base case, which disproportionately affects voclosporin + MMF. This is logical given there are more censored patients in the voclosporin + MMF arm, and most censoring occurs in response health states, which leads to an increase in transitions out of response states in addition to decreasing the likelihood of responding in the future. This would always have affected the voclosporin + MMF arm disproportionately more than the MMF arm, as more patients are in response states for voclosporin + MMF over the course of the AURORA trials. Relying on data in Table 25 (B6), one can see that at all points in time, VCS+MMF arm has a smaller proportion of patients in AD than MMF, starting with a difference of 22% at month 6. This is due to the additional patients being in response states. Over the course of the three-year period over which the AURORA trials are conducted, there are always more patients in CR and less patients in AD for VCS+MMF compared to MMF alone. As such, the assumption that all censored patients return to AD is unreasonably strong as it severely diminishes the benefits in efficacy observed in the clinical trials and can therefore only negatively affect the cost-effectiveness of voclosporin + MMF. As previously discussed, neither of the two scenarios should be considered a realistic possibility of lifetime model outcomes and the probabilistic survival analysis already accounts for the potential variation of trial results by stochastically sampling from Dirichlet distributions to vary the transitions observed in the trial. The PSA results reflect the

deterministic results of the base case and show that the distribution of efficacy and cost outcomes for VCS+MMF is similar to MMF and all other comparators.

Table 23. Economic model scenario: all transitions computed using LOCF

Technologies	Total costs (£)		Total QALYs		ICER (£/QALY)*	
	Base case	Scenario (i)	Base case	Scenario (i)	Base case	Scenario (i)
VCS + MMF	[redacted]	[redacted]	[redacted]	[redacted]	-	-
MMF	[redacted]	[redacted]	[redacted]	[redacted]	£19,876	£16,148
L-CYC	[redacted]	[redacted]	[redacted]	[redacted]	£11,392	£9,548
H-CYC	[redacted]	[redacted]	[redacted]	[redacted]	£10,897	£9,022
AZA	[redacted]	[redacted]	[redacted]	[redacted]	£15,855	£13,161
RTX + MMF	[redacted]	[redacted]	[redacted]	[redacted]	£18,716	£16,801
TAC + MMF	[redacted]	[redacted]	[redacted]	[redacted]	£18,169	£14,487
TAC	[redacted]	[redacted]	[redacted]	[redacted]	£17,803	£14,581

Abbreviations: AZA = azathioprine; H-CYC = high dose cyclophosphamide; ICER = incremental cost-effectiveness ratio; L-CYC = low-dose cyclophosphamide; MMF = mycophenolate mofetil; QALY = quality-adjusted life year; RTX = rituximab; TAC = tacrolimus; VCS = voclosporin

Table 24. Economic model scenario: all transitions computed with censored observations going into AD

Technologies	Total costs (£)		Total QALYs		ICER (£/QALY)*	
	Base case	Scenario (ii)	Base case	Scenario (ii)	Base case	Scenario (ii)
VCS + MMF	[redacted]	[redacted]	[redacted]	[redacted]	-	-
MMF	[redacted]	[redacted]	[redacted]	[redacted]	£19,876	£42,420
L-CYC	[redacted]	[redacted]	[redacted]	[redacted]	£11,392	£21,168
H-CYC	[redacted]	[redacted]	[redacted]	[redacted]	£10,897	£19,769
AZA	[redacted]	[redacted]	[redacted]	[redacted]	£15,855	£30,590
RTX + MMF	[redacted]	[redacted]	[redacted]	[redacted]	£18,716	£546,732
TAC + MMF	[redacted]	[redacted]	[redacted]	[redacted]	£18,169	£41,890
TAC	[redacted]	[redacted]	[redacted]	[redacted]	£17,803	£46,717

Abbreviations: AZA = azathioprine; H-CYC = high dose cyclophosphamide; ICER = incremental cost-effectiveness ratio; L-CYC = low-dose cyclophosphamide; MMF = mycophenolate mofetil; QALY = quality-adjusted life year; RTX = rituximab; TAC = tacrolimus; VCS = voclosporin

B6. The CS states: *"A second approach of calculating transition probabilities was also explored by fitting a multinomial logit model per transition per health state. However, the multinomial method provided unrealistic outcomes that did not match the trial data. Therefore, the multinomial method is not incorporated into the model."* (CS, Section B.3.3.2.1). Please can the company provide

further information relating to this analysis such that the EAG can understand why the 'count method' was preferred?

Multinomial logit models are estimated for the transition between all combinations of health states in CKD 1-3a and Death and thereby used to predict the probability of transitioning from one state to the other. This probability of transitioning from state 'r' to state 's' during a time period between 't' and 't+1' is as follows:

$$P(y_{t+1} = s|y_t = r) = \frac{exp(x_r\beta_{rs})}{\sum_{h=1}^{H} exp(x_r\beta_{rh})}$$

In multinomial logit models, 'r' and 's' are health states within the set of CKD stage 1-3a PR, CR, AD and Death, 'x_r' is a set of covariates used to estimate transition probabilities, and 'β_{rs}' is the estimated set of coefficients. This approach allows time to be considered with transitions, so no assumptions are needed for long-term transitions. However, the model fit was deemed to be poor, in terms of reflecting the first three years of AURORA 1 and AURORA 2 trial data and also the directionality of the transitions over time.

In particular over the first 2–5 years, the health state distribution of patients for VCS + MMF did not reflect the trial data whatsoever, nor the count data method. Most patients were in [redacted], with health state membership peaking at slightly less than [redacted]%. Therefore, the multinomial logit method represented an extreme overestimation of VCS + MMF efficacy.

When considering the multinomial logit method transition probabilities over time, the likelihood of staying in [redacted], and the transition probability approached [redacted]% for going from CR to AD. Similarly, the probability of staying in [redacted], leading to the transition probability approaching [redacted]% for going from AD to CR. In effect, [redacted] remained in their health state from the previous cycle, rather cycling between CR and AD in CKD 1-3a until progressing to CKD 3b-4. This occurred for both VCS + MMF and MMF, and therefore by extension for all comparators, as the transitions for comparators were based upon MMF. Since the multinomial logit models were fitted using all available data from AURORA 1 and AURORA 2, no more data was anticipated with which to potentially improve the model. Therefore, due to the unrealistic outcomes, specifically results not matching

the trial data, the multinomial logit method was abandoned in favour of the count data method, and treatment waning assumptions were explored.

The difference between the trial data, count data method and multinomial logit method over the first 36 months is presented below in Table 25. Please note that the multinomial logit method allowed for patients to transition out of CKD 1-3a in the first three years, so a direct comparison with the count data method is not possible. However, it can still be observed that the multinomial logit method does not capture the observed trial data distributions as accurately as the count data method does.

Table 25. Comparison between trial data, count data method, and multinomial logit method over 36 months, CR, PR and AD percentages

		VCS+MMF			MMF		
		Trial data*	**Count data method**	**Multinomial logit method**	**Trial data***	**Count data method**	**Multinomial logit method**
6 months	CR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	PR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	AD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
12 months	CR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	PR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	AD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
18 months	CR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	PR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	AD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
24 months	CR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	PR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	AD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
30 months	CR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	PR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	AD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
36 months	CR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	PR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	AD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

*Note that these percentages do not sum to 100% due to censoring and death

Abbreviations: AD = active disease; CR = complete response; MMF = mycophenolate mofetil; PR = partial response; VCS = voclosporin

B7. Priority question: The CS states that *"As such, the model assumes that upon discontinuation of VCS + MMF, patient health state transition probabilities wane to an average (i.e. midpoint) of those recorded within the AURORA 2 trial at Months 30 and 36 for the VCS + MMF arm, and those recorded at Months 30 and 36 months for the MMF alone arm."* (CS, Section B.3.2.2, Table B.3-2). Given that all patients discontinue treatment with VCS + MMF at 36 months, please can the company provide justification for the treatment waning assumption being a mid-point rather than applying the same transitions as either the VSC + MFF or the MMF arm entirely? Furthermore, please can the company provide a scenario where a 'full' waning effect is applied (i.e., that transitions from 36 months are applied based on the MMF arm only for both arms), such that it is possible to consider analyses that reflect assumptions of 'no waning', 'half waning', 'full waning' for VCS?

To date, we are not aware of any studies or data that explore a treatment waning effect in patients with lupus nephritis. There is also no evidence or data to support a treatment waning effect for voclosporin + MMF across AURORA 1, AURORA 2, AURA-LV or otherwise. On the contrary, a sustained separation of Kaplan-Meier curves has been observed for voclosporin versus placebo arms for both time to 50% reduction in UPCR and probability of UPCR ≤0.5mg/mg throughout the one-year treatment period in AURORA 1 (Document B: Figure B.2-4 and Figure B.2-5), while comparable CRR rates were observed for voclosporin + MMF at both one year of treatment (AURORA1: 40.8%) and at three years of treatment (AURORA 2: 50.9%), thereby indicating a sustained long-term treatment effect throughout the treatment period.[2,14]

The loss of treatment effect is unlikely to occur instantaneously following treatment discontinuation. In line with EULAR/ERA-EDTA and KDIGO guidelines; patients with lupus nephritis that respond to initial treatment may progress to a subsequent therapy to maintain response[29,30] and a Phase 3 study has indicated that maintenance of response can depend on the regimen in which an initial response was obtained.[31,32] Therefore, it would not be appropriate for patients distributed across response states to behave homogenously (i.e. all patients having the same transitions after 36 months) and fully wane immediately, as implied by a "full waning" scenario.

For the above reasons, we took a conservative approach whereby midpoint waning is applied to all regimens following initial treatment discontinuation, in such a way that the response after 36 months is equal to the midpoint between that regimen and MMF. While there are not yet any completed NICE technology appraisals for lupus nephritis treatments, a midpoint waning effect is a more conservative approach than taken within previous NICE technology appraisals for treatments recommended for CKD (dapagliflozin; TA775)[33] and SLE (belimumab; TA752).[34] In each appraisal, no treatment waning effect was applied for their respective economic analyses.[33,34]

B8. The CS explains that patients are able to transition from AD CKD Stages 1-3a to AD CKD Stages 3b-4, with a probability of 3.05% which does not vary by treatment arm (based on clinical expert feedback). Patients are unable to transition from the CR or PR 'sub-states' in CKD Stages 1-3a to CKD Stages 3b-4. Please can the company provide justification for the restriction on this transition only applying for patients with AD? In responding to this query, please can the company comment on this assumption with reference also to the model cycle length of 6 months. Furthermore, if deemed appropriate, please can scenario analyses be provided exploring the impact of the following edits to the model transitions, and if any of these scenarios are deemed inappropriate, please provide justification as to why:

- ***Allowing CKD progression from the CR and PR 'sub-states'***
- ***Allowing differential risks of CKD progression by treatment arm,***
- ***Allowing a combination of the above?***

The underlying logic for model transitions is based on cumulative kidney damage associated with LN. During the natural course of LN, patients transition to AD after experiencing a relapse (i.e., renal flare), and it takes some time for this flare to manifest in irreparable kidney damage. Therefore, before patients transition from CKD 1-3a to CKD 3b-4, they must go through a period of disease activity in order for their kidney to accumulate damage and for renal function to decrease. Clinical experts have verified the assumption that requires patients to first enter and spend some time in AD CKD 1-3a before transitioning to AD in CKD 3b-4. Therefore, scenario analyses that allow transition to CKD 3b-4 from CR and PR in CKD 1-3a

are not appropriate. In line with clinical expert advice, a 6-month cycle length is suitable to allow enough time to assess a patient's response (or non-response) to treatment. Also, 6 months allows time for a patient to progressively accumulate sufficient kidney damage to progress to the next stage of LN-related CKD.

On the other hand, analyses to allow for differential risks of CKD progression is something that was considered. However, no data has been identified which would allow for assumptions to be made on the differential risks of CKD progression.

B9. Table B.3-4 presents transition probabilities in CKD 3b-4 for all treatments. An estimate of 13.91% is obtained for transitions to CKD Stage 5, dialysis based on KOL expert feedback of a 95% probability over 10 years. Please can the company confirm that no evidence was identified to inform incidence of CKD Stage 5 from CKD Stage 3b/4? In addition, please can the company confirm that the value of 13.91% was estimated using a simple rate-to-probability calculation:

$$\mathbf{13.91\%} = \mathbf{1} - \boldsymbol{e}^{\frac{\mathbf{\log\,(1-95\%)}}{\mathbf{20 * 6\ month\ cycles}}}$$

- ***Further to this, please can the company confirm if the estimate of 95% over 10 years accounts for the competing risk of death?***

Tselios et al., 2020[35] was the only source identified for lupus nephritis patients which reported data on the transition between CKD 3b-4 and CKD 5, but when used in the model, led to very low transitions into CKD stage 5, such that the external validation from Tektonidou et al., 2016[36] and Gisca et al., 2021[37] was not met. Following the implementation of the clinical expert-advised transition between CKD 3b-4 and CKD 5, the proportion of patients which reach CKD 5 within 5 and 10 years was similar between the model and the aforementioned sources. While this is partially described in section B.3.3.2.2.1 of the submission, a comparison is presented below in Table 26.

Table 26. Validation of transitions with ESRD, literature and model outcomes

Percentage of patients in ESRD	Tektonidou et al., 2016[38]	Gisca et al., 2021[39]	Model for MMF
After 5 years	5.74%	5.02%	[redacted]
After 10 years	9.98%	10.96%	[redacted]

Abbreviations: ESRD = end-stage renal disease; MMF = mycophenolate mofetil.

When using the clinical expert estimate of 95%, which was transformed to 13.91% using a rate-to-probability calculation as shown above $(1 - \exp^{\frac{\log(1-0.95)}{20}})$, the model numbers were comparable to the sources identified, leading to the conclusion that these transition probabilities were more applicable than those reported by Tselios et al., 2020.[35] The clinical expert estimate was given with the understanding that 95% of patients which remained alive in CKD stages 3b-4 would be in CKD stage 5 after 10 years, accounting for the competing risk of death in the sense that the transition was only relevant for those patients which were alive.

B10. Priority question: In the CS, it states: *"UK-based KOL experts reported that 90% of LN patients who enter ESRD receive a transplant within two years. This is a higher rate than reported in the literature for CKD patients, as the average LN patient is younger and therefore more suitable for receiving a transplant."* (CS, Section B.3.3.2.4). For the avoidance of doubt, please can the company confirm that this estimate of 90% reflects the probability of receiving a transplant, and not the probability of requiring a transplant? In addition, please can the company comment on the possibility of patients receiving more than one transplant in practice, and if this is reflected within the model?

Yes, the estimate of 90% reflects the probability of receiving a transplant. It is expected that all patients on dialysis in CKD 5 require a transplant. The model allows for patients to receive more than one transplant, as KOL feedback indicated that the likelihood of a LN patient needing another transplant is low but not zero. Although there is a lack of data describing the rate of repeat transplant for patients with LN, a UK-based economic study was identified via a targeted literature search which reports that 6.0% of patients transition from transplant to pre-transplant (i.e. dialysis) (Palmer et al., 2004).[40] For the purposes of our economic model, this value has been converted to a 6-month probability whereby 2.96% of CKD 5 patients who have received a transplant, return to dialysis every 6 months.

Treatment discontinuation

B11. Please can the company comment on the decision to estimate parametric survival models for the outcome of TTD, and why the Kaplan-Meier estimate was not applied directly within the model (for the AURORA 1 and 2 scenario). Further to this, please can the company clarify why a combined TTD curve was preferred for the combination of VCS + MMF, and not each component of the regimen separately?

Parametric survival curves provide a smooth, continuous curve for time to treatment discontinuation (TTD) based on the underlying KM data. TTD is modelled because, by fitting to the stepwise Kaplan-Meier (KM) curve, it accounts for noise included within raw data. Using the KM curve by itself can lead to over or under-estimation, since only six time points are required by the model (6, 12, 18, 24, 30 and 36 months). Modelling TTD generates a continuous curve from which to sample these points and was therefore preferred over the KM curve.

A combined TTD curve for VCS + MMF was used, as if either component of the regimen was discontinued, then the entire regimen was considered to be discontinued. This is because taking oral MMF was a requirement for the study, meaning patients could not discontinue only MMF and remain in the AURORA trials, and naturally discontinuing the study drug (either VCS or placebo) was considered a discontinuation from treatment.[14] Therefore, modelling TTD separately (one curve for patients in the VCS+MMF arm on VCS and another for patients in the VCS+MMF arm on MMF) would lead to two identical curves, both of which are equal to the parametric fit currently in the model.

B12. Priority question: The company states that parametric models were fitted to TTD outcomes for both VCS + MMF and MMF from the AURORA 1 and AURORA 2 trials. Please can the company:

- ***Provide the curve parameters and Cholesky covariance matrix for all of the curve fits?***
- ***Provide a plot showing how each of the parametric curves compare with the Kaplan-Meier estimates of TTD for the observed period and the***

unobserved remainder of the time horizon for all parametric curves fitted?

- ***Justify the choice of the log-logistic curve to inform the TTD distribution (referring not solely to the AIC/BIC statistics provided)?***

- ***Provide four scenario analyses changing the base-case log-logistic TTD curve to the other four curves?***

The model specifications for all five parametric models fitted to the data are presented in Table 27; with requested plots presented below in Figure 4 (graphing the parametric fits for MMF) and

Figure 5 (graphing the parametric fits for voclosporin + MMF). It must be noted that parametric models are only used over the time period for which TTD data is available, so the fits are only compared to the KM period as there is no extrapolation of TTD used in the model.

Figure 4. TTD curves for all parametric models, MMF

Abbreviations: KM = Kaplan-Meier; MMF = mycophenolate mofetil; TTD = time to treatment discontinuation

Figure 5. TTD curves for all parametric models, VCS+MMF

Abbreviations: KM = Kaplan-Meier; MMF = mycophenolate mofetil; TTD = time to treatment discontinuation

Justification of the choice of log-logistic curve has been done systematically, as suggested in TSD 14[a].[41] Based on the log-cumulative hazard plots, Schoenfeld residuals and two proportional hazards test detailed in the CS, the hypothesis of proportional hazards is not rejected, so dependent models are fit. Based on visual inspection, the exponential and Weibull models seem to have the worst fit and are therefore excluded from further comparison. Additionally, when considering the MMF KM data, the log-normal curve seems to be underestimating the treatment discontinuation at 36 months and is therefore excluded from consideration. This leaves the log-logistic and generalised gamma parameterisations, which are difficult to distinguish from one another visually since they are primarily overlapping in both figures. Both the AIC and BIC for the log-logistic were more than 2 points below the respective AIC and BIC values for the generalised gamma, which indicates that the former is the best fitting model. Therefore, the log-logistic was used in the base case.

The results of the requested scenario analyses are provided below in Table 28,

[a] TSD14: "The fit of alternative models should be assessed systematically. Log-cumulative hazard plots (or suitable residuals plots), AIC/BIC tests (or other suitable tests of internal validity), and clinical plausibility based upon expert judgement, external data, or biological reasoning should be presented and assessed. Visual inspection should not be relied upon, but where it is used it is important to include numbers at risk data in diagrams of Kaplan Meier curves, as this aids the review of model fit via visual inspection."

Table 29, Table 30, Table 31, for the exponential, Weibull, log-normal and generalised gamma, respectively. All changes to results are minor, with exponential and Weibull parameterisations generally increasing the incremental cost-effectiveness ratio (ICER) relative to voclosporin, while the log-normal and generalised gamma parameterisations tended to decrease the ICER relative to voclosporin.

Table 27. Parameters and Covariance Matrices from each model

Modelled distribution	Results		Intercept	Treatment (Placebo)	MMF@Screening (No)	Scale	Shape
Exponential	Fitted Model	Model Parameters	[redacted]	[redacted]	[redacted]	[redacted]	
	Covariance Matrix	Intercept	[redacted]	[redacted]	[redacted]	[redacted]	
		Treatment (Placebo)	[redacted]	[redacted]	[redacted]	[redacted]	
		MMF@Sceening (No)	[redacted]	[redacted]	[redacted]	[redacted]	
		Scale	[redacted]	[redacted]	[redacted]	[redacted]	
Weibull	Fitted Model	Model Parameters	[redacted]	[redacted]	[redacted]	[redacted]	
	Covariance Matrix	Intercept	[redacted]	[redacted]	[redacted]	[redacted]	
		Treatment (Placebo)	[redacted]	[redacted]	[redacted]	[redacted]	
		MMF@Sceening (No)	[redacted]	[redacted]	[redacted]	[redacted]	
		Scale	[redacted]	[redacted]	[redacted]	[redacted]	
Log-Logistic	Fitted Model	Model Parameters	[redacted]	[redacted]	[redacted]	[redacted]	
	Covariance Matrix	Intercept	[redacted]	[redacted]	[redacted]	[redacted]	
		Treatment (Placebo)	[redacted]	[redacted]	[redacted]	[redacted]	
		MMF@Sceening (No)	[redacted]	[redacted]	[redacted]	[redacted]	
		Scale	[redacted]	[redacted]	[redacted]	[redacted]	
Log-Normal	Fitted Model	Model Parameters	[redacted]	[redacted]	[redacted]	[redacted]	
	Covariance Matrix	Intercept	[redacted]	[redacted]	[redacted]	[redacted]	
		Treatment (Placebo)	[redacted]	[redacted]	[redacted]	[redacted]	
		MMF@Sceening (No)	[redacted]	[redacted]	[redacted]	[redacted]	
		Scale	[redacted]	[redacted]	[redacted]	[redacted]	

Generalised Gamma	Fitted Model	Model Parameters	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Covariance Matrix	Intercept	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Treatment (Placebo)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		MMF@Sceening (No)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Scale	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Shape	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: MMF = mycophenolate mofetil

Table 28. Economic model scenario: exponential parameterisation for TTD

Technologies	Total costs (£)		Total QALYs		ICER (£/QALY)*	
	Base case	Exponential	Base case	Exponential	Base case	Exponential
VCS + MMF	[redacted]	[redacted]	[redacted]	[redacted]	-	-
MMF	[redacted]	[redacted]	[redacted]	[redacted]	£19,876	£20,582
L-CYC	[redacted]	[redacted]	[redacted]	[redacted]	£11,392	£11,892
H-CYC	[redacted]	[redacted]	[redacted]	[redacted]	£10,897	£11,383
AZA	[redacted]	[redacted]	[redacted]	[redacted]	£15,855	£16,435
RTX + MMF	[redacted]	[redacted]	[redacted]	[redacted]	£18,716	£19,891
TAC + MMF	[redacted]	[redacted]	[redacted]	[redacted]	£18,169	£18,894
TAC	[redacted]	[redacted]	[redacted]	[redacted]	£17,803	£18,567

Abbreviations: AZA = azathioprine; H-CYC = high dose cyclophosphamide; L-CYC = low-dose cyclophosphamide; MMF = mycophenolate mofetil; QALY = quality-adjusted life year; RTX = rituximab; TAC = tacrolimus; TTD = time to treatment discontinuation; VCS = voclosporin

Table 29. Economic model scenario: Weibull parameterisation for TTD

Technologies	Total costs (£)		Total QALYs		ICER (£/QALY)*	
	Base case	Weibull	Base case	Weibull	Base case	Weibull
VCS + MMF	[redacted]	[redacted]	[redacted]	[redacted]	-	-
MMF	[redacted]	[redacted]	[redacted]	[redacted]	£19,876	£20,107
L-CYC	[redacted]	[redacted]	[redacted]	[redacted]	£11,392	£11,564
H-CYC	[redacted]	[redacted]	[redacted]	[redacted]	£10,897	£11,064
AZA	[redacted]	[redacted]	[redacted]	[redacted]	£15,855	£16,055
RTX + MMF	[redacted]	[redacted]	[redacted]	[redacted]	£18,716	£19,120
TAC + MMF	[redacted]	[redacted]	[redacted]	[redacted]	£18,169	£18,418
TAC	[redacted]	[redacted]	[redacted]	[redacted]	£17,803	£18,066

Abbreviations: AZA = azathioprine; H-CYC = high dose cyclophosphamide; L-CYC = low-dose cyclophosphamide; MMF = mycophenolate mofetil; QALY = quality-adjusted life year; RTX = rituximab; TAC = tacrolimus; TTD = time to treatment discontinuation; VCS = voclosporin

Table 30. Economic model scenario: Log-normal parameterisation for TTD

Technologies	Total costs (£)		Total QALYs		ICER (£/QALY)*	
	Base case	Log-normal	Base case	Log-normal	Base case	Log-normal
VCS + MMF	[redacted]	[redacted]	[redacted]	[redacted]	-	-
MMF	[redacted]	[redacted]	[redacted]	[redacted]	£19,876	£19,682
L-CYC	[redacted]	[redacted]	[redacted]	[redacted]	£11,392	£11,250
H-CYC	[redacted]	[redacted]	[redacted]	[redacted]	£10,897	£10,759
AZA	[redacted]	[redacted]	[redacted]	[redacted]	£15,855	£15,691
RTX + MMF	[redacted]	[redacted]	[redacted]	[redacted]	£18,716	£18,382
TAC + MMF	[redacted]	[redacted]	[redacted]	[redacted]	£18,169	£17,962
TAC	[redacted]	[redacted]	[redacted]	[redacted]	£17,803	£17,586

Abbreviations: AZA = azathioprine; H-CYC = high dose cyclophosphamide; L-CYC = low-dose cyclophosphamide; MMF = mycophenolate mofetil; QALY = quality-adjusted life year; RTX = rituximab; TAC = tacrolimus; TTD = time to treatment discontinuation; VCS = voclosporin

Table 31. Economic model scenario: Generalised gamma parameterisation for TTD

Technologies	Total costs (£)		Total QALYs		ICER (£/QALY)*	
	Base case	Generalised gamma	Base case	Generalised gamma	Base case	Generalised gamma
VCS + MMF	[redacted]	[redacted]	[redacted]	[redacted]	-	-
MMF	[redacted]	[redacted]	[redacted]	[redacted]	£19,876	£19,939
L-CYC	[redacted]	[redacted]	[redacted]	[redacted]	£11,392	£11,439
H-CYC	[redacted]	[redacted]	[redacted]	[redacted]	£10,897	£10,943
AZA	[redacted]	[redacted]	[redacted]	[redacted]	£15,855	£15,910
RTX + MMF	[redacted]	[redacted]	[redacted]	[redacted]	£18,716	£18,826
TAC + MMF	[redacted]	[redacted]	[redacted]	[redacted]	£18,169	£18,237
TAC	[redacted]	[redacted]	[redacted]	[redacted]	£17,803	£17,875

Abbreviations: AZA = azathioprine; H-CYC = high dose cyclophosphamide; L-CYC = low-dose cyclophosphamide; MMF = mycophenolate mofetil; QALY = quality-adjusted life year; RTX = rituximab; TAC = tacrolimus; TTD = time to treatment discontinuation; VCS = voclosporin

B13. Please can the company explain why comparators other than MMF were assumed to have a TTD curve fixed at 100% until the end of treatment? Please provide sensitivity analysis where this assumption is varied (for example, assuming similar discontinuation to VCS + MMF or MMF)

Studies which reported on the regimens included within the model were searched, but no TTD data was found. Therefore, rather than making an assumption on the shape of the TTD curve, no discontinuation was used. Two scenarios are provided below: one with all comparators having the discontinuation of MMF (Table 32), and one where all comparators have the discontinuation of voclosporin + MMF (Table 33).

Table 32. Economic model scenario: all comparators with TTD of MMF

Technologies	Total costs (£)		Total QALYs		ICER (£/QALY)*	
	Base case	TTD of MMF	Base case	TTD of MMF	Base case	TTD of MMF
VCS + MMF	[redacted]	[redacted]	[redacted]	[redacted]	-	-
MMF	[redacted]	[redacted]	[redacted]	[redacted]	£19,876	£19,876
L-CYC	[redacted]	[redacted]	[redacted]	[redacted]	£11,392	£11,754
H-CYC	[redacted]	[redacted]	[redacted]	[redacted]	£10,897	£11,245
AZA	[redacted]	[redacted]	[redacted]	[redacted]	£15,855	£15,877
RTX + MMF	[redacted]	[redacted]	[redacted]	[redacted]	£18,716	£23,595
TAC + MMF	[redacted]	[redacted]	[redacted]	[redacted]	£18,169	£18,642
TAC	[redacted]	[redacted]	[redacted]	[redacted]	£17,803	£18,478

Abbreviations: AZA = azathioprine; H-CYC = high dose cyclophosphamide; L-CYC = low-dose cyclophosphamide; MMF = mycophenolate mofetil; QALY = quality-adjusted life year; RTX = rituximab; TAC = tacrolimus; TTD = time to treatment discontinuation; VCS = voclosporin

Table 33. Economic model scenario: all comparators with TTD of VCS + MMF

Technologies	Total costs (£)		Total QALYs		ICER (£/QALY)*	
	Base case	TTD of VCS+MMF	Base case	TTD of VCS+MMF	Base case	TTD of VCS+MMF
VCS + MMF	[redacted]	[redacted]	[redacted]	[redacted]	-	-
MMF	[redacted]	[redacted]	[redacted]	[redacted]	£19,876	£19,876
L-CYC	[redacted]	[redacted]	[redacted]	[redacted]	£11,392	£11,654
H-CYC	[redacted]	[redacted]	[redacted]	[redacted]	£10,897	£11,148
AZA	[redacted]	[redacted]	[redacted]	[redacted]	£15,855	£15,871
RTX + MMF	[redacted]	[redacted]	[redacted]	[redacted]	£18,716	£22,268
TAC + MMF	[redacted]	[redacted]	[redacted]	[redacted]	£18,169	£18,496
TAC	[redacted]	[redacted]	[redacted]	[redacted]	£17,803	£18,270

Abbreviations: AZA = azathioprine; H-CYC = high dose cyclophosphamide; L-CYC = low-dose cyclophosphamide; MMF = mycophenolate mofetil; QALY = quality-adjusted life year; RTX = rituximab; TAC = tacrolimus; TTD = time to treatment discontinuation; VCS = voclosporin

B14. Priority question: The CS makes repeated reference to a 36-month (3-year) stopping rule for VCS (e.g., Table B.3-2), which the EAG understands to be based on the study design of AURORA 1 and AURORA 2 (together providing follow-up data up to 3 years). Please can the company confirm if a 3-year stopping rule is expected to be followed in clinical practice, including any supporting evidence for the stopping rule? Furthermore, please can the company comment on the plausibility of a shorter treatment duration given the included scenario of a possible 18-month stopping rule (see Section B.3.3.5 of the CS)?

The AURORA clinical trial programme has demonstrated that voclosporin + MMF (alongside low-dose corticosteroids) is an effective and safe treatment option for LN for up to 3 years, with no requirement for regular therapeutic drug monitoring associated with other calcineurin inhibitors (CNIs).[2,14,42-45] In contrast to known safety risks with other CNIs, there was also no evidence suggestive of diabetes, renal toxicity, neurotoxicity or malignancy with long-term treatment with voclosporin.[2,14,46-50] Therefore, it is possible that clinicians would prescribe voclosporin for up to 3 years, as this is the longest period in which voclosporin has been shown to be effective and safe compared to MMF alone.

The 18-month scenario is informed by guidelines and a survey. According to the European Alliance of Associations for Rheumatology and European Renal Association–European Dialysis and Transplant Association EULAR/ERA-EDTA guidelines, treatment should be continued for a minimum of 24 weeks before assessing whether therapy should be continued.[29] Simultaneously, a survey of 96 US physicians found that 76% would keep patients on treatment for ≤1.5 years after achieving CRR.[51] Patients tend to respond quickly with voclosporin treatment. For example in AURORA-1, treatment with voclosporin + MMF resulted in a rapid reduction in UPCR, with a median time of 29 days to achieve a 50% reduction in UPCR from baseline.[14] Therefore, to assess the benefit of a time period between a minimum of 24 weeks (indicated by EULAR-ERA-EDTA guidelines) and a maximum of 1.5 years after CRR (indicated by physician survey), a scenario of 18 months was chosen. Results of the scenario suggest that voclosporin + MMF is also cost-effective over a shorter treatment horizon, and in line with a 36-month stopping rule, an 18-month stopping rule is clinically plausible given the data from AURORA 1 and 2.[2,14]

Since there is clinical data which suggests that the efficacy of voclosporin + MMF is maintained up to 36 months, a 36-month stopping rule is used as the base case. It must be noted that all ICERs in the scenario analysis of 18 months are reduced by more than 50%, suggesting that voclosporin + MMF becomes even more cost-effective over a shorter time horizon. This informed the choice to use a 36-month stopping rule in the base case, as it is a more conservative estimate of the value of voclosporin.

Utility values

B15. Please can the company explain why utility values were estimated independent of treatment arm and Grade 3 or 4 AE-related disutilities were incorporated separately, as opposed to estimating utility values by treatment arm? Further to this, please can the company undertake a scenario analysis including treatment arm in the utility regression analysis?

Disutilities from AEs were not explicitly captured in the study. Therefore, they are estimated separately, based on utility decrements and decrement length, and applied in the first model cycle. As is reported in the AURORA 1 CSR: Table 41,[14]

there was no significant difference between the treatment arm with regards to the both the SF-36 and LupusPRO.

Generally, there seems to be a misunderstanding in clarifications questions B15, B17, B18 and B19, that utility regression analysis was used in the final model. In fact, the Month 36 utilities from AURORA 2 are used in the base case, which correspond to a CR, PR and AD utility of 0.83, 0.80 and 0.71, respectively. In the literature, the only relevant utility identified was used to inform the ICER report (Mohara et al., 2014,[24,51]), with a decrement of 0.176 between AD and CR, and 0.09 between AD and PR. The Month 36 utilities used in the base case are therefore more conservative than the literature, with a base case decrement of 0.12 between AD and CR, and 0.08 between AD and PR utilised in the economic analysis.

At baseline for AURORA 2, the average utility is 0.70, which is the observation which is informed by the most data, 215 patients. After baseline there is a positive trend in utility for AD, increasing up to 0.79 before dropping to 0.71 at Month 36. We hypothesise that this could be due to a Hawthorne effect.[52] Therefore, Month 36 observations were used rather than the utility regression analysis, as the analysis makes use of all visits, which could potentially lead to bias being introduced. Additionally, the baseline observation of 0.7 for AD utility is based on the most data, and Month 36 has the closest AD utility estimate compared to all other months in addition to the expected utility hierarchy of CR, PR and AD.

The output of the linear mixed model is replicated in

Table 34 for completeness: as the reader can observe, the treatment effect was included in this model. However, with a p-value of 0.9261, the treatment effect is not statistically significant, and therefore no treatment effect on utilities was included in the model.

Table 34. Model parameters of linear mixed model for utilities

Covariate	Value of Covariate	Visit	Estimate	Standard Error	P-value
Intercept	N/A	-	[redacted]	[redacted]	[redacted]
Treatment (reference: voclosporin)	Placebo	-	[redacted]	[redacted]	[redacted]
Baseline EQ-5D	N/A	-	[redacted]	[redacted]	[redacted]
Response Category (reference: active disease)	Complete Response	-	[redacted]	[redacted]	[redacted]
	Partial Response	-	[redacted]	[redacted]	[redacted]
Age	N/A	-	[redacted]	[redacted]	[redacted]
Visit (reference: Month 36)	N/A	Month 6	[redacted]	[redacted]	[redacted]
		Month 12	[redacted]	[redacted]	[redacted]
		Month 18	[redacted]	[redacted]	[redacted]
		Month 24	[redacted]	[redacted]	[redacted]
		Month 30	[redacted]	[redacted]	[redacted]
Treatment * Visit	Placebo	Month 6	[redacted]	[redacted]	[redacted]
	Placebo	Month 12	[redacted]	[redacted]	[redacted]
	Placebo	Month 18	[redacted]	[redacted]	[redacted]
	Placebo	Month 24	[redacted]	[redacted]	[redacted]
	Placebo	Month 30	[redacted]	[redacted]	[redacted]
Baseline EQ-5D * Visit	N/A	Month 6	[redacted]	[redacted]	[redacted]
		Month 12	[redacted]	[redacted]	[redacted]
		Month 18	[redacted]	[redacted]	[redacted]
		Month 24	[redacted]	[redacted]	[redacted]
		Month 30	[redacted]	[redacted]	[redacted]
Response Category * Visit	Complete Response	Month 6	[redacted]	[redacted]	[redacted]
	Complete Response	Month 12	[redacted]	[redacted]	[redacted]
	Complete Response	Month 18	[redacted]	[redacted]	[redacted]
	Complete Response	Month 24	[redacted]	[redacted]	[redacted]
	Complete Response	Month 30	[redacted]	[redacted]	[redacted]
	Partial Response	Month 6	[redacted]	[redacted]	[redacted]
	Partial Response	Month 12	[redacted]	[redacted]	[redacted]
	Partial Response	Month 18	[redacted]	[redacted]	[redacted]

	Partial Response	Month 24	[redacted]	[redacted]	[redacted]
	Partial Response	Month 30	[redacted]	[redacted]	[redacted]
Age * Visit	N/A	Month 6	[redacted]	[redacted]	[redacted]
		Month 12	[redacted]	[redacted]	[redacted]
		Month 18	[redacted]	[redacted]	[redacted]
		Month 24	[redacted]	[redacted]	[redacted]
		Month 30	[redacted]	[redacted]	[redacted]

Abbreviations: EQ-5D = EuroQol 5-dimension scale; N/A = not applicable

B16. Please can the company comment on the face validity of the utility values for CR and PR in CKD Stages 3b-4 being higher than the utility value for AD CKD Stages 1-3a (though the EAG acknowledges that CR and PR in CKD Stages 3b-4 are not occupied at any time point in the company's base-case analysis)? Furthermore, please can the company comment on the implied utility for AD CKD Stages 1-3a from the analysis of the AURORA trial data, versus the reported utility for CKD Stages 1-2 from Jesky *et al.*, (2016), which is used as the basis for estimating decrements for CKD Stages 3b-4?

While the utility values of CR and PR in CKD 3b-4 are higher than the utility values of AD in CKD 1-3a, trial data and literature indicate that the achievement of response increases utility relative to active disease,[24,51] so this relationship may be maintained across CKD stages. However, due to data paucity, it is difficult to verify whether response in later CKD stages results in a higher utility than experiencing a renal flare during earlier CKD stages. This does not impact the economic modelling performed for the purpose of the submission, as these states are not used in the base case or any scenario.

The utility reported in Jesky et al., 2016 for CKD 1-2 is 0.85,[53] while the utility in AD from the AURORA 2 trial used in the model is 0.71. This difference is large because patients in CKD 1-2 unrelated to lupus nephritis are not comparable to patients with lupus nephritis. Lupus nephritis is the renal manifestation of systemic lupus erythematosus (SLE) which affects multiple bodily organs in addition to the kidney, often simultaneously,[54-56] whereby the QoL experienced by an SLE patient is baseline lower than a standard CKD patient.[57] Jesky et al., 2016 shows that utility decreases as CKD increases in severity,[53] a deterioriation which the model is designed to capture by defining the separate CKD stages, CKD 1-3a, CKD 3b-4 and CKD stage 5.

B17. For the final utility model used, please can the company confirm the exact equation and data formats used in the linear mixed model (LMM) as this is not immediately clear from the CS? For instance, are PR and CR dependent on stage? At present, the EAG expects this to be: (mapped) utility ~ factor (stage) + factor (response)

No utility regression analysis was used in the cost-effectiveness model, please see question B15 for additional clarification. The performed analysis had the following equation:

EQ-5D ~ Intercept + factor (Treatment) + numeric (Baseline EQ-5D) + factor (Response Category) + numeric (Age) + factor (Visit) + interaction term (Treatment * Visit) + interaction term (Baseline EQ-5D * Visit) + interaction term (Category * Visit) + interaction term (Age * Visit)

B18. For the final utility model used, please can the company provide a plot of predicted versus actual utility values?

Given that no utility regression analysis was used in the cost-effectiveness model, this has not been generated. Please see question B15 for additional clarification.

B19. For the final utility model used, please can the company provide the number of patients and observations informing each coefficient?

Given that no utility regression analysis was used in the cost-effectiveness model, this has not been generated. Please see question B15 for additional clarification.

B20. In considering the SF-36 data from the AURORA trial, were SF-6D utilities calculated? If so, please can the company provide information about these analyses to facilitate comparison with the mapped EQ-5D utility values? If not, please can the company explain why these utilities were not calculated?

Short-Form 6-Dimension (SF-6D) was not calculated. As specified in the NICE health technology evaluations manual,[58] "EQ-5D is the preferred measure of health-related quality of life in adults", so the decision was made to map the SF-36 utilities to EuroQol 5-Dimension (EQ-5D) using the method from Rowen et al., 2009.[59] In doing so, the SF-36 values are not mapped to the five domains of EQ-5D, but rather to one total EQ-5D utility. This reflected what was required for the model, as the model uses one utility value per health state.

B21. Please can the company provide summary statistics of the lupus-specific PRO(s) over time for the two arms, as well as a correlation plot against the estimated EQ-5D utilities?

The only lupus-specific patient-reported outcome measure included in the AURORA trials was LupusPRO v1.7, which was collected during AURORA 1 only. Since LupusPRO is collected over 12 domains (Lupus Symptoms, Cognition, Lupus Medications, Procreation, Physical Health, Pain Vitality, Emotional Health, Body Image, Desires-Goals, Social Support, Coping and Satisfaction with Care), the summary statistics from each of these domains is presented at baseline, 24 weeks and 52 weeks in Table 35.

Table 35. AURORA 1: Summary statistics for LupusPRO

Domain and timepoint	Summary Statistic	Voclosporin n=179	Placebo n=178
Lupus Symptoms			
Baseline	n	[redacted]	[redacted]
	Mean (SD)	[redacted]	[redacted]
	Median	[redacted]	[redacted]
	Min, Max	[redacted]	[redacted]
Week 12	n	[redacted]	[redacted]
	Mean (SD)	[redacted]	[redacted]
	Median	[redacted]	[redacted]
	Min, Max	[redacted]	[redacted]
Week 24	n	[redacted]	[redacted]
	Mean (SD)	[redacted]	[redacted]
	Median	[redacted]	[redacted]
	Min, Max	[redacted]	[redacted]
Week 52	n	[redacted]	[redacted]
	Mean (SD)	[redacted]	[redacted]
	Median	[redacted]	[redacted]
	Min, Max	[redacted]	[redacted]
Cognition			
Baseline	n	[redacted]	[redacted]
	Mean (SD)	[redacted]	[redacted]
	Median	[redacted]	[redacted]
	Min, Max	[redacted]	[redacted]
Week 12	n	[redacted]	[redacted]
	Mean (SD)	[redacted]	[redacted]
	Median	[redacted]	[redacted]
	Min, Max	[redacted]	[redacted]

Domain and timepoint	Summary Statistic	Voclosporin n=179	Placebo n=178
Week 24	n	[redacted]	[redacted]
	Mean (SD)	[redacted]	[redacted]
	Median	[redacted]	[redacted]
	Min, Max	[redacted]	[redacted]
Week 52	n	[redacted]	[redacted]
	Mean (SD)	[redacted]	[redacted]
	Median	[redacted]	[redacted]
	Min, Max	[redacted]	[redacted]
Lupus Medications			
Baseline	n	[redacted]	[redacted]
	Mean (SD)	[redacted]	[redacted]
	Median	[redacted]	[redacted]
	Min, Max	[redacted]	[redacted]
Week 12	n	[redacted]	[redacted]
	Mean (SD)	[redacted]	[redacted]
	Median	[redacted]	[redacted]
	Min, Max	[redacted]	[redacted]
Week 24	n	[redacted]	[redacted]
	Mean (SD)	[redacted]	[redacted]
	Median	[redacted]	[redacted]
	Min, Max	[redacted]	[redacted]
Week 52	n	[redacted]	[redacted]
	Mean (SD)	[redacted]	[redacted]
	Median	[redacted]	[redacted]
	Min, Max	[redacted]	[redacted]
Procreation			
Baseline	n	[redacted]	[redacted]
	Mean (SD)	[redacted]	[redacted]
	Median	[redacted]	[redacted]
	Min, Max	[redacted]	[redacted]
Week 12	n	[redacted]	[redacted]
	Mean (SD)	[redacted]	[redacted]
	Median	[redacted]	[redacted]
	Min, Max	[redacted]	[redacted]
Week 24	n	[redacted]	[redacted]
	Mean (SD)	[redacted]	[redacted]
	Median	[redacted]	[redacted]
	Min, Max	[redacted]	[redacted]
Week 52	n	[redacted]	[redacted]
	Mean (SD)	[redacted]	[redacted]
	Median	[redacted]	[redacted]
	Min, Max	[redacted]	[redacted]

Domain and timepoint	Summary Statistic	Voclosporin n=179	Placebo n=178
Physical Health			
Baseline	n	[redacted]	[redacted]
	Mean (SD)	[redacted]	[redacted]
	Median	[redacted]	[redacted]
	Min, Max	[redacted]	[redacted]
Week 12	n	[redacted]	[redacted]
	Mean (SD)	[redacted]	[redacted]
	Median	[redacted]	[redacted]
	Min, Max	[redacted]	[redacted]
Week 24	n	[redacted]	[redacted]
	Mean (SD)	[redacted]	[redacted]
	Median	[redacted]	[redacted]
	Min, Max	[redacted]	[redacted]
Week 52	n	[redacted]	[redacted]
	Mean (SD)	[redacted]	[redacted]
	Median	[redacted]	[redacted]
	Min, Max	[redacted]	[redacted]
Pain Vitality			
Baseline	n	[redacted]	[redacted]
	Mean (SD)	[redacted]	[redacted]
	Median	[redacted]	[redacted]
	Min, Max	[redacted]	[redacted]
Week 12	n	[redacted]	[redacted]
	Mean (SD)	[redacted]	[redacted]
	Median	[redacted]	[redacted]
	Min, Max	[redacted]	[redacted]
Week 24	n	[redacted]	[redacted]
	Mean (SD)	[redacted]	[redacted]
	Median	[redacted]	[redacted]
	Min, Max	[redacted]	[redacted]
Week 52	n	[redacted]	[redacted]
	Mean (SD)	[redacted]	[redacted]
	Median	[redacted]	[redacted]
	Min, Max	[redacted]	[redacted]
Emotional Health			
Baseline	n	[redacted]	[redacted]
	Mean (SD)	[redacted]	[redacted]
	Median	[redacted]	[redacted]
	Min, Max	[redacted]	[redacted]
Week 12	n	[redacted]	[redacted]
	Mean (SD)	[redacted]	[redacted]
	Median	[redacted]	[redacted]

Domain and timepoint	Summary Statistic	Voclosporin n=179	Placebo n=178
	Min, Max	[redacted]	[redacted]
Week 24	n	[redacted]	[redacted]
	Mean (SD)	[redacted]	[redacted]
	Median	[redacted]	[redacted]
	Min, Max	[redacted]	[redacted]
Week 52	n	[redacted]	[redacted]
	Mean (SD)	[redacted]	[redacted]
	Median	[redacted]	[redacted]
	Min, Max	[redacted]	[redacted]
Body Image			
Baseline	n	[redacted]	[redacted]
	Mean (SD)	[redacted]	[redacted]
	Median	[redacted]	[redacted]
	Min, Max	[redacted]	[redacted]
Week 12	n	[redacted]	[redacted]
	Mean (SD)	[redacted]	[redacted]
	Median	[redacted]	[redacted]
	Min, Max	[redacted]	[redacted]
Week 24	n	[redacted]	[redacted]
	Mean (SD)	[redacted]	[redacted]
	Median	[redacted]	[redacted]
	Min, Max	[redacted]	[redacted]
Week 52	n	[redacted]	[redacted]
	Mean (SD)	[redacted]	[redacted]
	Median	[redacted]	[redacted]
	Min, Max	[redacted]	[redacted]
Desires-Goal			
Baseline	n	[redacted]	[redacted]
	Mean (SD)	[redacted]	[redacted]
	Median	[redacted]	[redacted]
	Min, Max	[redacted]	[redacted]
Week 12	n	[redacted]	[redacted]
	Mean (SD)	[redacted]	[redacted]
	Median	[redacted]	[redacted]
	Min, Max	[redacted]	[redacted]
Week 24	n	[redacted]	[redacted]
	Mean (SD)	[redacted]	[redacted]
	Median	[redacted]	[redacted]
	Min, Max	[redacted]	[redacted]
Week 52	n	[redacted]	[redacted]
	Mean (SD)	[redacted]	[redacted]
	Median	[redacted]	[redacted]

Domain and timepoint	Summary Statistic	Voclosporin n=179	Placebo n=178
	Min, Max	[redacted]	[redacted]
Social support			
Baseline	n	[redacted]	[redacted]
	Mean (SD)	[redacted]	[redacted]
	Median	[redacted]	[redacted]
	Min, Max	[redacted]	[redacted]
Week 12	n	[redacted]	[redacted]
	Mean (SD)	[redacted]	[redacted]
	Median	[redacted]	[redacted]
	Min, Max	[redacted]	[redacted]
Week 24	n	[redacted]	[redacted]
	Mean (SD)	[redacted]	[redacted]
	Median	[redacted]	[redacted]
	Min, Max	[redacted]	[redacted]
Week 52	n	[redacted]	[redacted]
	Mean (SD)	[redacted]	[redacted]
	Median	[redacted]	[redacted]
	Min, Max	[redacted]	[redacted]
Coping			
Baseline	n	[redacted]	[redacted]
	Mean (SD)	[redacted]	[redacted]
	Median	[redacted]	[redacted]
	Min, Max	[redacted]	[redacted]
Week 12	n	[redacted]	[redacted]
	Mean (SD)	[redacted]	[redacted]
	Median	[redacted]	[redacted]
	Min, Max	[redacted]	[redacted]
Week 24	n	[redacted]	[redacted]
	Mean (SD)	[redacted]	[redacted]
	Median	[redacted]	[redacted]
	Min, Max	[redacted]	[redacted]
Week 52	n	[redacted]	[redacted]
	Mean (SD)	[redacted]	[redacted]
	Median	[redacted]	[redacted]
	Min, Max	[redacted]	[redacted]
Satisfaction with care			
Baseline	n	[redacted]	[redacted]
	Mean (SD)	[redacted]	[redacted]
	Median	[redacted]	[redacted]
	Min, Max	[redacted]	[redacted]
Week 12	n	[redacted]	[redacted]
	Mean (SD)	[redacted]	[redacted]

Domain and timepoint	Summary Statistic	Voclosporin n=179	Placebo n=178
	Median	[redacted]	[redacted]
	Min, Max	[redacted]	[redacted]
Week 24	n	[redacted]	[redacted]
	Mean (SD)	[redacted]	[redacted]
	Median	[redacted]	[redacted]
	Min, Max	[redacted]	[redacted]
Week 52	n	[redacted]	[redacted]
	Mean (SD)	[redacted]	[redacted]
	Median	[redacted]	[redacted]
	Min, Max	[redacted]	[redacted]

Abbreviations: SD = standard deviation
Source: Otsuka 2020[14]

LupusPRO can be summed into two total scores, the health-related quality of life (HRQOL), as well as non-health-related quality of life (non-HRQOL). Correlation pots for both have been presented against EQ-5D, at both baseline (

Figure 6 and

Figure 7) and month 12 (Figure 8 and

Figure 9). The Spearman's rank correlation coefficient was 0.706 at baseline and 0.685 at month 12 for HRQOL, and 0.338 at baseline and 0.370 at month 12 for non-HRQOL.

Figure 6. Correlation plot of HRQOL LupusPRO against EQ-5D, baseline

Abbreviations: EQ5D = EuroQoL 5-dimension scale; QoL = quality of life

Figure 7. Correlation plot of non-HRQOL LupusPRO against EQ-5D, baseline

Abbreviations: EQ5D = EuroQoL 5-dimension scale; QoL = quality of life

Figure 8. Correlation plot of HRQOL LupusPRO against EQ-5D, Month 12

Abbreviations: EQ5D = EuroQoL 5-dimension scale; QoL = quality of life

Figure 9. Correlation plot of non-HRQOL LupusPRO against EQ-5D, month 12

Abbreviations: EQ5D = EuroQoL 5-dimension scale; QoL = quality of life

B22. Please can the company confirm if the EAGs understanding of how the following decrements were calculated is correct?

- ***Decrement for CKD Stages 3b-4 - average of values reported in Table 3 of Jesky et al., (2016), assuming 50% in all states***
- ***Transplant - reported value in Table 3 of Lee et al., (2005)***
- ***Dialysis - average of values reported in Table 3 of Lee et al., (2005), assuming 50% peritoneal dialysis and 50% haemodialysis***

Yes, the understanding of the calculations is correct. The decrement between CKD 1-3a and CKD 3b-4 is calculated between a population of equal parts CKD 1/2 and CKD3a, and a population of equal parts CKD3b and CKD 4. Please note that for the last two points, these are not considered decrements from any state – they are utility values which represent the health state of CKD 5 transplant and CKD 5 dialysis, respectively.

Costs and medical resource use

B23. The CS states that PSSRU 2020 was used to inform costs within the model, yet the end-of-life costs within the model do not relate to PSSRU 2020 but instead are reported in PSSRU 2021. Please can the company confirm if PSSRU 2021 has been used throughout the CS and in the model?

All Personal Social Services Research Unit (PSSRU) costs included throughout the CS and the model are taken from PSSRU 2021. Any instances where PSSRU 2020 is mentioned can be considered as a mis-reference.

B24. Please can the company provide more information on how inputs from the PSSRU 2020 (or PSSRU 2021, depending on the response to the question above) have been used to inform costs for nurse visit, specialist visit, and psychologist visit. In responding to this question, please provide the following details:

- ***What (if any) assumptions were made to generalise reported costs to those included within the model?***
- ***Which category (or categories) of staff was (or were) used to inform the unit cost included within the model?***
- ***Were costs including or excluding qualifications used?***

Note: These three costs from the PSSRU were mistakenly inflated by the inflation index of 2021. This led to the costs being 0.2% higher. This error did not affect any other costs from the PSSRU. This has been adjusted and is reflected in the updated base case results in Section C.

Generally, attempts were made to pick the lowest band of service provider which would provide an adequate level of care. For nurse visit, this corresponded to a hospital-based Band 6 nurse, which is a nurse specialist able to perform the routine tests required for a lupus nephritis check-up. For specialist visit, this was a hospital-based doctor who specialised in either nephrology or rheumatology and was therefore attributed to the category “Consultant: medical.” For visits with a

psychologist, this corresponded to a clinical psychologist, i.e., Band 7 scientific and professional staff.

All unit costs are informed by two factors, an estimate of the time required and an hourly wage. KOL expert opinion indicated that a standard visit would require 40 minutes of nurse time and occur at a hospital. The hourly rate of a hospital-based Band 6 nurse is £51, equating to a cost of £34.00 to account for the 40 minutes of nurse time. For specialist visits, KOL expert opinion indicated 20 minutes of time are required for a hospital-based specialist visit. A hospital-based doctor had an hourly wage of £123, equating to a unit cost of £41.00 for 20 minutes of specialist time. For a psychologist, the average session time of 70 minutes was sourced from an NHS document.[60] The hourly wage for a clinical psychologist was £65 per hour, equating to the unit cost per psychologist visit of £75.83 (over 70 minutes). Please note that KOL expert opinion indicated that about 50% of LN patients in dialysis required a psychologist, so resource use frequency has been halved to account for this.

B25. The NHS reference costs provided within the table cannot be found within the provided reference file for YL20A, DIM007 and RD51A. Please can the company clarify how the values were obtained? Further to this, if a weighted average of the costs associated with each cost component was estimated, please can the company outline the methodology (e.g., was this weighted by the activity level)? Please can respective calculations be provided or cell references for the NHS reference costs.

The costs for YL20A, DIM007 and RD51A are given in the 'Total HRGs' sheet of the provided reference file deduced from the National Schedule of NHS (2019-20)- All NHS trusts and NHS foundation trusts.[61] The cell references for YL20A, DIM007 and RD51A are A3115, A3263, and A2594 respectively.[61] These costs are also mentioned across other sheets in the file but used from the 'Total HRGs' sheet.[61]

B26. In the CS, the study design of AURORA 1 implies that patients receive MMF 2g (plus oral corticosteroids) per day on both arms, yet in the model patients are assumed to incur the cost of MMF 2.5mg per day. Please can the company clarify the dosing of MMF both with respect to the AURORA 1 trial and expected use in clinical practice?

In AURORA-1, patients received MMF with a goal dose of 2 g/day, administered as 1 g twice daily. MMF-naïve patients were started at 0.5 g twice daily on days 1–7, then increased to 1 g twice daily on day 8, while those already on MMF continued their dose without interruption or adjustment.[14] As per the EULAR/ERA-EDTA guidelines, for patients with class III (±V) or IV (±V) LN, the recommended MMF target dose is 2–3 g/day.[29] Most studies and guidelines use MMF at a dosage of 2–3 g/day, which is in line to the dosage used in the AURORA clinical programme. Patients in the AURORA-1 trial were able to increase their MMF dosage to 3 g/day, if necessary, with approval by the Medical Monitor, and therefore the range of MMF in the AURORA 1 trial was 2-3 g/day.[14] In line with the approach taken for other ranges of treatment dosage, the mean was taken for the model, resulting in a dose of 2.5 g/day. As this dosing falls within the recommended bounds of EULAR/ERA-EDTA guidelines,[29] we assume that this value would be adequately reflective of clinical practice.

B27. In the model, relative dose intensity (RDI) for all non-AURORA 1 treatment arms is set to 100% except for tacrolimus + MMF which is assumed to have an RDI of 95%. Please can the company clarify the source of this estimate, and explain why all other treatments are assumed to have an RDI of 100%?

All non-AURORA 1 treatments besides tacrolimus + MMF are assumed to have a relative dose intensity (RDI) of 100% due to a lack of RDI being reported in the relevant trials. For tacrolimus + MMF, RDI of 95% was deduced from Liu et al., 2015,[62] which states that “95% of patients adhered to MMF and tacrolimus.” Rather than implementing this 95% compliance in the time to treatment discontinuation curve, RDI was set to 95% to allow for the same effect, i.e., treatment acquisition and administration costs are reduced by 5%. Please note that this option was mistakenly not connected for tacrolimus + MMF in the initial model version and has now been corrected. Therefore, the previous model version reported results with tacrolimus + MMF at 100%. Using the updated model, the ICER for VCS+MMF

versus tacrolimus + MMF shifts from £18,169 to £18,009 when RDI is increased from 95% to 100%, a decrease in ICER of 0.9%.

Adverse events

B28. The CS states that the cut off for which adverse events (AEs) were included in the model is specified by the probability of occurrence for a treatment-emergent AE, at Grade 3 or 4, of at least ≥1% in either treatment arm (see Section B.3.4.4). However, placeholders for some AEs not meeting these criteria are included within the model, but at a 0% probability of occurrence in the base case although they were present within the AURORA trials, or AEs noted throughout LN literature. Please can the company check and confirm that the AEs included in the model meet the stated inclusion criteria and make any necessary edits where appropriate?

The AEs included in the model are based on two criteria:

- Probability of occurrence for a serious TEAE of at least ≥1% in AURORA 1 for either treatment arm, OR
- Occurrence in a trial which has informed a comparator

Following review of the AURORA 1 CSR,[14] the AEs have been recalculated. Previous AE rates were based on severe treatment-emergent adverse events (TEAEs), not serious TEAEs. Serious TEAEs are considered Grades 3 and 4 AEs based on the Common Terminology Criteria for Adverse Events v5.0.[63] All AEs meeting the inclusion criteria for AURORA 1 are presented below, in

Table 36. In summary, two additional adverse events were added (urinary tract infection and bronchitis) and a single adverse event was removed (headache).

Table 36. AURORA 1: Serious TEAEs which affected ≥1% of either treatment arm

System organ class (Preferred term)	Voclosporin n=178	Placebo n=178
Infections and infestations, n (%)		
Pneumonia	7 (3.9)	8 (4.5)
Gastroenteritis	3 (1.7)	0 (0.0)
Urinary tract infection	2 (1.1)	1 (0.6)
Bronchitis	0 (0.0)	3 (1.7)
Renal and urinary disorders, n (%)*		
Acute kidney injury	4 (2.2)	2 (1.1)
Renal impairment	2 (1.1)	1 (0.6)
Lupus nephritis	1 (0.6)	4 (2.2)
Vascular disorders, n (%)**		
Hypertension	3 (1.7)	1 (0.6)
Hypertensive crisis	1 (0.6)	2 (1.1)
Blood and lymphatic system disorders, n (%)	1 (0.6)	0 (0.0)
Anaemia	3 (1.7)	0 (0.0)
Musculoskeletal and connective tissue disorders, n (%)*		
Systemic lupus erythematosus	3 (1.7)	3 (1.7)

*These TEAEs do not need to be considered separately within the model, as they are assumed to be a side effect of the lupus nephritis condition itself rather than either treatment arm

**Counted together as hypertension for the model

Abbreviations: TEAE = treatment-emergent adverse event

Source: Otsuka 2020[14]

The values informing these additional adverse events can be found in Table 37. Furthermore, the following adverse events have been removed, as they do not occur with any treatment included in the model: infections and infestations, respiratory, thoracic and mediastinal disorders, blood and lymphatic system disorders and nausea and vomiting. Relevant costs, disutilities and event durations have also been removed. Model formatting has also been updated so that the correct cells are hidden depending on the choice of AE incidence for comparators. Additionally, the reference in cell O34 has been updated.

Table 37. AE cost, utility decrement and duration

Adverse event	Category	Value	Reference
Bronchitis	Cost	£2,299	National Schedule of NHS costs (2019/20), DZ65E - Chronic Obstructive Pulmonary Disease or Bronchitis, with Single Intervention, with CC Score 0-4[61]
	Utility decrement	-0.069	Doyle S, Lloyd A, Walker M. 2008. Health state utility scores in advanced non-small cell lung cancer. Lung Cancer. 62,374-380.[64]
	Length	24 days	TA306[65]
Urinary tract infection	Cost	£2,418.10	National Schedule of NHS costs (2019/20), LA04M - Kidney or Urinary Tract Infections, with Interventions, with CC Score 0-2[61]
	Utility decrement	-0.124	TA250[66]
	Length	21 days	TA250[66]

Abbreviations: AE = adverse event; NHS = National Health Service; TA = Technology Appraisal
Source: NHS cost

B29. Please can the company justify the inclusion of only including Grade 3 or 4 treatment-emergent AEs within the model, if they occurred in at least ≥1% of patients in either treatment arm?

To restrict AEs to a manageable set, the aim is to identify those that are expected to have the largest impact on health-related quality of life and cost outcomes. Therefore, serious TEAEs were identified, as these are the highest-grade adverse events which occurred during treatment (assumed to correspond to Grade 3 or 4 in accordance with the Common Terminology Criteria for Adverse Events v5.0).[63] The following definition of TEAE comes from the AURORA 1 CSR: "A treatment-emergent adverse event (TEAE) was defined as an AE occurring on or after the first dose of voclosporin/placebo up to and including 30 days after the last dose of voclosporin/placebo."[14]

Reducing the number of AEs and ensuring that only those which occur in multiple patients within the same treatment arm is a common strategy and has been performed for other submissions. While there have been no other submission within lupus nephritis, TA775 in CKD used only serious AEs in their model,[67] whereas

TA623 for hyperkalaemia (a side effect of CKD) did not include any AEs in their initial model because none occurred frequently enough.[68]

Model settings and functionality

B30. Priority question: On the 'Transitions' sheet, alternative versions of the transition matrices are presented labelled as 'Costing transition matrices' (see cell range B19:CL31). Given that these alternative matrices are not described in the CS, please can the company explain their purpose and which aspects of the model they are intended to inform?

These transition matrices are used to derive the number of patients who are newly entering a health state. This breakdown of patients is required for resource use costs, as patients have differing costs based on whether they have remained in the health state ("Cycle 2+" on the Resource Use sheet) or have just entered the health state ("Cycle 1" on the Resource Use sheet). These matrices are not strictly transition matrices, since the rows do not add to 1. This is because they are equal to the transition matrices with the diagonal set to 0. In doing so, applying the patient trace to the costing transition matrices leads to the number of patients which are entering a health state for the first time, i.e., are in their first cycle in said health state.

B31. Priority question: The model includes an option to enable or disable wastage costs for vials only. Please can the company:

- ***Explain why this is disabled in the base-case analysis?***
- ***Confirm that this does not impact costs for oral therapies (since wastage is only considered in the model for vials)?***
- ***Provide a scenario in which wastage is also considered for oral therapies (for example, that discontinuing patients incur the cost of the remainder of a pack)?***

Our understanding is that vial wastage will primarily only increase the costs for comparators, making voclosporin + MMF more cost-effective. Therefore, vial wastage has been conservatively disabled in the base-case analysis. The reason vial wastage primarily increases costs for comparators is because vial wastage considers the cost of purchasing an entire vial (rather than paying for the cost based

on the quantity required by the patient) and only the IV treatments cyclophosphamide, rituximab and methylprednisolone are affected. As such, costs for oral therapies are not impacted.

A scenario is provided in Table 38 whereby vial wastage is turned on, and oral therapy pack wastage occurs for discontinuing patients due to them being charged the cost of the packs required in an average month in the first year of treatment. In this scenario, discontinuation is assumed equal to voclosporin + MMF for all comparators.

Table 38. Economic model scenario: vial and pack wastage included

Technologies	Total costs (£)		Total QALYs		ICER (£/QALY)*	
	Base case	TTD of MMF	Base case	TTD of MMF	Base case	TTD of MMF
VCS + MMF	[redacted]	[redacted]	[redacted]	[redacted]	-	-
MMF	[redacted]	[redacted]	[redacted]	[redacted]	£19,876	£20,555
L-CYC	[redacted]	[redacted]	[redacted]	[redacted]	£11,392	£11,891
H-CYC	[redacted]	[redacted]	[redacted]	[redacted]	£10,897	£11,331
AZA	[redacted]	[redacted]	[redacted]	[redacted]	£15,855	£16,459
RTX + MMF	[redacted]	[redacted]	[redacted]	[redacted]	£18,716	£23,414
TAC + MMF	[redacted]	[redacted]	[redacted]	[redacted]	£18,169	£19,043
TAC	[redacted]	[redacted]	[redacted]	[redacted]	£17,803	£18,757

Abbreviations: AZA = azathioprine; H-CYC = high dose cyclophosphamide; ICER = incremental cost-effectiveness ratio; L-CYC = low-dose cyclophosphamide; MMF = mycophenolate mofetil; QALY = quality-adjusted life year; RTX = rituximab; TAC = tacrolimus; TTD = time to treatment discontinuation; VCS = voclosporin

B32. On the 'Clinical Inputs' sheet, a validation section is provided. Please can the company confirm that the 'published' values labelled as 'PR' refer to 'CR and PR', whereas the 'count' and 'modelled' refer to PR alone? With respect to the 'published' and 'count' data, please can the company explain the apparent discrepancy between the 'published' CR+PR value for VCS + MMF of 70% (125/179) and the implied CR+PR 'count' value of 74.86% (134/179)?

The reference to the published data is Rovin et al., 2021 where PR and CR are reported differently than in the model and referred to as PRR and CRR respectively.[9] In the publication, as per the outcome definition, PR is not mutually exclusive from CR, and most but not all patients who achieved CR also achieved PR. However, in the model the states must be mutually exclusive, which has been defined using the

count data. This was done by classifying patients which are in both CR and PR as CR only. Therefore, the published PR value is not equal to the actual value of CR plus PR, but reflects 125 patients who were in PR. It can be inferred from 73 voclosporin + MMF patients being in CR and 61 patients in PR, that there were 64 patients in CR + PR who were classified as CR only.

B33. In the one-off treatment-emergent AE table within sheet 'Safety' in the model, the AE 'Placeholder 1' is shown to have a probability of occurrence in cells M27 and O27. Please can the company confirm if these cells are labelled incorrectly and/or if they should not be included within the model? Otherwise, please can the company provide the necessary information in order for the EAG to determine the relevance of these values to the model?

The cells, M27 and O27 (and P27 by virtue of a formula using O27) are labelled incorrectly under 'Placeholder 1'. The correct values under these should be 0%.

Section C: Textual clarification and additional points

In response to a request made by the EAG within the clarification question meeting, a corrected summary of serious treatment-related TEAEs for AURORA 1 (Table in main submission) is presented below.[14]

Table 39. AURORA 1: Serious treatment-related TEAEs

System organ class (Preferred term)	Voclosporin n=178	Placebo n=178
Any serious treatment-related TEAE, n (%)	8 (4.5)	8 (4.5)
Infections and infestations	4 (2.2)	6 (3.4)
Pneumonia	1 (0.6)	2 (1.2)
Upper respiratory tract infection	1 (0.6)	1 (0.6)
Acute sinusitis	1 (0.6)	0 (0.0)
Lung abscess	1 (0.6)	0 (0.0)
Pyeloneprhritis acute	1 (0.6)	0 (0.0)
Bronchitis	0 (0.0)	1 (0.6)
Herpes zoster disseminated	0 (0.0)	1 (0.6)
Pyelonephritis	0 (0.0)	1 (0.6)
Renal and urinary disorders	2 (1.2)	1 (0.6)
Renal impairment	1 (0.6)	1 (0.6)
Acute kidney injury	1 (0.6)	0 (0.0)
Vascular disorders	2 (1.2)	0 (0.0)

Hypertension	2 (1.2)	0 (0.0)
Blood and lymphatic system disorders	1 (0.6)	0 (0.0)
Anaemia	1 (0.6)	0 (0.0)
Neoplasms benign, malignant and unspecified*	0 (0.0)	1 (0.6)
Schwannoma	0 (0.0)	1 (0.6)

*including cysts and polyps

Abbreviations: TEAE = treatment-emergent adverse event

Source: Otsuka 2020[14]

The following table details the new base case results. This includes the following changes: updates to adverse events, resource use costs, NMA results for PR, connecting RDI for TAC+MMF and fixing the error on the Outcomes sheet.

The outcomes error can be explained as follows: in the Outcomes sheet, there are some numbers in column A which are used as indices for arrays of results. One of these numbers is incorrect: A23 is 5 but should be 6. This affects the total cost of the "Resource Use" category, and therefore affects the ICERs for all treatments.

Table 40. Updated base case results (discounted)

Technologies	Total			Incremental			ICER (£/QALY)*
	Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs	
VCS + MMF	[redacted]	[redacted]	[redacted]	-	-	-	-
MMF	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£19,876
L-CYC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£11,392
H-CYC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£10,897
AZA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£15,855
RTX + MMF	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£18,716
TAC + MMF	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£18,169
TAC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£17,803

*ICER for VCS + MMF vs comparator

Abbreviations: AZA = azathioprine; CYC = cyclophosphamide; ICER = incremental cost-effectiveness ratio; L-CYC = low-dose CYC; H-CYC = high-dose CYC; LYG = life years gained; MMF = mycophenolate mofetil; QALYs = quality-adjusted life years; RTX = rituximab; TAC = tacrolimus; VCS = voclosporin

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NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Voclosporin with immunosuppressive therapies for treating lupus nephritis [ID3962]

Patient Organisation Submission

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type. [Please note that declarations of interests relevant to this topic are compulsory].

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

NICE National Institute for Health and Care Excellence

About you

1.Your name	[redacted]
2. Name of organisation	AOFAC Foundation
3. Job title or position	
4a. Brief description of the organisation (including who funds it). How many members does it have?	Anthonia Oyindamola Folakemi Afelumo Coshare (AOFAC) Foundation is a charity registered in England and Wales, we are a patient advocacy group in the area of Thrombotic Thrombocytopenic Purpura (TTP) with interest in Sickle Cell Disease and Lupus SLE. We've had funding from Lottery fund and Sanofi
4b. Has the organisation received any funding from the company bringing the treatment to NICE for evaluation or any of the comparator treatment companies in the last 12 months? [Relevant companies are listed in the appraisal stakeholder list.] **If so, please state the name of the company, amount, and purpose of funding.**	No
4c. Do you have any direct or indirect links	No

with, or funding from, the tobacco industry?	
5. How did you gather information about the experiences of patients and carers to include in your submission?	**We normally gather information from Groups and patients that are linked with the disease**

Living with the condition

6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	Living with = Fatigue-task are difficult, pain, stress, Anxious/depress mood Carers experience = Big live adjustment, stress

Current treatment of the condition in the NHS

7. What do patients or carers think of current treatments and care available on the NHS?	**No comment**
8. Is there an unmet need for patients with this condition?	**No comment**

Advantages of the technology

9. What do patients or carers think are the advantages of the technology?	**No comment**

Disadvantages of the technology

10. What do patients or carers think are the disadvantages of the technology?	**No comment**

Patient population

11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	**No comment**

Equality

12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	**No comment**

Other issues

13. Are there any other issues that you would like the committee to consider?	NA

Key messages

14. In up to 5 bullet points, please summarise the key messages of your submission.	• The more options of medications for treatment the better • • • •

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

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NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Voclosporin with immunosuppressive therapies for treating lupus nephritis [ID3962]

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- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you

1.Your name	[redacted]
2. Name of organisation	LUPUS UK
3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	LUPUS UK is the only national registered charity supporting people affected by lupus. The charity produces high-quality information for patients, carers, employers and clinicians. Through volunteer-led regional groups the charity provides support group meetings and raises awareness of the disease within local communities. LUPUS UK also funds medical research and Specialist Lupus Nurses in UK hospitals. The charity has approximately 4,000 subscribed members, however, we are here for all people affected by lupus and therefore engage with many more people with the disease in the UK.
4b. Has the organisation received any funding from the company bringing the treatment to NICE for evaluation or any of the comparator treatment companies in the last 12 months? [Relevant companies are listed in the appraisal stakeholder list.] **If so, please state the name of the company, amount, and purpose of funding.**	LUPUS UK has received no funding from the company bringing the treatment to NICE. The charity has also not received any funding from companies providing comparator treatments listed as stakeholders for the appraisal. In the interest of transparency, the charity has received the following funding from pharmaceutical companies in the past 12 months: • £5,000 of restricted funding from Janssen Pharmaceuticals in January 2022. This funding was to assist LUPUS UK in the development of an initiative to engage more patients in research, particularly covering the costs of a new CRM database and staff time. • £7,685.64 of restricted funding from GlaxoSmithKline in May 2021 to help LUPUS UK to develop and provide a series of interactive virtual patient education seminars. This is part of LUPUS UK's digital outreach initiative in response to the COVID-19 pandemic to ensure that lupus patients are still able to access important patient education and support throughout social distancing restrictions. The virtual patient education seminars were developed and produced independently from GSK. The company had no editorial oversight of the contents. The virtual seminars are unrelated to belimumab.
4c. Do you have any direct or indirect links	No

with, or funding from, the tobacco industry?	
5. How did you gather information about the experiences of patients and carers to include in your submission?	In the process of identifying suitable candidates to nominate as Patient Experts for the appraisal committee meeting, we selected a small group of people living with lupus nephritis who were happy to share their experiences and contribute to this submission. Each individual was provided with some questions about their experiences and views, which has helped to guide or response. Some anonymised quotations from these people have been included in our submission. A broader range of experiences and views from across the community have been collected through various surveys in recent years: • LUPUS UK conducted an anonymous online survey which was completed by 67 respondents between 30/09/2020 – 30/10/2020. The survey was open to people living with SLE and their carers in the UK. The survey asked a range of questions about the experiences of living with lupus and treatment. • Results from a previous LUPUS UK membership survey were also used in this submission. The survey was completed by 2,527 patients who were members of the charity in 2014 and the results were subsequently analysed by The Arthritis Research UK Centre for Epidemiology, University of Manchester and accepted for publication in the journal 'Lupus' on 16 November 2017 - https://journals.sagepub.com/doi/10.1177/0961203317749746 • Evidence was also taken from the Rare Autoimmune Rheumatic Diseases Alliance (RAIRDA) report, "Reduce, Improve, Empower" published in February 2018 and available at https://rairdaorg.files.wordpress.com/2020/06/rairda-survey-report-2018.pdf. The report followed a survey completed by 2,101 RAIRD patients, of which 1,098 reported having a diagnosis of lupus. • Five people living with lupus nephritis in the UK were provided with short questionnaires for them and their partner/carer in April 2022. These questionnaires were based upon the topics within this framework to help guide our submission. The final draft of the submission was circulated to LUPUS UK's Board of Trustees to review and provide additional comments. Our Board of Trustees is entirely formed of people who either have personal lived experiences of lupus or close family members living with the disease.

Living with the condition

6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	The day-to-day symptoms of lupus nephritis are similar to those of other kidney diseases and can include: 1. Changes to urine (including appearing dark, containing blood or being foamy) 2. Increased frequency of urination, especially at night 3. Puffiness/swelling in the feet, ankles, and legs that worsens over the course of the day 4. Gaining weight 5. High blood pressure The outlook for people with lupus nephritis varies. Many people may experience intermittent symptoms and their kidney damage may only be noticed through routine urine testing. However, some will have more severe disease and progress to end-stage renal disease (ESRD). A. Mahajan 2020 (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7425376/) found from analysing studies that 4–28% of patients with lupus nephritis developed ESRD. The key predictors for progression to ESRD included high serum creatinine (>1.5 mg/dL) at disease onset; hypocomplementaemia; class III, IV and VI of lupus nephritis; higher chronicity index; high systolic blood pressure; older age; male sex; and black race. M. Hui 2013 (https://pubmed.ncbi.nlm.nih.gov/23386411/) undertook a 15-year review at three UK centres in the East Midlands from 1995-2010. 61 patients with lupus nephritis were identified with biopsy-proven lupus nephritis (class III-V). Of these, 8.2% developed end-stage renal failure. Whilst lupus nephritis most commonly occurs at presentation or within 5-years of onset of systemic lupus erythematosus (SLE), it is important to maintain continued vigilance for lupus nephritis in all SLE patients because it can occur, and flare, after many years. Lupus nephritis is a common and severe manifestation of systemic lupus erythematosus (SLE). As such, people with lupus nephritis will typically experience a wide range of symptoms affecting other systems in addition to their kidney involvement. SLE is a disease which varies significantly in presentation, is often unpredictable and difficult to successfully manage with medication. In our survey of LUPUS UK members, respondents reported fatigue (81%) and joint pain/swelling (60%) as the most difficult symptoms to live with. In our online survey, respondents reported that the most challenging aspects of living with lupus are the symptoms (particularly fatigue and joint/muscle pain), the impact on their ability to work and their mental wellbeing. *“The worst thing is the chronic fatigue. No matter how much sleep I get, I wake up every day knowing I don’t have enough energy to face the day. I have to ration my energy. Daily, I have to push myself to do tasks that most people do absent-mindedly because I feel so lethargic. Working is extremely important to me, but I know working full-time means most of my energy goes on my job, meaning I must sacrifice hobbies and socializing etc. because I don’t have the energy after work.”*

	The symptoms of lupus can limit a person's mobility and independence. In our online survey, over 58% of respondents indicated that they require assistance with household care, over 43% require assistance with mobility and 1-in-3 said they need assistance with their personal care. *"[Being a carer] can be difficult at times, a lot of the time you feel so helpless. It is a 24/7 illness, there are days when their joints are so swollen that I need to do everything; bathe, help dress, prepare meals. They need to rest often, especially after doing activities that a healthy person does without much thought. We don't socialize as much as most people we know as they need time to recover after work. I do have to take time off work to attend appointments or help when they are unwell, which I am more than happy to do but it can be a constant worry, checking blood results or biopsy results. And they can get down at times when their body can't keep up with their willpower, which is hard to watch. I'm always amazed at what they do despite all they endure to do it."* An important area that is often impacted by lupus is a person's ability to maintain employment. LUPUS UK's member survey revealed that almost 1-in-4 respondents had retired on medical grounds and just over half were receiving welfare benefits. In our online survey approximately 58% of respondents indicated that they found maintaining employment 'difficult' or 'very difficult'. *"Had to retire from work 10 years early. Major financial and mental hardship as a result. Have to rely on reduced pension and demean myself for PIP."* *"The number of appointments can affect employment, particularly if an employer does not understand the importance/necessity of appointments. As lupus nephritis is an invisible illness, I feel that employers do not a) understand the condition, b) take time/effort to understand the condition, c) arrange appropriate discussion for the benefit of all parties when it comes to employing those with disabilities. Over the last couple of years, both my study and employment have been impacted by the pandemic because of having lupus nephritis. Immunosuppressive medication and having severe CKD put my studies behind by 6 months because university felt it was unsafe for me to be out on placement at this time. This impacted not only study time, but pushed me starting employment back by 6 months. Not only did this financially impact me but my personal wellbeing was also impacted by this."* The social and psychological impact of having lupus is also reported as being very significant, with mental health problems such as depression & anxiety and loss of confidence/self-esteem being ranked as some of the most challenging aspects of living with the disease. In many cases, lupus presents with few visible symptoms (if any) making it difficult for family, friends, colleagues and medical professionals to appreciate the extent to which fatigue, pain and other symptoms have an impact. RAIRDA's 2018 report found that lupus patients were likely to feel isolated, with 24% feeling that way every day and 57% at least once a week. *"It does affect friendships and relationships because the truth is, I don't have the energy to maintain them; I can't keep up. I have a tight group of close friends, but I don't see them anywhere near as often as I should because as stated above, I don't have the energy."* The impact of caring for someone with lupus can be significant. This may be especially true for those with severe lupus that hasn't responded well to standard therapy – those who could potentially benefit most from voclosporin. Fatigue, pain and weakness can be limiting factors in the mobility and capacity for activities for someone living with lupus. This often means a

	partner or carer will need to provide additional assistance with transport for medical appointments and essential personal and household care. RAIRDA's 2018 report showed that 25% of respondents to their survey indicated that either they or their partner/carer had reduced working hours as a result of their condition. A further 20% reported that either they or a partner/carer had been forced to give up working due to their condition. *"The greatest impact it has on my life is the fatigue and joint and muscle pain symptoms. This doesn't allow us to make any plans for the future and more often than not means we have to cancel plans last minute. If my partner didn't have other carers, I feel I would have to give up work to care for them."* RAIRDA's 2018 report indicated that 50% of lupus patients feel that their condition has a negative effect on their family.

Current treatment of the condition in the NHS

7. What do patients or carers think of current treatments and care available on the NHS?	Treatments can be used to slow the course of lupus nephritis but standard therapy is not always effective in controlling the symptoms of lupus and may not be tolerated well by all patients. *"When you've tried almost all the available treatment options there is the fear that you're running out of options and your lupus is starting to become untreatable. That fear is even bigger when you have lupus nephritis as your kidneys are suffering and time is running."* The side-effects from currently available treatments often have a significant impact on the lives of lupus patients. Steroids are renowned for their many side-effects with weight gain and changes to sleeping patterns being reported as the most difficult side-effects to tolerate. Other medication side-effects reported as being most difficult to tolerate by people with lupus include fatigue, nausea, hair loss, and changes in mood. *"I have tried many different medicines and treatment over the years, but the main ones have been cyclophosphamide and rituximab. Cyclophosphamide was horrible, I was very sick with it, extremely tired and it just left you feeling terrible. I hated it. Rituximab's side effects weren't as severe, but I still felt exhausted the initial period after, probably driven by the long day in hospital. That is the big downside for me; both medications must be given in hospital, so it involves time off work and days just spent sitting in hospital. I much prefer medication you can manage yourself at home. I now have secondary-immunodeficiency as a result of the immunosuppressant treatment I have had, meaning I now have to inject myself weekly with donated antibodies and need to see an immunologist."* Many people with lupus will have been prescribed several different medications to try and manage their condition. It is often the case that a treatment does not sufficiently control symptoms or causes adverse effects that cannot be tolerated. Many lupus treatments can take months before the full benefit may be experienced, meaning a significant period with a lower quality of life. *"[My partner's] care has always been fantastic, and I am amazed at some of the treatments available, like the antibody treatment she receives. Prior to that she was constantly on antibiotics battling infections so that has been great. In terms of lupus treatment, it is a shame there isn't specific treatment available. Some of [my partner's] previous treatments have left her extremely incapacitated, which massively impacts her ability to have a normal life and gets her down both physically and mentally. They are extremely harsh treatments that have led to additional issues that she now has to deal with."* In our online survey, the areas that respondents most reported their treatment as having a negative impact were "managing current treatment (collecting prescriptions, checking for interactions etc.)", "social activities" and "changes to diet/lifestyle". *"Contraindications have caused friction and difficulties between different specialist hospital departments - I am stuck in the middle and often left with sorting things out. There is little co-ordination/communication between them - This has made everything more complicated and stressful than it should or needs to be. Again, my physical and mental health have been adversely affected. I regularly have to literally spend days phoning around regarding prescriptions, explaining complex issues, locating medications etc."*

	The provision of care for lupus patients in England is inconsistent. Many patients living closer to larger cities and able to access a specialist centre with multidisciplinary clinics report a much higher level of satisfaction with the care they receive. Most lupus nephritis patients without access to specialist lupus services will be required to attend additional consultations split between nephrology, rheumatology and possibly multiple other specialties. This is often accompanied by poor communication between clinicians, a lack of a coordinated care plan and barriers to accessing some treatments, such as biologic therapies. RAIRDA's 2018 report indicated important findings related to treatment of people with RAIRDs (including lupus): • Only 34% of patients received all their routine care at the same hospital in the past year. • Two-thirds of patients routinely visit two or more hospitals for their care, with 1-in-20 visiting five or more hospitals in the past year for their care. • 8% of patients reported regular journeys of two or more hours for their treatment. • 93% of patients see clinicians from multiple specialisms as part of their routine treatment, yet among those people, less than 1-in-5 were able to see multiple specialists at a joint clinic. • 46% of lupus patients stated that they do not feel the different professionals involved in their care have a plan for their treatment. In our online survey, we asked, "How would you rate your overall treatment and care from the NHS for your lupus?" On a scale from one (very poor) to ten (very good) the average score was six. Approximately 25% of respondents in our online survey stated that their current treatment was a "large" or "very large" interruption to work/study. *I've been treated with prednisolone, rituximab, mycophenolate, cyclophosphamide and others. I've found the benefits of these to be frustratingly slow with highly uncertain outcomes. Whilst rituximab and mycophenolate have been easy to deal with, prednisone and cyclophosphamide are extremely invasive in terms of their collateral side effects on quality of life. Additionally, the timelines for recovery are long. In my first bout of lupus nephritis on these drugs it took 5 years for a full recovery, I am 12 months into my current flare. There are various treatment options available on the NHS, however these are often treatments not specifically designed for lupus nephritis but have been found to have positive effects. From my perspective, it can be unsettling to not have a drug which is specifically designed for the condition as from the perspective of the patient, it can sometimes seem like one is trying random drugs and hoping for the best."*

8. Is there an unmet need for patients with this condition?	Earlier diagnosis of lupus is needed to allow for faster intervention with treatment, the prevention of damage accumulation and improved outcomes and quality of life for patients. LUPUS UK's member survey indicated that the average length of time to obtain a diagnosis after the initial onset of symptoms was 6.4 years. In addition to delays in diagnosis, people with lupus often experience delays in seeing a specialist. RAIRDA's 2018 report found that just over half (54%) of patients were seen by a specialist in under three months, while almost a quarter (22%) reported that they had waited longer than six months for their specialist appointment. These findings suggest that waiting time targets continue to be missed for people with rare autoimmune rheumatic diseases (including lupus). Additionally, there is real concern that these targets themselves do not adequately reflect the need for prompt diagnosis of rare diseases to reduce the risk of irreversible organ damage occurring prior to treatment. *"My main issue would be for all patients to have a better way of talking to a nurse or doctor in between appointments that can be every 9 months or yearly. I am lucky to have a dedicated nurse line I can call but I have heard from others that this is not the norm, so if some need help and advice they have to go to their GP – and my personal experience is that they tend to refer you back to the rheumatologist or they downplay how you feel. I would say that support is the biggest need."* Cardiovascular disease (CVD) is the leading cause of mortality in lupus patients, with the condition representing a significant risk factor. Effective treatments to control lupus inflammation and reduce the development of CVD are essential to the length and quality of life for those with SLE. Many treatments used in lupus suppress the immune system and leave patients more at risk from infection. These treatments (particularly rituximab) can also reduce the efficacy of some vaccines, leaving patients vulnerable to otherwise vaccine-preventable illnesses. This has been of concern during the COVID-19 pandemic. Treatments that effectively control the disease whilst not making patients vulnerable to infection are needed. Treatments can be used to slow the course of lupus nephritis, but they are not always successful. Systematic review found that the mean renal remission/response rate was less than 50% for most standard therapy[1]. Importantly, despite improvements in therapeutic strategies, decreased mortality rate and an improvement in the disease prognosis, the percentage of patients progressing into end-stage renal disease (ESRD) remains steady[2]. The risk of ESRD in lupus nephritis improved between the 1970s and the mid-1990s and then plateaued, with an increase in the late 2000s[3]. This pattern suggests limitations in the effectiveness of, or access to, current treatments. *"[My partner] now has Stage 4 kidney diseases and her last biopsy confirmed she will need a transplant in the future. That to me shows there isn't a treatment that adequately manages lupus nephritis or she wouldn't be in this position. She has suffered from the illness since she was 10 years old, has tried so many different medications and the end result is still going to be renal failure. Her care is brilliant so you can't fault the doctors. The issue is there is no treatment that has managed to control her lupus well enough to avoid this position."* There is a need for treatments which will reduce the over-reliance on glucocorticoids in the management of lupus nephritis. Standard care makes significant use of glucocorticoids as induction treatment and is typically part if maintenance treatment for at least 3-5 years after complete remission. Lupus nephritis most commonly occurs as an early-onset symptom of SLE and is much

	more prevalent in juvenile-onset lupus. This means that the lifetime burden of glucocorticoids and risk of adverse events and steroid-associated comorbidities is significant. *"Current treatments for lupus nephritis for me personally have felt limited. It has felt like prednisolone has been the mainstay of treatment and while I understand its importance, the side effect profile of this treatment makes taking steroids difficult and very unpleasant."* *"My long-term steroid use means I have osteopenia and in my hip I'm on the cusp of osteoporosis. That's the thing with all the treatments, they harm the little bit of healthy body you have and lead to additional issues. I don't fault the NHS or my care, two occasions I would confidently say the NHS has saved my life and my consultants are incredible, but they only have the tools available to them and when your only option is bad or worse, you are going to opt for bad."* Stratified medicine is needed for lupus because of its heterogeneous nature and unpredictable response to treatment. Stratified medicine could aid newly diagnosed patients in accessing the treatment most likely to be effective for them earlier, saving months or years of trial and error with side-effects, poorly managed disease, and disruption to their life. Rituximab is frequently used in the management of lupus nephritis but there is uncertainty about the longer-term safety and efficacy, especially for young patients who will require management of their disease for many decades. The long-term effect on B-cell depletion and subsequent use of other biologic therapies is poorly understood.

Advantages of the technology

9. What do patients or carers think are the advantages of the technology?	*"For me the big perk is the fact it is a medication you take yourself at home. It's also designed for lupus nephritis with proven better results than the alternatives currently available. It doesn't have the awful side effects of the likes of cyclophosphamide and rituximab (fertility, sickness, hair loss etc.) I think it would have a massive positive impact on day to day life with lupus nephritis; for the individual but also for their family, not having to take time off for hospital trips or to care for the patient post-treatment."* For those patients who experience a significant improvement in the management of their condition because of voclosporin, it could have a massive impact on their quality of life. It could potentially mean they are able to continue in employment and experience further benefits to their social and psychological wellbeing. With their lupus nephritis better controlled, it could reduce the number of hospital visits and admissions they may otherwise have needed which would be a positive change for them and their family/carers. It is important to remember that many of the patients who may be considered for treatment with voclosporin have severe lupus nephritis which may not have responded adequately to standard therapy. It may therefore provide an additional option and hope. *"[Voclosporin] is a lupus nephritis specific medication so is designed to target and fight that specific issue. That is a huge deal. The side effects do not appear to be anywhere near as severe as the other treatments [my partner] has tried and results are extremely promising. Also the fact you can manage it at home, I know [my partner] hates the constant hospital appointments and hates having to take time off work to attend so that would be hugely beneficial."* *"Any drugs or processes that target specific lupus issues would be highly appreciated and there would be a lot of comfort in knowing that there are targeted drugs."*

Disadvantages of the technology

10. What do patients or carers think are the disadvantages of the technology?	Lupus presents differently in each patient and response to treatment can vary similarly. A treatment that works well for one patient will not necessarily work for another. Adverse reactions to medications are seen in many people with SLE, resulting in a need to switch to another treatment option. It is therefore likely that some patients will not be able to tolerate voclosporin or will not respond as hoped.

Patient population

11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	Whilst voclosporin is currently only indicated for treating adults, lupus nephritis is much more prevalent in juvenile-onset SLE (JSLE)[4]. JSLE is also recognised to have a more active disease course when compared with adult-onset disease and patients have a worse long-term survival. Kidney remission remains suboptimal with only 40–60% of patients achieving complete remission. Kidney flares are seen in over a third of patients. The rate of chronic kidney disease (CKD) 5 is reported to be up to 15% and the presence of lupus nephritis has an established link with an associated increase in mortality. Findings show that current treatment regimens are unable to completely halt the kidney inflammatory process in the majority of patients and this contributes to damage accumulation. (HERE) Lupus nephritis is also more prevalent and severe within some ethnic groups. A UK study (HERE) examining incidence and prevalence of lupus nephritis across ethnic groups in North West England identified dramatic differences in prevalence according to ethnicity with an increasing gradient from the white population to the Indo-Asian, Afro-Caribbean, and Chinese populations. The estimated proportion of white SLE patients with lupus nephritis was 10%. A much higher proportion of Indo-Asian patients with SLE (27%) and an even higher proportion of Afro-Caribbean patients with SLE (58%) were estimated to have lupus nephritis. In addition the severity of disease and progression to renal failure in patients with lupus nephritis is significantly greater in black and Chinese patients[5-8].

Equality

12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	As an orally administered treatment voclosporin presents fewer barriers to access than other comparator treatments which may involve hospital-administered infusions. Treatments such as rituximab and belimumab typically need to be administered at a specialist centre, which further increases barriers to access. A Rare Disease UK study (HERE) has previously shown that only 27% of patients with rare diseases are cared for in specialist centres. This presents a barrier to access for some patients who may live a considerable distance from a specialist centre or have difficulty travelling due to their ill-health and/or disability. As such, those living in more remote parts of the country, those with mobility issues, those in employment or with childcare needs, and those on lower incomes may be disproportionately disadvantaged if voclosporin is not approved. Lupus nephritis affects people of all ethnic groups but is more prevalent in people of African, Caribbean and Asian heritage. People from these ethnic groups are also more likely to experience severe disease and higher rates of premature mortality. In addition people from these ethnic groups are already at a high risk of developing diabetes and hypertension. It should be considered whether steroid-sparing treatments such as voclosporin could have additional advantages over standard treatments by reducing some adverse effects and risks of comorbidities. SLE disproportionately affects women and commonly presents in those of childbearing age. Most immunosuppressive and biologic treatments are not safe during pregnancy and breast-feeding. Cyclophosphamide is still used to treat lupus nephritis despite presenting a risk of infertility. The role of voclosporin in the treatment of young women should be carefully considered.

Other issues

13. Are there any other issues that you would like the committee to consider?	*"I think if there are cost considerations that drive reluctance to approve this medication, it is important to also account for the additional costs the current treatments result in, for example, now that I have SID I require weekly antibody treatment which is expensive, also the cost of having an individual admitted as an in-patient."* Due to the rare and heterogeneous nature of lupus, meeting clinical trial endpoints can be extremely challenging. It has been observed that clinical trial recruitment uses increasingly strict eligibility criteria. This is likely an attempt to demonstrate significant benefit from trial compounds when compared to standard treatment alone. These trial populations no longer reflect the real-world lupus patient population. A recently published paper found 63% of patients in the BILAG BR were ineligible to participate in non-renal SLE trials and 43% with active lupus nephritis would be ineligible for lupus nephritis trials (HERE). Despite this, strict eligibility criteria are being applied to commissioned treatments because there is only sufficient evidence to support treatment for the sub-populations enrolled in the trials. This is creating inequality between antibody-positive and antibody-negative lupus patients. Without changes to the eligibility criteria, it is unlikely sufficient data will be collected to demonstrate how new therapies could benefit the lupus patient community more widely. *"I know first-hand the positive impact this treatment could have on patients and their loved ones. The difference it makes to have the hope of a new and effective drug I can't even begin to put into words. I've always taken my good health for granted but now I have the experience of seeing what it's like to not have that, I think it's shameful if we don't approve something that could help ease their suffering and improve their quality of life."* *"At what stage of kidney disease from lupus nephritis can voclosporin be used in? With some other treatments used, they are felt unjustified when there is a certain amount of scaring and damage to the kidney and therefore patients at certain stages of the disease process are currently left with very little medication to help their illness. It would be amazing if voclosporin could be considered for use for those with later stage disease."*

Key messages

14. In up to 5 bullet points, please summarise the key messages of your submission.	• Lupus nephritis (and associated symptoms of SLE) often has a significant impact on the lives of people with the disease and their close family. It also represents a risk of early mortality. • In recent decades the percentage of patients progressing into end stage renal disease (ESRD) remains steady despite improvements in therapeutic strategies. This pattern suggests limitations in the effectiveness of, or access to, current treatments. • Voclosporin offers an additional treatment option, representing hope for those with active disease who do not respond to standard therapy. • Current standard therapy is over-reliant on glucocorticoids as induction and maintenance therapy for lupus nephritis. This has a significant negative impact on patients through both short and long term side effects. • As an orally-administered therapy, voclosporin presents significantly fewer barriers to access for many people who may currently be disadvantaged due to geographical location, lack of mobility, work or childcare commitments, or financial constraints.

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APPENDIX:	1. A. Singh 2016 (https://systematicreviewsjournal.biomedcentral.com/articles/10.1186/s13643-016-0328-z#MOESM6) found in a systemic review that the mean renal remission/response rate was less than 50% for most standard therapy with ciclosporin, mycophenolate-mofetil (MMF), and rituximab combined with MMF being the only treatments with better response rates. 2. M. Gasparotto 2020 (https://academic.oup.com/rheumatology/article/59/Supplement_5/v39/6024733) discusses how, even though retrospective cohort studies report a decreased mortality rate and an improvement in the disease prognosis, the percentage of patients progressing into end stage renal disease (ESRD) remains steady despite improvements in therapeutic strategies. 3. M Tektonidou 2016 (https://pubmed.ncbi.nlm.nih.gov/26815601/) shows the risk of ESRD in lupus nephritis improved between the 1970s and the mid-1990s and then plateaued, with an increase in the late 2000s. 4. N Ambrose 2016 (https://pubmed.ncbi.nlm.nih.gov/27147622/) assessed data from the UK JSLE Cohort and compared it to the UCLH SLE cohort. A total of 924 individuals were compared (413 JSLE, 511 adult-onset SLE) and they found renal disease in 44% of JSLE compared to 33% of adult SLE. 5. Neuman et al. (HERE) found the 5-yr renal survival was 72% for black patients with lupus nephritis compared with 91% for white patients (P = 0.001). Renal outcome and the level of immunosuppressant use in Asians were comparable to Afro-American black patients in some studies. Asian patients were also found to have higher overall damage scores compared with white patients. (HERE) 6. Contreras *et al.* (HERE) found that black patients were almost twice as likely to have WHO class IV lesions as white patients (51% *versus* 30%). In addition, black patients were three times more likely to double their serum creatinine or reach ESRD (31 *versus* 10%; $P < 0.05$) than white patients. 7. Austin et al. (HERE) suggested that the poorer renal prognosis in black patients with severe lupus nephritis resulted from the fact that they were more than twice as likely to have “high risk” histology, that is the presence of cellular crescents and interstitial fibrosis, as white patients (29 versus 13%; P < 0.05). 8. Patients with HLA-DRB1*15, uniquely found in black patients, have a greater likelihood of renal disease. In addition, the presence of FcγRIIA-R131, an allelic variant of the IgG receptor FcγRIIA that results in decreased ability to clear immune complexes, is significantly more frequent among black patients with lupus nephritis.

NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Voclosporin with immunosuppressive therapies for treating lupus nephritis [ID3962]

Professional organisation submission

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

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- Your response should not be longer than 13 pages.

About you

1. Your name	[redacted]
2. Name of organisation	UK Kidney Association
3. Job title or position	Consultant Nephrologist
4. Are you (please select Yes or No):	An employee or representative of a healthcare professional organisation that represents clinicians? Yes A specialist in the treatment of people with this condition? Yes A specialist in the clinical evidence base for this condition or technology? Yes Other (please specify):
5a. Brief description of the organisation (including who funds it).	UK Kidney Association is the professional body for the UK renal community delivering leadership and professional advice, research, education, training, audit and quality improvement, guidelines and working in partnership alongside patients. It is a charity.
5b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.] **If so, please state the name of manufacturer, amount, and purpose of funding.**	No
5c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No

The aim of treatment for this condition

6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	Lupus nephritis is one of the most serious, life-threatening manifestations of SLE. The risk of chronic kidney disease and end-stage renal failure (ESRF) is significant with 10% of patients reaching ESRF at 5 years and 20% at 15 years. Current treatment options not only have a significant number of adverse effects (for example corticosteroid use), but do not result in a sustained remission in a significant proportion of patients. The aim of treatment in lupus nephritis is to achieve a sustained remission. This can be defined as normal kidney function with a reduction in proteinuria (<0.5-0.7g/day) by 12 months, which is only achieved in around 20-30% of patients after 6-12 months of treatment. Treatment can be divided into induction phase of treatment to induce a disease remission followed by maintenance treatment to prevent flares and further risk of chronic kidney damage. Treatment with immunosuppression has duration of several years due to the chronic, relapsing nature of SLE.
7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	A significant response can be divided into a partial remission or a complete remission, with no renal flares while not exposing the patient to serious adverse complications of therapy. A complete response is defined as normalisation of serum creatinine with urine protein <0.5g/day. A partial response is generally defined as a creatinine clearance no more than 10% below baseline, or normal, with a 50% reduction in urine protein (or a decrease from nephrotic range proteinuria to non-nephrotic). Renal survival (remaining free of dialysis), chronic kidney disease and mortality are also significant factors with respect to long term follow-up and the success of treatment.
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	There is a significant unmet need for further therapies in this condition. Only a minority of patients achieve a complete and long lasting remission. Not achieving a remission puts the patient at risk of further renal damage and the associated morbidity and mortality associated with CKD and ESRF. Additionally, the current treatments have significant treatment associated complications and adverse effects. Corticosteroids are associated with many adverse effects, and non-adherence is a significant factor with respect to poor treatment outcomes. Immunosuppressive agents such as cyclophosphamide have an important role in the treatment of this disease but are associated with decreased fertility which is a factor in a disease which predominantly affects women of child-bearing age. Steroids, cyclophosphamide and also mycophenolate mofetil are all associated with infectious complications. Although medications such as rituximab also have a very important role, its use can be limited in the lupus population due to serious infusion (allergic) reactions. There is therefore an unmet need for further therapies in patients with difficult to treat- resistant disease.

What is the expected place of the technology in current practice?

9. How is the condition currently treated in the NHS?	All patients with lupus nephritis are treated with hydroxychloroquine Non-immunosuppressive treatments include: blood pressure control (for example with ACE-inhibition), bone protection, addressing cardiovascular risk factors. 1st line immunosuppression treatment for patients with Class III and IV lupus nephritis - Prednisolone with mycophenolate mofetil - Depending on disease activity/disease severity and renal function (and patient choice taking into account fertility): prednisolone and low dose intravenous cyclophosphamide (500mg every 2 weeks for a total of 6 doses then switch to mycophenolate mofetil) - In those patients with a previous high burden of immunosuppression with cyclophosphamide, additionally in those patients of Asian, Hispanic or African ancestry, MMF may be a preferred option. - Addition of a calcineurin inhibitor (such as ciclosporin or tacrolimus) is reserved in those patients who may not tolerate high doses of MMF, or in which cyclophosphamide is not desirable. - MMF is used for maintenance therapy. 2nd line - Use of azathioprine if MMF, CNI, cyclophosphamide not tolerated - Azathioprine used if pregnancy planned in a patient in remission Biological therapy- Rituximab Despite disappointing trial evidence (LUNAR), Rituximab is an incredibly useful agent in the treatment of lupus nephritis Rituximab will be added to treatment (prednisolone and MMF) in those patients with active disease who:- (i) Poor response to steroids and MMF (ii) Adverse effects of high dose steroids as a steroid sparing/minimising agent (iii) Unable to tolerate higher doses of MMF and needing an escalation in immunosuppression

	(iv) high risk disease and reluctance for a cyclophosphamide based regime, can be added to prednisolone and MMF. Biological therapy- Obinutuzumab (and Ofatumumab) - Given individual named patient basis and great difficulties due to lack of funding in NHS. Fully humanised anti-CD20 used in select patients when rituximab contraindicated. Biological therapy belimumab - BLISS-LN trial added belimumab to standard treatment and increased the response rate at 2 years compared to standard treatment - currently not 1st line treatment for lupus nephritis. Can consider especially in those patients unable to tolerate rituximab and intravenous therapy preferred rather than oral. Immunosuppression in patients with Class V lupus nephritis - Similar to Class III/Class IV treatment - Higher use of CNI, and addition to prednisolone and mycophenolate in membranous (class V) LN.
9a. Are any clinical guidelines used in the treatment of the condition, and if so, which?	Joint European League Against Rheumatism (EULAR) and European Dialysis and Transplant Association (ERA/EDTA) recommendations for the management of lupus nephritis: 2019 Update KDIGO updated guidelines for treatment of glomerular disease draft 2020.
9b. Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	Many patients are treated within renal units or specialist lupus clinics attended by nephrologists and rheumatologists working together. There maybe some regional variation in treatment depending on access to infusion suits for intravenous treatment and drug availability (for example rituximab, tacrolimus) but within specialist lupus nephritis clinics there should not be variation. Due to well defined treatment protocols, the pathway of care is well defined.

9c. What impact would the technology have on the current pathway of care?	Voclosporin would be a useful addition to the current care pathways and would be added to prednisolone and mycophenolate (as per the clinical trial data AURA-LV and AURORA1). The trial data has demonstrated an increase in complete and partial kidney response at one year, supporting the addition to the pathways above Voclosporin would also replace the current use of tacrolimus or ciclosporin in the treatment protocols above.
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Voclosporin would replace the current use of tacrolimus and ciclosporin. Due to the positive trial results and also the lack of drug level monitoring required, it will likely be used more frequently than tacrolimus or ciclosporin.
10a. How does healthcare resource use differ between the technology and current care?	The current treatment includes drugs such as tacrolimus which in theory would use more healthcare resources due to the drug monitoring required during treatment with tacrolimus. One significant advantage would be that voclosporin does not require monitoring with drug levels in this manner. However, these patients are monitored frequently anyway due to active kidney disease so there would be little difference in resource use. Additionally with a reported lower incidence of complications such as diabetes and adverse lipids compared to tacrolimus, there may also be less healthcare resources utilised with voclosporin. However, this is a group of patients who are susceptible to disease and treatment related complications and as a result require close monitoring and frequent hospital visits.
10b. In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Voclosporin will be used within the setting of specialist lupus nephritis clinics
10c. What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	No additional investment would be required.

11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	The trial data has demonstrated that when added to standard of care, the addition of voclosporin provides clinical effectiveness. At 1 year, more patients in the drug arm compared to placebo achieved a reduction in proteinuria and allowed a rapid decrease in steroids. There was a significant difference in complete response rates at both 24 weeks and 48 weeks (AURA-LV Phase 2 trial and AURORA Phase 3). The benefit of a reduction in proteinuria is well characterised and described. Patients achieving a renal response have a more favourable long term renal outcome with lower risk of CKD and ESRF, and the complications associated with chronic kidney disease. Additionally, there are many clinical benefits from allowing a sustained decrease in corticosteroid exposure. The trial reports short term outcomes, so with respect to long term data (renal survival, mortality at 5 to 10 years of follow-up), this is currently unknown. However, it is well recognised that the best predictor of long term outcome (reduced risk of flares, reduced risk of ESRF, and a reduction in the risk of death) is the early reduction in proteinuria
11a. Do you expect the technology to increase length of life more than current care?	The current trial evidence investigated outcomes at 52 weeks. With respect to long term life expectancy, this has not been assessed in the current data. However, the trial data demonstrates improved renal outcome with respect to proteinuria and therefore improvements in activity of lupus nephritis with a decrease in the risk of long term complications of lupus nephritis. Decreasing proteinuria in the long term is associated with improved renal survival. One of the most significant impacts on morbidity and mortality is the presence of chronic kidney disease. By decreasing the risk of CKD, and the significant complications associated with CKD and ESRF requiring renal replacement therapy (RRT), this drug potentially will increase life expectancy.
11b. Do you expect the technology to increase health-related quality of life more than current care?	The addition of voclosporin to standard of care resulted in a higher response rate. This will impact quality of life by:- (i) Allowing a rapid and sustained decrease (in the short and medium term: long term unknown) of corticosteroids. High doses of steroids have a severe impact on the wellbeing of patients especially with respect to mental health and also adverse effects including weight gain, skin changes, bone density, mood changes including the risk of psychosis with high doses

	(ii) By improving the current response rate, this will result in a lower use of more potent therapies such as cyclophosphamide in some patients. Cyclophosphamide is associated with decreased fertility, infections as well as frequent visits to the hospital infusion ward for treatment. (iii) Non-responders (or partial response) risks kidney failure and the decreased quality of life associated with renal replacement therapy for which there is a higher risk of poor kidney outcomes in the standard group compared to the addition of voclosporin.
12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	The current trial data was not powered to detect differences in treatment between race and ethnicity. There was post-hoc analysis for race and ethnicity. Patients of African ethnicity have a worse outcome in lupus nephritis, and are at higher risk of ESRF. The trial included a racially diverse population, and it is noticeable (and very encouraging) that patients recognised to have more difficult disease to treat, and at higher risk of adverse outcomes, had a similar response. This suggests that patients of African ethnicity would benefit from this treatment Additionally, voclosporin has an improved profile with respect to risk of diabetes and adverse lipid profiles which is beneficial in those patients at risk of diabetes or cardiovascular complications.

The use of the technology

13. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use	Voclosporin will be easier to use than the current CNIs in use. This is because there is no monitoring of drug levels required. There will need to be monitoring of renal function, but this is part of standard of care and is not in addition to the current monitoring. The drug is metabolised via CYP3A4 pathway hence the need for care when prescribing other medications and the potential for drug interactions. The same applies for tacrolimus and ciclosporin.

or additional tests or monitoring needed.)	
14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Renal function will need to be monitored, like all CNIs with the potential for stopping and re-starting at a lower dose if there are changes in renal function. However, these patients have active renal disease and are being closely monitored anyway due to the combination of treatments (such as steroids and MMF), so this is likely not to require significant additional testing.
15. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	Patients of ethnic minorities, as well as patients living in more deprived areas, are disproportionally affected by lupus nephritis as well as having poor renal outcomes and at higher risk of kidney failure. A drug that has a similar response compared to lower risk patients is very encouraging and this benefit should be taken into account.
16. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	There is currently a large unmet need in the treatment of lupus nephritis due to the low proportion of patients achieving either (i) a complete remission, or (ii) a sustained, relapse-free remission.
16a. Is the technology a 'step-change' in the management of the condition?	This is a rare disease with limited treatment options. This drug is a useful addition to current treatment options.
16b. Does the use of the technology address any particular unmet need of the patient population?	There is a low proportion of patients who have a complete response to treatment in lupus nephritis. The addition of other therapies maybe limited. For example, in patients with a previous high burden of cyclophosphamide, or in patients who wish to preserve fertility, cyclophosphamide will need to be avoided. Additionally, a significant proportion of patients cannot be given rituximab due to severe reactions. In these scenarios, treatment options are

	very limited. Voclosporin would be a useful addition especially in those patients who cannot be given alternative immunosuppressants. Additionally, due to the reported lower incidence of diabetes and adverse lipid profile compared to other CNIs, this drug would be useful in those patients at risk of diabetes.
17. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Hypertension and a decrease in GFR are recognised side effects. The reduction in GFR has been described as generally mild and occurring early after initiation but does require careful monitoring if this occurs with possible dose adjustment or discontinuation. There is also a risk of neurotoxicity. These include headaches, tremor, dizziness and parathesia which will all have a negative impact on a patient's quality of life. Any immunosuppressant will increase the risk of infection. The trial evidence does not suggest an unacceptable risk of infection (similar to placebo group). The early trial did have a higher mortality rate but this was reassuringly not replicated in the subsequent Phase III trials.

Sources of evidence

18. Do the clinical trials on the technology reflect current UK clinical practice?	Yes. The current trials have the same standard of care used in the UK. Additionally, the trial included an ethnically diverse population of patients which is applicable to the population of patients in some parts of the UK with a diverse ethnicity of patients with lupus nephritis.
18a. If not, how could the results be extrapolated to the UK setting?	NA
18b. What, in your view, are the most important outcomes, and were they measured in the trials?	The most important outcome is the risk of CKD, ESRF and mortality. The trial data has limited follow-up so these questions remain unanswered. Additionally, the risk of future renal flares/relapses remains unanswered so far. However, the renal response with respect to renal function and proteinuria at 1 year are the most important outcomes in the short term and these have been answered by the trial. Additionally, the trial data has looked at rescue medication and escalation in steroid use. The use of steroids is particularly important due to the significant risk of steroid related toxicity as well as the severe impact on a patients quality of life.

	Patients with lupus nephritis can have a significant nephrotic syndrome are at risk of complications of nephrotic syndrome such as thromboembolic disease (requiring anti-coagulation prophylaxis) as well as significant oedema. The trial did not assess parameters such as the time taken to improve oedema (comparing diuretic use for example), or improvements in serum albumin over 52 weeks. This trial also did not include patients with severe renal disease, but in this cohort voclosporin will likely not be recommended.
18c. If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	The outcome in the trial was renal response by 52 weeks which was a composite of urine protein creatinine ratio and stable renal function with no rescue medication and a protocolised use of steroids. With respect to the renal outcomes. Proteinuria at 12 months is one of the best predictors of long term outcome. Additionally renal function after 12 months and the presence of abnormal renal function is a good indicator of the risk of CKD and therefore long term renal survival. The use of rescue therapies would be a worrying indicator of more resistant disease therefore putting the patient at risk of a long term poor clinical outcome.
18d. Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	Not that I am aware of. This drug now has approval in the USA so any potential adverse effects not observed in clinical trials may come to light in the near future. As the drug is a CNI, it will be imperative to assess the risk of long term renal function and risk of renal damage with voclosporin.
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
20. How do data on real-world experience compare with the trial data?	Approved in USA in January 2021 (not yet used in UK/EU) so there is a lack of real world data so far.

Equality

21a. Are there any potential equality issues that should be taken into account when considering this treatment?	As previous written, patients from ethnic backgrounds are at higher risk of poor long term renal outcomes. There is also some evidence that patients of African ethnicity may respond better to a MMF based regime rather than cyclophosphamide. The trial data demonstrates better renal outcomes when voclosporin is added to prednisolone and MMF. Although the trials were not powered to investigate responses in the different race and ethnic groups, the good response of patients particularly of African ethnicity who are at higher risk of poor long term renal outcomes should be taken into account.
21b. Consider whether these issues are different from issues with current care and why.	

Key messages

22. In up to 5 bullet points, please summarise the key messages of your submission.	• When added to standard care, there are improved renal outcomes at 52 weeks • Voclosporin does not require drug level monitoring unlike other CNIs (ciclosporin and tacrolimus) • There is a lower risk of diabetes and adverse lipids unlike other CNIs • Decreasing proteinuria is the best predictor of long term renal outcome • There is not a significant safety signal in the trial data

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Single Technology Appraisal

Voclosporin with immunosuppressive therapies for treating lupus nephritis [ID3962]

Professional organisation submission

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

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- Your response should not be longer than 13 pages.

About you

1. Your name	[redacted]
2. Name of organisation	UK Renal Pharmacy Group [redacted]
3. Job title or position	[redacted]
4. Are you (please select Yes or No):	An employee or representative of a healthcare professional organisation that represents clinicians? Yes A specialist in the treatment of people with this condition? Yes A specialist in the clinical evidence base for this condition or technology? No Other (please specify):
5a. Brief description of the organisation (including who funds it).	UK Renal Pharmacy Group is a non-profit organisation that sits within UK Kidney Association. UK Renal Pharmacy Group works in partnership with colleagues across specialties to contribute to and promote national guidance, pharmaceutical research, audit and innovation in renal medicine and pharmacy practice.
5b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.] **If so, please state the name of manufacturer, amount, and purpose of funding.**	None
5c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	None

The aim of treatment for this condition

6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	To treat active lupus nephritis and achieve complete renal response
7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	Target proteinuria of < 0.5- 0.7g/24 hours within the first year of treatment
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	No

What is the expected place of the technology in current practice?

9. How is the condition currently treated in the NHS?	Dependent on classification of lupus nephritis (brief overview): - Steroid plus MMF or IV cyclophosphamide or rituximab - Steroid plus CNI or Azathioprine or MMF - CNI and MMF

	- RAS blockade +/- MMF or IV cyclophosphamide
9a. Are any clinical guidelines used in the treatment of the condition, and if so, which?	1. Kidney Disease: Improving Global Outcomes (KDIGO) Glomerulonephritis Work Group. KDIGO Clinical Practice Guideline for Glomerulonephritis. Kidney inter., Suppl. 2021; 100: 753-779. 2. Fanouriakis A, et al. 2019 Update of the Joint European League Against Rheumatism and European Renal Association–European Dialysis and Transplant Association (EULAR/ERA–EDTA) recommendations for the management of lupus nephritis. Ann Rheum Dis 2020;79:713–723. doi:10.1136/annrheumdis-2020-216924
9b. Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	Yes, pathway of care is established and well defined.
9c. What impact would the technology have on the current pathway of care?	Offering an additional treatment option to those are unsuitable or contraindicated in existing treatment options.
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Yes, voclosporin will be prescribed under hospital specialists or shared care guidelines similar to other oral immunosuppressive therapies such as CNIs, MMF or azathioprine.
10a. How does healthcare resource use differ between the technology and current care?	Prescribing budget may need to be expanded to accommodate the prescribing of voclosporin. In the US, the cost per patient per year is estimated to be around $92,000. The cost of voclosporin is significantly higher compared to other existing CNIs, such as ciclosporin (Vanquoral) which is estimated to be around £500 - £800. Cost pressure would also be significantly affected by the duration of treatment.
10b. In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Voclosporin should be initiated and continued under supervision of nephrologists under secondary/tertiary care settings or under shared care guidelines if agreed.

10c. What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	Additional blood tests required for eGFR assessment as part of voclosporin monitoring.
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Limited evidence to show this.
11a. Do you expect the technology to increase length of life more than current care?	Limited evidence to show this.
11b. Do you expect the technology to increase health-related quality of life more than current care?	Limited evidence to show this.
12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Voclosporin may be less effective for the following patient groups: 1. pregnancy: alcohol contents contained within the drug formulation 2. poor adherence: high pill burden (vocloposrin is only available in 7.9mg capsule and the starting dose is 23.7mg twice daily. Therefore, total quantity required per day is 6 capsules) 3. swallowing difficulty: Voclosporin capsules can only be swallowed whole. Oral administration may be challenging in those with nil oral route or swallowing difficulties. Other comparators such as tacrolimus can be given in an alternative route, such as sublingually or intravenously. And ciclosporin (Neoral) is available in oral solution, therefore dose can be administered via enteral feeding tube if required.

The use of the technology

13. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	Therapeutic drug monitoring is not required for voclosporin compared to other CNIs, such as tacrolimus and ciclosporin. However, regular eGFR assessment is still necessary according to the product literature (e.g., every 2 weeks for the first month, and every 4 weeks thereafter).
14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	No additional testing is required to make changes to the treatment. The treatment will be guided by renal response, proteinuria, renal function testing as well as patient tolerability.
15. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	Limited evidence to show this.
16. Do you consider the technology to be	Limited evidence to show this.

innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	
16a. Is the technology a 'step-change' in the management of the condition?	No
16b. Does the use of the technology address any particular unmet need of the patient population?	N/A
17. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	N/A

Sources of evidence

18. Do the clinical trials on the technology reflect current UK clinical practice?	- Comparable safety profile compared to other immunosuppressants - Racially diverse population included in the trial and therefore reflecting the diverse UK population treated - Primary and secondary endpoints in the trial comparable to the treatment outcomes outlined in the international guidelines
18a. If not, how could the results be extrapolated to the UK setting?	N/A

18b. What, in your view, are the most important outcomes, and were they measured in the trials?	Renal response and proteinuria – both objectives were measured in the trial.
18c. If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	Insufficient data to conclude the long-term safety and efficacy outcomes
18d. Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	N/A
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	N/A
20. How do data on real-world experience compare with the trial data?	- No data on response to treatment in patient with new-onset versus relapsed lupus nephritis therefore difficult to know which patient group may receive the maximal benefit from voclosporin. - Limited evidence to suggest for use in patients with eGFR <45ml/min therefore may not be suitable for use in patients with eGFR<45ml/min.

Equality

21a. Are there any potential equality issues that should be taken into account when considering this treatment?	No
21b. Consider whether these issues are different from issues with current care and why.	N/A

Key messages

22. In up to 5 bullet points, please summarise the key messages of your submission.	• Limited evidence to suggest for use in patients with eGFR <45ml/min • No therapeutic drug monitoring is required however regular eGFR assessment is recommended • High cost - Blueteq may be considered to ensure the appropriateness of its prescribing • Safety profile may be comparable to the existing immunosuppressants commonly used in this condition

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Voclosporin with immunosuppressive therapies for treating lupus nephritis [ID3962]:

A Single Technology Appraisal

Produced by	Peninsula Technology Assessment Group (PenTAG) University of Exeter Medical School South Cloisters St Luke's Campus Heavitree Road Exeter EX1 2LU
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Author Contributions:	
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Ash Bullement	Critical appraisal of the economic evidence and analysis submitted by the company, conducted additional economic analyses and drafted sections of the report
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Sophie Robinson	Critical appraisal of the literature search strategies
Dominic Taylor	Clinical advice and review of draft report
Preetham Boddana	Clinical advice and review of draft report
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G.J. Melendez-Torres	Critical appraisal of the company submission, writing and editorial input
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Abbreviations

ACR	American College of Rheumatology
AD	active disease
AE	adverse event
AZA	azathioprine
BID	twice daily
BT	background therapy
CEAC	cost-effectiveness acceptability curve
CI	confidence interval
CKD	chronic kidney disease
CNI	calcineurin inhibitor
CRD	Centre for Reviews and Dissemination
CRR	complete renal response
CQ	clarification question
CSR	clinical study report
CS	company submission
CYC	cyclophosphamide
DIC	deviance information criterion
DP	decision problem
DSA	deterministic sensitivity analysis
EAG	Evidence assessment group
eGFR	estimated glomerular filtration rate
EQ-5D	EuroQol five dimension
EMA	European medicines agency
ERA-EDTA	European Renal Association – European Dialysis and Transplantation Association
ESRD	end-stage renal disease
EULAR	The European Alliance of Associations for Rheumatology
GFR	glomerular filtration rate
HR	hazard ratio
HRQoL	health-related quality of life
HTA	health technology assessment
H-CYC	high dose cyclophosphamide
ICER	incremental cost-effectiveness ratio
ICER	Institute for Clinical and Economic Review

ACR	American College of Rheumatology
ICH	International conference on harmonisation
IQR	interquartile range
ITC	indirect treatment comparison
ITT	intention-to-treat
IV	intravenous
LN	lupus nephritis
LOCF	last observation carried forward
L-CYC	low dose cyclophosphamide
LY	life-year
MCAR	missing completely at random
MD	mean difference
mg	milligram
MHRA	Medicines and Healthcare products Regulatory Agency
MMF	mycophenolate mofetil
MPA	mycophenolic acid
NA	not applicable
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NMA	network meta-analysis
NMB	net-monetary benefit
NR	not reported
OR	odds ratio
OWSA	one-way sensitivity analysis
PAS	patient access scheme
PBO	placebo
PRR	partial renal response
PSA	probabilistic sensitivity analysis
PSS	Personal Social Services
QALY	quality adjusted life year
RCT	randomised controlled trial
RDI	relative dose intensity
RR	relative risk
RTX	rituximab
SAE	serious adverse event

ACR	American College of Rheumatology
SD	standard deviation
SF-36	Short Form (36) health survey
SLE	systemic lupus erythematosus
SLR	systematic literature review
SmPC	Summary of product characteristics
TA	technology appraisal
TAC	tacrolimus
TEAE	treatment-emergent adverse event
TSD	Technical support document
TTD	time to treatment discontinuation
UK	United Kingdom
UPCR	Urine Protein Creatinine Ratio
USA	United States of America
VCS	voclosporin
Vs	versus
WTP	willingness to pay

1. EXECUTIVE SUMMARY

This summary provides a brief overview of the key issues identified by the Evidence Assessment Group (EAG) as being potentially important for decision-making. It also includes the EAG's preferred assumptions and the resulting incremental cost-effectiveness ratios (ICERs).

Section 1.1 provides an overview of the key issues. Section 1.2 provides an overview of key model outcomes and the modelling assumptions that have the greatest effect on the ICER. Sections 1.3 to 1.6 explain the key issues in more detail. Background information on the condition, technology and evidence and information on non-key issues are in the main EAG report.

All issues identified represent the EAG's view, not the opinion of NICE.

1.1. Overview of the EAG's key issues

A brief overview of the key issues identified by the EAG in their appraisal of the company submission (CS) is provided in Table 1. Further detail of the issues is provided in Sections 1.3, 1.4, 1.5, and 1.6.

Broadly speaking, the key issues related to the company's cost effectiveness model, including limitations with the model structure, estimates of health-related quality of life, and assumptions related to long-term treatment effects. In addition, the EAG highlighted uncertainty in the way voclosporin would be used in practice, leading to uncertainty about the generalisability of the company's model and of clinical effectiveness estimates.

Table 1: Summary of key issues

ID	Summary of issues	Report sections
Key Issue	Network meta-analysis estimates may not be reliable and should better account for heterogeneity	3.3, 3.4
Key Issue	The company's model structure	4.2.2, 4.2.6
Key Issue	The long-term treatment effect of voclosporin + MMF and its comparators is unknown	4.2.2, 4.2.6
Key Issue	The utility estimates used in the company's model are inappropriate	4.2.7

ID	Summary of issues	Report sections
Key Issue	The company has not appropriately calculated the costs of treatment in the model	4.2.6, 4.2.8
Key Issue	There is a lack of transparency around the inputs used in the company's model	5.3
Key Issue	Uncertainty in how voclosporin will be used in practice	2.4, 3.2.2, 3.2.3.2, 3.3.3, 4.2.3, 0

The key differences between the company's preferred assumptions and the EAG's preferred assumptions are outlined in Table 2.

Table 2: Key differences between the company's preferred assumptions and EAG's preferred assumptions

	Company's preferred assumption	EAG preferred assumption	Report Sections
Utilities	Various see CS B.3.4 for specific details	Amendments to health state utility values for CKD stage 1-3a AD,PR,CR, CKD stage 5 dialysis and transplant	4.2.7
Costs	Various see CS B.3.5 for specific details	Updates to the treatment costs incorporated RDI and amending the MMF dose to 2g daily. Updates of cost inputs to align with sources. Updates to wastage assumptions	4.2.8
Transition probabilities from CKD 1-3a to CKD 3b-4	No movement from CKD 1-3a to CKD 3b-4 in the first 36 months	Movement from CKD 1-3a to CKD 3b-4 in the first 36 months	4.2.6.7
Long-term transition probabilities (36months+)	Application of 'treatment waning' using average of VCS+MMF transitions with MMF transitions applied to VCS+MMF arm	Application of average VCS+MMF and MMF transitions applied to both arms after 36 months	4.2.6.3
Risk on LN deaths in CKD stage 1-3a	Deaths observed within the AURORA 1 and 2 trial are assumed to inform LN related death in CKD stages 1-3a	Removal of 'LN related' deaths from the model transition probabilities from earlier CKD stages 1-3a assuming that death at this stage is non-disease specific and captured by	4.2.6.6

	Company's preferred assumption	EAG preferred assumption	Report Sections
		general population mortality	

Abbreviations: CKD, chronic kidney disease; CS, company submission; LN, lupus nephritis; MMF, mycophenolate mofetil; RDI, relative dosing intensity, VCS, voclosporin

1.2. Overview of key model outcomes

NICE technology appraisals compare how much a new technology improves length (overall survival) and quality of life in a quality-adjusted life year (QALY). An ICER is the ratio of the extra cost for every QALY gained.

Overall, the technology is modelled to affect QALYs by:

- Increasing the rate of CRR
- Increasing the rate of PRR
- Reducing the risk of CKD progression

Overall, the technology is modelled to affect costs by:

- Drug acquisition costs for voclosporin
- Avoiding/delaying time to more expensive health states related to CKD (such as kidney transplant and dialysis associated with CKD stage 5)

The modelling assumptions that have the greatest effect on the ICER are:

- The application of LN related mortality within the company's model, which may overestimate the number of patients with LN who die as a result of disease (with subsequent impacts on the total costs and QALYs obtained)
- The long-term treatment effect assumptions applied to voclosporin+MMF and MMF. These are primarily:
    - The premise that voclosporin+MMF maintains some level of treatment effect relative to MMF for the entire duration of the modelled time horizon (72 years)

- The assumption that transition probabilities from the within trial period will be maintained once all patients are removed from treatment at 36 months for the remainder of the model duration

1.3. The decision problem: summary of the EAG's key issues

The EAG did not identify a key issue solely related to the decision problem; however, in Key Issue 7 (Uncertainty in how voclosporin will be used in practice) the EAG highlights uncertainty about how voclosporin will be used in practice, including where it will be used in the treatment pathway. This affects the most appropriate comparators for voclosporin.

1.4. The clinical effectiveness evidence: summary of the EAG's key issues

Key Issue 1: Network meta-analysis estimates may not be reliable and should better account for heterogeneity

Report sections	Sections 3.3 and 3.4
Description of issue and why the EAG has identified it as important	Network meta-analyses (NMAs) drew on a heterogeneous evidence base including diverse outcome definitions, follow-up times and populations. However, the company chose to present fixed effects NMAs on the basis that random effects NMAs were judged as not converging. The EAG did not regard that the company had substantiated this claim.
What alternative approach has the EAG suggested?	The EAG suggested exploring informative priors for between-study variance parameters that are appropriate to this context in order to appropriately capture the heterogeneity in the evidence.
What is the expected effect on the cost-effectiveness estimates?	Expected cost-effectiveness estimates are not expected to change substantially, but uncertainty is more likely to be appropriately captured in probabilistic analyses.
What additional evidence or analyses might help to resolve this key issue?	NMAs that use appropriate informative priors, or otherwise clear evidence that no plausible random effects model would lead to convergent estimates in the base case.

Abbreviations: EAG, Evidence Assessment Group; NMA, network meta-analysis

1.5. The cost effectiveness evidence: summary of the EAG's key issues

Key Issue 2: The company's model structure is subject to a number of structural limitations

Report sections	Sections 4.2.2 and 4.2.6
Description of issue and why the EAG has identified it as important	The company's model is associated with a number of restrictive settings and assumptions which preclude in-depth investigation of the impacts these aspects of the model have on cost-effectiveness results. These features include: • CKD progression is only possible from an 'active disease' sub-state (and so patients with renal response are not subjected to a risk of CKD progression) • No CKD progression events in AURORA 1 or AURORA 2, and so CKD progression is disabled in the company's base-case analysis for the first 3 years, but this is not expected to align with clinical practice • Transitions in the first 3 years are based on the 'count method', which is subject to limitations mostly due to sample size • Very few within-trial deaths, and cause of death is not explicitly captured but is modelled to incur differential costs
What alternative approach has the EAG suggested?	The EAG has explored a range of sensitivity analyses where possible within the confines of the company's model structure to investigate these aspects of the model further. These scenarios include permitting CKD progression from 0 years and removing within-trial deaths. However, some scenarios are not possible within the model structure (such as allowing CKD progression for patients with renal response, and re-analysing transition probabilities using a different approach other than the 'count method').
What is the expected effect on the cost-effectiveness estimates?	The scenarios that were possible to explore generally led to an increase in the ICER (further details presented in Section 6.2 of this report). When combined, these scenarios have the potential to lead to a much larger ICER compared with the company's base-case analysis. However, the impact of changing the model structure beyond edits possible for the EAG to make remains unclear.
What additional evidence or analyses might help to resolve this key issue?	Additional structural uncertainty analysis, considering sensitivity analysis allowing different transitions to occur and/or re-analysing the AURORA 1 and AURORA 2 trial data to obtain different transition probabilities may help resolve uncertainty associated with the model structure.

Abbreviations: CKD, chronic kidney disease; EAG, Evidence Assessment Group; ICER, incremental cost-effectiveness ratio.

Key Issue 3: The long-term treatment effect of voclosporin + MMF and its comparators is unknown

Report sections	Sections 4.2.2 and 4.2.6
Description of issue and why the EAG has identified it as important	There is uncertainty in the long-term effect of VCS+MMF and how this compares to the long-term effect of MMF alone, as well as other comparators. The company's model requires extrapolation of transition matrices over a lifetime horizon (equivalent to 69 years beyond the initial 3 years of follow-up data available from the AURORA 1 and AURORA 2 studies). The company's application of independent transition matrices from the trial data makes two important assumptions: (1) that short-term data are sufficient to generalise to the

Report sections	Sections 4.2.2 and 4.2.6
	longer term, and (2) that the short-term data while patients are on treatment are reflective of longer-term outcomes when patients are no longer receiving the same treatment up until 3 years. The company has assumed a 'waning' effect which takes the average effects across both arms and applied this to the VCS+MMF arm indefinitely. The EAG considered this approach to be inappropriate and unjustified in the absence of long-term data and clear justification within the CS.
What alternative approach has the EAG suggested?	The EAG has explored a range of alternative treatment waning effects, and ultimately prefers to assume the same conditional probabilities for renal response across both arms after 3 years.
What is the expected effect on the cost-effectiveness estimates?	The EAG's preferred approach causes the ICER to increase (further details presented in Section 6.2 of this report).
What additional evidence or analyses might help to resolve this key issue?	The EAG feels there is no such evidence that would likely resolve the uncertainty associated with long-term treatment effects, other than longer-term follow-up data or clinical expert opinion.

Abbreviations: CKD, chronic kidney disease; CS, company submission; EAG, Evidence Assessment Group; ICER, incremental cost-effectiveness ratio; MMF, mycophenolate mofetil; VCS, voclosporin.

Key Issue 4: The utility estimates used in the company's model are inappropriate

Report sections	Section 4.2.7
Description of issue and why the EAG has identified it as important	The EAG has a number of reservations about the appropriateness of the utility values used to populate the model. These include a lack of appropriate analysis methods to derive utility values from the AURORA 1 and AURORA 2 studies, omission of a large quantity of data from AURORA 1 and AURORA 2 from the estimation of utility values, and use of literature-based utility values for later states that reflect a different group of patients.
What alternative approach has the EAG suggested?	Where possible, the EAG undertook sensitivity analyses using alternative utility values attempting to address some limitations of the company's analysis (e.g., using all values from AURORA 1 and AURORA 2, and not just values collected around the end of follow-up in AURORA 2).
What is the expected effect on the cost-effectiveness estimates?	The EAG's preferred utility values cause the ICER to increase slightly (further details presented in Section 6.2 of this report).
What additional evidence or analyses might help to resolve this key issue?	The EAG would prefer the company to re-analyse its utility data collected in AURORA 1 and AURORA 2 in line with standard convention, most likely adopting a regression analysis to explicitly incorporate multiple observations at the patient level.

Abbreviations: EAG, Evidence Assessment Group; ICER, incremental cost-effectiveness ratio.

Key Issue 5: The company has not appropriately calculated the costs of treatment in the model

Report sections	Sections 4.2.6 and 4.2.8
Description of issue and why the EAG has identified it as important	The company's model includes a number of assumptions made with respect to costing VCS, MMF, and other comparators included via the indirect comparison. The EAG considered there to have been a fundamental misinterpretation by the company with respect to the difference between RDI and TTD, which means that while premature discontinuation is captured within the model (through TTD), any dose adjustments are not reflected (through RDI, or an equivalent measure). RDI is not clearly reported in the CS, nor is it contained within the AURORA 1 or AURORA 2 clinical study reports provided within the CS reference pack. For MMF, the company costed this assuming a dose of 2.5 g/day, whereas in AURORA 1 and AURORA 2 this was dosed at 2 g/day. Moreover, in AURORA 2, MMF dose reductions were permitted per protocol, and this is not reflected within the company's model. For other comparators, TTD is assumed to be 100% which the company justified based on a lack of data to quantify premature treatment discontinuation. The EAG considered this to be inappropriate given that some patients are expected to discontinue treatment due to lack of efficacy or occurrence of AEs.
What alternative approach has the EAG suggested?	The EAG has incorporated a number of edits to address some of the costing issues, and has explored a variety of scenarios to address areas of outstanding uncertainty. These are described throughout Section 6 of this report.
What is the expected effect on the cost-effectiveness estimates?	Incorporating RDI adjustments (assuming 95% for all treatments) causes the ICER to decrease, whereas all other edits to costs generally caused the ICER to increase slightly. However, combining all changes causes the ICER to increase, with details provided in Section 6.2 of this report.
What additional evidence or analyses might help to resolve this key issue?	The EAG notes there is no such evidence that would likely resolve the uncertainty associated with the incorporation of costs within the model unless the company had relative dosing information available, but expects the various changes and sensitivity analyses warrant further discussion at technical engagement and/or by the committee to determine the most suitable basis to inform decision making.

Abbreviations: CS, company submission; EAG, Evidence Assessment Group; ICER, incremental cost-effectiveness ratio; MMF, mycophenolate mofetil; RDI, relative dose intensity; TTD, time-to-treatment-discontinuation; VCS, voclosporin.

Key Issue 6: There is a lack of transparency around the inputs used in the company's model

Report sections	Section 4.2
Description of issue and why the EAG has identified it as important	The EAG identified a number of issues with respect to transparency of reporting in both the CS and the company's model, which impacted its ability to verify a variety of aspects of the CS. Issues included hardcoded values which did not match source material (due to inflation and/or converting outputs for use within the model), misalignment in source costs with those used in the model, inconsistencies in apparent inflation indices used to adjust costs, and non-

Report sections	Section 4.2
	systematic identification of drug costs leading to some costs that were higher than other available sources (e.g., prednisolone sourced from BNF and not eMIT).
What alternative approach has the EAG suggested?	The EAG has included edits to model inputs where it could clearly identify discrepancies between source data and intended values for the model. However, it was not possible for the EAG to reconcile all apparent discrepancies with information provided to the EAG, and the timeframe available for the EAG to conduct its review.
What is the expected effect on the cost-effectiveness estimates?	The impact on cost-effectiveness estimates for making these edits is small, if the EAG is correct in its interpretation of the intended use of costs and other inputs, and if any outstanding issues are clarified by the company. However, the EAG considered it important to raise this issue with transparency since the EAG has highlighted numerous instances of input parameters which are not clearly referenced and therefore could contain errors but that the EAG could not verify.
What additional evidence or analyses might help to resolve this key issue?	The EAG encourages the company to verify the model input parameters referred to throughout this report to provide reassurance to the committee that the values used are accurate and appropriate to inform decision making.

Abbreviations: BNF, British National Formulary; CS, company submission; EAG, Evidence Assessment Group; eMIT, electronic market information tool.

1.6. Other key issues: summary of the EAG's views

Key Issue 7: Uncertainty in how voclosporin will be used in practice

Report sections	**2.4, 3.2.2, 3.2.3.2, 3.3.3, 4.2.3, 0**
Description of issue and why the EAG has identified it as important	The treatment pathway and the way in which treatments are administered to people with LN is highly variable across the population. The choice of treatment is tailored to patients' needs, and there is a lack of clear evidence about the optimal duration of treatment with immunosuppression. The evidence presented by the company represents one way in which voclosporin may be used: administered at either first or second line (after MMF monotherapy), and with a target duration of 3 years (with a small number of trial participants permitted to withdraw due to response after 2 years of treatment). Clinical effects are based on a combined population of people receiving voclosporin at different lines of treatment, and mostly receiving treatment for close to 3 years. Clinical advice to the EAG is that this may not be how voclosporin is used in practice, as clinicians may seek to continue existing flexibility with treatment choice and duration. Moreover, using voclosporin routinely at first line would be a change in practice, since other CNIs are usually administered later such as when people do not respond to MMF alone. Where variations in practice existed within the trials of voclosporin (such as prior treatment with MMF or treatment discontinuation < 3 years), a lack of statistical power meant that the company was unable to evaluate how these variations influenced the treatment effect. The EAG considered it uncertain but plausible that the effect of voclosporin may vary according to the way it is used. Subgroup analyses from AURORA 1 and AURA-LV suggested that line of treatment may have a significant impact on the magnitude of treatment effect, but the findings

Report sections	2.4, 3.2.2, 3.2.3.2, 3.3.3, 4.2.3, 0
	between studies were conflicting, and neither the company nor the EAG were able to resolve the reason behind this. The EAG is also aware that variation in the duration of immunosuppression treatment can affect the risk of relapse, but this evidence does not provide a clear steer on the length of time people should receive immunosuppressive treatment. Due to uncertainty in the way treatment for LN is administered, it is likely that further evidence may arise that guides the duration and withdrawal of voclosporin and other treatments. Together, the EAG was unable to rule out that the effect of voclosporin may vary according to how it is used, which has implications for the clinical and cost effectiveness of voclosporin in a way that cannot be fully understood at present.
What alternative approach has the EAG suggested?	While acknowledging the lack of statistical power in the included trials, and quality issues with AURA-LV that affect the feasibility of a pooled meta-analysis, at clarification, the EAG requested further sensitivity analyses from the company to explore the effect of voclosporin according to line of treatment [CQ A15]. The company restricted their response to analyses already presented in the CS, and did not present additional data e.g. for other outcomes or using data from AURORA 2. It is possible that further analyses may have been informative for this matter (e.g. a consistent pattern in effects across outcomes may had increased confidence in the presence of an effect), however, multiple post-hoc analyses that are also under-powered would not have generated estimates with sufficient confidence for decision-making. Furthermore, if differences between the design of AURA-LV and AURORA 1 contributed to the conflict in findings, further analyses would perpetuate these differences without providing insight into the reasons for conflict. Overall, the EAG considered that the company's trial evidence did not sufficiently explore how variation in the use of voclosporin would affect its effect for people with LN, and this is challenging to resolve at this stage.
What is the expected effect on the cost-effectiveness estimates?	Transitions in the company's model are derived from transitions observed within AURORA 1 and AURORA 2, and therefore represent the way in which voclosporin was used within those trials. Separate data were not presented according to whether participants were or were not using MMF at baseline, or according to a different approach to treatment duration. The EAG have no reliable estimates for how the effect of voclosporin may vary across populations and variations in its use, and within the model structure, the EAG was unable to explore how altering the magnitude of treatment effect for voclosporin would affect cost effectiveness. Overall, the EAG considered that the company model likely does not represent solely the way in which voclosporin would be used in practice, but is unable to determine how this has affected cost effectiveness estimates for voclosporin without further analyses from the company.
What additional evidence or analyses might help to resolve this key issue?	The EAG considered that, due to limitations in the trial evidence, this issue cannot be resolved without further evidence generation. However, the company may be able to provide further evidence to inform the committee in its decision-making. For example, the company may be able to provide further analyses that explore the effect of changes to the treatment pathway; such as the position of voclosporin in the treatment pathway, and variation in the duration of treatment. The company may also be able to provide data for the model separated according to MMF use at baseline, which may give an indication for how cost effectiveness may vary according to its use.

Abbreviations: CQ, clarification question; CS, company submission; EAG, Evidence Assessment Group; LN, lupus nephritis; MMF, mycophenolate mofetil

1.7. Summary of EAG's preferred assumptions and resulting ICER

A summary of the ERG's preferred assumptions and resulting ICER is provided in Table 3.

Table 3: Summary of EAG's preferred assumptions and ICER

Preferred assumption	Incremental cost	Incremental QALYs	Cumulative ICER £/QALY
Company base-case			*£19,876*
Company base-case with fix applied	[redacted]	[redacted]	***£19,897***
Align resource use, AE, EOL and drug costs	[redacted]	[redacted]	*£20,114 (£217)*
Add in ½ pack wastage for voclosporin	[redacted]	[redacted]	*£20,413 (+£516)*
Update trial utilities to weighted average from AURORA 1 and AURORA 2 observations	[redacted]	[redacted]	*£21,401(+£1,504)*
Update literature-based utilities for transplant from Li et al.2017	[redacted]	[redacted]	*£20,152(+£255)*
Update literature-based utilities for dialysis from meta-analysis of Cooper et al. 2020	[redacted]	[redacted]	*£19,984(+£87)*
Apply 95% RDI to all treatments	[redacted]	[redacted]	*£18,699 (-£1,198)*
Removal of LN death in CKD stage 1-3a	[redacted]	[redacted]	*£23,497 (+£3,600)*
Allow transitions CKD stage 3b-4 in first 36 months	[redacted]	[redacted]	*£14,811 (-£5,086)*
Use average long-term transition probabilities from VCS+MMF and MMF applied to both arms	[redacted]	[redacted]	*£45,446(+£25,549)*
EAG base case	[redacted]	[redacted]	*£40,029 (+£20,132)*

Abbreviations: CKD, chronic kidney disease; EAG, Evidence Assessment Group; ICER, incremental cost-effectiveness ratio; LN, lupus nephritis; MMF, mycophenolate mofetil; QALY, quality adjusted life year; RDI, relative dosing intensity, VCS, voclosporin

Modelling errors identified and corrected by the EAG are described in Section 6.1. For further details of the exploratory and sensitivity analyses done by the EAG, see Section 6.2.

2. INTRODUCTION AND BACKGROUND

2.1. Introduction

In this report, the Evidence Assessment Group (EAG) provides a review of the evidence submitted by Otsuka Pharmaceuticals in support of voclosporin (Lupkynis) in combination with immunosuppression therapy for the treatment of lupus nephritis.

Lupus nephritis (LN) is a common complication of systemic lupus erythematosus (SLE), which is an autoimmune condition affecting an estimated 60,000 people in England and Wales. [1] LN is experienced by between 33% - 60% of people with SLE, with higher incidence in people with high-risk disease or those with prior kidney injury. LN occurs when chronic inflammation within the glomerular affects the ability of the kidney to filter waste and excess substances including proteins from the blood. This leads to kidney damage, which can lead to end stage renal disease (ESRD), and serious health outcomes such as heart attacks and strokes. People with LN have a higher standardised risk of mortality compared to the general population (6 – 6.8 vs. 2.4), and have a shorter life expectancy compared to people with SLE who do not have LN. [2]

LN typically develops within 5-years of diagnosis of SLE, though 25% - 50% of people show signs of LN at the time of SLE diagnosis, [3] which may be due to general under-diagnosis of SLE. Data describing the prevalence and incidence of LN in the UK are currently limited. Among publicly available data, the most recent UK-specific study was a 2001 retrospective analysis conducted in England, which reported overall LN prevalence and incidence rates of 4.4 and 0.4 per 100,000 of the population, respectively. [4] While SLE is generally more common amongst females, in general studies report that males with SLE are at higher risk of developing LN. Additional risk factors include people within certain Black, Asian and Hispanic ethnic groups, juvenile onset of SLE, and the presence of high risk genetic markers. In general, 5-yr risk of ESRD in people in LN is 11% (95% CI 10–12%), 10-yr is 17% (95% CI 16–18%), and 15-yr is 22% (95% CI 20–23%). The risk is higher in developing nations, particularly for 15-yr risk. Also higher risk for those with higher class LN, with highest risk in class IV: 5-year, 10-year, and 15-year risks of 19% (95% CI 12–29%), 33% (95% CI 22–44%), and 44% (95% CI 32–56%).[5]

Treatment for LN is similar to the approach used for SLE, and includes high-dose corticosteroids to rapidly control inflammation, followed by immunotherapy (including mycophenolate mofetil [MMF] and cyclosphosphamide). Sometimes additional treatment with a calcineurin inhibitor (CNI; such as tacrolimus), an anti-malarial (hydroxychloroquine), or with

rituximab is indicated. Controlling the inflammation may limit damage to the kidney and reduce the risk of ESRD; however, a third of patients who experience a complete response to treatment nevertheless relapse. Treatments for LN also carry their own risks, and drug-induced toxicity and the increased risk of infections are associated with early mortality and morbidity.

Voclosporin is a novel CNI which, like other CNIs used to treat LN, blocks T-cell activation instrumental in causing inflammation, and independently decreases proteinuria by reinforcing the integrity of podocytes in the glomeruli. Voclosporin does not currently have a licence for use in the UK; in November 2021 the European Medicines Agency (EMA) requested further information from the company, to which it is still preparing its response (as of January 2022).[6] If the company receive a positive decision for voclosporin from the EMA, [redacted].

2.2. Critique of the company's description of the underlying health problem

The EAG considered that the company's description of LN was representative of the condition, and included consideration of relevant available evidence.

2.3. Critique of the company's overview of current service provision

The company accurately summarised treatment recommendations for LN published by EULAR/ERA-EDTA.[7] Clinical advice to the EAG was consistent with statements from the company that people with LN typically receive hydrochloroquine, and that tacrolimus is the CNI treatment most used. However, clinical advisors noted that cyclophosphamide (CYC) is now rarely used within the NHS, due to toxicity. As shown by the EULAR/ERA-EDTA recommendations, initial immunosuppressive treatment for LN is MMF or MPA. The company noted that other treatments, including CNIs, may be used at first-line in certain circumstances, for example if standard doses of MMF or MPA are contra-indicated, or for those with nephrotic-range proteinuria. Clinical advisors to the EAG also noted that an alternative to MMF may be used in case of planned pregnancy. However, advice to the EAG was that alternatives to MMF and MPA in the first-line are rarely used. Advisors also noted that consideration for using a CNI would depend on a person's kidney function, since CNIs are associated with a risk of kidney damage.

Clinical advisors to the EAG noted that, while treatment of LN is evidence-driven, the evidence does not support a one-size-fit-all approach to management. As shown in the EULAR/ERA-

EDTA recommendations reported by the company, there are multiple options available at each stage, and clinicians choose a strategy according to patient preferences, their disease severity and response to previous treatments, and their vulnerability to the safety profile of specific products. EULAR-ERA-EDTA also note that there is yet insufficient evidence to determine the optimum duration of treatment, which should balance the protective effects of treatment for controlling progression of kidney damage with safety risks. Clinicians can vary in their approach to management: one clinical advisor to the EAG reported that they would consider discontinuing treatment after 15- to 18-months, while another of their team typically discontinued after 1-year. Another clinical advisor to the EAG noted that treatment administered longer than 3-years would be consistent with EULAR/ERA-EDTA guidance.

2.4. Critique of company's definition of decision problem

The company submission (CS) was aligned with the decision problem (see Table 4). At clarification, the company noted that the expected licence for voclosporin would be in combination with MMF, which is consistent with the evidence presented.

The EAG were uncertain where in the treatment pathway voclosporin would typically be used. As described in Section 2.3, treatment with a CNI would typically be administered after patients had not responded to treatment with MMF/MPA alone, or if first-line treatment with MMF/MPA was contraindicated. In this case, the main comparators for voclosporin would be azathioprine, rituximab, or tacrolimus. The company do not present a direct comparison between voclosporin and these technologies, and therefore comparative efficacy is demonstrated through the company's network meta-analysis (NMA; Section 3.4). The company proposed that in this position, voclosporin would be used as an alternative to tacrolimus, as both are CNIs are therefore offer a similar mechanism for treating the disease, and potentially carry a similar safety profile (though the company suggested that the safety profile of voclosporin is improved compared to tacrolimus). The company also proposed that voclosporin be considered as an alternative to MMF/MPA in the first-line position. The EAG are unclear if the company intend for voclosporin to be used in the first-line in the same way other CNI therapies are used (i.e. if MMF/MPA is contra-indicated), or whether they intend for voclosporin to be used as an alternative to MMF/MPA in a larger group of patients with LN. Half of all participants included in the AURORA 1 and AURA-LV trials were not receiving MMF at screening for the trial, and it is unclear whether or why these patients were therefore receiving voclosporin as first-line treatment, or if they had previously received and discontinued MMF/MPA. It is therefore

plausible that the company wish the committee to consider a broader use of voclosporin than for other CNIs, though the EAG did not consider the company had substantiated this.

Table 4: Summary of decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comment
Population	Adults with active lupus nephritis	As per scope	N/A	The evidence submitted by the company was appropriate to the NICE scope
Intervention	Voclosporin with immunosuppressive therapies	As per scope	N/A	The evidence submitted by the company was appropriate to the NICE scope. The evidence presented evaluated the effectiveness of voclosporin in combination with MMF and immunosuppressive therapies. At clarification, the company confirmed that this is consistent with the expected licence for voclosporin.
Comparator(s)	Standard therapy for lupus nephritis without voclosporin including the following induction treatments, followed by maintenance treatment with mycophenolate plus corticosteroids or azathioprine plus corticosteroids:	As per scope	N/A	The evidence submitted by the company was appropriate to the NICE scope. As stated in Key Issue , the EAG were uncertain which comparators would be most appropriate for voclosporin, as it was unclear where in the treatment line voclosporin would be used.

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comment
	• mycophenolate plus corticosteroids • cyclophosphamide plus corticosteroids • azathioprine plus corticosteroids • rituximab • a calcineurin inhibitor plus mycophenolate and corticosteroids.			
Outcomes	The outcome measures to be considered include:	As per scope	N/A	The evidence submitted by the company was appropriate to the NICE scope
Economic analysis	The NICE reference case stipulates that: • the cost-effectiveness should be expressed as cost per quality-adjusted life year in a cost-utility analysis framework with fully incremental analysis where required • the model time horizon should be sufficiently long to fully capture all differences in costs and outcomes being compared between the technologies • Costs should be considered from an NHS	The EAG considered that the economic analysis largely matched the analysis outlined within the scope: • Cost effectiveness was expressed as a cost per quality adjusted life year • A lifelong time horizon was considered • Costs were considered from an NS and Personal Social Services perspective • Health effects were mapped to the EQ-5D • Costs and health effects were discounted	N/A	Mostly in line with the NICE scope, with concerns relating to model structure and the utility values obtained (see Section 4.2). Incremental analyses were not presented but have been provided by the EAG in Section 5.

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comment
	and Personal Social Services perspective • Health effects should be expressed in QALYs with the EQ-5D being the preferred measure in adults with sources of data being a representative sample of UK patients • Costs and health effects should be discounted at 3.5%			
Subgroups	None specified	N/A	N/A	N/A
Special considerations including issues related to equity or equality	None specified	N/A	N/A	N/A

Abbreviations EAG, Evidence Assessment Group; NICE, National Institute for Health and Care Excellence; N/A, not applicable

3. CLINICAL EFFECTIVENESS

3.1. Critique of the methods of review(s)

The company undertook a systematic literature review (SLR) to identify evidence from randomised controlled trials (RCTs) for voclosporin and its comparators for the treatment of active class III-IV LN. Overall, the EAG considered the review methods used by the company to be acceptable, though raised some concerns about the company's literature search strategy and its methods of quality appraisal. The EAG did not consider that issues with the company's search strategy would have a major impact on the findings of the review, as it considered it likely that all relevant evidence for voclosporin had been identified. This evidence includes a direct comparison with MMF, and a search of recent literature reviews by the EAG suggested that the company's review also included all relevant trials of tacrolimus + MMF, which the EAG considered the other principal comparator of interest. However, the EAG did have concerns about aspects of the quality assessment conducted by the company, which it considered underestimated risk of bias of the included trials.

Table 5: Summary of EAG's critique of the methods implemented by the company to identify evidence relevant to the decision problem

Systematic review step	Section of CS in which methods are reported	EAG assessment of robustness of methods
Searches	Appendix D (D1.1.1)	The company literature searches were carried out in Proquest, which the EAG were unable to access and so searches were not tested. The company searched several databases together in one strategy, which is not best practice as, for example, terms can vary between databases. Moreover, the RCT filter that was used by the company is not the recognised, validated filter from the Cochrane Handbook; in clarification the company stated that they used a mixture of different filters, though that is not how they are designed to be used[8] and this makes the effectiveness of the search uncertain. Overall, the EAG considered it likely that the company's search strategy missed relevant papers. Clinical trials registers were not searched so relevant (unpublished, ongoing) trials may have been missed. The company stated that targeted PubMed searches were carried out for adverse events but the strategies were not provided in clarification, therefore it was not possible to assess the effectiveness of these. It is possible that exclusion of cohort, case-control, cross-sectional and case series as publication types in the literature searches (due to the use of an RCT filter) meant that papers reporting adverse events have been missed.
Inclusion criteria	Appendix D (D1.1.2)	The inclusion criteria were appropriate to the aims of the review and consistent with NICE methods. The criteria were limited to RCT evidence; while RCTs are the gold standard for determining relative efficacy, they often lack external validity, and in some topic areas, restriction to RCT evidence can result in a limited evidence base. New NICE guidance[9] allows for inclusion of non-randomised studies to supplement a limited evidence base, provide a counterpoint to RCT evidence, and provide insight into any concerns about the generalisability of trial evidence. Given the small evidence base for treatments for LN, the EAG considered it may have been valuable for the company to have broadened their SLR to include non-randomised evidence. However, the EAG were unable to identify non-randomised studies either of voclosporin, or including a comparison of tacrolimus+MMF (a comparator of interest for which there is no direct RCT evidence). The company also confirmed at clarification [A19] that it had been unable to find a non-randomised comparison of tacrolimus plus MMF. Ultimately therefore, the EAG considered it unlikely that the inclusion of non-randomised evidence would have contributed significantly to the evidence base.

Systematic review step	Section of CS in which methods are reported	EAG assessment of robustness of methods
Screening	Appendix D (D1.1.2)	Screening methods were described in full, and were conducted according to gold standard practice.
Data extraction	NR	Methods for extraction of clinical effectiveness data were not reported
Tool for quality assessment of included study or studies	CS B.2.5	Critical appraisal of the trials of voclosporin and those included in the company's NMA was conducted using an appropriate checklist (NICE quality appraisal tool). The company did not nuance their appraisal according to outcome, which is a limitation in their approach. Overall the EAG judged the company's quality appraisal to be acceptable, though disagreed with several of their assessments, judging that these underestimated the risk of bias of the included trials. Moreover, the EAG noted that a response to an item in their appraisal of AURORA 2 was incongruent with the risk of bias under assessment. The company's quality appraisal of trials included in the NMA highlighted several issues with the included studies, though these were not discussed by the company.
Evidence synthesis	Paired meta-analysis: CS B.8. Network meta-analysis: CS B.2.9	The company did not conduct a substantial narrative synthesis of treatment effects across the included trials of voclosporin. The company did conduct a paired meta-analysis of data from comparable treatment arms in AURORA 1 and AURA-LV in an effort to capitalise on a larger sample size. The outcomes considered by the analysis were limited in scope, which limited the utility of the analysis in the appraisal. The utility of the analysis was also limited by concerns about the potential imbalance between treatment arms in AURA-LV. The company NMAs to evaluate the comparative effectiveness of voclosporin versus other treatments for LN. The analyses were restricted to two outcomes only (complete renal response and partial renal response), which despite being non-independent were analysed separately. The EAG considered that a multivariate analysis to include both outcomes would have been preferable. The EAG also considered that the findings of random effects models should have been prioritised in the base case, and that alternative priors should have been explored.

Abbreviations: CS, Company submission; EAG, Evidence Assessment Group; LN, lupus nephritis; MMF, mycophenolate mofetil; NMA, network meta-analysis; NR, not reported; RCT, randomised controlled trial; SLR, systematic literature review

3.2. Critique of trials of the technology of interest, the company's analysis and interpretation (and any standard meta-analyses of these)

3.2.1. Studies included in the clinical effectiveness review

The CS described three trials of voclosporin that were identified by the company's SLR (**Error! Not a valid bookmark self-reference.**). These comprise a phase III, double-blind, placebo-controlled RCT (AURORA 1) and its extension (AURORA 2), and a Phase IIb, double-blind, placebo-controlled, three-armed RCT (AURA-LV). The company also conducted a pooled meta-analysis using data from AURORA 1 and AURA-LV (using those participants from AURA-LV who were randomised to the low dose arm). An overview of the methods of the included trials is provided in the following sections.

Table 6: Clinical trials included in the CS

Study name and acronym	Study design	Population	Intervention	Comparator	Location
AURORA 1	Phase III, double-blind, parallel-group, two-arm, multicentre RCT Follow-up: 52 weeks	Adult patients with SLE and LN class III – V as determined by a kidney biopsy, and who were considered to require high-dose corticosteroid and immunosuppressive treatment N=357	Voclosporin (23.7 mg BID) with MMF (2g) and low-dose corticosteroids	Placebo with MMF (2g) and low-dose corticosteroids	International (Europe 40 sites; USA 29 sites; Latin America 32 sites, South Africa 3 sites, Asia 38 sites). Sites in the UK: 0
AURORA 2	Phase III extension to AURORA 1. Double-blind, parallel-group, placebo-controlled, multicentre extension to a RCT Follow-up: 2 years	Patients recruited for AURORA 1 who completed 52 weeks of treatment in either arm N=216	Voclosporin (23.7 mg BID up to 12 months, then patients with controlled UPCR become eligible for a dose reduction to 15.8mg BID for the final 12 months; otherwise dosage remains the same) with MMF (2g) and low-dose corticosteroids	Placebo with MMF (2g) and low-dose corticosteroids	International (Europe 30 sites; USA 24 sites; Latin America 23 sites; South Africa 3 sites; Asia 25 sites) Sites in the UK: 0
AURA-LV	Phase IIb double-blind placebo-controlled, three-arm, multicentre study Follow-up: 48 weeks	Adult patients with SLE and LN class III – V N=265	Voclosporin 23.7mg BID or Voclosporin 39.5 mg BID, with MMF (2g) and low-dose corticosteroids	Placebo with MMF (2g) and low-dose corticosteroids	International (Europe, Americas, Asia) Sites in the UK: 0

Abbreviations: BID, twice daily; LN, lupus nephritis; MMF, mycophenolate mofetil; RCT, randomised controlled trial; SLE, Systemaic Lupus Erythematosus; UPCR, Urine Protein Creatinine Ratio

3.2.2. Description and critique of the design of the studies

3.2.2.1. Design of the studies

None of the trial sites were based in the UK, which at clarification the company stated was due to an understanding during the feasibility assessment of the trial that interest in the clinical trial of voclosporin in the UK would be less than elsewhere in Europe. Clinical advisors to the EAG were unable to explain why this might be the case but did not consider management of LN to vary greatly between countries. However, they noted that the incidence of prognostic markers in the LN population may vary between locations (for example, variation in the proportion of the population from certain ethnic minority groups).

AURORA 1 was an international multicentre placebo-controlled RCT with follow-up of one year. The EAG considered that the trial was of high quality (see Section 0), however had concerns about the length of follow-up and the lack of statistical power.

The EAG considered that the follow-up for the trial was short given that voclosporin (and its comparators) may be expected to be administered over several years. The company implemented a target for 3-years of treatment with voclosporin, and during AURORA 1 participants were permitted to withdraw or reduce their dose only for safety concerns (withdrawal after 2-years of treatment due to response was possible for those participants who continued from AURORA 1 into AURORA 2). The use of voclosporin over multiple years is consistent with current use of other immunosuppression treatments; this is done to ensure a complete renal response (CRR) and to protect against renal flares. The EMA advise that rates of renal response may be detected within 1-year of treatment, [10] though a minority of people may experience a response after more than 1-year of treatment. [11] For this reason the EAG considered it reasonable that a difference in renal response would be detected during the follow-up of AURORA 1, but that it was plausible that some but not all renal responses would be identified. The EAG were more concerned that AURORA 1 would be unable to detect incidence of renal flares, which would require follow-up of longer than 1 year. [10] Clinical advice to the EAG was also that the follow-up of the included trials may be limited for detecting differences how response to treatment may be sustained over time, and the effect of treatment on CKD progression. The company noted that only a minority of participants would be expected to transition from CKD stages 3b - 4 to CKD stage 5 within 1 year (CS, p.116). For adverse events (AE), the EAG considered that a 1 year follow-up would capture initial tolerance to the

treatments, but would not capture longer term toxicity effects associated with immunosuppressant therapy, such as infections and malignancies.

AURORA 1 was the largest of the included trials, but this trial only had sufficient statistical power for detecting change in its primary outcome, and was not powered for subgroup analyses. This seriously limits the scope of the evidence base for exploring variation in treatment effect across groups of interest, such as according to line of treatment, geographical location, and disease staging at baseline.

Participants in ***AURORA 2*** were those that completed the treatment regime in AURORA 1, chose to participate in the follow-on study, and met the trial inclusion criteria (see Section 3.2.2.2). Group allocation was maintained as in AURORA 1, and participants continued to be blinded. Follow-up was 2 years, thus completing follow-up for the target 3-year treatment period of voclosporin. There was a substantial loss of participants between AURORA 1 and AURORA 2: a total of 39.5% of participants did not participate (35.2% of the voclosporin arm and 43.8% of the placebo arm). The reasons for participants not continuing with AURORA 2 are summarised in Table 7; the major reasons were due to AEs, lack of efficacy, and a withdrawal of physician or participant consent. High levels of attrition, particularly where these are related to treatment, increase the risk of bias associated with trial data (see Section 3.2.2.5). This is attenuated slightly as the rate of discontinuation was comparable between arms, as were the reasons for discontinuation, though the EAG noted that the rate of withdrawal due to a lack of efficacy was greater in the placebo arm. Overall, the EAG concluded that absolute rates of events for all outcomes from AURORA 2 were subject to a high risk of bias, as they do not include consideration of participants who chose to discontinue treatment prior to AURORA 2. Relative risk estimates from AURORA 2 may be more reliable, provided that treatment effects are stable across LN populations; this is typically the case, though the EAG did not have clear evidence for this within LN. Finally, the EAG noted that AURORA 2 was underpowered to detect statistical significance in any clinical outcome, including primary trial outcomes, and no subgroup analyses were conducted. This further limits the utility of the AURORA 2 trial.

Table 7: Reasons that participants from AURORA 1 did not enrol in AURORA 2

	AURORA 1	
	VCS (n=63)	PbO (n=78)
Permanent treatment discontinuation	[redacted]	[redacted]

	AURORA 1	
	VCS (n=63)	PbO (n=78)
AE	[redacted]	[redacted]
Protocol non-compliance	[redacted]	[redacted]
Pregnancy	[redacted]	[redacted]
Physician decision	[redacted]	[redacted]
Prohibited medication required	[redacted]	[redacted]
Lack of efficacy	[redacted]	[redacted]
Other	[redacted]	[redacted]
Withdrew from AURORA 1 prematurely	[redacted]	[redacted]
Intolerable AE	2 (1.1)	0 (0.0)
Death	1 (0.6)	5 (2.8)
Lost to follow-up	1 (0.6)	3 (1.7)
Physician decision	2 (1.1)	3 (1.7)
Prohibited medication required	1 (0.6)	0 (0.0)
Pregnancy	1 (0.6)	0 (0.0)
Protocol non-compliance	1 (0.6)	1 (0.6)
Withdrawal of consent	7 (3.9)	14 (7.9)
Lack of efficacy	0 (0.0)	1 (0.6)
'Other'	0 (0.0)	4 (2.2)
Administrative reasons	[redacted]	
Did not give consent due to life circumstances	[redacted]	
Not recorded	[redacted]	

Abbreviations: AE, adverse event; PbO, placebo; VCS, voclosporin

^rates for each arm not reported; * note that sub-categories total more than 15. EAG is unclear whether this is because a participant gave more than one reason for discontinuing; #the EAG cannot account for 10 participants missing from AURORA 2 in the breakdown of reasons provided by the company

Source: Table B.2-5 of the CS, p.37; company clarification response A10

AURA-LV was an international multicentre phase IIb dose-finding trial, comparing two doses of voclosporin with each other and with a matching placebo. The trial appeared well-conducted, however an anomalous high mortality rate in the low-dose arm of voclosporin led to the company concluding that a chance imbalance in randomisation had undermined the internal validity of the trial. At clarification [A26] the company provided a report summarising the deliberations of an internal board that reviewed the mortality data in AURA-LV, which concluded that the deaths were unrelated to treatment, and may have resulted from an imbalance in

disease severity and treating centre. [12] The EAG accepted the conclusions of the report, noting that chance imbalances in baseline characteristics can occur no matter how rigorous the methods used, particularly for smaller trials. However, the EAG considered that the findings of the AURA-LV trial are therefore at a higher risk of bias, as where one imbalance is noted, more may be present and undetected.

3.2.2.2. Population

Trial inclusion criteria

Population inclusion and exclusion criteria for the included trials are provided in Table 8. The EAG considered that these criteria were reasonable and aligned with the target patient population for voclosporin. While the criteria excluded people with significant comorbid health conditions and a medical history with severe infections or cardiovascular conditions, clinical advice to the EAG was that these criteria would not exclude a high proportion of people with LN in clinical practice. This is because many people with LN are younger and are less likely to have these serious conditions.

People with CKD stage 3b and above at screening were also excluded, as were those who were expected to need a transplant during the trial duration. The EAG considered that this was also consistent with the intended use of voclosporin.

Table 8: Key inclusion/exclusion criteria for the included trials

	AURORA 1	AURORA 2	AURA-LV
Inclusion	Adults aged 18 – 75 years Diagnosis of SLE (per ACR criteria) LN, as defined as class III-V, including mixed class Active LN according to a kidney biopsy* Requires high-dose corticosteroids and immunosuppression therapy	Completed 52 weeks of treatment with study drug in the AURORA 1 study, including anyone who had discontinued and re-started treatment. Continued immunosuppressive therapy was required	Adults aged 18 – 75 years Diagnosis of SLE (per ACR criteria) LN, as defined as class III-V, including mixed class Active LN according to laboratory findings# Requires high-dose corticosteroids and immunosuppression therapy
Exclusion	eGFR ≤45 ml/min/1.73 m2 at screening Requires renal dialysis at screening or during the trial period	Requires renal dialysis at screening or during the trial period Planned kidney transplant	eGFR ≤45 ml/min/1.73 m2 at screening Requires renal dialysis at screening or during the trial period

	AURORA 1	AURORA 2	AURA-LV
	Previous or planned kidney transplant Current or medical history of malignancy^ or severe viral infection. Current severe active conditions, including infections requiring antibiotics, severe cardiovascular disease, liver disease	A medical condition with increased risk to the patient or may interfere with assessments	Previous or planned kidney transplant Current or medical history of malignancy^ or severe viral infection. Current severe active conditions, including infections requiring antibiotics, severe cardiovascular disease, liver disease

Abbreviations: ACR, American College of Rheumatology; eGFR, estimated glomerular filtration rate; LN, lupus nephritis; SLE, systemic lupus erythematosus

*within 2 years or 6 months prior to baseline, depending on UPCR rate (see Table B.2-3, p. 31 CS); # Further details in table B.2-13, p.49 CS)

Baseline characteristics

Key baseline characteristics for the included trials are summarised in

Table 9.

The EAG considered that the trial populations appeared comparable with the target LN population for voclosporin: participants were mostly female and in early to mid-age, were in biopsy class III-IV and IV, and had active LN at the time of screening. Baseline measurement of eGFR and UPCR was consistent with active LN and concurrent kidney damage. Trial participants had been diagnosed with LN approximately 3 to 5 years prior to the trials.

The EAG considered that the company had reported a reasonable scope of baseline characteristics, though noted the omission of some characteristics that have prognostic value (e.g. incidence of those with juvenile-onset, high risk biomarkers), and that there was a lack of information about the previous treatment received by those in the trials. As treatment efficacy may vary according to the aggressiveness of a person's disease and their previous treatment, the EAG considered it could not rule out differences between trials and trial arms that may have affected trial outcomes. This concern was bolstered given that disease characteristics for those in the low-dose voclosporin arm of AURA-LV appeared comparable to those in the other arms and trials using the characteristics reported, but they subsequently had a higher risk of mortality, which may in part have been due to higher disease severity. [12]

Participants were randomised to treatment arms on a 1:1 ratio, stratified by biopsy class (class V or other), MMF use at baseline (yes/no), and region (North America vs Latin America vs Europe and South Africa vs Asia-Pacific). Within AURORA 1, trial arms were reasonably well-balanced (noting the concern above). Fewer characteristics were reported for participants entering AURORA 2, though in the characteristics reported there was also reasonable balance. The EAG noted that those in the placebo arm of AURORA 2 were more likely to be in biopsy class III, and those in the voclosporin arm were more likely to be in biopsy class IV; such differences would be unsurprising given attrition between AURORA 1 and 2 effectively breaking randomisation, and the overall trial sample size. Several minor differences between trial arms were noted within AURA-LV: median age in the placebo arm was lower, and more participants in the low dose voclosporin arm were treated within Asian settings, and were White or Asian.

Overall, the EAG considered that the trial arms appeared well-balanced across most characteristics, including disease severity, but could not conclude that participants were entirely comparable due to missing details for some characteristics (e.g. previous treatment), and because of the lack of stable prognostic measures within LN.

Table 9: Demographic characteristics of included trial samples

	AURORA 1		AURORA 2			AURA-LV	
	VCS	Placebo	VCS	Placebo	VCS (low dose)	VCS high dose	Placebo
Age, median (range), years	31 (18–62)	32 (18–72)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Female, n (%)	161 (90)	152 (85)	[redacted]	[redacted]	76 (85.4)	81 (92.0)	73 (83.0)
Region (%)	Asia Pacific 29% Europe and South Africa 29% Latin America 27% North America 15%	Asia Pacific 29% Europe and South Africa 29% Latin America 27% North America 15%	NR	NR	Asia: 58.4% Europe: 28.1% Americas 13.5%	Asia: 48.9% Europe: 28.4% Americas: 22.7%	Asia: 39.8% Europe: 38.6% Americas: 21.6%
Race	White 38% Black 15% Asian 30% Other 18%	White 34% Black 11% Asian 31% Other 24%	[redacted]	[redacted]	White: 33.7% Black: 3.4% Asian Indian subcontinent: 24.7% Asia other: 33.7% Other: 4.5%	White: 40.9% Black: 6.8% Asian Indian subcontinent: 22.7% Asia other: 27.3% Other: 2.3%	White: 47.7% Black: 5.7% Asian Indian subcontinent: 20.5% Asia other: 20.5% Other: 5.7%
Ethnicity	Hispanic or Latino 32% Other 68%	Hispanic or Latino 33% Other 66% Unknown 1%	[redacted]	[redacted]	Hispanic or Latino 10.1% Other 89.9%	Hispanic or Latino 14.8% Other 85.2%	Hispanic or Latino 14.8% Other 85.2%
Time since initial LN diagnosis, mean (SD), years	4.6 (5.1)	4.7 (4.9)	[redacted]	[redacted]	4.2 (5.1)	3.2 (4.4)	3.5 (4.0)
Time since SLE diagnosis, mean (SD), years	6.6 (6.4)	6.9 (6.1)	NR	NR	[redacted]	[redacted]	[redacted]

		AURORA 1		AURORA 2		AURA-LV	
Biopsy class, n (%)	Pure class III: 11% Pure class IV: 51% Pure class V: 14% Class II and V only: 0% Class III and V only: 13% Class IV and V only: 11%	Pure class III: 16% Pure class IV: 43% Pure class V:14% Class II and V only: <1% Class III and V only: 11% Class IV and V only: 15%	[redacted]	[redacted]	Pure class V: 13.5% Class III/IV: 62.9% Class III+V or IV+V: 23.6%	Pure class V: 15.9% Class III/IV: 71.6% Class III+V or IV+V: 12.5%	Pure class V: 14.8% Class III/IV: 67% Class III+V or IV+V: 18.2%
Baseline eGFR Mean (SD), mL/min/1.73 m²	92.1 (30.6)	90.4 (29.0)	[redacted]	[redacted]	95.3 (28.4)	104.0 (27.3)	100.2 (27.1)
Mean (SD) baseline UPCR, mg/mg	4.14 (2.71)	3.87 (2.36)	[redacted]	[redacted]	5.16 (4.2)	4.48 (3.0)	4.43 (3.6)
SELENA-SLEDAI, mean (SD); n	13.2 (6.5); n=177	11.8 (6.1); n=177	NR	NR	NR	NR	NR
MMF use at screening, n (%)	100 (56)	96 (54)	NR	NR	31 (34.8)	29 (33.0)	32 (36.4)

Abbreviations: eGFR, estimated glomerular filtration rate; LN, lupus nephritis; MMF, mycophenolate mofetil; SD, standard deviation; UPCR, urine protein/creatinine ratio; VCS, voclosporin

Source: CS; AURORA 2 CSR; AURA-LV CSR

3.2.2.3. Intervention and comparator

Treatment characteristics and dose modifications for the included trials are summarised in Table 10. Additional details about the tapering of MMF for those not receiving this at baseline are provided in the CS, along with a list of permitted concomitant therapies (AURORA Table B.2-4, p. 34; ADD other refs).

Intervention characteristics for AURORA 1 were the same as those used in the low dose (23.7mg) arm of AURA-LV. In AURORA 2, intervention characteristics were similar but different rules about dose modification were used to account for participants having received treatment for 1-year prior to the trial. All three trials permitted dose modification due to safety events, but in AURORA 2, participants receiving voclosporin with controlled UPCR could also receive a reduction in dose to 15.8mg (2 capsules, twice daily). [redacted] in each arm were receiving a reduced dose by the end of AURORA 2 ([redacted] in the voclosporin arm and [redacted] in the placebo arm), though [redacted] participants received a reduced dose due to UPCR being well controlled ([redacted] after two years of treatment). Compliance to voclosporin across trials was high (>99%).

Exposure to MMF and corticosteroids were provided by the company at clarification (A18). Exposure to MMF was [redacted]. Median exposure to oral prednisone [redacted].

The comparator to voclosporin for all three trials was a matching number of capsules containing a placebo. All other treatment details were the same as the intervention arm. Dose reductions in placebo were managed by altering the number of capsules administered.

Table 10: Intervention characteristics of the included trials

	AURORA 1		AURORA 2		AURA-LV		
Voclosporin and comparator	23.7 mg voclosporin (administered as three 7.9 mg capsules) BID	Matching placebo	23.7 mg voclosporin (administered as three 7.9 mg capsules) BID	Matching placebo	23.7 mg voclosporin (administered as three 7.9 mg capsules) BID	39.5 mg voclosporin (administered as five 7.9 mg capsules) BID	Matching placebo (three or five capsules BID)

	AURORA 1	AURORA 2	AURA-LV
Treatments administered to both arms	2g MMF daily Days 1&2: IV methylprednisolone once daily (0.25 – 0.5g according to weight) Day 3: Oral prednisone (20 - 25mg/day according to weight). Tapering to begin on subsequent days Week 16: Oral prednisone 2.5mg/day	2g MMF daily Days 1&2: IV methylprednisolone once daily (0.25 – 0.5g according to weight) Day 3: Oral prednisone (20 - 25mg/day according to weight). Tapering to begin on subsequent days Week 16: Oral prednisone 2.5mg/day	2g MMF daily Days 1&2: IV methylprednisolone once daily (0.25 – 0.5g according to weight) Day 3: Oral prednisone (20 - 25mg/day according to weight). Tapering to begin on subsequent days Week 16: Oral prednisone 2.5mg/day
Dose modification	Modification was permitted due to a decrease in renal function, increased blood pressure, or an abnormal heart rhythm.	After 1 year in AURORA 2 (i.e. 2 years of treatment), participants were permitted to reduce the dose of voclosporin to 15.8mg (2 capsules) provided UPCR was controlled. Dose modification was also permitted due to adverse events, included but not limited to those specified for AURORA 1.	Modification was permitted due to a decrease in renal function, increased blood pressure, or an abnormal heart rhythm.

Abbreviations: BID, twice daily; MMF, mycophenolate mofetil; mg, milligram; UPCR, urine protein/creatinine ratio

3.2.2.4. Outcomes

The outcomes reported in the trials are summarised in

Table 11. Outcomes measured consistently across trials were CRR, PRR, change in serum creatinine, urine protein, UPCR and eGFR, immunology parameters, and SELENA-SLEDAI (SLE disease activity). All trials also captured safety outcomes. AURA-LV measured a broader range of outcomes related to CRR and PRR, such as time to event outcomes and the rate of sustained response. In AURORA 1 and 2, these outcomes were replaced by measures specific to UPCR. HRQoL was measured in AURORA 1 and 2; both trials measured generic HRQoL using the SF-36, while AURORA 1 also reported disease-specific HRQoL using the Lupus Pro measure.

The EAG concluded that the definitions of CRR and PRR used within the trials were clinically relevant. Data for each of the outcomes making up the composite CRR outcome were provided by the company for AURORA 1, and were provided for AURORA 2 and AURA-LV at clarification. EULAR/ERA-EDTA (2019) guidelines note that proteinuria and serum creatinine in particular are strongly associated with long-term kidney outcomes, and that treatment should aim for ≥25% reduction in proteinuria at 3 months, ≥50% at 6 months and complete renal response (<500–700 mg/day) at 12 months. Thresholds for change in UPCR used by the company were therefore considered to be predictive of longer-term outcomes. On the whole, advice to the EAG was that smaller changes in renal response7 outcomes are generally considered to be unreliable, due to natural fluctuation in measurements over time.

The EAG noted that the company varied the threshold at which safety events were reported across trials, and that this variation was not justified by the company, pre-specified in trial protocols, or tied to the sample size:

- AURORA 1: TEAEs at ≥4%, serious TEAEs at ≥2 patients; TEAEs leading to discontinuation or dose modification at ≥2%; no threshold for all others.
- AURORA 2: TEAEs at ≥3%, serious TEAEs at ≥2%; no other thresholds
- AURA-LV: TEAEs at ≥5%; serious TEAEs at ≥2 patients, TEAEs leading to discontinuation at ≥2%.

A different threshold for AEs was also used in the company model (grade 3 or 4 AEs were included where these were reported by ≥1% of participants). Variation in reporting thresholds across outcomes and trials is an indication of reporting bias (see Section 0), as it may occlude events and patterns in events across trials. In this case, the EAG were concerned that variation

in threshold was occluding AE events that were high severity but low incidence; however, the EAG did not identify evidence of this from the trial CSRs.

Table 11: Outcomes measured by the included trials

	AURORA 1 Final follow-up: 1 year	AURORA 2 Final follow-up: 2 years	AURA-LV Final follow-up: 1 year	Pooled analysis of AURORA 1 and AURA-LV
CRR, defined as all the following: • 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 • no more than 10 mg prednisone equivalent per day for ≥3 consecutive days or for ≥7 days in total during final 8 weeks	✓	✓	✓	✓
Time to CRR	×	×	✓	×
Duration of CRR	×	×	✓	×
PRR, defined as 50% reduction in UPCR from baseline	✓	✓	✓	✓
Time to PRR	×	×	✓	×
Duration of PRR	×	×	×, though measured	×

	AURORA 1 Final follow-up: 1 year	AURORA 2 Final follow-up: 2 years	AURA-LV Final follow-up: 1 year	Pooled analysis of AURORA 1 and AURA-LV
			'sustained' PRR	
Reductions in UPCR	✓	×	×	✓
Time to reductions in UPCR	✓	×	×	✓
Duration of reductions in UPCR	✓	×	×	×
Change in serum creatinine, urine protein, and eGFR from baseline	✓	✓	✓	×
Change from baseline in immunology parameters (complement 3 (C3), C4, and anti-ds DNA) at weeks 24 and 52	✓	✓	✓	×
Renal flares	✓	✓	×	×
Extra-renal flares	×	✓	×	×
Generic HRQoL (SF-36)	✓	✓	×	×
Disease specific HRQoL (LupusPRO)	✓	×	×	×

	AURORA 1 Final follow-up: 1 year	AURORA 2 Final follow-up: 2 years	AURA-LV Final follow-up: 1 year	Pooled analysis of AURORA 1 and AURA-LV
SLE disease activity (SELENA-SLEDAI)	✓	✓	✓	×
Safety	✓	✓	✓	×
Subgroup analyses conducted (including age, gender, race, biopsy class, region, MMF use at baseline)	✓	×	✓	✓

Abbreviations: AE, adverse event; CRR, complete renal response; eGFR, estimated glomerular filtration rate; g, gram; MMF, mycophenolate mofetil; PRR, partial renal response; SAE, serious adverse event; UPCR, urine protein/creatinine ratio

^ provided at clarification at request of the EAG

3.2.2.5. Critical appraisal of the design of the studies

The company provided quality assessment ratings of the included trials using the critical appraisal checklist recommended by NICE, [13]. Although this is an acceptable tool, ratings presented by the company did not include consideration of how risk of bias may vary across outcome. Of relevance for the included trials, risk of bias ratings may vary between objective (e.g. clinical measures) and subjective outcomes (e.g. HRQoL), and risk of bias may be greater for some outcomes due to specific issues with their measurement. The company's ratings were reported in Section B.25 of the CS.

The EAG agreed with most of the ratings provided by the company, but considered there were some items of note:

- All trials were described as double-blind, and the company stated that patients, clinicians and all trial personnel were blinded to treatment allocation throughout the trials. It was unclear to the EAG which of the trial personnel were un-blinded, and therefore preventing the trials from being characterised as triple blind. On the whole, the EAG did not consider any lack of blinding to affect the measurement of most trial outcomes, though (depending on which personnel were not blinded and their role), this could affect subjective outcomes such as the two measures of HRQoL.
- The EAG did not consider that the company appraisal had sufficiently considered the impact of drop-out between AURORA 1 and AURORA 2 on the randomisation process of AURORA 2. As AURORA 2 was conducted as a separate trial to AURORA 1, and participants who started treatment in AURORA 1 but discontinued prior to AURORA 2 were not included in analyses of AURORA 2, this breaks the randomisation process. Few baseline characteristics were reported to determine the comparability of participants remaining in AURORA 2 across trial arms, and while reasons for discontinuation appeared comparable across arms, the EAG nevertheless considered the break in randomisation to be a high risk of bias in AURORA 2. Absolute rates of clinical outcomes were considered to be at particular risk of bias, though the EAG did not have evidence to confirm that relative effects would be stable once participants choosing to discontinue treatment were removed from the analysis. The EAG further noted that the company's response to the item on whether prognostic characteristics for AURORA 2 were balanced across arms was irrelevant and did not address the issue.
- The EAG were unclear why thresholds for reporting safety events varied across trials, when these were not explained, pre-specified in trial protocols, or appeared to be connected to

sample size. Changing thresholds across trials and/or outcomes is a signal of reporting bias, as thresholds may be changed to occlude patterns in the data. However, the EAG inspected the original safety data in the trial CSRs and did not identify any clear pattern of effect of concern.

- Sample sizes for AURORA 1 and AURA-LV were powered for the primary outcome only, which meant that it was not possible for the company to detect a reliable difference in effect on outcomes requiring greater power (e.g. those with low event rates), or to detect variation in effect across subgroups. AURORA 2 included only those participants who chose to continue from AURORA 1, and due to a high level of attrition at this time, AURORA 2 was under-powered for all its analyses.

3.2.3. Description and critique of the results of the studies

3.2.3.1. Clinical effectiveness results

Clinical effectiveness data for key outcomes from the included trials are shown in Table 12.

Renal response outcomes

Participants in both arms of the included trials experienced CRR, though the rate of CRR was higher for those receiving CRR across the trials. The breakdown in the composite outcome for CRR showed that voclosporin was beneficial for all outcomes, but the biggest effect was shown for proteinuria. This is exemplified by data from AURORA 1 showing that more than two thirds of those in the placebo arm met the required CRR criteria for eGFR and the use of rescue medication and prednisone, but only 23% of them also showed the required reduction in UPCR. A larger effect of voclosporin for proteinuria is consistent with voclosporin having an additional independent mechanism for reducing proteinuria in addition to its immunosuppressant mechanism. Clinical advice to the EAG was that both mechanisms – an improvement in kidney functioning as shown across outcomes of the CRR composite, and an independent reduction in proteinuria – would be beneficial for kidney function. Proteinuria is also a validated prognostic marker of longer-term kidney functioning.[7] However, clinical advice also cautioned that a reduction in proteinuria that does not result in disease modification may result in a corresponding level of nephrotoxicity.

There were limited data concerning the time to response, but some data from AURA-LV (time to response) and AURORA 1 (time to UPCR ≤0.5mg/mg) suggested that voclosporin may also lead to an earlier renal response, though this varied from a difference of weeks in AURA-LV to

days in AURORA 1. Clinical advisors to the EAG were uncertain whether this difference would be of clinical benefit to patients, noting that this may be the case for some participants who are experiencing a rapid decline in kidney function prior to treatment. There was a paucity of data concerning the duration of response; though on the whole, the EAG considered that the evidence did not demonstrate that duration of effect would differ between arms. In both arms of AURORA 2, the number of participants in CRR reduced between years 1 and 3, suggesting that participants began to relapse. However, the EAG also noted that the relative effect of voclosporin for CRR fluctuated in magnitude over the follow-up of AURORA 2, which may be consistent with the fluctuating nature of LN. Independent PRR data was not reported for AURORA 2 or AURA-LV, and were not calculable by the EAG on the data provided, but at clarification [A9] the company provided independent PRR data for AURORA 1. These data showed that amongst participants who did not achieve a CRR within 1 year, more participants in the voclosporin arm exhibited a PRR, though these effects were not statistically significant. Overall, the EAG concluded that the primary advantage of voclosporin was that people with LN may be more likely to achieve a renal response than with MMF and immunosuppressive treatment alone.

Renal relapse/flares

Data from AURORA 2 did not show a difference in the risk of renal flares up until end of the trial. The EAG concluded that these data suggested that those additional participants in the voclosporin arm who achieved a CRR were not more likely to relapse within 3 years of starting treatment. However, clinical advice to the EAG was that this follow-up is nevertheless still short for determining the long-term impact of renal response, including the nature and impact of relapse.

Table 12: Trial outcomes for renal response

		AURORA 1 Final follow-up: 1 year		AURORA 2 Final follow-up: 2 years		AURA-LV Final follow-up: 1 year	
	VCS (N=179)	**Placebo (N=178)**	**VCS (N=116)**	**Placebo (N=100)**	**VCS (N=89)**	**VCS high dose (N=88)**	**Placebo (N=88)**
CRR							
CRR	Week 24 32.4% OR 2.23 (1.3, 3.7)*	Week 24 19.7%	18 months [redacted]	18 months [redacted]	Week 24 32.6% OR 2.03 (1.01, 4.05)*	Week 24 27.3% OR NR	Week 24 19.3%
	Week 52 73 (40.8%) OR 2.65 (1.6, 4.3)*	Week 52 40 (22.5%)	24 months [redacted]	24 months [redacted]	Week 48 49.4% OR 3.21 (1.68, 6.13)*	Week 48 39.8% OR 2.10 (1.09, 4.02)*	Week 48 23.9%
			30 months [redacted]	30 months [redacted]			
			36 months [redacted]	36 months [redacted]			
Time to CRR	-	-	-	-	Median time: 19.7 weeks (16.1, 36.1) HR 2.26 (1.45, 3.51)*,≠	Median time: 23.4 weeks (13.7, 33.4) HR 2.25 (1.46, 3.47)*,≠	Median time: NR
Sustained CRR	-	-	-	-	[redacted]	[redacted]	[redacted]
Duration of CRR	-	-	-	-	[redacted]	[redacted]	[redacted]
Composite of CRR							
UPCR ≤ 0.5 mg/mg	52 weeks 81 (45.2%) OR 3.11 (1.9, 5.0)*	52 weeks 41 (23.0%)	[redacted]	[redacted]	[redacted]	[redacted]	NR

		AURORA 1 Final follow-up: 1 year		AURORA 2 Final follow-up: 2 years		AURA-LV Final follow-up: 1 year	
			[redacted]	[redacted]			
			[redacted]	[redacted]			
			[redacted]	[redacted]			
eGFR of ≥60 ml/min/1.73^2 or no confirmed eGFR decrease of >20% from baseline	52 weeks 147 (82.1%) 1.50 (0.9, 2.5)	52 weeks 135 (75.8%)	[redacted]	[redacted]	[redacted]	[redacted]	NR
			[redacted]	[redacted]			
			[redacted]	[redacted]			
			[redacted]	[redacted]			
Received no rescue medication for LN	52 weeks 163 (91.1%) 1.62 (0.8, 3.2)	52 weeks 154 (86.5%)	[redacted]	[redacted]	[redacted]	[redacted]	NR
Did not receive > 10 mg/day prednisone for ≥ 3 consecutive days or for ≥ 7 days in total during Weeks 44 through 52	52 weeks 156 (87.2%) 1.26 (0.7, 2.3)	52 weeks 152 (85.4%)	[redacted]	[redacted]	[redacted]	[redacted]	NR
PRR							

		AURORA 1 Final follow-up: 1 year		AURORA 2 Final follow-up: 2 years		AURA-LV Final follow-up: 1 year	
PRR (all patients who achieved a PRR)	24 weeks 126 (70%) OR 2.43 (1.56, 3.79)*	24 weeks 89 (50%)	18 months [redacted]	18 months [redacted]	24 weeks 69.7% OR 2.33 (1.26, 4.33)*,≠	24 weeks 65.9% OR 2.03 (1.10, 3.76)*	24 weeks 49.4%
	52 weeks 125 (70%) 2.26 (1.45, 3.51)*	52 weeks 92 (52%)	24 months [redacted]	24 months [redacted]	48 weeks NR	48 weeks NR OR 2.68 (1.43, 5.02)*,≠	48 weeks NR
			30 months [redacted]	30 months [redacted]			
			36 months [redacted]	36 months [redacted]			
PRR (patients who only achieved a PRR; i.e. did not achieve a CRR during follow-up)^	[redacted]	[redacted]	NR	NR	NR	NR	NR
Time to PRR	-	-	-	-	Median time: 1.3 weeks (2.6, 5.9) HR 1.63 (1.16, 2.27) *,≠	Median time: 4.4 weeks (4.1, 6.1) HR 1.74 (1.25, 2.43) *,≠	Median time: 6.6 weeks (4.6, 8.6)
Additional outcomes							
Time to UPCR of ≤0.5 mg/mg	Median 169 days HR 2.0 (1.5, 2.7) 64.8% of patients reached this at some point	Median 372 days 43.8% of patients reached this at some point	-	-	-	-	-
Time to 50% reduction in UPCR from baseline	Median 29 days 96.6% HR 2.05 (1.6, 2.6)*	Median 63 days 75.8%	-	-	-	-	-

		AURORA 1 Final follow-up: 1 year		AURORA 2 Final follow-up: 2 years		AURA-LV Final follow-up: 1 year	
Duration of UPCR of ≤0.5 mg/mg	Mean 163.3 days (1, 356)	Mean 158.8 days (1, 358)	-	-	-	-	-
Flares							
Renal flares (after achieving a UPCR of ≤0.7 mg/mg)	[redacted]	[redacted]	[redacted]	[redacted]	-	-	-
			[redacted]	[redacted]			
			[redacted]	[redacted]			
Extra-renal flares	-	-	[redacted]	[redacted]	-	-	-
			[redacted]	[redacted]			
			[redacted]	[redacted]			
			[redacted]	[redacted]			

Abbreviations: AE, adverse event; CRR, complete renal response; eGFR, estimated glomerular filtration rate; g, gram; HR, hazard ratio; MD, mean difference; MMF, mycophenolate mofetil; OR, odds ratio; NR, not reported; PRR, partial renal response; SAE, serious adverse event; UPCR, urine protein/creatinine ratio; VCS, voclosporin

Notes: * statistically significant (i.e. p value <0.05); ^analysis requested by the EAG; ≠ compared with placebo

Source: CS; clarification response [A7]

Health-related quality of life

HRQoL data as assessed using SF-36 were reported in appendices to the CS (Appendix N2), though disease –specific HRQoL data measured by Lupus Pro were not reported. Data from AURORA 1 were provided to the EAG by the company within the trial CSR, though this was not the case for AURORA 2, as while the trial CSR was provided, the accompanying data tables were not. The data for AURORA 1 showed that there was no difference in HRQoL between treatment arms at any timepoint, as measured using SF-36

and LupusPro. Change in HRQoL showed that there was a mean increase in HRQoL in both trial arms, though this was highly variable across the trial sample. The company reported that there was also no difference in HRQoL between treatment arms in AURORA 2. Clinical advice to the EAG was that it is plausible that people can experience a response to treatment that is clinically meaningful to their condition without showing a corresponding benefit in HRQoL. This is because the impacts of active disease and receiving immunosuppressive treatment can be detrimental to HRQoL, and improvements in HRQoL may not be seen until a response is stable and people have been withdrawn from treatment.

Additional clinical outcomes of interest

There was no difference in SLE disease activity between trial arms.

	AURORA 1 **Final follow-up: 1 year**		**AURORA 2** **Final follow-up: 2 years**		**AURA-LV** **Final follow-up: 1 year**		
	VCS (N=179)	Placebo (N=178)	VCS (N=116)	Placebo (N=100)	VCS (N=77)	VCS high dose (N=82)	Placebo (N=79)
SELENA-SLEDAI	Week 24 Mean change: -4.5 (5.4, -3.7) MD: -0.5 (-1.6, 0.6)	Week 24 Mean change: -4.1 (-5.0, -3.2)	[redacted]	[redacted]	Week 24 Mean change (range): -6.3 (5.86; -25, 6)*	Week 24 Mean change (range): -7.1 (7.41, -26.10)*	Week 24 Mean change (range):-4.5 (7.09, -26.12)
	Week 52 Mean change -6.0 (-6.7, -5.2)	Week 52 Mean change -5.5 (-6.3, -4.7)			Week 48 Mean change (range):-7.9 (6.39, -25.8)*	Week 48 Mean change (range): -8.3 (6.93, -26.6)*	Week 48 Mean change (range): -5.3 (6.85, -28.8)

	AURORA 1 **Final follow-up: 1 year**		**AURORA 2** **Final follow-up: 2 years**		**AURA-LV** **Final follow-up: 1 year**		
	MD: -0.5 (-1.4, 0.4)						

Abbreviations: MD, mean difference; VCS, voclosporin

Pairwise meta-analyses

The company presented pooled data for AURORA 1 and AURA-LV for a limited set of outcomes up to 1 year, using participants from AURA-LV who received the low (target) dose of voclosporin. Generally speaking, pooled analyses are preferred data as they draw upon a larger body of evidence, and have greater statistical power for conducting sensitivity analyses. However, few outcomes were considered within the pooled analysis, and therefore these data were considered by the EAG alongside the data from each of the included trials. Subgroup analyses from the pooled data were not provided in the CS, but were included in a confidential document submitted by the company with the CS (Aurinia Pharmaceuticals data on file, 2021).[14]

The results of the pairwise meta-analyses for CRR are shown in Table 13. The results were generally consistent with those reported for the individual trials. Data for change in eGFR and serum creatinine were discussed in a confidential file provided to the EAG by the company, but the tables containing the data were not accessible.

Table 13: Results of the pairwise meta-analyses

	Voclosporin	**Placebo**
CRR	24 weeks: 31.7% OR 2.01 [redacted]^* 52 weeks:43.7% OR 2.76 [redacted]^*	24 weeks: 20.3% 52 weeks: 23.3%
PRR	24 weeks: 70.1% OR 2.42 [redacted]52 weeks: 69.4% OR 2.26 [redacted]	24 weeks: 49.8% 52 weeks: 50.6%
≥50% UPCR reduction	52 weeks: 93.7% Median time to reduction: 29 days HR 1.96 [95% CI [redacted]	52 weeks: 75.2% Median time to reduction: 58 days
UPCR ≤0.5mg/mg	[redacted]	[redacted]
Change in UPCR	[redacted]	[redacted]

Abbreviations: CRR, complete renal response; HR, hazard ratio; NE, not estimable; OR, odds ratio; PRR, partial renal response; UPCR, urine protein/creatinine ratio

^ compared to placebo; *statistically significant at p<.05

Source: CS, clarification response [A17], and additional confidential data provided by the company[14]

3.2.3.2. Subgroup analyses

All subgroup analyses conducted by the company evaluated whether rates of CRR varied across population subgroups. Due to a formatting issue in the CS, at clarification the EAG requested that the company re-submit all subgroup and covariate analyses with their response [A14] to ensure completeness. In addition, the EAG expressed an interest in further subgroup analyses to explore the effect of previous MMF treatment at screening on the treatment effect (for example across additional outcomes, and/or using data from AURORA 2 [A15]). Finally, the EAG requested the company conduct a subgroup analysis limited to centres within Europe [A16]. The company re-submitted the subgroup analyses for CRR from AURORA 1 and AURA-LV, and conducted the requested analysis within European centres. The company did not expand their choice of analyses to explore variation in effect according to MMF use at baseline.

Overall, subgroup analyses showed that participants receiving voclosporin had a greater chance of achieving a CRR than those in the placebo arm across all population subgroups. The EAG noted some variation in the magnitude of effect across groups, though in most cases this was inconclusive, and due to limitations in statistical power the EAG did not draw firm conclusions about variation in effect across these populations. However, the EAG did note that the subgroup analyses appeared to show a smaller effect of voclosporin amongst White participants and those in Europe. There is evidence that people with LN from certain minority ethnic groups have an increased likelihood of having a more aggressive course of LN, which may explain the smaller effect in White trial participants. However, there was no further evidence to consider this further.

In addition, the EAG noted a difference in the magnitude of effect according to whether participants were receiving MMF at baseline in AURORA 1 or AURA-LV. In those receiving MMF at baseline in AURORA 1, [redacted] of those receiving voclosporin achieved a CRR compared to only [redacted] in the placebo arm; however in those not receiving MMF at baseline, rates of response were [redacted] ([redacted] in the voclosporin arm and [redacted] in the placebo arm). However, in AURA-LV, rates of response were greater in the voclosporin arm regardless of MMF use at baseline, and in contrast to the AURORA 1 data, a larger treatment effect was noted amongst those not receiving MMF at baseline. Pooling of the two data points generated a pooled effect consistent with the AURORA 1 findings, but given the unexplained heterogeneity between the two trials, the EAG were concerned about the validity of the pooled estimate. Neither the company nor the EAG were able to explain the conflicting findings. At clarification

[A15], the company suggested the difference in effect between those receiving and not receiving MMF at baseline was due to random variation, and therefore not indicative of a true difference in effect. The EAG accepted that random variation may explain the large difference in effect in both trials, and the conflicting findings between trials, but did not consider that other causes had been satisfactorily explored. For example, as noted in Section 3.2.2.2, the company did not collect data about previous treatments received by participants, and while all participants receiving MMF at baseline were receiving this for the treatment of LN (confirmed by the company to CQ 15), they did not collect information about the length of time they had been receiving it. It was therefore not possible for the EAG to compare whether the trial samples differed in their use of MMF at baseline. Clinical advice to the EAG was that a different magnitude of response might be seen between those who had only recently started MMF, and those who had received MMF for some time and who had not achieved a response or had relapsed. As noted in Section 3.2.2.2, the EAG also considered it plausible that samples differed in characteristics that were unmeasured at baseline, such as those related to disease prognosis. A clinical advisor to the EAG considered it more likely that treatment with voclosporin would have a greater effect at the first-line, as at subsequent lines there may be greater resistance to response in the population. This view may support the findings from AURORA 1, where a greater rate of CRR was seen in those not receiving MMF at baseline who received placebo ([redacted] vs. [redacted] amongst those already receiving MMF), and so explains why the relative benefit of voclosporin was not statistically different. However, the EAG's other advisor did not consider there was yet sufficient evidence to determine why rates of CRR appeared to differ according to MMF use at baseline. Overall, the EAG considered it plausible but uncertain that the magnitude of treatment effect for voclosporin may vary according to the way it is used. This uncertainty is covered by Key Issue 7.

3.2.3.3. Adverse effects

Safety data were presented by the company for each of the included trials within the CS, though rates of serious treatment-related TEAEs were re-submitted by the company at clarification (Section C) due to an error in the CS. The EAG considered that safety data presented for AURORA 1 were the most reliable: safety data from AURORA 2 were considered to be flawed as they do not include participants from AURORA 1 who chose not to continue with the trial; data from AURA-LV were affected by a potential imbalance in disease characteristics and treating centre, which a panel concluded may have contributed to the high mortality rate in the low-dose arm. [12]

The evidence did not show that the addition of voclosporin resulted in an unacceptable rise in safety events: while treatment-related adverse events were reported in the voclosporin arm, there was no difference in the number of serious adverse events. Moreover, while acknowledging the limitations in the AURORA 2 data, treatment–related AEs were comparable between arms by the end of AURORA 2, supporting the company's claim that these events were temporary and/or treatable.

Voclosporin appears to be associated with an increased risk of gastrointestinal and skin disorders, and a higher risk of hypertension, which may be of interest given the increased risk of cardiovascular disorders amongst people with SLE. Notably however, there was no increase in the risk of infections within the trials. As noted in Section 3.2.2.4, the EAG did not consider the follow-up of the trials to be sufficient to conclude whether voclosporin was associated with an increased risk of malignancy. Paradoxically, the EAG noted that voclosporin was associated with an increased risk of a decline in kidney function, including GFR decreases, renal impairment, and proteinuria. This is a known risk associated with prolonged use of CNIs, and clinical advisors to the EAG suggested that people with LN receiving voclosporin should receive similar monitoring for kidney function as those who receive treatment with other CNIs.

Table 14: Key safety data for voclosporin across all included trials

	AURORA 1		AURORA 2		AURA-LV		
	VCS (n=178)	Control (n=178)	VCS (n=116)	Control (n=100)	VCS low dose	VCS high dose+	Control
Any AE	162 (91%)	158 (88.8%)	[redacted]	[redacted]	82 (92.1)	85 (96.6)	75 (85.2)
Any serious AE	37 (20.8)	38 (21.3)	[redacted]	[redacted]	25 (28.1)	22 (25.0)	14 (15.9)
AE leading to discontinuation	20 (11.2)	26 (14.6)	[redacted]	[redacted]	16 (18.0)	14 (15.9)	9 (10.2)
AE leading to dose adjustment	80 (44.9)	47 (26.4)	[redacted]	[redacted]	48 (53.9)	51 (58.0)	28 (31.8)
All cause death	0	3 (1.7)	[redacted]	[redacted]	10 (11.2)	2 (2.3)	1 (1.1)
Treatment-related AE	80 (44.9)	45 (25.3)	[redacted]	[redacted]	45 (50.6)	55 (62.5)	15 (17.0)
Serious treatment-related AE	8 (4.5)	8 (4.5)	[redacted]	[redacted]	4 (4.5)	7 (8.0)	1 (1.1)
Treatment-related AE leading to discontinuation	-	-	-	-	11 (12.4)	8 (9.1)	2 (2.3)
Treatment-related death	0	0	[redacted]	[redacted]	0 (0.0)	0 (0.0)	0 (0.0)
Any infections or infestation	115 (64.6)	101 (56.7)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Any gastrointestinal	83 (46.6)	61 (34.3)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
GFR decrease	43 (24.2)	15 (8.4)	[redacted]	[redacted]	27 (30.3)	27 (30.7)	12 (13.6)
Renal impairment	13 (7.3)	6 (3.4)	[redacted]	[redacted]	Acute renal failure: 5 (5.6)	Acute renal failure: 8 (9.1)	Acute renal failure: 0 (0.0)
Proteinuria	0 (0.0)	8 (4.5)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	AURORA 1		AURORA 2		AURA-LV		
Lupus nephritis	2 (1.1)	12 (6.7)	[redacted]	[redacted]	0 (0.0)	1 (1.1)	3 (3.4)
Anaemia	21 (11.8)	10 (5.6)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hypertension	36 (20.2)	15 (8.4)	[redacted]	[redacted]	15 (16.9)	16 (18.2)	8 (9.1)
Skin disorders	42 (23.6)	31 (17.4)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Neoplasm	[redacted]	[redacted]	-	-	[redacted]	[redacted]	[redacted]

Abbreviations: AE, adverse event; GFR, glomerular filtration rate; VCS, voclosporin

Source: CS, trial CSRs, and clarification response [Section C]

3.3. Critique of trials identified and included in the indirect comparison and/or multiple treatment comparison

The company identified a total of 17 trials to include in their network meta-analyses (NMAs), as well as an additional two trials providing 'non-essential' data on comparators. NMAs focused on CRR and PRR outcomes only, and thus trials not including these outcomes were excluded; moreover, base case NMAs excluded the two trials providing 'non-essential' data, which the EAG judged was appropriate as these comparators were not most relevant to the decision problem. Appraisals of the 19 trials were presented in CS Table B.5-22, in which summary judgments by risk of bias item were tabulated without justification. It is notable that 12 of the 17 key trials did not include blinding of providers, participants or outcome assessors; otherwise, risk of bias domains did not suggest any additional notable threats to validity.

The company undertook an assessment of heterogeneity in included trials. Key features relevant to assessing transitivity in NMAs related to variation in dosages of MMF, which was the reference treatment for all NMAs; six trials with exclusively Asian patients; variable length of follow-up; and outcome definitions for CRR and PRR. The last two points are considered in depth below.

3.3.1. Follow-up times

According to the CS, the longest available follow-up was included in analyses, with a maximum of two years and a modal follow-up time of six months; thus, AURORA-2 was excluded from NMAs (CS document B, p. 84). In the base case, all longest follow-ups were pooled, though it was not clear from the information provided exactly which follow-up points were used in the base case NMA, precluding a clear view as to the inconsistency of follow-up times across networks. This is a potential threat to transitivity if follow-up times are unbalanced over nodes in the evidence networks. A related issue arose from the digitization of curve data from two trials to include in NMAs. The choice of time points for digitization, and how this accounted for censoring where appropriate, created an additional source of ambiguity in the analysis.

3.3.2. Outcome definitions for CRR and PRR

Included trials defined CRR and PRR in a range of ways. As acknowledged in the CS (appendix D, p. 51), though most definitions of CRR included a proteinuria component, the stringency of this component (e.g. proteinuria of <0.5 g/day, or of <0.3 g/day) varied; and more recent trials included eGFR as part of CRR definitions. CRR definitions were tabulated in Table B.5-10. At

clarification, the EAG requested a similar tabulation for PRR definitions; this was presented as clarification Table 20. PRR definitions were considerably heterogeneous, including in the components included; for example, several trials defined PRR as response from baseline (e.g. in UPCR or proteinuria), whereas others defined PRR with respect to specific thresholds (e.g. urinary protein excretion).

While CRR and PRR definitions were broadly consistent within group in considering improvements in renal function, it was not clear that CRR and PRR definitions would be consistent enough to generate measures equivalent between studies in the effectiveness of included comparators. The company asserted in response to CQ A20 that clinical experts were consulted as to the similarity of definitions, and that the company regarded outcome definitions were similar across trials on the basis of inclusion of components such as assessment of proteinuria or UPCR. However, several trials used different combinations of renal function measures to assess PRR, so that even if the component measures included were similar, trials differed in the 'ways' patients could meet effectiveness thresholds.

This is important because it is a threat to transitivity in evidence networks. If a drug would appear more effective under one definition of CRR as compared to another definition but the favourable definition is more prevalent with respect to some nodes in the network as compared to others, then the resultant comparative effectiveness estimates will be biased in favour of the drug meeting an 'easier' threshold for effectiveness. However, the small number of trials relative to the number of nodes precludes any formal or qualitative investigation of this problem.

Relatedly, it is not obvious that CRR and PRR are ordinal outcomes, as might be expected. In response to CQ A23, the company notes that patients achieving CRR are not necessarily subsets of patients achieving PRR. This is a conceptual challenge to interpreting the results of included trials collectively and was reflected in the company's analytic strategy for the NMA.

3.3.3. Similarity of trial populations across the network

A final point relates to the distribution of effect modifiers across the network on the basis of the characteristics of patient populations in the included trials. First, and possibly most importantly, trials in the network include combinations of patients on first, second and third line treatment. This is not explicitly formalised in the table of characteristics for included trials, but it does mean that comparative effectiveness estimates may not be proper to a line of treatment, and if imbalanced over the network, lines of treatment may generate biased estimates of comparative

effectiveness. Moreover, the company acknowledges that a potential source of heterogeneity is the subset of trials enrolling exclusively Asian patients; however, it appears possible, if not likely, that disease characteristics are unequally distributed over the network. Presented in Table B.5-9 (CS Appendix D), the baseline characteristics of patients enrolled in NMA-included trials represent a wide variety of disease characteristics. The range of patients in biopsy class IV ranges from 0% to 100%, with many trials not reporting biopsy results. Demographically, the sex of patient samples ranges from 55% to 100% female. It is unclear how this would influence effectiveness estimates from NMAs.

3.4. Critique of the indirect comparison and/or multiple treatment comparison

3.4.1. Methods used to undertake NMAs

Network meta-analyses (NMAs) were undertaken using standard methods as described in TSD2. [15] CRR and PRR were modelled separately using a logit link, with standard Markov chain Monte Carlo methods implemented using Rstan. The company used generally appropriate and standard statistical methods to estimate both base case and scenario NMAs. Code and data supplied by the company were fully reproducible, and confirmed that the number of iterations used after burn-in was sufficient to achieve convergence for base case NMAs. As noted in Section 3.3.2, CRR and PRR were not regarded by the company to be ordinal outcomes and thus these outcomes were analysed separately. The EAG noted that even if an ordinal model was considered unsuitable, a multivariate NMA might have improved the stability of estimates. The company did not appear to consider this option. Missingness across included trials was also not discussed in sufficient depth to understand how this was addressed.

Fixed effects models and random effects models both used weakly informative priors for treatment effects. Random effects models additionally used an informative prior for between-study standard deviation (half normal with mean 0 and standard deviation 5). At clarification, the EAG questioned the choice of informative prior for between-study standard deviation; in response to CQ A22, the company specified that the source was an example used in TSD2 related to beta blockers, and that further informative priors were not considered. The EAG did not regard this was sufficient justification, especially given the availability of more plausible 'off the shelf' priors (from e.g. Turner (2015)). [16] The company did not present random effects models for base case NMAs, asserting that this was due to lack of convergence. However, this claim was not substantiated with respect to specific model diagnostics, and the EAG could not

trace where and to what degree the company detected evidence of non-convergence. Thus, the EAG presents random effects estimates alongside fixed effects estimates below. This is important as well because the heterogeneity in both NMAs suggests that a random effects model more appropriately reflects the included data.

Consistency checks did not reveal evidence of inconsistency in the PRR NMA; however, the company noted some evidence of inconsistency in the CRR NMA arising from a small trial providing direct evidence of the comparison between MMF and L-CYC. Because of the Bayesian framework used to undertake analyses, consistency was checked by comparing unrestricted mean effects models against the base case estimate. The EAG agreed that the evidence of inconsistency in the CRR NMA was ultimately not consequential enough to invalidate the model, as evidenced by DIC values that were approximately 3 points apart between the fixed effects and unrestricted mean effects models.

The company's critical appraisal of trials included in the NMA identified several issues with the included trials, including: a lack of information about whether appropriate methods for randomisation and allocation concealment were used; imbalance in prognostic factors across trial arms; and analyses not using an ITT approach. These issues are known to affect the reliability of treatment effects.

3.4.2. NMA results

Pairwise odds ratios for each comparator against MMF are presented below, both for the company's fixed effects model and the EAG's random effects model.

Findings from the fixed effects NMA (see Table 15) suggested that voclosporin with MMF is the only treatment statistically superior to MMF in achieving CRR. Pairwise odds ratios suggested that voclosporin with MMF was statistically superior to all comparators with the exception of azathioprine. Unsurprisingly, a random effects model generated substantially wider confidence intervals, though with qualitatively similar point estimates. Voclosporin with MMF was still the only treatment statistically superior to MMF in achieving CRR.

Table 15: Pairwise odds ratios vs MMF for CRR network meta-analysis

	Fixed effects OR (95% CrI)	Random effects OR (95% CrI)
VCS+MMF	[redacted]	[redacted]
AZA	[redacted]	[redacted]
H-CYC	[redacted]	[redacted]

	Fixed effects OR (95% CrI)	Random effects OR (95% CrI)
L-CYC	[redacted]	[redacted]
RTX+MMF	[redacted]	[redacted]
TAC	[redacted]	[redacted]
TAC+MMF	[redacted]	[redacted]
Model fit	Residual deviance 41.8, pD 24.3, DIC 66.1	Residual deviance 39.3, pD 27.7, DIC 67.0

Abbreviations: AZA = azathioprine; CrI = credible Interval; CRR = complete renal response; DIC = deviance information criterion; H-CYC = high-dose cyclophosphamide; L-CYC = low-dose cyclophosphamide; MPR = methylprednisolone; MMF = mycophenolate mofetil; OR = odds ratio; pD = parameters; PR = prednisolone; RTX = rituximab; TAC = tacrolimus; VCS = voclosporin

Source: CS Table B.2-31, EAG calculations

At clarification, the company disclosed that NMAs for PRR were incorrectly estimated due to data extraction errors. The revised estimates, presented in response to CQ A9, are presented below (see Table 16). Only rituximab with MMF was significantly better than MMF at producing PRR outcomes in the fixed effects NMA, with few meaningful differences between the remaining comparators in effectiveness. Unsurprisingly, estimates from the random effects NMA did not suggest any significant differences between any comparators in effectiveness.

Table 16: Pairwise odds ratios vs MMF for PRR network meta-analysis

	Fixed effects OR (95% CrI)	Random effects OR (95% CrI)
VCS+MMF	[redacted]	[redacted]
H-CYC	[redacted]	[redacted]
L-CYC	[redacted]	[redacted]
RTX+MMF	[redacted]	[redacted]
TAC	[redacted]	[redacted]
Model fit	Residual deviance 17.9, pD 15.2, DIC 32.3	Residual deviance 17.9, pD 16.5, DIC 34.4

Abbreviations: AZA = azathioprine; CrI = credible Interval; DIC = deviance information criterion; H-CYC = high-dose cyclophosphamide; L-CYC = low-dose cyclophosphamide; MPR = methylprednisolone; MMF = mycophenolate mofetil; OR = odds ratio; pD = parameters; PR = prednisolone; PRR = partial renal response; RTX = rituximab; TAC = tacrolimus; VCS = voclosporin

Source: Clarification Table 6, EAG calculations

Of note is that for both outcomes, random effects models suggested similar fit as compared to fixed effects models, especially as measured by the deviance information criterion (DIC). One approach would be to state that when two models have similar fit indices, the more parsimonious model should be chosen. However, the EAG regards that based on heterogeneity in outcome definition and follow-up time, there is a strong conceptual basis to prefer a random

effects model; and indeed, TSD3 notes that information criteria alone should not determine choice of model in the face of a conceptual rationale for model choice.

A range of scenario analyses were provided for both CRR and PRR outcomes, including restricting follow-up to six months or 12 months; excluding trials with a significantly different outcome definition; and excluding trials with 100% Asian populations (presented in CS Appendix D.1.1.4.1.9 for CRR, and in clarification responses for PRR). Results were qualitatively similar to base case NMAs.

3.5. Additional work on clinical effectiveness undertaken by the EAG

The EAG reproduced base case NMAs for CRR and PRR outcomes, including scrutiny of model diagnostics and results. The EAG were unable to consider alternative base cases using, for example, informative prior distributions for the between-study variance due to time and resource constraints.

3.6. Conclusions of the clinical effectiveness section

The EAG considered the clinical evidence to demonstrate that treatment with voclosporin + MMF is associated with an increased likelihood of renal response than treatment with MMF alone. There was a lack of reliable data for the effectiveness of tacrolimus + MMF, however evidence from the company's NMA appeared to demonstrate that voclosporin + MMF was more effective for renal response. Evidence from the clinical trials suggested that the addition of voclosporin to MMF did not increase rates of serious adverse events, though prolonged use of voclosporin may carry similar risks to kidney function as other CNIs. Within the trial follow-up, people receiving voclosporin + MMF did not show an improvement in HRQoL compared to those treated with MMF alone. If longer-term evidence demonstrated that voclosporin was associated with a higher rate of sustained response, clinical experts to the EAG considered that improvements in HRQoL may be seen later, following discontinuation from treatment.

There are several limitations with the trial evidence for voclosporin, including a chance but meaningful imbalance in the trial arms of AURA-LV, issues with the selection of participants in AURORA 2, and the lack of statistical power in the trials. While the EAG considered the length of trial follow-up to be acceptable for evaluating renal response, the trials were too short to detect the medium- to long-term implications of treatment, including the impact of treatment on CKD progression, and outcomes following discontinuation from voclosporin. The EAG also highlighted uncertainty about the generalisability of trial evidence to the way voclosporin would

be used in practice (Key Issue 7), and considered that the treatment effect may vary according to variation in the treatment pathway and the duration of treatment. The possibility of effect modification could not be explored within the clinical trials, and this issue was also present in the NMAs.

4. COST-EFFECTIVENESS

4.1. EAG comment on company's review of cost-effectiveness evidence

The company carried out a SLR, using a single search strategy, to identify existing cost-effectiveness evidence, HRQoL evidence, and cost and resource use evidence for voclosporin in LN. A summary of the EAG's critique of the methods implemented by the company to identify relevant evidence is presented in Table 17.

Table 17. Summary of EAG's critique of the methods implemented by the company to identify health economic evidence

Systematic review step	Section of CS in which methods are reported			EAG assessment of robustness of methods
	Cost-effectiveness evidence	HRQoL evidence	Cost and resource use evidence	
Searches	Appendix G	Appendix G	Appendix G	Search strategies by the company were provided in clarification [CQ B1]. The company literature searches were carried out in Proquest which we do not have access to so searches cannot be tested; several databases were searched together in one strategy which is not best practice, it is likely that the strategy may have missed some relevant papers. The cost effectiveness filter that was used does not appear to be a tested filter; [17] this makes the effectiveness of the search uncertain and it is possible that some relevant papers may have been missed. It appears as if the company conducted additional 'targeted' searches for evidence, including data relevant for input into the company model, however the details of these searches were not provided.
Inclusion criteria	Appendix G (Section G.1.1.1.1)	Appendix G (Section G.1.1.1.1)	Appendix G (Section G.1.1.1.1)	Inclusion criteria for the company's SLR were appropriate. Inclusion criteria for any targeted searches conducted by the company were not provided, though the EAG understands this included a search for data on re-transplantations rates (CQ B10) and a search for AE disutility values (though no such data were identified; CQ A5).

Systematic review step	Section of CS in which methods are reported			EAG assessment of robustness of methods
Screening	Appendix G (Section G.1.1.1.2)	Appendix G (Section G.1.1.1.2)	Appendix G (Section G.1.1.1.2)	Screening methods were described in full, and were conducted according to gold standard practice
Data extraction	Appendix G (Section G.1.1.1.3)	Appendix G (Section G.1.1.1.3)	Appendix G (Section G.1.1.1.3)	Data extraction was described in full, and was conducted according to gold standard practice
QA of included studies	Appendix G (Section G.1.1.1.4)	NA	NA	Quality appraisal of economic evaluations reported in full-text publications was conducted using the Drummond checklist, [18] as per best practice. The evidence submitted was consistent with the NICE reference case

Abbreviations: CQ, clarification question; CS, Company Submission; EAG, Evidence Assessment Group; HRQoL, health-related quality of life; NA, not applicable; QA, quality assessment

At clarification stage, the company confirmed that four published cost-effectiveness models and a cumulative cost analysis for LN were identified within its SLR, and that commonalities across these models were used by the company to inform the health states and the decision to build a Markov model to inform this submission (CQ B3). The EAG highlighted that only one of the identified studies considered a comparison of VCS+MMF to MMF, which is discussed further alongside the company's chosen model structure in Section 4.2.2 of this report.

Overall, the EAG was satisfied that the company's health economic SLR was broadly appropriate, and it is unlikely that any cost-effectiveness, cost and resource use, or HRQoL evidence that is directly related to this appraisal was not identified from the searches run. In spite of this, the EAG noted that various sources are used to populate the model that were not identified from the SLR, owing to model's use of data from a non-LN population for various input parameters (e.g., utility values and unit costs). These are discussed in turn in the relevant sub-sections of Section 4.2 of this report.

4.2. Summary and critique of company's submitted economic evaluation by the EAG

4.2.1. NICE reference case checklist

Table 18: NICE reference case checklist

Attribute	Reference case	EAG comment on company's submission
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers	✓ No comment
Perspective on costs	NHS and PSS	✓ No comment
Type of economic evaluation	Cost–utility analysis with fully incremental analysis	× The model only presents pairwise analyses not a fully incremental analysis and the EAG has considerable concerns with the chosen model structure
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	✓ No comment
Synthesis of evidence on health effects	Based on systematic review	× Utility obtained from one time point in the AURORA 2 study via mapping, though inappropriate analysis methods used. Dialysis and transplant utilities deemed unsuitable
Measuring and valuing health effects	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of health-related quality of life in adults.	✓ Health effects expressed as QALYs (although captured from SF-36 mapped to EQ-5D)
Source of data for measurement of health-related quality of life	Reported directly by patients and/or carers	× The approach taken although informed by patients within the AURORA-2 trial was analysed using methods inappropriate for decision making
Source of preference data for valuation of changes in health-related quality of life	Representative sample of the UK population	× Generalisability of data unknown as trial did not have any UK centres
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	✓ No comment

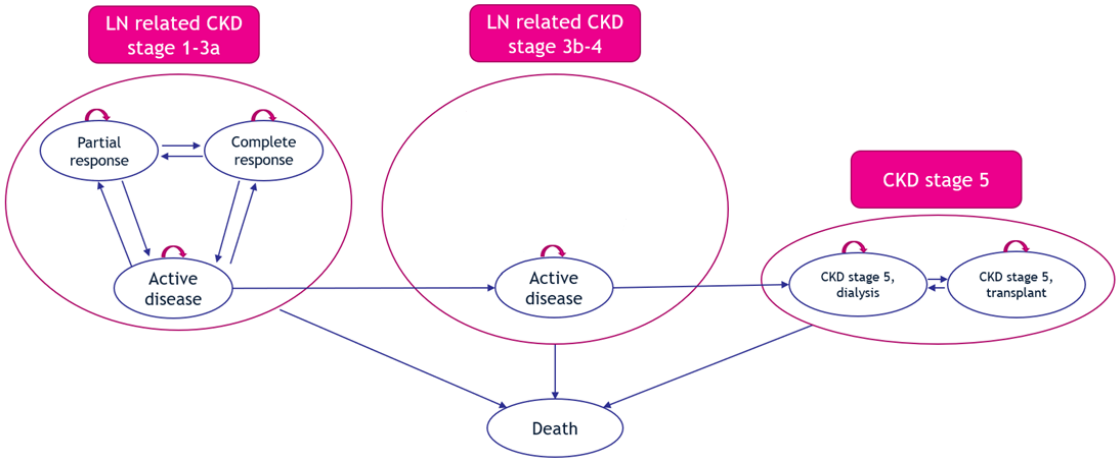
Attribute	Reference case	EAG comment on company's submission
Evidence on resource use and costs	Costs should relate to NHS and PSS resources and should be valued using the prices relevant to the NHS and PSS	✓ No comment
Discounting	The same annual rate for both costs and health effects (currently 3.5%)	✓ No comment

Key: EQ-5D, EuroQol 5 dimension; HRQoL: health-related quality of life; NHS, National Health Service; PSS, Personal Social Services; QALY: quality-adjusted life year; TA: technology appraisal

4.2.2. Model structure

The company developed a *de novo,* cohort-level state-transition Markov model to estimate the cost-effectiveness of voclosporin + MMF (VCS+MMF) versus placebo + MMF (referred to simply as 'MMF' henceforth) in adult patients with LN. A schematic of the submitted model is provided in Figure 1 (replicated based on Figure B.3-1 from the CS with health states removed which are not considered in the model base case).

Figure 1: Cost-effectiveness model structure (company base case)



Source: Adaptation of Figure B.3-1 in the CS, adapted to remove health states not considered in the model base case

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

In its submission, the company describes how its cost-effectiveness model structure was informed by previously published models (identified via SLR) due to no previously established NICE guidance concerning people with LN (CS Section B.3.2.2). Although the company states

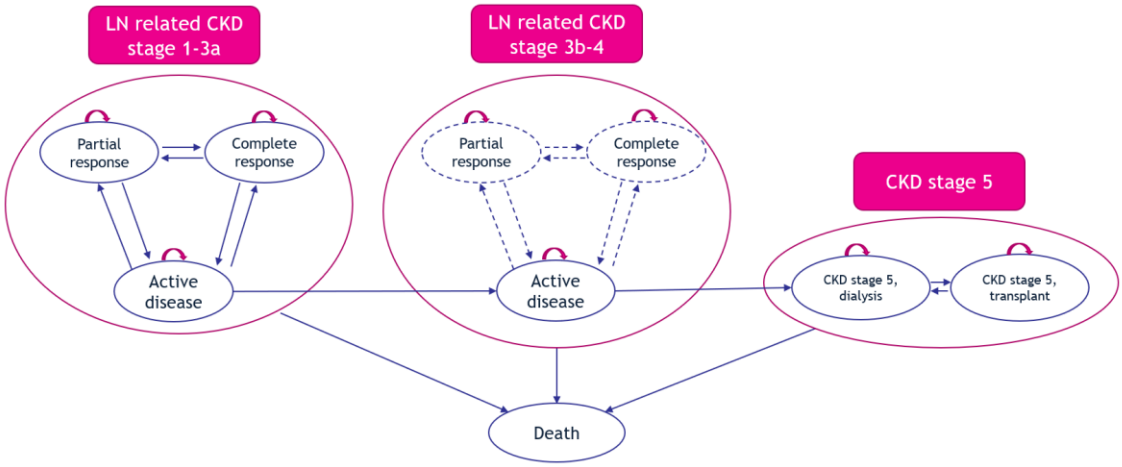
that its model is based on structures identified from studies identified via the SLR, the specific papers are not cited within the CS as to disclose which previously implemented models were used to inform this latest approach.

At clarification, the EAG highlighted the ICER report, to seek justification for the differences in modelling approaches between this paper and the structure used by the company (CQ B3). The company noted that the model in this report did not aptly consider CKD stages, consequently not capturing renal flares. Within a report by the Institute for Clinical and Economic Review (ICER) about its cost-effectiveness analysis of LN treatments, renal flares were included as a parameter and so were explicitly captured within the modelling; although patients receiving belimumab did experience fewer renal flares, the difference between the amount experienced between this arm and the placebo arm was not statistically significant. [19]

Consistent with the expected licence and use for VCS, people are assumed to enter the model in the CKD stage 1-3a active disease (AD) health state. Within CKD stage 1-3a, transitions between partial (renal) response (PR), complete (renal) response (CR) and active disease (AD) health states may occur, with movements between any of these states deemed possible. Importantly, people in either of the response states (i.e., PR or CR) must return to AD before they progress to CKD stage 3b-4 (see Figure 1 for the EAG's edited version of the company's model structure to illustrate non-zero transitions). Here, the EAG highlights the arrow connecting the two AD states, which illustrates that patients must progress through the AD states to move into CKD stage 3b-4.

Although not in the company's base case analysis, it is possible (in terms of model functionality) for patients to move between AD, PR, and CR states within CKD stage 3b-4 (see Figure 2 for the model-permitted transitions, including movements into CR and PR in CKD stage 3b-4 which are set to 0% in the company's base-case analysis and hence enabling this transition has no impact on cost-effectiveness results).

Figure 2: Cost-effectiveness model structure (provided by the company, including scenario analysis health states)



Source: CS Figure B.3-1, Section B.3.2.2.

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

Owing to the progressive nature of CKD, the company's base-case analysis does not permit movements from later stages to earlier stages of CKD. CKD stage 5 establishes health states by either use of dialysis or undergoing kidney transplant, in which the company have demonstrated that movements between the two may occur (e.g., patients could undergo transplant but then later require dialysis). People can die while in any model health state.

At clarification stage, the EAG raised concerns with the following features of the company's model structure:

- The recurrent transitions within CKD stage 5 in the model between dialysis and transplant health states given that patients have a 90% probability of receiving a kidney transplant within two years (CS Section B.3.3.2, Table B.3-5) (CQ Question B10)
- The movement (or lack thereof) between various health states within CKD stage 1-3a and stage 3b-4 (CS Section B.3.3.2.2, Table B.3-3) (CQ Question B8)
- The capturing of renal flares within the model (CS Section B.3.2) (CQ Question B4)

The EAG consideration of these features of the model are discussed in the sections that follow.

4.2.2.1. Dialysis and transplant

As described above, the company's model includes the possibility of patients requiring dialysis or undergoing kidney transplantation upon experience of CKD progression to stage 5. Both dialysis and kidney transplant are associated with substantial medical resource use costs, and by extension have important impacts on the overall modelled costs reflected by the company's model.

The company's model includes an estimated probability of undergoing kidney transplant which is equivalent to 90% of patients receiving a kidney transplant within two years from developing stage 5 CKD (estimate obtained from clinical opinion provided to the company). Based on these estimates, the company estimated a per-cycle probability of transplant for patients with CKD stage 5 receiving dialysis of 43.77%. A clinical advisor to the EAG indicated it may be feasible that LN patients could receive transplant more quickly than other patients requiring a transplant as LN patients tend to be relatively younger and fitter, and so would usually be considered more suitable candidates for transplant versus an all-comer population with stage 5 CKD. Despite this, advice from the EAG's clinicians indicated that 90% appeared high, and the EAG were advised that 65% per 2-years may be more reflective of practice. A value of 65% per 2-years translates to a per 6-month cycle rate of 23.08%.

An important feature of the Markov model structure is that it is possible for patients to incur the costs of several kidney transplants, as patients can move between the CKD stage 5 dialysis and transplant states repeatedly. The company noted this within its submission (Table B.3-5) and assumed 2.96% of transplant patients move to dialysis, after which they experience the same probability of transplant (i.e., 43.77% as described above). The EAG considered it unlikely that the transitions between dialysis and transplant in the model are reflective of UK clinical practice, principally owing to the memoryless property of the model as well as the fact that a subsequent transplant is associated with the same probability of occurring versus a first transplant.

The EAG believes that modelling transplants in this way could have been avoided by having a series of sub-models to track (some) event history, which patients could enter upon developing CKD stage 5. This could therefore avoid the 'memoryless' property of the originally imposed Markov model and avoid the possibility that patients may experience multiple transplants. Within the timeframe the EAG had to conduct its review, it was not possible for it to restructure the company's model to explore this further; however, the EAG conducted a sensitivity analysis to

limit patients to only one transplant to ascertain the impact on the ICER of reducing transplant rates in the model (see Section 6.2 for further details).

4.2.2.2. Health states within CKD stages 1-3a and 3b-4

People enter the model within CKD stage 1-3a and may progress from this stage to either death or CKD stage 3b-4. As previously noted, it is crucial to note that movement from PR and CR within the LN related CKD stage 1-3a health state to any sub-state within LN related CKD stage 3b-4 is impossible, i.e., it is only possible to progress to CKD stage 3b-4 if patients have AD due to initial structural decisions made by the company (further discussed in Section 4.2.6). Relatedly, patients cannot achieve a PR or CR from AD CKD stage 3b-4, as these transition probabilities are set to 0% in the company's base-case analysis (given that no patients in AURORA 1 or AURORA 2 developing CKD stage 3b-4 during the period of follow-up).

The EAG received clinical expert advice that it is possible for patients to progress from any health state within CKD stage 1-3a (i.e., AD, PR, or CR) to CKD stage 3b-4, rather than limiting this to only movements from CKD stage 1-3a AD to CKD stage 3b-4 AD. As with the inclusion of non-base case functionality between health states within CKD 3b-4, the EAG believe that it may be useful to include similar capabilities for transitions between all health states, despite the limited data from the AURORA 1 and AURORA 2 trials. After receiving clinical expert advice indicating that patients may be able to progress CKD stage without the presence of AD, the EAG requested justification for the inability to transition between CKD stages (CQ Question B8). The company acknowledged that a person must "*go through a period of disease activity in order for their kidney to accumulate damage*", which is in line with logic regarding how people experience renal flares (CQ Question B8 p.80).

With respect to achieving PR or CR from AD in the CKD stage 3b-4 state, the company chose to use a 'conservative approach' in the model on the basis of feedback from clinical experts that response is rare in patients who reach CKD 3b-4 (CS Section B.3.2.2, p.112). While the EAG acknowledges that there are no data from the AURORA 1 or 2 studies to populate these transitions, the EAG considered it plausible that a PR or CR could theoretically be achieved by patients in either arm, potentially as a result of subsequent therapy use. Therefore, by disabling these transitions, tied with the fact that the PR and CR states have a 'protective' property with respect to CKD progression, it may instead be the case that disabling these transitions introduces a bias in favour of VCS+MMF. However, owing to the paucity of evidence to determine response rates to subsequent therapies in a more advanced CKD population, the

EAG did not explore this feature of the model further, and on balance considered the fact that these transitions are set to 0% in the company's base-case analysis to be reasonable (yet still subject to uncertainty).

4.2.2.3. Capturing renal flares

Renal – and extra-renal – flares are mentioned on several occasions within the CS, included as an outcome specified in the final scope issued by NICE (CS Section B.2.2, Table B.2-1) and equally reported as a key secondary outcome (CS Section B.2.3.2.1, Table B.2-7).

Within the CS, renal flares and extra-renal flares are only reported as an efficacy outcome for the AURORA 2 trial as the follow-up data from AURORA 1 were deemed too short to be considered meaningful (CS Section B.2.6.2). Upon initial inspection of the CS, the EAG could not readily identify precisely how the company's model captures renal flares, therefore the EAG queried how the company captured flares within the model for the avoidance of doubt (CQ Question B4). The company did not clarify whether flares were captured in the model from the AURORA 1 trial; however, justification was provided for how flares were captured.

Based on clinical advice provided to the EAG, renal flares are recognised to be an important aspect of LN, reflecting a key aspect of the natural course of the disease. The CS explains that *"in order to be considered to have experienced a renal flare, patients must first achieve an adequate renal response"*, thus people experiencing renal flares are assumed to be a sub-population of the people with this adequate renal response (CS Section B.2.6.2.3, p.66). A number of patients in AURORA 1 and AURORA 2 were reported to have experienced flares in Table B.2-24 (CS Section B.2.6.2.3). Reporting of flares was limited in both AURORA 1 and AURORA 2, especially given that not all patients from AURORA 1 enrolled in AURORA 2, and so the EAG was unable to fully verify how accurately the company's model captures flares, but considered this an important limitation of the company's model (given the importance of flares in clinical practice).

4.2.3. Population

The population included within the model reflects the population of the AURORA 1 study. Although the company's model classifies patients in terms of CKD stage and renal response, patients must also have been experiencing LN classes III, IV and V or mixed classes of III/V and IV/V to meet the inclusion criteria of AURORA 1. The model does not explicitly capture LN class, but these classes would be expected to be referred to in NHS clinical practice in order for

patients to be deemed suitable candidates for treatment with VCS (in combination with MMF). Owing to the need to capture the downstream costs and effects associated with CKD progression, the EAG considered it appropriate to have not constructed model health state around LN class, but highlights for completeness that LN class is used in clinical practice but is not an explicit feature of the company's model.

Within the CS, the company clarifies that treatment using VCS + MMF should be considered for all active LN patients, *"including patients at initial diagnosis of LN, those with newly flaring disease (previously in remission), and those previously diagnosed but inadequately treated for LN"* (CS Section B.1.3.8, p.26). Patients enrolled in the AURORA 1 study were screened for LN both with and without prior MMF use, and those who experienced successful treatment could progress into the subsequent AURORA 2 follow-on 2-year trial. Approximately 60.5% of patients enrolled in AURORA 2 after completing AURORA 1 (see Section 3.2.2). All patients entered the economic model with CKD stage 1-3a. The model base case was informed using the combined AURORA 1 and AURORA 2 population using data across 36-months. The use of data from both studies is discussed further in Section 4.2.6, and prior use of MMF highlights a key issue for this appraisal concerning the positioning of VCS+MMF in NHS practice (see Section 1.6, Key Issue 7).

4.2.4. Interventions and comparators

The intervention considered, VCS, is described in the CS as being used in combination with background immunosuppressive therapies. At clarification stage, the company confirmed that the licensed indication for VCS will likely restrict background immunosuppressive therapies to MMF specifically, in line with the use of VCS in AURORA 1 and AURORA 2. The cost-effectiveness model considered VCS + MMF as the intervention and as such, the model is therefore aligned with both the AURORA 1 and AURORA 2 trials as well as the anticipated marketing authorisation for VCS.

VCS is administered as 7.9 mg oral tablets (capsules), dispensed in pack sizes of 180. Patients require six capsules daily to achieve a total daily dose of 47.4 mg. Dosing within the cost-effectiveness model is aligned with that of the AURORA 1 and AURORA 2 trials.

In combination with VCS, patients receive MMF (also orally administered). Within the AURORA 1 trial, for patients who had not previously received MMF prior to randomisation, 1 g/day would be administered initially, increasing to 2 g/day starting from day 8. Conversely, for patients who

had been taking MMF prior to the commencement of AURORA-1, a dose of 2g/day was administered. In AURORA 1, 54.9% of patients had experienced prior MMF use at screening. The company's cost-effectiveness model differs from the clinical trial dosing with regard to MMF dosing, as MMF is assumed to be dosed at 2.5g/day irrespective of prior use.

The final scope for the appraisal outlined that several treatments should be considered comparators to VCS:

- MMF
- Cyclophosphamide
- Azathioprine
- Rituximab
- A calcineurin inhibitor + MMF

The CS stated that MMF was regarded as the most commonly used initial therapy, however all comparators listed in the final scope were incorporated into the cost-effectiveness analysis. The company submission compared VCS + MMF with seven comparator regimens:

- MMF
- Low-dose cyclophosphamide
- High-dose cyclophosphamide
- Azathioprine
- Rituximab + MMF
- Tacrolimus + MMF
- Tacrolimus

Clinical advice to the EAG emphasised that MMF was the primary treatment used in current clinical management of LN. Clinicians highlighted that rituximab and tacrolimus are occasionally used if the patient is pregnant or contemplating pregnancy.

To inform the cost-effectiveness analysis, trial data were used to inform several inputs for VCS+MMF and MMF. For other comparators, an NMA was conducted to compare VCS+MMF to other relevant comparators included within the final scope due to a lack of direct evidence for each of these comparators versus VCS+MMF (see Section 3.4).

4.2.5. Perspective, time horizon and discounting

The company's model adopts an NHS and PSS perspective on costs and outcomes, discounted at 3.5% per annum in line with the NICE methods manual.[9] The model output refers to QALYs, LYs and pairwise ICERs for VCS+MMF versus each comparator. Overall, the EAG were satisfied that the perspective adopted, and discounting applied are aligned with the NICE reference case.

The model calculates costs and outcomes over 72 years, which is considered to be a 'lifetime' horizon. The company justify the use of 72 years as based on the extrapolated outcomes, it is the point at which <0.1% of patients are alive. With a mean starting age of patients being 33.2 years (based on the average from the AURORA-1 study),[20] this equates to a maximum age within the model of 105.2 years. The EAG therefore considered a 72-year time horizon to be sufficiently reflective of the lifetime of patients.

The company applied a 6-month cycle length (with a half-cycle correction), justified on the basis of clinical expert advice (CQ Question B8). The company stated at clarification that, in line with clinical expert advice, 6-month cycles were adequate to assess patient response and progression, whilst half-cycle correction accounted for the incidence of events not occurring at the beginning or end of every cycle (CQ Question B8) (CS Section B.3.2.2).

The EAG believe that a 6-month cycle length is suitable for decision making within the company's model but draw attention to two factors that should be considered. Firstly, the duration of treatment effect after the 3-year stopping rule may not be reflected with such long cycle lengths, thus implications of treatment waning may not be correctly gauged (further discussed in Section 4.2.6.3). Secondly, the long length of cycle could potentially mask differences in resource use and treatment costs, which may be inflated in a real-world scenario with a shorter cycle length.

4.2.6. Treatment effectiveness and extrapolation

4.2.6.1. Overview of treatment effectiveness reflected within the model

The company's model captures the impact of treatment through transitions between health states linked with renal response (CR, PR, and AD), as well as CKD stage (1 to 3a, 3b to 4, and 5), details of which are provided in CS Section B.3.3. Of note, the transitions between the renal response health states were derived from data collected in the AURORA 1 and AURORA 2 clinical trials, whereas transitions associated with CKD stage were based on external evidence (i.e., not based on data from AURORA 1 and AURORA 2). No data from the AURA-LV trial were considered in the company model, which was considered appropriate given some of the quality issues associated with this trial (see Section 4.2.6.2).

To facilitate comparisons to other comparators not included in the AURORA 1 and AURORA 2 clinical trials, the company undertook an NMA. A detailed critique of the NMA can be found in Section 3.4 of this report. The company also included within its model assumptions about long-term transitions, both with respect to extrapolation in general and extrapolation of treatment effects. Finally, the company performed time-to-event analyses of treatment discontinuation data to populate its model.

The following sub-sections contain the EAG's critique of these aspects of the company's model.

4.2.6.2. Renal response transitions

All patients enter the model with AD and CKD Stages 1-3a. Then, in terms of renal response, patients can either remain in AD, or achieve either a PR or CR. Transitions up to 36 months were derived from data collected in AURORA 1 (0 to 12 months) and AURORA 2 (12 to 36 months). After 36 months, transitions estimated in the final one or two model cycles were then assumed to be 'carried forward' and applied to later model cycles (discussed further in later parts of this sub-section). Consideration was also given to the possibility of treatment effect waning, described further in Section 4.2.6.3 of this report.

Transitions for the first 36 months were estimated using the 'count method', using data for patients residing in a given health state at the end of each model cycle to then determine movements from the previous cycle. As an example, at baseline all patients in the VCS+MMF arm were in the AD state (n=179 patients).[21] At 6 months, based on information contained within the company's model, there were n=[redacted] patients still evaluable for renal response, of which n=[redacted] achieved and maintained a CR, n=[redacted] achieved and maintained a PR, and n=[redacted]

remained in AD (either following a temporary renal response, or no change in terms of their renal response). Using this information, the transition probability from baseline to 6 months for the movement AD to CR was estimated as [redacted].

Related to the above, the EAG highlights the following excerpt from the CS: *"A transition probability was then generated for each transition within the CKD stages 1-3a by dividing the number of transitions from health state A to health state B by the total number of patients starting in health state A at the beginning of the six-month period."* (CS Section B.3.3.2.1). Here, it is implied that transitions are calculated based on patients being in a given health state at the start of a model cycle. However, instead of this, the model calculates transitions on the basis of patients being in a given health state at the end of a model cycle, which is of particular relevance for the first transition matrix since all patients enter the model in the AD CKD stage 1-3a health state. This is an important distinction to make since some patients can be lost to follow-up part-way through a model cycle.

At clarification stage, the EAG asked the company to provide further information about the approach taken to censoring patients with missing data to inform the 'count' method. In response, the company confirmed that censored observations were essentially removed from the analysis, by subtracting the relevant number of patients with missing data from both the numerator and denominator (company's response to CQ B5). This means that patients are assumed to be missing completely at random (MCAR) and can therefore be effectively removed from the analysis with no adjustment to the resultant transitions other than to re-scale the probabilities so that they sum to one.

The EAG asked the company to provide two alternative analyses to explore the impact of missing data on the transition probabilities, and in particular attempting to account for the potential reasons for the data being missing. These scenarios were:

- To allocate patients with missing data to the health state they last occupied (i.e., a last observation carried forward [LOCF] -type approach)
- To allocate patients with missing data to the AD state (i.e., a 'worst-case scenario' approach)

As the company notes in its response, both of these analyses should be interpreted with caution, since they involve imputing missing data while making explicit assumptions about what the missing data are mostly likely to have been if they were not missing. Furthermore, while the

company provided results for all comparators, the EAG's commentary is limited here to only the comparison of VCS+MMF to MMF since it is not possible to produce 'fair' comparisons to the other treatments given that individual patient-level data are not available to the company nor the EAG for other treatments.

The company notes that censoring affects the MMF arm mostly in the AD state, whereas censoring affects the VCS+MMF arm mostly in the CR and PR states (company's response to CQ B5, Table 22). Therefore, the company explains that the LOCF-type approach is expected to benefit VCS+MMF (i.e., 'carries forward' patients in broadly better response states), whereas the 'worst-case scenario' approach is expected to disadvantage VCS+MMF (i.e., 'forces' more VCS+MMF patients into the worse AD state, relative to the MMF arm). While the EAG is broadly in agreement with the company's view of these exploratory analyses, these interpretations should be viewed as being relative to the company's base-case approach (i.e., an alternative censoring approach may appear to advantage or disadvantage VCS+MMF versus the company's base-case approach, but all three approaches are estimates and are not 'true' data).

A further complication with the 'count method' in addition to determining how to account for censoring is the need to 'switch' from using AURORA 1 data (up to 12 months) to AURORA 2 data (after 12 months). This is challenging since not all patients that were followed up until the end of AURORA 1 continued in/ transferred to the AURORA 2 study. More specifically, taking the VCS+MMF arm as an example, n=162 patients completed AURORA 1 (CS Section B.2.3.1.5.1), and only n=116 entered AURORA 2 (CS Section B.2.3.2.5.1), meaning that n=46 VCS+MMF patients completed 52 weeks of study follow-up in AURORA 1 but did not enrol in AURORA 2. The CS contains information about different reasons that some patients did not enrol in AURORA 2 (CS Section B.2.3.2.5.1), discussed further in Section 3.2.2.1 of this report.

As AURORA 2 does not provide long-term follow-up data for all patients enrolled in AURORA 1, it was necessary for the company to impose an assumption about the impact on transitions for 'removing' the patients effectively lost to follow-up (by virtue of recruiting less than 100% of patients into AURORA 2; or in other words, that 116 ≠ 162). In the model, it is assumed that patients that did not enrol in AURORA 2 could be taken as uninformative censored observations. By extension, this means that data about these patients' long-term renal response outcomes are assumed to be MCAR (i.e., the same rationale of missing data was assumed to apply here as per the assumption made for patients lost to follow-up in general).

Given the above commentary related to the sample size and designs of AURORA 1 and AURORA 2, the EAG has prepared a simple schematic to illustrate the number of patients 'at risk' for specific transitions from a given health state at each model cycle from 0 to 36 months, shown in Figure 3. As can be inferred from this diagram, there is a large proportion of patients considered 'missing' from AURORA 2 (either due to censoring, death, or non-enrolment from AURORA 1 to AURORA 2) when making the switch from AURORA 1 to AURORA 2 data in the company's model. It may also be speculated that the proportion of patients in AD at the end of AURORA 1 was greater than the proportion of patients in AD that entered AURORA 2 [redacted].

Figure 3: Patients by renal response category over time

Abbreviations: AD, active disease; CR, complete (renal) response; MMF, mycophenolate mofetil; PR, partial (renal) response; VCS, voclosporin.

Note: This figure presents data for all AURORA 1 patients until 12 months, and then all AURORA 2 patients from 12 to 36 months. 'Missing' refers to a patient no longer being considered in either CR, PR, or AD for any reason (including death, loss to follow-up, not enrolling in AURORA 2, etc.).

It is the EAG's view that the approach taken to censoring patients from AURORA 1 who did not enrol in AURORA 2 has the potential to have led to overly optimistic estimates of transition probabilities between 12 and 36 months (and therefore, by consequence, for the remainder of the modelled time horizon). This is because these latter transitions are based only on AURORA 2 patients, and patients who did not enrol in AURORA 2 may be more likely to either continue with AD (if they were in AD at the end of AURORA 1) or 'lose' their renal response (by virtue of having VCS+MMF or MMF either at 12 months [when completing the study], or prior to 12 months [if they discontinued treatment prematurely]). The company did not provide alternative analyses to account for this aspect of censoring as part of the EAG's request for clarification about the overall approach taken to account for missing data (CQ B5).

An alternative statistical analysis approach was noted in the CS, with further details provided by the company at clarification stage. In summary, the company explained that a multinomial logit model was considered to derive transition probabilities, but found that model fit was poor, both in terms of reflecting the available trial data and the direction of transitions over time (company's response to CQ B6). In response, the company explained that there were issues with model fit in this analysis, and in particular that *"…the health state distribution of patients for VCS + MMF did not reflect the trial data whatsoever…"* (company's response to CQ B6). The EAG agreed with the company's general summary of the model fit being poor and therefore not useful to inform the model, though the EAG would have ideally preferred the company to elaborate further as to the reason(s) why the fit was so poor. The EAG speculated that the poor fit was likely caused by a small number of patients at risk for each transition over time.

For completeness, the EAG observes that the company provided a scenario analysis in which transitions were estimated using data from AURORA 2 only. While this analysis avoids the issue relating to 'switching' from AURORA 1 to AURORA 2 data, there is a clear issue with this approach in that randomisation is not only broken, but the comparability of the two groups is determined on the basis of a measure taken post-baseline (more specifically, at 12 months). Patients only entered AURORA 2 if they completed 12 months of treatment as part of AURORA 1), and so it would therefore be expected that transitions from 0 to 12 months based on AURORA 2 data only would appear more favourable (in terms of achieving PR or CR, for either treatment arm) versus including data for all AURORA 1 patients. Consequently, the EAG does not consider this scenario analysis further.

Based on the structure of the company's model, achieving either a PR or CR is associated with a 'protective' property in terms of CKD progression – in other words, patients can only progress from CKD stage 1-3a to CKD stage 3b-4 if they have AD, whereas patients with PR or CR must first 'lose' their renal response before being eligible to transition from CKD stage 1-3a to CKD stage 3b-4. This feature of the company's model is especially noteworthy given the specification of a relatively long model cycle length of 6 months. In theory, a hypothetical patient could 'lose' their renal response at any time within a 6-month period but would only be subject to the risk of CKD progression in the next cycle (i.e., it is not possible within the company's base case model for a patient with renal response to experience CKD deterioration to stage 3b-4 without first moving to AD, and so this takes place over a 12-month period [PR/CR CKD stage 1-3a $\xrightarrow[6\ months]{}$ AD CKD stage 1-3a $\xrightarrow[6\ months]{}$ CKD stage 3b-4]).

At clarification stage, the company explained that this feature of the model was designed to reflect cumulative kidney damage associated with LN, and that during the natural course of disease, patients with LN transition to AD after experiencing a relapse (i.e., renal flare), and it can take some time for the flare to manifest in irreparable kidney damage i.e., progression of CKD (company's response to CQ B8). The company clarified that analyses in which CKD progression are permitted from the CR and PR health states are *"not appropriate"* and that *"clinical experts have verified the assumption that requires patients to first enter and spend some time in AD CKD* [stage] *1-3a before transitioning to AD in CKD* [stage] *3b-4"* (company's response to CQ B8). Therefore, such analyses were not provided as part of the company's response to this request.

Contrary to the view expressed by the company in its response to the aforementioned CQ, based on clinical opinion provided to the EAG it is expected that some patients could experience CKD progression outside of experiencing renal flare (i.e., it is entirely possible for patients with CR or PR to experience CKD progression outside of a renal flare). The EAG acknowledges that all models represent a simplification of reality, and so the decision to only allow CKD progression to occur from the AD state in CKD stage 1-3a may be reasonable, yet there is no other evidence provided in the CS to further substantiate this structural feature of the model. As the requested sensitivity analyses to explore this further within the company's model were not provided (per the EAG's request in CQ B8), and it is beyond the remit of the EAG to re-structure the company's model to permit such transitions, the EAG highlights this as a limitation of the company's model structure, and the impact of this restriction of the model structure on results is unclear.

As described previously, from 36 months, transitions that were estimated for the previous one or two model cycles were assumed to be 'carried forward' and applied to later model cycles. In the base-case analysis, the 'average' transitions from 24 to 30 months and 30 to 36 months were assumed to serve as the renal response transitions for the remainder of the modelled time horizon. However, limited explanation concerning the calculation of these long-term transition probabilities is provided in the CS, though calculations were clearly presented in the company's model in order to understand how they were estimated.

Let us consider the transition AD CKD stage 1-3a to CR CKD stage 1-3a. For the VCS+MMF arm, the transition probability applied in the base-case analysis for 24 to 30 months is [redacted] (call this x_{24}) and for 30 to 36 months is [redacted] (call this x_{30}). The transitions estimated for 24 to 30

months were based on a sample of n=[redacted] patients residing in the AD CKD stage 1-3a health state (call this n_{24}), which decreased to n=[redacted] patients for 30 to 36 months (call this n_{30}). Therefore, in the base-case analysis, the transition probability estimated to apply from 36 months (call this x_{36+}) is calculated as follows:

$$x_{36+} = \frac{(x_{24} \times n_{24}) + (x_{30} \times n_{30})}{(n_{24} + n_{30})}$$

Or

[redacted]

In this worked example, x_{36+} is estimated to be [redacted]. While the EAG raises no issues with the calculation approach to obtain these 'average' transitions, the approach in general is heavily reliant on small numbers of patients still considered to be 'at risk' for a given set of transitions. Taking the example above, for 24 to 30 months n=[redacted] of n=[redacted] patients moved from AD CKD stage 1-3a to CR CKD stage 1-3a*, but for 30 to 36 months n=[redacted] of n=[redacted] patients experienced the same transition. The EAG noted that in response to CQ B14, the company explained that patients *"tend to respond quickly with* [VCS] *treatment"*, [redacted]. Therefore, the EAG highlights that the long-term transitions included within the model are subject to substantial uncertainty and appear to lack a degree of face validity in terms of how renal response is likely to be achieved in the long term after cessation of treatment with VCS+MMF or MMF.

The EAG has undertaken further exploratory analyses concerning the duration of treatment effect, and how this impacts transitions within the model. Further details of these analyses are provided within Section 6 of this report, and additional discussion pertaining to the expected duration of treatment effect is contained within Section 4.2.6.3 of this report.

* Note: the 'final' transition probability of [redacted] is not equal to [redacted] as the model also accounts for the risk of death. Mortality model inputs and calculations are discussed further in Section 4.2.6.6 of this report.

4.2.6.3. Treatment efficacy waning

The company describes within its submission how *"uncertainty related to any sustained efficacy following treatment discontinuation…"* was *"… accounted for by applying a long-term treatment waning effect to* [VCS + MMF] *and all comparators"* (CS Section B.3.3.2.1, p.116). Further detail concerning the application of treatment efficacy waning is provided in Table B.3-2 in the CS. In summary, the model assumes that when all patients permanently discontinue VCS + MMF (assumed to be 36 months in the base-case analysis), transition probabilities 'wane' to reflect an average of the estimated probabilities for the last two model cycles across both treatment arms from AURORA 2 (i.e., VCS + MMF versus MMF). The EAG noted that this application is based on transition probabilities from VCS+MMF and MMF whilst patients remain on treatment and does not capture what happens to patients who discontinue treatment on either arm. These transition probabilities based on patients receiving treatment are applied for the remainder of the time horizon (i.e., from 36 months to 72 years).

Second to this, the EAG also notes that while this aspect of the model transitions reflects *some* loss of treatment effect from 36 months, it should not be mistaken as an assumption of loss of *all* treatment effect (since some residual treatment effect is maintained from 36 months). In the context of the model, here 'loss of treatment effect' refers to the difference between treatment arms for transitions between PR, CR, and AD after cessation of treatment (at 36 months in the company's base-case analysis). The company's base-case approach to capturing long-term treatment effect means that patients that received VCS+MMF are associated with 'better' transition probabilities for the remainder of their lifetime – for example, a lower risk of losing their renal response. At clarification stage, the EAG asked the company to provide further information concerning the application of treatment effect, and to provide scenarios such that the model can reflect partial, total, or no treatment effect waning (clarification question B7).

In response, the company explained that any loss of treatment effect is *"unlikely to occur instantaneously following treatment discontinuation"*, as well as adding that it was unaware of any data or studies concerning treatment waning effects in an LN population (company's response to CQ B7). The company did not provide any of the requested sensitivity analyses concerning differential approaches to capturing potential treatment waning effects within its model.

The EAG highlights a study by Jourde-Chiche *et al.*, (2022) [11] which reports findings from the WIN-Lupus trial: a multicentre RCT investigating weaning of maintenance immunosuppressive

therapy in LN. While the EAG acknowledges that this study was published after the company made its submission, the study provides some evidence related to the waning of treatment effects over time for immunosuppressive therapies in an LN population. Acknowledging a number of limitations of this study and its direct relevance to this appraisal (different treatments, non-inferiority study, limited sample size of n=88 patients, amongst others), the EAG highlights the following conclusion reached by the authors of this study: *"*[Immunosuppressive therapy] *discontinuation was associated with a higher risk of severe* [systemic lupus erythematosus] *flares (renal or extra-renal) requiring induction* [immunosuppressive therapy]*"* (Jourde-Chiche *et al.*, [2022], p.4). [11] The EAG therefore considered it entirely possible that the effect of treatment (with either VCS+MMF or MMF alone) could indeed wane over time, and that there is no guarantee that it would persist over a lifetime.

The EAG contends that there are different ways one could hypothesise about the long-term effect of VCS+MMF treatment, relative to MMF alone, after discontinuation. Of note, the EAG highlights the importance of separating two distinct concepts:

- loss of effect in terms of assuming an immediate loss of renal response
- loss of effect in terms of assuming no further difference in gaining or losing renal response over time

The first concept above is not reflected by the model, which the EAG agrees is appropriate and does not advocate any immediate reversal of renal response upon discontinuation of treatment effect. However, the second concept is *partially* reflected by the model, but the EAG maintains its view expressed at clarification stage that scenarios reflecting 'no' waning or 'full' waning may be suitable scenarios to consider within decision making.

A related issue with respect to long-term treatment effect is that by carrying forward transition probabilities after patients have discontinued treatment, patients can continue to achieve a renal response. The EAG concedes that this may be possible in reality due to the use of subsequent therapies (costs for which are captured within the model). However, the effects of subsequent therapies are not explicitly captured within the model, and there is no guarantee that subsequent therapy would yield 'similar' response rates to those implied by the latter transition matrices estimated from the AURORA 2 trial data. This is especially important to consider in light of the fact that subsequent therapy use is not directly linked to renal response health state within the company's model.

Overall, the EAG considered the duration of treatment effect, and the method most appropriate to reflect this, as a key area of uncertainty inherent within the company's model and has therefore conducted additional exploratory analyses to investigate this further. Details of the scenarios undertaken, and associated results are provided in Section 6.2 of this report.

4.2.6.4. Indirect treatment comparison

A full critique of the company's network meta-analysis (NMA) is provided in Section 3.4 of this report, but here the EAG focuses on the application of the NMA of odds ratios (ORs) comparing the probability of transitioning from AD CKD stage 1-3a to either PR or CR (separate ORs for each transition). As discussed in Section 3.4 of this report, the EAG would have preferred an analysis that used random effects, likely with a better choice of informative prior to improve the credibility of estimates. Though the EAG present estimates from a random effects NMA, the fixed effects NMA is used pending resolution of questions about optimal estimation of the NMA.

Overall, the EAG has no major concerns with the application of the NMA outputs within the company's model but highlights two relatively minor points for completeness below.

The first of these pertains to the comparison of VCS+MMF versus MMF. In the company's model, while ORs are presented to compare MMF with VCS+MMF, these do not inform any model calculations. Instead, transitions for the VCS+MMF arm are based solely on the patient-level data from the AURORA 1 and AURORA 2 studies. While the EAG considered this approach to be sensible in light of the availability of individual patient-level data for both arms, it is evident that transitions for VCS+MMF would be different if the ORs were used to derives transitions instead of estimating transitions from the AURORA 1 and AURORA 2 trial data, if only because the OR provides a summary measure assuming a time-invariant difference in transitions over the course of the modelled time horizon.

The second point relates to a specific transition probability for the MMF arm, which serves as the baseline from which the ORs are applied. Over the time period 18 to 24 months, n= patients in the MMF arm transitioned from AD CKD stage 1-3a to CR CKD stage 1-3a. [redacted]. Similar to aspects of the model highlighted earlier in this report, this is another example of where the model calculations are adversely affected by the number of patients at risk of a given transition at a given time point across the 36 month-period over which data are available from AURORA 1 and AURORA 2. However, the EAG noted that this specific issue affects only one transition at one model cycle.

4.2.6.5. Time to treatment discontinuation and stopping rule

To inform treatment discontinuation rates within the model, the company undertook parametric survival analyses of time to treatment discontinuation (TTD) data for VCS+MMF and MMF. Additional information was provided by the company at clarification stage, at the request of the EAG, concerning the overall approach taken, provision of supporting plots, statistical goodness-of-fit scores, and justification of the base-case model selected (CQs B11 and B12).

Initially, the EAG was unsure why a parametric model was fitted to these data, given that all patients are subjected to a stopping rule at 36 months, and that trial follow-up was sufficient to allow estimation of drug costs without needing to fit a parametric model. In response to the EAG's request for further information, the company explained the benefit of parametric survival models providing a 'smooth' curve, versus a stepped Kaplan-Meier estimate. The EAG accepts that a parametric model has this advantage, but notes that a sensitivity analysis using the Kaplan-Meier estimate may have also been helpful to consider for completeness.

The company selected a log-logistic model, based on visual fit, statistical goodness-of-fit scores, and consideration of proportional hazards. The EAG considered the choice of a log-logistic model to be acceptable, though asked the company to provide alternative analyses at clarification stage for completeness. The company provided additional results with four alternative parameterisations (exponential, generalised gamma, lognormal, and Weibull), which had very little impact on the company's base-case ICER. As such, the company's base-case approach was deemed acceptable and is maintained in the EAG's preferred analysis.

For all comparators within the model except for MMF, a TTD curve was not considered, and all patients were assumed to receive treatment until they stopped treatment (i.e., there was no treatment discontinuation for any proportion of patients for reasons such as adverse events or lack of efficacy). The EAG considered this to be a very limited analysis which will likely overestimate costs associated with all other comparators (except MMF). As such an exploratory scenario analysis is considered by the EAG (outlined in Section 6.2) which assumes that all comparators follow the same TTD curve as the observed MMF data.

In the company's base-case analysis, patients are assumed to receive treatment with either VCS+MMF or MMF until 36 months. The stopping rule of 36 months was chosen by the company on the basis of the AURORA 1 and AURORA 2 trials providing follow-up until this point in time and based on clinical expert opinion provided to the company. Independent clinical expert feedback provided to the EAG suggested that 36 months was likely a suitable stopping

rule in most cases. However, the EAG was also advised about the heterogeneous nature of LN and how different patients respond to treatment, meaning that some patients may discontinue earlier than 36 months, or potentially (if permitted according to both the marketing authorisation for VCS and the recommendation reached by NICE) could be treated beyond 36 months. The draft SmPC included within the CS states with respect to treatment duration: "[redacted]" (CS, Appendix C, p.1). Consequently, the EAG highlights that there is currently no restriction made within the SmPC that would limit the maximum duration of treatment with VCS+MMF to 36 months. At clarification stage, the EAG asked the company to confirm the rationale behind the 36-month stopping rule, and in response it reaffirmed that this was in keeping with the available data from AURORA 1 and AURORA 2, as well as clinical expert opinion it received.

Taking into consideration the position of the company (informed by both trial data and advice from its clinical experts), as well as the views expressed by the EAG's clinical advisers, the EAG tentatively adopts a 36-month stopping rule to inform its preferred analysis. The EAG considered treatment duration as a key issue with regard to positioning for voclosporin+MMF and the long-term efficacy assumptions related to a 36-month stopping rule (see Key Issue 3 and Key Issue 7), in so far as an imposed stopping rule constitutes a restriction of the use of VCS+MMF in practice relative to its licensed indication. However, this restriction may also mean that some patients would need to discontinue treatment at 36-months who may have otherwise continued in the absence of a stopping rule. Further to this, for MMF and the analysis of the data from AURORA 1 and 2, and inclusion within the model, the imposed stopping rule by the company does not take into consideration the duration of therapy for patients who were receiving MMF prior to entering the trial, again bringing into question the appropriate positioning of MMF for cost-effectiveness estimates.

As a scenario analysis, the company included within its model the ability to impose an early stopping rule at 18 months. This earlier stopping rule was explored as a result of findings from a US-based survey of 96 clinicians, which was contained within feedback provided as part of ICER's independent assessments of VCS and belimumab for the treatment of LN. For complete context, the exact quote included in the feedback is as follows: *"Underpinning this, a survey of 96 treating U.S. physicians suggests that the majority would keep patients on treatment for no more than 1.5 years after achieving a complete renal response"* (Aurinia Comments on the Institute for Clinical and Economic Review's Draft Evidence Report, p.1-2). [22]The EAG highlights

that the time point of 18 months refers to treatment after achieving a CR, not from initiation of treatment prior to response.

The EAG highlights that the 18-month stopping rule scenario comprises (i) a simple 'cap' on the treatment duration curve used within the company's model to affect costs, and (ii) use of transitions up until 18 months (with the 'carrying forward' approach of the base-case analysis applied relatively earlier). While this scenario happens to yield [redacted] QALYs compared with the company's base-case analysis, the EAG investigated results accounting for all possible ranges of treatment duration from 12 months to 36 months, in 6-month intervals, to investigate the relationship between outcomes and duration of treatment in the company's model.

The results of this analysis are presented in Figure 4. As can be inferred from this figure, there is a non-linear relationship between the imposed stopping rule and the total QALYs estimated by the model. In reality, it would be expected that a longer duration of treatment should yield increasing QALYs, and so this analysis sheds further light of the overall uncertainty in the company's model with respect to transitions based on limited trial data, and how these impact on lifetime estimates of QALYs (including the approach taken to account for treatment waning, as discussed in Section 4.2.6.3 of this report) over the modelled time horizon.

Figure 4: Total QALYs by treatment arm based on duration of treatment

Abbreviations: MMF, mycophenolate mofetil; QALY, quality-adjusted life year; VCS, voclosporin.

4.2.6.6. Mortality

In the company's model, background mortality was applied for all health states before any other transitions between health states occurred, which was independent of health state occupancy. However, additional mortality risk was included for specific health states in the model at all model cycles for the following health states:

- **AD CKD stage 1-3a:** Based on patient-level data for the MMF arm from AURORA 1 and AURORA 2, a probability of [redacted] per 6-month model cycle was estimated on the basis of [redacted] deaths being recorded over a total of [redacted] 'at risk' periods of 6 months
- **AD CKD stage 3b-4:** Based on a study by Sugrue *et al.*, (2019), [23] a probability of 3.92% per 6-month model cycle was estimated. The population included in the study by Sugrue *et al.* reflected a broader CKD population, and so this estimated mortality risk may be higher than the 'true' value expected for a relatively younger LN population
- **CKD stage 5 (dialysis):** Based on Sugrue *et al.*, (2019), [23] 7.47% per model cycle
- **CKD stage 5 (transplant):** Based on Sugrue *et al.*, (2019), [23] 2.62% per model cycle

No excess mortality risk was applied for patients residing in either the PR or CR health states for every model cycle. However, for specific model cycles, some specific transition matrices included non-zero probabilities for death for the PR and CR health states, based on the count method. Owing to the low number of deaths that occurred during follow-up in the AURORA 1 and AURORA 2 studies, these mortality risks are small.

The EAG considered the company's overall approach to incorporating mortality within the model to be appropriate but given the small number of observed deaths in the AURORA 1 and AURORA 2 studies, it is important to acknowledge that the incorporation of these deaths within the first 36 months of follow-up in the model can have a marked impact on results due to sample size of AURORA 1 and AURORA 2. For example, in the MMF arm [redacted] with PR CKD stage 1-3a died between 24- and 30-months, and because [redacted] were still at risk at this time, this ultimately translated to a [redacted] probability of death in this cycle specifically, versus [redacted] for the VCS+MMF arm [redacted]. Moreover, the EAG considered it counter-intuitive that patients can die of their disease from the PR or CR states (i.e., there is at

least one non-zero transition from either the PR or CR CKD stage 1-3a state to Dead, on at least one treatment arm), but cannot experience CKD progression from this same state.

A further issue with the application of mortality data from the AURORA 1 and AURORA 2 studies is that deaths from CR and PR are factored into the model using a different approach versus deaths from AD (all in CKD stages 1-3a). Deaths from CR or PR are both time-varying and arm-specific (i.e., could be different values for each model cycle, and can be different for VCS+MMF versus MMF), whereas deaths from AD are applied based on count data from AURORA 1 and 2 varying over time (and arm-specific) with a further additional constant over time independent of treatment arm (i.e., one transition probability is applied to both arms, across all model cycles).

The EAG considers the description of how mortality is captured within the company's model via the CS to be somewhat misleading, as the application of mortality risk for AD CKD stages 1-3a is described very briefly, and within a sub-section titled: "Transitions between AD CKD 1-3a and AD CKD 3b–4". The relevant text in the CS states: *"In addition, the transition probability from AD CKD 1-3a to death could be informed by mortality data collected in the MMF arm in AURORA 1 and AURORA 2 ([redacted]% per 6-month cycle")"* (CS, Section B.3.3.2.2, p.116-117). Here, the CS acknowledges that the same probability is applied by treatment arm but is based only on data collected for the MMF arm. No explanation is provided for why this specific transition probability was estimated only using data for the MMF arm, nor is it clear why this particular probability was necessary to consider fixed over time.

Given the small number of deaths that occurred during the follow-up period of AURORA 1 and AURORA 2, the EAG prefers the approach taken to capture deaths from AD over the time-varying/ arm-specific approach taken for PR and CR deaths, but both approaches are subject to both misinterpretation given both the description provided within the model and uncertainty given the small numbers of events within the trial. As such, the impact of LN deaths is explored further as part of the EAG's exploratory analysis.

4.2.6.7. CKD progression transitions

In its base-case analysis, the company assumes that progression from CKD stage 1-3a to CKD stage 3b-4 is not possible in the first 36 months of the model (i.e., 3 years). This is justified by the company in its submission on the basis of no patients in AURORA 2 progressing to CKD stage 3b-4 over the course of three years of follow-up. The EAG noted that while it is correct that no patients in AURORA 2 experienced progression to CKD stage 3b-4, it is clinically

plausible that patients *could* progress to CKD stage 3b-4 in the first 3 years of the model, and arguably the most likely patients to progress within the first 3 years of treatment would be those patients that discontinued treatment before 12 months, or those that completed AURORA 1 but did not enrol in AURORA 2 (including, 13 patients (of n=55) who discontinued due to a lack of efficacy – see responses to CQ A10). In addition, the EAG noted that 54.9% of the AURORA 1 population were already receiving MMF at screening, and so may be considered to have been 'at risk' for CKD progression prior to enrolment (though if they had already progressed to CKD stage 3b-4, would not have met the inclusion criteria of the study). This restriction within the company model structure emphasises why the positioning of voclosporin within the treatment pathway is a key consideration and noteworthy to the EAG (see Key Issue 7).

In light of the considerations above, while the EAG acknowledges the rationale behind disabling this transition for the first 3 years of the model, it expects that in reality this transition should be considered possible, as there is no biological basis from which to assume CKD progression cannot occur until after 3 years of treatment (with any regimen included within the model). This transition is therefore permitted within the EAG's preferred analysis, presented in Section 6 of this report.

After 3 years, patients are permitted to experience progression from CKD stage 1-3a to CKD stage 3b-4. As discussed previously, the company's model includes a 'protective' property linked with renal response, such that patients cannot progress to CKD stage 3b-4 unless they currently reside in AD. This means that by extension, VCS+MMF is associated with an indirect benefit in terms of CKD progression through keeping patients in either PR or CR for longer versus MMF. Given the irreversible nature of CKD progression, this indirect treatment effect constitutes an important assumption within the company's model. Advice from clinical experts to the EAG indicated that it may be possible for patients to progress CKD stage whilst still maintaining renal response.

For patients with AD, the risk of progressing to CKD stage 3b-4 is fixed at 3.05% per 6-monthly model cycle. This value was estimated on the basis of clinical expert opinion that approximately 6% of patients in CKD stage 1-3a will progress to CKD stage 3b-4 per year (CS Table B.3 3). The EAG noted that this probability was not estimated using empirical evidence, but rather was derived from clinical expert opinion (with further details about elicitation of this opinion not clear from the CS), and so it is subject to uncertainty. Nevertheless, the EAG understands that there is a paucity of evidence available concerning the long-term disease progression for patients with

LN (confirmed also by the fact that the EAG was also unable to identify relevant evidence to inform CKD progression rates within the company's model for an LN population), and so recognises the need to rely on experts to populate these aspects of the model. However, the EAG's principal concern relating to this transition is about the 'protective' property of renal response in the model with respect to CKD progression.

Once patients have progressed to CKD stage 3b-4, a risk of progressing to CKD stage 5 is included within the model. CKD stage 5 is separated by 'Dialysis' and 'Transplant', with patients initially moving to 'Dialysis' from CKD Stage 3b-4. The probability of moving into 'Dialysis' from CKD stage 3b-4 is fixed at 13.91% per 6-month model cycle, applied across both arms equally, based on clinical opinion provided to the company (CS Table B.3-4). Similar to the EAG's commentary concerning movements from AD CKD stage 1-3a to AD CKD stage 3b-4, there is a paucity of evidence to inform this latter aspect of the model, yet it is clear that this transition probability is subject to substantial uncertainty.

Of greater concern, however, are transitions between 'Dialysis' and 'Transplant'. The probabilities applied in the model for these transitions are as follows:

- From 'Dialysis' to 'Transplant': 43.77% (based on clinical opinion)
- From 'Transplant' to 'Dialysis': 2.96% (based on Palmer *et al.*, [2004]) [24]
- From 'Dialysis' to 'Dead': 7.47% (based on Sugrue *et al.*, [2019]) [23]
- From 'Transplant' to 'Dead': 2.62% (based on Sugrue *et al.*, [2019]) [23]

Taking these probabilities together, it is possible to track over a given time horizon how many transplants would be modelled for a hypothetical cohort of patients starting in the 'Dialysis' health state. Taking a 10-year time horizon as an example, the average patient starting in 'Dialysis' would be modelled as receiving 1.12 transplants over 10 years, and slightly more than half (50.5%) of the starting cohort would be modelled to have died by 10 years. While these estimates are hypothetical, the EAG considered it important to acknowledge that due to the memoryless property of the company's Markovian model, many surviving patients will undergo at least one transplant, and a notable proportion will have two or more transplants over their lifetime. Overall, the EAG has concerns with the face validity of the estimated number of transplants that occur within the company's model, owing mostly to the specification of a time-

invariant probability of transplant occurring from the dialysis health state, and a lack of consideration of event history when considering eligibility for re-transplantation.

Ideally, the EAG would have preferred the company's model structure to introduce an element of memory to better account for the probability of additional transplants, and potentially adjust the subsequent chance of transplant success or failure. In lieu of a model structure that explicitly captures differences in outcomes based on re-transplantation rates, the EAG has conducted an exploratory analysis to ascertain the impact on results if re-transplantation is disabled within the company's model (see Section 6.2 of this report).

4.2.7. Health-related quality of life

4.2.7.1. Overview of HRQoL within the model and EAG critique

The AURORA 1 and AURORA 2 trials included both the SF-36 (v2) and the LupusPRO (v.1.7) disease-specific measure. In order to generate health state utilities, the company used a mapping from the SF-36 to generate EQ-5D utilities (Rowen et al., 2009). [25] Given the EQ-5D was not directly measured this does provide reference case utilities, albeit with uncertainty inherent through the use of a mapping algorithm. In response to CQ B20, the company confirmed that SF-6D utilities[26] had not been generated, and thus there remains uncertainty regarding the validity of the mapping in this patient population as the mapping was derived in different disease areas, and may not reflect the specific issues faced by people with LN. The company however did provide plots comparing the LupusPRO and mapped EQ-5D utility (CQ B21), which appear to support the mapped EQ-5D values reflecting the patient experience according to the disease specific measure.

Although the company used data collected from the AURORA trial programme to populate the model, the approach used to estimate health state utilities for use in the economic model is methodologically wrong, certainly biased, with the resulting values unreliable for decision making. The EAG has used the values provided by the company in some instances due to the lack of other values in the company submission, however the EAG has substantial reservations regarding the conduct of the utility analysis, and consequently the robustness of the utility values provided.

To populate the model, a mix of trial data and data from the literature was used. For CR/PR/AD in CKD stages 1-3a, the approach taken by the company was to use only the utility values from AURORA 2 observed in Month 36. These were split by patients in CR, PR and AD, and the

mean utility in each of the groups used (taking values of 0.83, 0.80, and 0.71, respectively). For values not available from the AURORA 1 and AURORA 2 trials (i.e., CKD stage 3b-4, CKD stage 5 [dialysis and transplant]), literature values were used. For CR/PR/AD in CKD stages 3b-4, a study by Jesky *et al.,* (2016)[27] was used. This is a study of a broader population of patients with CKD (the most common cause being diabetes), where a decrement of 0.055 was assumed to apply relative to the values derived from the AURORA trials. This appears to have been derived from Table 3 of the Jesky *et al.*, (2016) study, though the exact methodology is not clear from the CS. In response to clarification (CQ B.22), the company confirm the EAG's understanding that the approach taken was to average the EQ-5D Index scores between CKD stages 1/2 and 3a and deduct the average score from stage 3b and 4.

Further utilities are then used for patients receiving dialysis and post-transplant, taken from a publication by Lee *et al.,* (2005).[28] This study used the EQ-5D in transplant recipients and compared results between groups, finding that transplant recipients had a higher utility (0.71) than patients receiving haemodialysis (0.44) or peritoneal dialysis (0.53). The company then assumed an equal 50:50 split between the two forms of dialysis, giving a mean utility of 0.485 for dialysis.

The company considered the application of disutilities associated with AEs for VCS+MMF and MMF, which were applied as a one-off disutility at the start of the model. Disutilities were estimated based on incidence of AEs observed within AURORA 1 and reported as Grade 3/4 TEAEs with an incidence of ≥1% with impact on HRQoL and assumed duration of each AE sourced from the literature. For comparators outside of the trial, an assumption was made by the company that regimens which contain MMF would have the same disutility as MMF, with all other comparator disutilities associated with AEs set to zero. The company considered this a conservative approach (with respect to comparisons against VCS+MMF).

The EAG has major concerns with all of the approaches/sources used for utility data, which are addressed in turn throughout this section. The EAG presents alternative approaches to informing health-state utility values within the model with a description outlined in Section 6.2.

4.2.7.2. Issues relating to the analysis of trial data

By taking the mean values of month 36 data to derive health state utility values by CR/PR/AD, the company's approach omits all other trial HRQoL data from consideration. The uncertainty associated with these values is therefore likely higher than implied by the stated SDs/SEs, any patients who did not provide a value at month 36 are not represented in the analysis, and if

patients have provided multiple observations, the correlation between these is not used. To underline how much data are omitted, it is the EAG's understanding that not a single value from AURORA 1 informs the estimates used in modelling (CQ B15 and CS Table B.3-10).

The company justifies its approach by stating that utilities increase then decrease in the period between months 0 and 36 (CQ B15). However not including this 'area under the curve' ignores any differences seen within the study period and is highly inappropriate, and unsuitable for use in calculating either the within trial period (given values are not stable), or for use extrapolating the likely outcomes seen in patients over time. There would appear to be two obvious appropriate methods for analysing the trial utility data (neither of which have been provided): either to analyse in a regression model by timepoint, or to estimate health state utility values from all data. The equations for such regressions are shown below for clarity:

$$MappedUtility \sim as.factor(response) + as.factor(time\ period)$$

$$MappedUtility \sim as.factor(response)$$

The first of these methods would specify a regression model incorporating time periods for which the relevant utility values would be estimated (e.g., by model cycle and response status), with values then used in the relevant model periods. The second method would specify a regression with only response status, and all values able to inform the estimate, to generate an overall health state utility value for each response category (i.e., CR, PR, and AD). The huge amount of omitted data (every observation apart from month 36) and lack of appropriate analysis method means that the EAG does not consider the utility values estimated to provide a reliable basis from which to inform decision making. Given the non-linear nature of the model, and unknown effects of proper analysis, it is not possible to speculate whether the result is biased, and in which direction any bias would impact the analysis.

Even given the company approach, there are further issues with the values used. The values presented in CS Table B.3-10 appear to be a tabulation of the mean (and SDs) of all observations which exceed the number of patients at risk in each time period. This implies multiple observations per patient were available and used in calculations of values – however the patient level values will be correlated, again meaning that SDs (and indeed means) are also unreliable. Thus, even the simplistic analysis performed by the company is inappropriate in mean values, with incorrect SDs, and is unsuitable for use in decision making.

4.2.7.3. Issues relating to the use of a decrement for CKD stages 3b-4

Although the issues relating to this assumption are of less concern to the EAG than those regarding the analysis of trial data, the approach used by the company is also limited.

The first limitation regarding this decrement is that the population in the Jesky *et al.* [27] study is a much older population (age at baseline 64 years, versus 31 years in the AURORA 1 VCS+MMF arm), predominantly with diabetes, and as such it is a strong assumption that the same decrement would apply (confirmed in CQ B22). Notwithstanding this limitation, the approach taken to uncertainty by the company is to assume the SE of the newly calculated decrement is "SE assumed to be 20% of utility value due to no SE reported in publication", however this relates to the decrement, and not the overall value.

This uncertainty is exacerbated further as utilities are then age adjusted using the often cited Ara & Brazier (2011) study. [29] Although age-adjustment applies to all health states, as CKD stage 3b-4 patients have already had a decrement applied (from an older age group), they may be impacted to a larger degree.

4.2.7.4. Issues relating to the utilities used for dialysis and transplant

In addition to the above issues, the EAG has further concerns about the approach taken to populating the model with dialysis and transplant utilities. As noted above, the company makes use of values from a study by Lee *et al.,* (2005). [28] The date of publication of this study (2006) should be acknowledged, as the underlying data informing the analysis by Lee *et al.* are now (at the time of writing) approximately 20 years old, and as with the Jesky *et al.* study, [27] the data are not specific to a population with LN, which constitutes a further limitation, but not the only concern relating to the approach.

Firstly, the company assume a 50:50 split between haemodialysis and peritoneal dialysis. Based on data reported by UK Renal Registry in its 23rd Annual Report (published in 2019), [30] 87.6% of all UK dialysis patients receive haemodialysis dialysis. This would impact the weighted utility and costs.

The second concern is the data source used. This compares the utility values cross-sectionally, which, when used directly in the model, implicitly assumes patients are similar between groups. This is unlikely to be the case in practice, where receiving a transplant is informative, and patients are generally younger and healthier i.e., they would be expected to have higher utility than non-recipients, regardless of the receipt of a transplant. This can be seen in the Lee *et al.*

study where the transplant recipients were around 10 years younger than the dialysis patients (53 versus 60-67 years [depending on sex and timing of dialysis]). [28]

These issues arose in the recent NICE appraisal of imlifidase for enabling transplant [ID1672], where the EAG identified a number of relevant references which warrant consideration in this appraisal. This includes a systematic review of utility weights through different stages of CKD by Cooper *et al.*, (2020), [31] and a regression analysis of utility values in patients waiting for transplants by Li *et al.*, (2017). [32] This latter paper by Li *et al.* presents seven regression models with various characteristics which would appear relevant to this appraisal (predominantly female, nondiabetic, younger patients), and the impact of transplant on the same patients (i.e., not comparing cross-sectionally with data taken from the UK).

4.2.7.5. Issues relating to the disutilities associated with AEs

As noted previously, the company's model included disutilities for AEs based on incidence of AEs observed within AURORA 1 and reported as Grade 3/4 TEAEs with an incidence of ≥1% with impact on HRQoL and assumed duration of each AE sourced from the literature. For treatments other than VCS+MMF or MMF, the company assumed that disutilities for MMF apply to all comparators containing MMF.

The EAG noted that a coding error was found in the company's model (in the versions provided at company submission and the revised model provided at clarification stage) which incorrectly adjusts the disutilities applied within the model based on the 6-month cycle length. The approach to estimate disutilities associated with AEs already captures the assumed duration from the literature, and therefore duration is already captured in the one-off value applied. The subsequent adjustment in the calculation for cycle length is inaccurate and halves the disutilities associated with AEs. The EAG has provided an updated analysis as part of Section 6.1.

4.2.8. Resources and costs

4.2.8.1. Overview of costs reflected within the model

The company's model includes costs relating to treatment and comparators, medical resource use, the resolution of AEs, background therapy and death (death from background mortality or death as a result of underlying LN). The costs captured by the model are discussed in turn below.

4.2.8.2. Treatment costs

All costs were presented within the model in terms of either the number of packs or vials (dependent on whether each drug was to be orally or intravenously administered).

Voclosporin

As stated within the CS, the indicative NHS list price of VCS is [redacted] per pack. At the time of writing, a proposed commercially-sensitive simple patient access scheme (PAS) is applied to the cost of VCS in the company's model. The discount is equivalent to a [redacted] discount on the list price of VCS equating to a final price of [redacted] per pack. Functionality to apply this discount to VCS is included in the model. However, the EAG noted that the PAS discount has been applied to the cost per mg rather than the cost per pack. Given the discount is based on the price per pack, the application within the model should be aligned. Within the scope of the model, acknowledging that there is only one pack size of VCS included and the dose is fixed over time, this application of the PAS discount has no impact on any cost-effectiveness analyses and is therefore not discussed further within this report.

The EAG noted that the cost of VCS is applied in the company's model based on a fixed supply of treatment with the assumption that there is no wastage associated with treatment discontinuation. In reality, it is expected that some product wastage would arise for patients that discontinue treatment part-way through a pack of treatment, though this is not explicitly reflected with the company model. For simplicity, the EAG has explored a sensitivity analysis which adds on half a pack cost of voclosporin treatment to reflect wastage of the treatment (please refer to Section 6.2 for further details).

MMF

MMF is costed within the model differently dependent on the treatment arm considered. For MMF and VCS+MMF, the dosing assumed within the model is 2.5 g/day, despite dosing schedules in AURORA 1 and AURORA 2 considering MMF at a dose of 2 g/day. Explanation for the assumption of a 2.5 g/day dose was provided at clarification (CQ B26), where reference was made to the EULAR/ERA-EDTA guidelines where the recommended dose for MMF was between 2-3 g/day. [7] The company took the average of the upper and lower bounds to inform its base-case analysis.

Within both AURORA 1 and AURORA 2 trials, a dose of 2 g/day for MMF was predominant. The EAG believes that efficacy data based on this 2 g/day dose should have informed the model rather than the 2.5 g/day dose the company implemented within its model. This is further explored in Section 6.2 where a scenario analysis using a 2 g/day dose of MMF is presented.

Comparator treatment costs

The EAG cross-checked the company's calculations of the cost per mg for each treatment within the model. Comparator costs were aligned with those referenced.

Application of relative dosing intensity (RDI)

The company applied an RDI of 100% for all treatments except for tacrolimus + MMF, which instead had an RDI estimate of 95%. In response to CQ B27, the company emphasised that treatment with tacrolimus + MMF was adjusted for TTD by instead setting RDI to 95%. Justification for the decision to substitute TTD compliance for RDI was purely cost-based, since the company stated that: *"treatment acquisition and administration costs are reduced by 5%"*, thus treatment efficacy or informative dropouts for tacrolimus + MMF adherence will not be accounted for (Company's response to CQ B27).

In the absence of mean RDI reported in the CSRs of AURORA 1 and AURORA 2, the EAG was unable to adjust the company's model to account for dose adjustments for VCS + MMF or MMF. Within the CS, the company addressed treatment discontinuation in Section B.2.3.2.3.3, highlighting that patients may have their dose reduced after 12 months within the AURORA 2 trial (i.e., after 2-years of treatment) on consultation with the Medical Monitor at the Investigator's discretion: in these instances, patients taking 23.7 mg BID of VCS could have their dose reduced to 15.8 mg BID (from three down to two capsules).

The EAG believed that there is a fundamental misinterpretation between the use of the TTD curve and the application of RDI in the model since the two are not interchangeable. Therefore, the EAG considered the company's approach to capture treatment costs to be inappropriate. The length of time that patients received treatment is not comparable to how much treatment a patient obtained relative to the anticipated (or 'target') dose, and as such the analysis presented is limited. In the absence of alternative information, the EAG has undertaken a simplified scenario analysis outlined in Section 6.2.7.

4.2.8.3. Administration costs

Administration costs were incorporated within the model if patients were administered treatment as an intravenous infusion (IV). IV costs were split into two separate costs for IV *first attendance* and IV *subsequent cycles*. Oral administration was assumed to have a cost of £0. Within the CS, it is noted that "*costs have been adjusted for inflation using the NHS cost inflation index*" (CS, Table B.3-16, pp.134). Both IV costs were sourced from the NHS National Schedule 2019/20 (version 1).

The two administration costs associated with IV attendance (first and subsequent using costs SB14Z and SB15Z respectively) could not be validated alongside the original source. For IV first attendance, the company used a cost of £404.89 in their model but referenced the SB14Z currency code on the "Total HRGs" sheet which was priced at £406.04, while the company used a cost of £339.75 within the model for the subsequent administration cycle cost, however the original source indicated that this cost would be £341.30. [33,34] Given the company states that costs were adjusted for inflation, and the NHS cost inflation index are positive, the EAG are unsure why the costs included in its model are lower than those reported in the source documentation. Further to this, as the costs are hardcoded inputs within the model (rather than inputted using the original source and inflated within the model for transparency), it is unclear to the EAG how the respective IV administration costs have been obtained given the reported references. However, the EAG accepts that these differences are relatively minor (in the region of £1-£2) and so are unlikely to have a marked impact on model results.

4.2.8.4. Background therapy (BT) costs

BT costs are applied to each comparator based on receiving tapered glucocorticoids (with dosing options from either the AURORA 1 and AURORA 2 trials, or the literature) and hydroxychloroquine. Glucocorticoids referred to methylprednisolone and prednisolone. The EAG's main concern regarding BT is the difference between tapered glucocorticoids from either the AURORA trials or the literature. These were dosed differently within the model, with a higher dose of up to 2,500 mg used outside of the AURORA 1 and AURORA 2 trials. The AURORA trial protocols outlined rapid glucocorticoid tapering to 2.5mg/day at week 16. No justification was provided in the CS as to why glucocorticoid tapering would not be considered for the alternative comparators.

Costs associated with BT were aligned except for a few instances of prednisone, where the company referenced the British National Formulary (BNF) as their cost source of this drug;

however, on inspection, only predniso*lone* was available. If the company did use predniso*lone* costs instead of predniso*ne*), the EAG identified lower price alternatives for this via eMIT. For simplicity, the EAG considered predniso*ne* to be interchangeable with predniso*lone* for costing purposes. A comparison of the company's costs of prednisone/prednisolone versus the costs sourced on eMIT are reported in Table 19, however due to the low cost of the treatment, the EAG did not anticipate this to be a driver of the cost-effectiveness results.

Table 19: Alternative prednisolone costs sourced from eMIT

Company reported costs from the BNF			Costs sourced from eMIT		
Dose	Packsize	Price	Dose	Packsize	Price
Prednisolone 1mg	28	£0.88	Prednisolone 1mg	28	£0.16
Prednisolone 2.5mg	30	£1.42	Prednisolone 2.5mg	28	£0.71
Prednisolone 5mg	30	£0.95	Prednisolone 5mg	28	£0.41
Prednisolone 10mg	30	£1.90	Prednisolone 10mg	N/A	N/A
Prednisolone 20mg	30	£3.80	Prednisolone 20mg	28	£3.30
Prednisolone 25mg	56	£40.00	Prednisolone 25mg	56	£17.72
Prednisolone 30mg	28	£29.12	Prednisolone 30mg	N/A	N/A

Abbreviations: BNF, British National Formulary; eMIT, electronic market information tool; mg, milligram; N/A not applicable.

4.2.8.5. Resource use and monitoring

4.2.8.5.1. CKD-based health states

The model considers a cost per cycle related to the occupancy of each CKD-based health state and LN stage:

- CKD stage 1-3a
    - AD
    - PR
    - CR

- CKD stage 3b-4
    - AD
    - PR (only included in scenario analysis – see Section 4.2.2.2)
    - CR (only included in scenario analysis – see Section 4.2.2.2)
- CKD stage 5
    - Dialysis
    - Transplant

Two types of costs are included per health state – a cost of health state entry (referred to as cycle 1 in the company model) and a cost applied within the health state thereafter (referred to as cycle 2+ in the company model). This distinction in costs by cycle of entry (cycle 1) versus later cycles (cycle 2+) allows for the specification of additional costs that are applied upon a particular movement, typically reflecting initial additional monitoring/ investigations. Resource use categories and frequency estimates were applied per cycle and based on clinical guidelines and KOL expert feedback to the company, with key assumptions listed:

- Given there was a paucity of evidence to inform resource use for the PR health state, the resource use frequency is an average of CR and AD (which reflect patients with an absence of flare or AD and patients in an AD health state).
- Urinalysis, complete blood count and anti-dsDNA, C3 and C4 levels monitoring occur every visit
- Serum immunoglobulin measurement, antibody tests, chronic infection screening and cholesterol and lipid monitoring occur every visit in AD, and every second visit in CR

In addition to these assumptions, the CS also states that *"resource use is identical between response states across different CKD stages, except for CKD-specific categories"* (CS, Section B.3.5.2, p.136).

A list of the resource use frequency per health state was provided in Table B.3-18 of the CS. As outlined above, resource use differed by health state, and differential resource use was applied on entry to the model health state. Entrance to the health state was determined by 'Costing

transitions' presented within the company model which used the transition probabilities to derive entrants to new health states. Overall, the EAG was satisfied with the approach taken to estimating medical resource use costs by CKD stage.

4.2.8.5.2. Additional monitoring for CNI-based treatments

In addition to CKD-based health state resource use, a further monitoring cost is applied to tacrolimus. The company did not consider it relevant to apply to the VCS+MMF arm, despite VCS being a CNI, due to an improved immunosuppressive potency, tolerable safety profile and broader therapeutic index which the company explained eliminates the need for regular therapeutic drug monitoring (CS Section B.3.5.2). This additional cost was assumed to apply at every nurse and specialist visit, with frequency dependent on CKD-stage. The EAG has explored a scenario analysis where this cost is also applied to the VCS+MMF treatment arm (given that VCS is also a CNI treatment), which is described further in Section 6.2.

As is the case for a variety of costs included within the company's model, the CS states that the costs for additional monitoring for CNI-based treatments have been adjusted for inflation indices from the NHS cost inflation index from the PSSRU 2021, however the company include no description of the exact indices used and the value incorporated within the model is a hardcoded input within the model. Without transparent explanation, the EAG is unable to cross-check the application.

4.2.8.5.3. Resource use costs incorporated within the model

Resource use costs were calculated predominantly using three sources; the PSSRU 2021, [34] NHS National Schedule 2019/2020[33] and an NHS report by Kerr (2012) [35] on costs for CKD in England.

Costs incorporated within the model were reported in Table 3.4-17 of the CS. PSSRU costs were included to account for costs associated with primary care (e.g., nurse visits). The PSSRU was also used to inflate costs to 2021 costs where appropriate. The NHS National Schedule 2019/2020 was predominantly used to inform non-Kidney specific secondary care costs and testing (e.g., ultrasound scans). The report by Kerr (2012) relating to CKD in England was used to inform CKD-specific costs (predominantly those related to transplant).

On cross-checking of the model inputs, the EAG found that costs from the NHS National Schedule 2019/2020 could not be matched with their original source. Although these costs were inputted as hard coded values, on further inspection, the EAG were able to back calculate that

the costs included were taken from the NHS National Schedule 2019/2020 version 1 and uplifted by an inflationary factor of 1.002 to reflect current prices. The 1.002 inflationary factor can be obtained from the PSSRU 2020/2021 Hospital and Community Health Services (HCHS) prices inflation index (with a NHSCII Pay & Price index of 2.21 for the year) 2019/2020. Therefore, the EAG have assumed that this was the process undertaken for informing NHS National Schedule costs within the model.[34] Despite querying some anomalous costs, and clarification provided by the company (CQ B25), there still remained a few instances where the costs included within the model could not be matched using the same methodology; these are provided in Table 21 for transparency.

The EAG was also unable to consolidate costs used from Kerr (2012).[35] An inflation rate of 1.2636 seemed consistent amongst most costs taken from this document by the company (for urinalysis, initial assessment for kidney transplant, waiting list clinic attendance, post-kidney transplantation year 2+ and anti-hypertensive medication). This cost was calculated within the model by dividing the cost included in the model for each resource unit cost by the corresponding price within the '*CKD in England'* reference. Although this rate is consistent within the model, the EAG could not re-calculate this rate of inflation (by taking the product of inflation rates provided within the relevant PSSRU resources). Calculations are provided in Table 20 below.

Table 20: Inflation rates as calculated by the EAG using PSSRU 2021 inflation indices

Sector	Years of inflation included in product	Overall inflation rate from year specified to 2021
HCHS prices	Inflation rate 2013-2021 inclusive	1.1549
	Inflation rate 2011-2021 inclusive	1.2359
HCHS pay & prices	Inflation rate 2013-2021 inclusive	1.1743
	Inflation rate 2011-2021 inclusive	1.2350

Abbreviations: EAG, evidence assessment group; HCHS, hospital and community health services; PSSRU, Personal Social Services Research Unit

Inflation rates in Table 20 were derived from taking the product of 2011-2021 inflation rates inclusive (since several costs were taken from 2010) and 2012-2021 inflation rates inclusive (publication year of this guidance) using both HCHS prices and HCHS pay & prices.

4.2.8.6. AE costs

Adverse events (AE) costs were again predominantly calculated using the NHS National Schedule 2019/20. The EAG followed calculations provided by the company, however some costs could not be matched. The EAG present a table of the costs of AEs set by the company (Table 21), highlighting differing costs upon re-calculation. Some discrepancies are thought to be rounding errors, and the EAG anticipated the impact on the model results would be minimal.

Table 21: Costs for treatment-emergent Grade 3/4 adverse events shown in company model and re-calculated by the EAG

Adverse event	Value in model	EAG re-calculated value	EAG comments
Pneumonia	£2,701.93	£2,701.93	N/A
Gastroenteritis	£2,490.47	£2,490.30	Potential rounding error
Urinary tract infection	£2,418.10	£2,423.42	Cost was not inflated
Hypertension/hypertensive crisis	£640.41	£640.22	Potential rounding error
Anaemia	£872.29	£1,352.15	Calculated using same weighted average method as for epilepsy (weighting non-elective long stay, non-elective short stay and day-case costs, then inflated by a factor of 1.0022)
Neutropenia	£619.36	£673.88	Cost could not be matched
Bronchitis	£2,299.17	£2,304.23	Cost was not inflated
Herpes zoster/ Varicella zoster virus	£8,868.09		Could not find within reference
Upper respiratory tract infection	£1,458.20	£1,458.21	Potential rounding error
Epilepsy	£1,472.93	£1,472.93	N/A
Septicaemia / Sepsis	£2,422.00	£2,422.00	N/A

Abbreviations: EAG, external assessment group; N/A; not applicable.

4.2.8.7. Second-line therapy costs

Although not explicitly outlined in the CS, subsequent therapy costs were incorporated within the model structure based on a proportion of patients receiving either MMF, azathioprine, rituximab+MMF or tacrolimus+MMF. Proportions were informed based on data from Otsuka

Pharmaceutical market estimates considerations for VCS+MMF and MMF. The assumption was made that all other model comparators would have the same subsequent treatments as MMF. A further assumption was made that besides MMF, patients would not be able to receive the same subsequent therapy as they received in the prior line (for example, patients receiving tacrolimus on the comparator arm would not receive tacrolimus as a second-line treatment). A summary of the proportions are provided in Table 22 alongside the assumed treatment duration.

Whilst the EAG do not have any major concerns with the approach taken by the company, the EAG do note two minor details of the approach taken which lack justification. Firstly the assumption that no patients can receive the same second-line therapy as they had first line – this seems justified, however the approach is not taken for MMF and it's assumed that [redacted] of patients on the MMF arm have receive subsequent MMF. Second to this, the company patients cannot receive the same second-line therapy as their first-line therapy (and this proportion is removed from the model except in the case of MMF). The EAG considered that this may be implausible and instead alternative regimens may have been administered. A different approach could have been taken by the company to redistribute the removed patients to the alternative second-line treatment options.

Table 22: Second-line therapies applied within the CEM

Comparator	**Subsequent treatment**			
	MMF	Azathioprine	Rituximab+MMF	Tacrolimus + MMF
Assumed treatment duration	8 weeks	8 weeks	6 weeks	2 weeks
Voclosporin+MMF	[redacted]	[redacted]	[redacted]	[redacted]
MMF	[redacted]	[redacted]	[redacted]	[redacted]
L-CYC	[redacted]	[redacted]	[redacted]	[redacted]
H-CYC	[redacted]	[redacted]	[redacted]	[redacted]
Aza	[redacted]	[redacted]	[redacted]	[redacted]
Rituximab+MMF	[redacted]	[redacted]	[redacted]	[redacted]
Tacrolimus+MMF	[redacted]	[redacted]	[redacted]	[redacted]
Tacrolimus	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: H-CYC, high dose cyclophosphamide; L-CYC, low dose cyclophosphamide; MMF, mycophenolate mofetil;

4.2.8.8. Mortality costs

Within the CS, end-of-life (EOL) care costs was costed differently depending on whether deaths were LN-related mortality or assumed to be background mortality.

4.2.8.8.1. LN-related mortality

If a death was classed as LN-related, the company costed these events at £12,636. In PSSRU 2021, this was the average cost in the final year of life for a patient diagnosed with renal failure. LN-related deaths were defined as those that either occurred during the period of follow-up in AURORA 1 or AURORA 2, or based on a mortality risk explicitly linked to a CKD-based health state. Deaths captured from background mortality rates were considered separately.

KDIGO guidelines define CKD stage 5 as synonymous with kidney failure. [36] This implies that, within the model, this cost should only relate to people within CKD Stage 5 (i.e., at a point of needing a transplant), and as a result LN-related mortality costs may be overestimated. Some deaths were recorded within AURORA 1 and AURORA 2 (described further in Section 4.2.6), and as mentioned are defined as LN-related within the context of the model. These deaths incur the 'renal failure' EOL cost of £12,636. The EAG noted that deaths that occurred in AURORA 1 or AURORA 2 could be linked to any cause, and could in theory be partially linked to LN (e.g., a cardiovascular event associated with CKD, since CKD is associated with increased risk of cardiovascular events), [37] but could plausibly be any other cause not associated with LN.

The EAG highlights that since no patient in AURORA 1 or AURORA 2 was recorded as having progressed to CKD stage 3b-4 (and by consequence, no patient progressed to CKD stage 5 either), this EOL cost is likely inappropriate because not all deaths within the trial are LN-related and none appear to fulfil the traditional definition of renal failure. The EAG considered a scenario where the LN-related mortality cost within the model is the same as the background mortality cost, £9,590 taken sourced from the PSSRU 2021 and defined as 'any diagnosis'.

4.2.8.8.2. Background related mortality

The company applied a cost of £9,590 to people in their final year needing hospital care for a non-LN-related death. Again, to reiterate the point above, it is unclear how patients should incur this cost in comparison to the renal failure cost since cause of death is not explicitly modelled. Ultimately, the EAG highlights that all patients in the model reside within a CKD-related health state for the duration of the model time horizon, and so to an extent, it could be argued that a

large proportion of deaths are likely to be linked to either LN or CKD, yet it is less clear if this should result in a large difference in EOL costs across arms.

4.2.8.8.3. Issues related with company's approach to mortality costing

Taking into consideration the points raised above, the EAG believed it is unjustified to differentiate between EOL mortality costs since all patients must either be within a CKD stage thus experiencing a "renal failure" death, or a death unrelated to LN, in which case could experience an "any diagnosis" death (acknowledging that it is hard to capture EOL LN costs from this source). As part of EAG exploratory analyses, LN-related deaths are removed from the earlier CKD stages (1-3a). This analysis mitigates (to an extent) this issue of EOL costs, although these will still be applied for CKD states 3b-4 and 5.

5. COST-EFFECTIVENESS RESULTS

5.1. Company's cost-effectiveness results

5.1.1. Base case results

An updated model was provided by the company at clarification stage with several edits provided to the cost-effectiveness calculations. These are described by the company as:

- Updates to AEs
- Updates to the medical resource use costs
- Updates to NMA results for PR
- Connecting RDI for TAC+MMF
- Fixing the error on the Outcomes sheet described as 'some numbers in column A which are used as indices for arrays of results

The results presented within the model did not consistently align with the results presented alongside the CQs (see Table 40 – clarification response). The EAG has assumed that results within the model file are correct, and any discrepancies in results presented in the company's clarification response were minor typographical or copy/paste errors. The results within the company model are shown in Table 23. The deterministic ICER for VCS+MMF versus MMF alone was £19,876. Updated probabilistic results were not provided by the company and therefore have been run and presented by the EAG using the company's updated model provided at clarification (also as part of Table 23).

All results versus the listed comparators were presented by the company as pairwise analyses, not incremental analyses, therefore the EAG has provided full incremental analysis of the comparators listed (shown in Table 24).

Table 23: Company base case results

	Discounted costs	Discounted QALYs	Incremental discounted costs	Incremental discounted QALYs	Pairwise cost per QALY gained
Company deterministic base case (results taken from EAG from updated company CEM provided at clarification stage)					

	Discounted costs	Discounted QALYs	Incremental discounted costs	Incremental discounted QALYs	Pairwise cost per QALY gained
VCS + MMF	[redacted]	[redacted]		[redacted]	
MMF	[redacted]	[redacted]	[redacted]	[redacted]	£19,876
L-CYC	[redacted]	[redacted]	[redacted]	[redacted]	£11,411
H-CYC	[redacted]	[redacted]	[redacted]	[redacted]	£10,914
AZA	[redacted]	[redacted]	[redacted]	[redacted]	£15,855
RTX + MMF	[redacted]	[redacted]	[redacted]	[redacted]	£18,848
TAC + MMF	[redacted]	[redacted]	[redacted]	[redacted]	£18,169
TAC	[redacted]	[redacted]	[redacted]	[redacted]	£17,833
Company probabilistic base case (analysis run by EAG from updated company CEM provided at clarification stage)					
VCS + MMF	[redacted]	[redacted]	[redacted]	[redacted]	-
MMF	[redacted]	[redacted]	[redacted]	[redacted]	£21,086
L-CYC	[redacted]	[redacted]	[redacted]	[redacted]	£11,962
H-CYC	[redacted]	[redacted]	[redacted]	[redacted]	£11,458
AZA	[redacted]	[redacted]	[redacted]	[redacted]	£17,041
RTX + MMF	[redacted]	[redacted]	[redacted]	[redacted]	£20,683
TAC + MMF	[redacted]	[redacted]	[redacted]	[redacted]	£18,364
TAC	[redacted]	[redacted]	[redacted]	[redacted]	£18,331

Abbreviations: AZA = azathioprine; CEM, cost-effectiveness model; CYC, cyclophosphamide; H-CYC, high-dose CYC; L-CYC, low-dose CYC; MMF, mycophenolate mofetil; QALY, quality adjusted life year; RTX, rituximab; TAC, tacrolimus; VCS

Table 24: Full incremental analysis of voclosporin+MMF versus comparators – company base case

Treatment	Total discounted costs	Total discounted QALYs	Incremental discounted costs	Incremental discounted QALYs	ICERs (following re-baseline)
Company incremental base case (results taken by EAG from updated company CEM provided at clarification stage)					
MMF	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
AZA	[redacted]	[redacted]	[redacted]	[redacted]	Strictly Dominated
TAC + MMF	[redacted]	[redacted]	[redacted]	[redacted]	Extendedly dominated

Treatment	Total discounted costs	Total discounted QALYs	Incremental discounted costs	Incremental discounted QALYs	ICERs (following re-baseline)
TAC	[redacted]	[redacted]	[redacted]	[redacted]	Extendedly dominated
L-CYC	[redacted]	[redacted]	[redacted]	[redacted]	Strictly Dominated
H-CYC	[redacted]	[redacted]	[redacted]	[redacted]	Strictly Dominated
RTX + MMF	[redacted]	[redacted]	[redacted]	[redacted]	Extendedly dominated
VCS + MMF	[redacted]	[redacted]	[redacted]	[redacted]	£19,897

Abbreviations: AZA = azathioprine; CEM, cost-effectiveness model; CYC, cyclophosphamide; H-CYC, high-dose CYC; L-CYC, low-dose CYC; MMF, mycophenolate mofetil; QALY, quality adjusted life year; RTX, rituximab; TAC, tacrolimus; VCS

5.2. Company's sensitivity analyses

5.2.1. Deterministic sensitivity analysis

The company presented the results of a one-way sensitivity analysis to explore the sensitivity of the base case results by varying key parameters within plausible 95% confidence intervals. The included parameters are respective ranges presented as an Appendix to the company submission document (CS Appendix O). The EAG noted that as part of the original submission the company did not present DSA results against any comparison besides VCS+MMF vs. MMF. Further to this, in response to the CQs, the company did not provide an updated deterministic sensitivity analysis, following revisions to the model. The EAG have therefore re-ran the analysis presented within the model for VCS+MMF vs MMF and results are presented in Figure 5, Figure 6 and Figure 7 for the impact on the incremental costs, incremental QALYs and the ICER respectively.

Figure 5: DSA: Incremental costs from company model (analysis ran by EAG on the updated company CEM provided at clarification stage)

Abbreviations: AD, active disease; CKD, chronic kidney disease; LN, lupus nephritis; MMF, mycophenolate mofetil

Figure 6: DSA: Incremental QALYs from company model (analysis ran by EAG on the updated company CEM provided at clarification stage)

Abbreviations: AD, active disease; CKD, chronic kidney disease; partial response; MMF, mycophenolate mofetil; QALY, quality-adjusted life year

Figure 7: DSA: ICER from company model (analysis ran by EAG on the updated company CEM provided at clarification stage)

Abbreviations: AD, active disease; CKD, chronic kidney disease; ICER, incremental cost-effectiveness ratio; MMF, mycophenolate mofetil

The EAG has a fundamental issue with the company's DSA. Firstly, the inclusion of interlinked parameters within the DSA (for example transition probabilities from AD CKD 1-3a to death). Whilst important to test parameter uncertainty associated with such transitions, this parameter is linked with several other transitions within the model to ensure that the transition probabilities sum to 100%. As the model contains adjustments to account for differences in transition probabilities, varying this probability to death has a knock-on implication for other transition probabilities from the AD CKD 1-3a health states (for patients remaining in AD CKD 1-3a). This is illustrated in Table 25 which shows the transition probabilities when varying this parameter at its lower and upper bound, and the impact on the VCS+MMF 6-month transition probabilities. Given the parameters are interlinked, the description provided by the company of a deterministic one-way sensitivity analysis is inaccurate as all parameters were not varied one at a time. This is problematic for two of the top ten results in the DSA ('AD CKD 1-3a -> Death' and 'AD CKD 1-3a -> AD CKD 3b-4'). It is the opinion of the EAG that interlinked parameters should not be included in a DSA framework and instead should be explored through PSA and scenario analysis to avoid misinterpretation of results.

Table 25: CKD 1-3a AD transition probability at 6-months for VCS + MMF

To:		From CKD 1-3a AD		
		Deterministic	**Upper bound**	**Lower bound**
CKD 1-3a	**CR**	[redacted]	[redacted]	[redacted]
	PR	[redacted]	[redacted]	[redacted]
	AD	[redacted]	[redacted]	[redacted]
CKD 3b-4	**CR**	[redacted]	[redacted]	[redacted]
	PR	[redacted]	[redacted]	[redacted]
	AD	[redacted]	[redacted]	[redacted]
CKD 5	**Dialysis**	[redacted]	[redacted]	[redacted]
	Transplant	[redacted]	[redacted]	[redacted]
Death		[redacted]	[redacted]	[redacted]
Sum		[redacted]	[redacted]	[redacted]

Abbreviations: AD, active disease; CKD, chronic kidney disease; CR, complete response; PR, partial response

Second to this issue, the EAG believed that in other instances parameters lacked face validity when tested at their lower and upper bound and may substantially over-estimate the volume of uncertainty each parameter is associated with. For example, the utility value for CR CKD Stage 1-3a is varied between bounds of 0.433 and 0.997 (with a deterministic input of 0.83). Given the utilities were derived from the SF-36 in AURORA 2 (at Month 36), it is probably that a realistic lower bound of the CR CKD Stage 1-3a utility would also translate to a similarly lower utility for patients in the PR and AD health states (which remain constant in the DSA framework at 0.8 and 0.71 respectively), implying that a patient has a substantially lower HRQoL in the best health state feasible within the model (CR in CKD stage 1-3a); this lacks face validity.

Finally, the EAG considered that the company should have considered presenting DSA in the context of a net-monetary benefit (NMB) as opposed to the ICERs, given results produce negative values. In the context of negative ICERs, it is not possible without further investigation to understand where on a cost-effectiveness plane the results are positioned (i.e., is the intervention less costly and more effective and therefore dominant, or conversely less effective and more costly and therefore dominated by the comparator).

In summary, the EAG does not consider the specific outputs of the DSA to be relevant for decision making except to illustrate that parameters included (isolated and linked) impact model results, and edits should be made to exclude inappropriate parameters before results can be interpreted in a meaningful way.

5.2.2. Probabilistic sensitivity analysis

The company conducted a probabilistic sensitivity analysis (PSA) to explore parameter uncertainty with 1,000 iterations conducted. The company did not provide an updated PSA as part of the response to clarification and therefore the EAG have re-ran the analysis on the updated model provided by the company at clarification stage. In line with the format presented by the company in the submission, the EAG provide Figure 8, Figure 9 and Figure 10 which illustrate the PSA results in a PSA scatterplot for total discounted costs and QALYs, the PSA scatterplot for incremental discounted costs and QALYs and the cost effectiveness acceptability curve (CEAC) respectively.

Figure 8: Cost-effectiveness plane – total discounted costs and QALYs (analysis re-ran by the EAG in the updated company's CEM provided at clarification stage)

Abbreviations: AZA = azathioprine; CEM, cost-effectiveness model; CYC, cyclophosphamide; H-CYC, high-dose CYC; L-CYC, low-dose CYC; MMF, mycophenolate mofetil; QALYs, quality adjusted life years; RTX, rituximab; TAC, tacrolimus

Figure 9: Cost-effectiveness plane – incremental discounted costs and QALYs (re-ran by the EAG in the updated company's CEM provided at clarification stage)

Abbreviations: AZA = azathioprine; CEM, cost-effectiveness model; CYC, cyclophosphamide; H-CYC, high-dose CYC; L-CYC, low-dose CYC; MMF, mycophenolate mofetil; QALYs, quality adjusted life years; RTX, rituximab; TAC, tacrolimus

Figure 10: CEACs (re-run by the EAG in the updated company's CEM provided at clarification stage)

Abbreviations: AZA = azathioprine; CEM, cost-effectiveness model; CYC, cyclophosphamide; H-CYC, high-dose CYC; L-CYC, low-dose CYC; MMF, mycophenolate mofetil; RTX, rituximab; TAC, tacrolimus

Given the number of comparators included within the graphs, the EAG provide a further diagram (Figure 11) which illustrates the parameter uncertainty within the PSA for VCS+MMF vs. MMF. In addition to this, for ease of interpretation, the EAG have also added in the deterministic result and the average result from the 1,000 iterations to the graph taken from the updated company model provided at clarification stage. As illustrated within the revised diagram, the incremental

costs associated with VCS+MMF vs. MMF alone are always positive (indicating that VCS+MMF costed more in each of the 1,000 iterations) and vary between £2,872 and £32,411. Incremental QALYs associated with VCS+MMF vs MMF alone varied between -1.17 and 3.591 cross the 1,000 iterations. These results indicate that there is a wide range of parameter uncertainty within the company model and selected model base case. Overall, the deterministic and probabilistic mean values were similar with similar incremental costs and slightly lower probabilistic incremental QALYs.

The individual diagrams for VCS+MMF vs the other comparators included within the model are provided as an Appendix (Appendix A).

Figure 11: Cost-effectiveness plane for voclosporin+MMF vs MMF

Abbreviations: MMF, mycophenolate mofetil; QALYs, quality adjusted life years

5.2.3. Scenario analyses

The company undertook a range of scenario analyses to consider alternative data sources and assumptions within the economic model. Full details of this are provided in CS Section B.3.11.3. The company provide scenario analysis of voclosporin+MMF versus MMF related to:

- Time horizon
- Discount rates
- Stopping rules
- Utilities

- TTD
- Wastage

The EAG considered the range of scenarios presented by the company to be limited in range, and hence have limited ability to wholly explore structural uncertainty within the model and decision problem.

5.3. Model validation and face validity check

An overview of the company's approach taken to validate the submitted cost-effectiveness analysis is provided in Section B.3.14.1 of the CS. The company notes that a technical validation of the model was undertaken internally to ensure that calculations of the model were correct prior to submission. The company also stated that an external health economist reviewed the CS with feedback incorporated prior to submission. Details of the technical validity were not provided by the company, nor were details of the type of review undertaken by the external health economist, and so the EAG does not discuss this further. However, further details of the EAG's corrections and adjustments to the company's model are provided in Section 6.1 of this report.

In addition to the technical validation, the company also sought to compare data from AURORA 1 to the outputs of the model as an internal validation exercise (CS Section B.3.14.1). The company presented estimates of the proportion of patients with PR or CR at 12 months in the model, versus the 'true' results of AURORA 1 (CS Table B.3-28). At clarification stage (CQ B32), the EAG queried an apparent discrepancy between the 'published' PR value for VCS + MMF of 70% (125/179, from Rovin *et al.*, 2021) and the implied CR+PR 'count' value of 74.86% (134/179, which can be inferred from CS Table B.3-28). In response, the company explained that PR is not mutually exclusive from CR using the definition of response in Rovin *et al.*, (2021), and that most but not all patients who achieved CR also achieved PR. The EAG therefore does not consider this discrepancy to be an error, but instead highlights the difficulties associated with comparing PR and CR rates, given that most but not all CRs can also be considered PRs.

With respect to the internal validation exercise, the EAG again noted that because of the designs of AURORA 1 and AURORA 2, the company could not present the results of an equivalent internal validation exercise for a time horizon longer than 1 year. Consequently, the

EAG considered the internal validation to have limited merit beyond confirming that the 'count method' yields transition probabilities that largely reflect the data collected in AURORA 1.

Outside of the remit of model validation, the EAG highlighted that the company's model included a number of apparent input parameters which have no influence on model calculations. The EAG considered the inclusion of these parameters to be problematic in terms of transparency; however, since they do not compromise the model calculations, these 'unused' parameters are not considered further as part of the EAG's critique.

6. EVIDENCE REVIEW GROUP'S ADDITIONAL ANALYSES

Due to the size and complexity of the model, paired with limited description within the CS, a thorough cell-by-cell inspection of the model was not feasible within the timeframe available. However, the EAG conducted black box (i.e., face validity) tests on the model in Excel alongside a crosscheck of inputs included within the model. The structure of the company's model was somewhat rigid in terms of how it captured health and cost outcomes associated with LN. Given the rigid structure, the EAG's ability to incorporate additional flexibilities to adequately understand uncertainty associated with the decision problem was limited.

This section is organised as follows: Section 6.1 details the impact of errors identified in the EAG's validation of the executable model (focused mostly on 'black box' tests and crosschecking input parameters). Section 6.2 details a series of scenario analyses exploring the areas of concern identified by the EAG (as discussed throughout Section 4 of this report). A summary of the scenarios explored by the EAG are provided at the end of Section 6.2. Following identification of corrections and investigation of the scenarios undertaken by the EAG, combined with alternative functionality included by the company in its submitted model, the EAG presents its preferred base-case analysis in Section 6.3. Finally, Section 6.4 presents the EAG's conclusions of the cost-effectiveness section of the CS.

6.1. EAG corrections and adjustments to the company's base case model

Below is a short list of errors that the company identified after submission and resolved in a revised model provided at clarification stage:

- RDI for tacrolimus+MMF was taking a value of 100% rather than 95% as intended
- Error in inflationary costs
- Error in results sheet where resource use was referring to incorrect cell ranges
- Error in NMA application for PRR

EAG also noted an error found in application of disutilities, as these values were mistakenly halved. The disutilities associated with AEs affect the 'QALYs' sheet, on rows 5:6 columns Q, AB, CP, DA. While this errors only affects MMF containing regimens, since VCS+MMF contains MMF the company's base-case results are affected as a result of resolving this error. Table 26 provides a summary of the EAG-corrected company base-case results, and Table 27 provides a

breakdown of revised incremental analysis. All scenarios provided by the EAG are with the correction for disutilities applied. While the EAG consider MMF to be the main comparator for consideration and hence provide a breakdown of results for voclosporin+MMF versus MMF, advice to the EAG indicated that tacrolimus may also be a comparator of interest. As such, for the EAG corrected base case and the summary of EAG preferred base case, full incremental analysis is presented which shows a comparison of voclosporin+MMF versus all comparators within the model (including the key comparators of interest, MMF and tacrolimus).

Table 26: EAG-corrected company base case results

	Discounted costs	Discounted QALYs	Incremental discounted costs	Incremental discounted QALYs	Cost per QALY gained
EAG corrected company deterministic base case					
VCS + MMF	[redacted]	[redacted]	-	-	-
MMF	[redacted]	[redacted]	[redacted]	[redacted]	£19,897
L-CYC	[redacted]	[redacted]	[redacted]	[redacted]	£11,468
H-CYC	[redacted]	[redacted]	[redacted]	[redacted]	£10,966
AZA	[redacted]	[redacted]	[redacted]	[redacted]	£15,947
RTX + MMF	[redacted]	[redacted]	[redacted]	[redacted]	£18,882
TAC + MMF	[redacted]	[redacted]	[redacted]	[redacted]	£18,189
TAC	[redacted]	[redacted]	[redacted]	[redacted]	£17,969
EAG corrected company probabilistic base case					
VCS + MMF	[redacted]	[redacted]	-	-	-
MMF	[redacted]	[redacted]	[redacted]	[redacted]	£21,508
L-CYC	[redacted]	[redacted]	[redacted]	[redacted]	£12,191
H-CYC	[redacted]	[redacted]	[redacted]	[redacted]	£11,754
AZA	[redacted]	[redacted]	[redacted]	[redacted]	£17,422
RTX + MMF	[redacted]	[redacted]	[redacted]	[redacted]	£21,854
TAC + MMF	[redacted]	[redacted]	[redacted]	[redacted]	£18,782
TAC	[redacted]	[redacted]	[redacted]	[redacted]	£19,186

Abbreviations: AZA = azathioprine; CEM, cost-effectiveness model; CYC, cyclophosphamide; H-CYC, high-dose CYC; L-CYC, low-dose CYC; MMF, mycophenolate mofetil; QALYs, quality adjusted life years; RTX, rituximab; TAC, tacrolimus; VCS

Table 27: EAG corrected: Full incremental analysis of voclosporin+MMF versus comparators – company base case –

Treatment	Total discounted costs	Total discounted QALYs	Incremental discounted costs	Incremental discounted QALYs	ICERs (following re-baseline)
Company incremental base case (results taken by EAG from updated company CEM provided at clarification stage with fix applied)					
MMF	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
AZA	[redacted]	[redacted]	[redacted]	[redacted]	Strictly Dominated
TAC + MMF	[redacted]	[redacted]	[redacted]	[redacted]	Extendedly dominated
TAC	[redacted]	[redacted]	[redacted]	[redacted]	Extendedly dominated
L-CYC	[redacted]	[redacted]	[redacted]	[redacted]	Strictly Dominated
H-CYC	[redacted]	[redacted]	[redacted]	[redacted]	Strictly Dominated
RTX + MMF	[redacted]	[redacted]	[redacted]	[redacted]	Extendedly dominated
VCS + MMF	[redacted]	[redacted]	[redacted]	[redacted]	£19,897

Abbreviations: AZA = azathioprine; CEM, cost-effectiveness model; CYC, cyclophosphamide; H-CYC, high-dose CYC; L-CYC, low-dose CYC; MMF, mycophenolate mofetil; QALY, quality adjusted life year; RTX, rituximab; TAC, tacrolimus; VCS

6.2. Exploratory and sensitivity analyses undertaken by the EAG

The EAG have undertaken a range of alternative exploratory analyses within the company's model. Whilst some exploratory analysis links to functionality already within the model provided by the company, further model edits have also been undertaken to try to explore structural uncertainty, where possible. Each model scenario is discussed in turn throughout this section.

6.2.1. Scenario 1: Amending the approach to applying trial-based utility values to CKD states 1-3a (AD, PR and CR)

In the company's model, the heath state utility values were based on 36-month data from AURORA 2. The EAG considered this approach to be inappropriate as it ignores all data from month 0 to month 36 (see Section 4.2.7.2). Based on this, the EAG considered an analysis which produces a weighted average utility value per health state (CKD stage 1-3a for AD, PR and CR) based on the information provided within the company submission (CS Table B.3-10)

and applied the calculated values as health state utilities within the model. Table presents a summary of the utility values obtained and applied within the EAG analysis.

Table 28: EAG scenario - weighted average of mapped utility values

Health state	Health state utility values applied in company base case	Health state utility values applied in EAG analysis
CKD Stage 1-3a CR	0.830	0.814
CKD Stage 1-3a PR	0.800	0.800
CKD Stage 1-3a AD: Non-response	0.710	0.749

Abbreviations: AD, active disease; CR, complete response; PR, partial response

As shown in the approach the company have taken, the utilities for the CR health state are higher (+0.162) than when applying a weighted average, and the AD value is lower (-0.385). The EAG considered that this approach may favour the VCS+MMF arm within the model where CR rates are higher. Whilst the differences may appear small between the two methods, the company's base case ICER for VCS+MMF versus MMF increases from £19,897 to £21,401 (+£1,504) when applying the weighted values. In the absence of a regression model, the EAG considered this scenario to represent a more reasonable approach to modelling utility values based on the data available.

6.2.2. Scenario 2: Amending health state utility values for CKD Stage 5 (transplant and dialysis)

As outlined in Section 4.2.7.4, the EAG had concerns regarding the approach taken to populating the model with dialysis and transplant utilities. The company makes use of values from a study by Lee *et al.,* (2005) [28], which, as the EAG outlined previously, has limitations in comparability with the LN patient population relevant to this appraisal (e.g., 53 versus 60-67 years [depending on sex and timing of dialysis]).

The EAG identified Cooper *et al*., 2020[31] which was a systematic review of utility weights through different stages of CKD, and a study by Li *et al.,* (2017), [32] which presents regression models with various characteristics relevant for consideration in an LN setting (e.g., predominantly female, nondiabetic, younger patients).

The EAG explored three alternative approaches to applying health state utility values for the CKD Stage 5 transplant and dialysis utility values.

6.2.2.1. Scenario 2A: the EAG applied a transplant utility value taken from the Li *et al.* [32] regression analysis

Within the Li *et al.,* 2017 publication[32] eight regression analyses are presented which include predictive variables on health state utility values for waiting list patients and transplant recipients. The EAG considers 'model 7' to be the most relevant for consideration with transplant values versus waiting list, age, gender and diabetes status. Using the regression model with the average age (33.2†) and proportion female (87.7%) from the company model, a revised estimate for transplant patients was estimated using the following formula (assuming no patients were diabetic):

$$Transplant\ utility = baseline\ (0.830) + age + diabetic + female + transplant$$

$$Transplant\ utility = 0.830 + (-0.036) + 0 + \ (-0.033 * 0.877) \ + \ (+0.053)$$

$$Transplant\ utility = 0.818$$

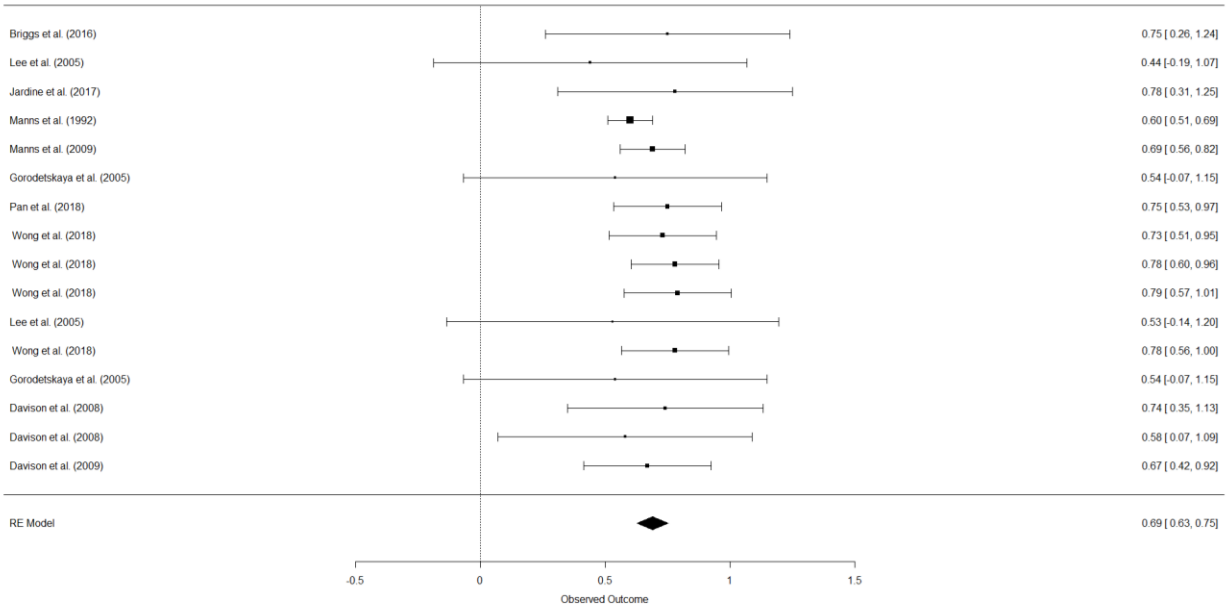
The company's base case ICER for VCS+MMF versus MMF increases from £19,897 to £20,152 (+£255) when applying the alternative transplant value.

6.2.2.2. Scenario 2B: the EAG applied a dialysis utility value taken from a meta-analysis of values presented within Cooper et al. [31]

In the systematic review by Cooper *et al.,* [31] utility weights through different stages of CKD are presented. Within the paper, Table 4 presents a summary of all CKD Stage 5 utilities, split by dialysis and transplantation. The EAG meta-analysed the dialysis values presented in Cooper *et al.* to obtain a mean estimate of 0.69. This scenario explored the impact of applying the meta-analysed value to the CKD stage 5 dialysis health state. Using this value increases the company base case ICER by £87 (from £19,897 to £19,983 for VCS+MMF versus MMF).

† Age is a categorical variable in 'model seven' from Li *et al.*, (2017)

Figure 12: Meta-analysis of dialysis utilities outlined in Cooper et al. 2020[31]



6.2.2.3. Scenario 2C: the EAG apply a dialysis utility value taken from the largest source of EQ-5D data for dialysis patients with an applied utility increment for transplant patients (taken from Li *et al*. [32])

In this final scenario, the EAG amended both the CKD stage 5 (dialysis and transplantation) values simultaneously. This scenario uses the 0.75 dialysis value from Briggs *et al.,* 2016 as presented in Cooper *et al.,* (2020) [31] This was selected as the largest source of EQ-5D-3L data. The transplantation utility was calculated by using the Briggs et al 0.75 value and applying the transplant increment reported in Li et al. (+0.053 as outlined in 'model 7'). [32] The resulting change in the company ICER when this scenario is applied is a slight increase of £334 (£19,897 to £20,230 for VCS+MMF versus MMF).

6.2.3. Scenario 3: Wastage applied to voclosporin

Voclosporin is expected to be dispensed in packs providing a 30-day supply (180 tablets of 7.9mg dose). However, in the company's model, patients are modelled to incur the cost of treatment based on the half-cycle corrected LYs within a model cycle and based on a time-to-treatment discontinuation curve. Hence, patients are costed to receive the precise number of tablets within a model cycle that are needed, with no rounding to account for the number of tablets dispensed. In reality, it is expected that some product wastage for voclosporin would arise for patients that discontinue due to any cause part-way through a pack. As this is not

explicitly modelled within the company base case, the EAG has explored a simple analysis which adds on half of an additional pack of voclosporin to the overall incremental costs projected by the model to ascertain the potential impact of including wastage within the model results. This analysis causes the company's base case ICER to increase from £19,897 to £20,413 (+£516).

6.2.4. Scenario 4: 2g dose of MMF

The company base case applied a 2.5g dose of MMF daily based on referenced guidelines from EULAR/ERA-EDTA, which suggested a recommended dose between 2-3g. To align with the AURORA 1 and AURORA 2 trial, the EAG considered a scenario applying a 2g dose. The impact of this scenario is minimal on the base case results producing a revised ICER that is £13 less than the deterministic result (£19,897 versus £19,884).

6.2.5. Scenario 5: Additional monitoring for CNI treatment applied to voclosporin

As outlined within Section 4.2.8.5.2, the company included additional monitoring for CNI treatments (tacrolimus). The company did not consider it relevant to apply this additional cost to the VCS+MMF arm, despite VCS being a CNI, as they state it has an improved immunosuppressive potency, a tolerable safety profile and broader therapeutic index. Expert advice to the EAG suggested that, based on the current available evidence, voclosporin would be considered comparable to other CNIs with regard to monitoring. Therefore, for completeness the EAG has explored a scenario where the cost is applied to all CNI treatments within the model (i.e., the VCS+MMF and tacrolimus arms).

This scenario increases the company base case ICER from £19,897 to £20,862 (+£965).

6.2.6. Scenario 6: Amendments to cost inputs to align with referenced sources

As outlined throughout Section 4.2.8, there were several instances where the company's description of a given cost did not align with the original sources. As such, the EAG conducted a scenario that aligned the costs to the original sources, applied cheaper drug cost prices where available, and inflated costs to current prices where relevant. In addition to this, the EAG also adjusted the LN-related mortality cost to be aligned with 'any diagnosis' end of life cost as reported within the PSSRU 2021. The rationale for this was two-fold: firstly, the description of renal failure within the PSSRU may relate to the later CKD stages (i.e., CKD stage 5), and

therefore death from earlier states may be overestimating costs applied; second to this, the costs included within the PSSRU account for costs within the final year of life, and resource use within the model already varies by health state, and as such these differences may already be captured within the model resource use calculations. A description of the amendments made are shown in Table 29. Whilst the amendments to the costs are small, the resulting impact is a +£217 on the company base case ICER (from £19,897 to £20,114).

Table 29: EAG amended costs

Cost type	Cost description	Company model cost	EAG scenario cost
AE cost	Urinary tract infection	£2,418.10	£2,423.42
	Anaemia	£872.29	£1,352.15
	Neutropenia	£619.36	£673.88
	Bronchitis	£2299.17	£2,304.23
Resource use costs	Initial assessment for kidney transplant	£3,205.72	£3,135.49
	Waiting list clinic attendance (pre-transplant)	£3,754.12	£3,617.87
	Post-kidney transplantation year 2+	£9,246.94	£9,044.35
	Anti-hypertensive medication	£166.79	£163.14
Prednisone/prednisolone costs	1mg	£0.88 (28 pack)	£0.16 (28 pack)
	2.5mg	1.42 (30 pack)	£0.71 (28 pack)
	5mg	£0.95 (30 pack)	£0.41 (28 pack)
	20mg	£3.80 (30 pack)	£3.30 (28 pack)
	25mg	£40 (56 pack)	£17.72 (56 pack)
EOL cost	LN related death	£12,636	£9,590

Abbreviations: AE, adverse event; LN, lupus nephritis

6.2.7. Scenario 7: Amendments to estimating treatment costs for the intervention and comparators

The company applied an RDI of 100% for all treatments except for tacrolimus + MMF, which instead had an RDI estimate of 95%. Further to this, TTD curves were applied to the VCS+MMF and MMF arms but all other comparators were assumed to have no treatment discontinuation. Based on responses to clarification questions (and outlined in Section 4.2.8.2), the EAG believe

that there is a fundamental misinterpretation between the use of the TTD curve and the application of RDI in the model with regard to estimating treatment costs. A TTD curve provides information about the duration of time that patients spend on treatment before permanent discontinuation, whereas RDI provides an estimate of the proportion of treatment that was administered relative to the planned dose (for those patients still receiving treatment). As such the EAG has conducted two additional scenarios in relation to estimating treatment costs within the economic model. These are discussed in turn.

6.2.7.1. Scenario 7A: the EAG assuming an RDI of 95% for all comparators

In this scenario, the EAG apply an RDI value of 95% for all treatment options included in the model (i.e., all comparators and VCS+MMF). Whilst a simplified scenario using an arbitrary number (though the estimate of 95% was applied to tacrolimus within the company base case), in the absence of alternative data, either from the literature or from the AURORA studies, this scenario considered that not all patients will receive 100% of the planned dose.

Though the EAG acknowledges the limitations of using essentially arbitrary values to inform RDI, in the absence of an alternative approach which exhibits face validity, the EAG deems the use appropriate for exploration. The application of the 95% RDI reduces the ICER from £19,897 to £18,699 (-£1,198) within the comparison of VCS+MMF versus MMF.

6.2.7.2. Scenario 7B: the EAG assuming TTD equivalent to MMF for all other model comparators

In this scenario, the model assumes that for all comparators (but not the VCS+MMF arm), that TTD is equivalent to the curve informing the MMF arm. Similar to the scenario above (7A), this scenario serves as an exploratory analysis to illustrate that not all patients are likely to remain on treatment throughout the duration of the model and may discontinue for a plethora or reasons (including but not limited to lack of efficacy and occurrence of adverse events).

Table 30 reports the impact of this scenario in comparison to the company base case. The largest impact is on the VCS+MMF versus rituximab+MMF scenario, where the ICER increases by £4,922. All other comparisons have a relatively small impact on the ICER (varying from £22 difference for VCS+MMF versus AZA, to £681 for VCS+MMF versus tacrolimus).

Table 30: EAG exploratory analysis: comparison of ICERs when applying a treatment costing scenario assuming TTD for non-MMF comparators is equivalent to MMF

Comparisons	Company base case ICER	EAG treatment costing scenario: assuming TTD for comparators is equivalent to MMF
VCS + MMF vs MMF	£19,897	£19,897
VCS + MMF vs L-CYC	£11,468	£11,833
VCS + MMF vs H-CYC	£10,966	£11,316
VCS + MMF vs AZA	£15,947	£15,968
VCS + MMF vs RTX + MMF	£18,882	£23,804
VCS + MMF vs TAC + MMF	£18,189	£18,663
VCS + MMF vs TAC	£17,969	£18,649

Abbreviations: AZA = azathioprine; CEM, cost-effectiveness model; CYC, cyclophosphamide; H-CYC, high-dose CYC; L-CYC, low-dose CYC; MMF, mycophenolate mofetil; RTX, rituximab; TAC, tacrolimus; TTD, time-to-treatment discontinuation; VCS, voclosporin.

6.2.8. Scenario 8: Exploratory impact of restricting movement from CKD 5 transplant back to CKD 5 dialysis

As outlined within Section 4.2.6.7, the memoryless nature of the Markovian model and the ability for patients to move backwards and forwards between the CKD stage 5 health states (dialysis and transplant), means that it is possible for patients to undergo multiple transplants (with the same probability per model cycle) over the modelled lifetime horizon. The EAG considered this to lack face validity, and as such have explored a scenario (already existing within the company model) which disables movement from re-transplantation. This analysis in isolation had a low impact on the modelled ICER with a difference of +£460 from the company base case (£20,357 and £19,897 respectively).

6.2.9. Scenario 9: Reduction in transplantation rates (CKD 5 dialysis to CKD 5 transplant)

Advice to the EAG indicated that transplantation rates included within the company's base case model may be too high (90% of patients receiving a kidney transplant within two years from developing stage 5 CKD – translating to a per-cycle rate of 43.77%). Expert advice suggested that 65% (within two years) may serve as a better reflection of current clinical practice. As such, the EAG have considered a scenario which reduces the transplantation rate to be 65% over two

years (translating to a per cycle rate of 23.08%). This exploratory scenario has a relatively small impact on the base case ICER for VCS+MMF versus MMF (£19,897 in the base-case compared to £19,526).

6.2.10. Scenario 10: Removal of LN related deaths for CKD stages 1-3a

The EAG previously highlighted limitations of including LN-related mortality within the model for the early CKD stages (1-3a). The EAG has therefore conducted a scenario which removes LN death from the model in the first 36 months from CR and PR CKD stages 1-3a (Scenario 10A), and another scenario removing LN death from the model in the first 36 months from CR, PR, *and* AD CKD stages 1-3a (Scenario 10B). The rationale for undertaking these scenarios is two-fold. Firstly, the LN-related deaths incorporated within the company's cost-effectiveness model were based on a small number of observed deaths in AURORA 1 and AURORA 2, and the methodology used to estimate transition probabilities within the model means that the deaths can have a marked impact on results, which may not be a true reflection of reality and instead an artefact of a within trial analysis and small sample size. This issue is exacerbated further by the fact that the approach taken to capture LN-related deaths differs according to health state (i.e., CR and PR deaths are estimated as time-varying and arm-specific, whereas AD deaths are constant over time, and equal across arms). Secondly, the EAG considered it counter-intuitive that it was infeasible within the model structure for patients to progress CKD stage within the 36-month window however they could experience LN-related death. Based on this, the EAG believe it is possible that LN-related death could be overestimated within the model, and with the application of mortality specific costing (see Section 4.2.8.8), this could in turn overestimate total costs within the model and underestimate total QALYs gained across treatment arms.

6.2.10.1. Scenario 10A: Remove LN deaths for CR and PR, CKD stages 1-3a using count method

In this scenario, the EAG removed the impact of the 'count method' deaths that apply to some model cycles for the CR, PR and AD health states (in CKD stages 1-3a) based on data from only AURORA 1 and 2. The removal of the LN-related deaths for CR, PR and AD, CKD stages 1-3a, has a substantial impact on the company's modelled ICER, increasing the base-case ICER from £18,897 to £23,497 (+£3,600). The removal of these deaths adjusts the ICER, however LN death still occurs due to an additional model parameter (explored in Scenario 10B).

6.2.10.2. Scenario 10B: Remove LN deaths for CR, PR, and AD, CKD stages 1-3a using count method and additional model scenario

As an alternative to Scenario 10A, in Scenario 10B the EAG assumed that the risk of death in each of the CKD stage 1-3a states (for first 36-months of the model) would be captured by background mortality (which is also accounted for within the company base case model), however two methods are used to remove early-stage CKD deaths from the model. This scenario involves the adjustments to the 'count method' outlined in Scenario 10A, with a further adjustment to a switch within the company's model labelled "Transitions shared between all treatments, AD CKD 1-3a -> Death". The company base case inputs the count data method and a further proportion of 1.729% also referenced as being count method data. Therefore, without further description the EAG considered there could be potential risk of double counting of deaths within the model for CKD stages 1-3a. The removal of the LN related deaths for CR, PR and AD, CKD stages 1-3a, in the 36-month transition probabilities as well as amending the additional parameter to 0% has an strikingly large impact on the company's modelled ICER, increasing the base-case ICER from £18,897 to £38,125 (+£18,228).

6.2.11. Scenario 11: Inclusion of transitions into CKD 3b-4 and 5 in the first 36 months

Within the company base case, the model framework does not allow patients to experience CKD progression within the first 36 months of the time horizon. Whilst CKD progression was not observed within the AURORA 1 and AURORA 2 trial follow-up, the EAG considered it feasible that some patients may experience CKD disease progression, and this transition may be of particular relevance for those patients who do not respond to treatment (and hence remain in an AD health state). This 'protective' assumption by the company may be particularly problematic when considering patients who have received prior treatment with MMF (54.9% of the AURORA 1 population), and who still do not achieve response (e.g., within the current model framework and based on the anticipated patient population, it is feasible that a patient could have been receiving MMF for several months with no response to treatment, enters the model, receives VCS+MMF, still does not achieve response, and yet their CKD is still contains a protective property which means their CKD cannot progress for 36 months).

The EAG therefore explored a scenario analysis which already exists within the company's economic model allowing patients to transition from CKD stages 1-3a to 3b-4 within the first 36 months. The transition in this scenario is only considered for movements from AD and patients

in a PR and CR health state are still 'protected' from CKD progression unless they lose response (i.e., move to AD). The movement from CKD stage 1-3a AD to CKD stage 3b-4 AD is 3.05%, which the company derived from KOL expert feedback which indicated that the probability of patients progressing CKD stage was 6% per year.

The inclusion of this scenario has a large impact on the company ICER and reduces the base case ICER for VCS+MMF versus MMF from £19,897 to £14,811 (-£5,086) highlighting the extent of structural uncertainty within the model.

6.2.12. Scenario 12: Long-term transition probabilities for VCS+MMF and MMF and the implementation–

The company describe how uncertainty related to sustained efficacy within the model was captured by applying a long-term waning effect for VCS+MMF which assumed that when patients stopped treatment at 36-months within the model, transition probabilities were averaged between the treatment arms from AURORA 2 (i.e., VCS+MMF and MMF). The EAG considered two main limitations with this application:

1. This application of a treatment waning effect is still based on patients receiving treatment in the AURORA 2 trial (and therefore the implicit assumption is made that the treatment effect for both VCS+MMF and MMF alone would be maintained after stopping treatment at 36-months for the remainder of the 72 year time horizon within the model).

2. The assumption made by the company is not that the treatment effect of VCS wanes for all patients, but rather is that an average between the two arms is taken (inherently assuming that some treatment effect is maintained for VCS+MMF versus MMF).

With a lack of longer-term data, the EAG are unable to explore uncertainty with regard to how VCS+MMF would compare to MMF once patients have stopped treatment. Despite this, findings from the literature (Jourde-Chiche 2022[11] – as outlined in Section 4.2.6.3) found evidence related to the waning of treatment effectiveness over time in an LN-specific population. As such, the EAG consider it reasonable to assume that the effect of VCS+MMF or MMF alone could wane over time and there is no guarantee that the transition probabilities observed within the AURORA 2 trial would be maintained over the remainder of the model.

The EAG explored two scenarios related to the long-term transition probabilities within the model. These scenarios make the implicit assumption that differences beyond 36 months are

driven by the patient health state occupancy at 36-months rather than the treatment arm i.e., a higher proportion of patients achieving CR on the VCS+MMF arm would still translate to a more favourable long-term outcome as the transition probabilities for progression of CR are more favourable than those patients with AD. The approach is slightly different between the two scenarios; scenario 12A assumes that VCS+MMF has the same long-term transition probabilities as MMF, which are derived from the MMF arm of the AURORA 2 data, while scenario 12B assumes that VCS+MMF has the same long-term transition probabilities as MMF, which are derived from averaging the VCS+MMF and MMF transition probabilities from AURORA 2 data.

6.2.12.1. Scenario 12A: the EAG assumed that long-term transition probabilities for voclosporin + MMF are the same as the long-term transition probabilities for MMF

The first scenario assumes that the point where patients are removed from voclosporin treatment within the model (36 months), thus transition probabilities thereafter are based on the MMF arm alone. This scenario could be considered conservative in the sense that it assumes there is no long-term treatment effect associated with voclosporin specifically in terms of the risk of achieving or losing response. However, the counter to this argument is that this scenario *does* in fact assume that there is a long-term effect of MMF which is applied beyond 36-months (despite the assumption that patients are no longer on treatment), as health state occupancy differs between the two arms at 36 months, and transition probabilities are a function of the current health state.

This scenario has a dramatic increase on the company's base case more than doubling the ICER (£18,897 to £46,412). This analysis indicates how sensitive the model results are to key structural uncertainties relating to the long-term transition probabilities within the model and the assumption that VCS+MMF not only maintains a level of treatment effect over time, but that this is maintained when patients are no longer receiving treatment.

6.2.12.2. Scenario 12B: the EAG assumed that the long-term transition probabilities for voclosporin+MMF and MMF are the same and the average is taken from AURORA-2

The second scenario considered by the EAG applied the average transition probabilities from the AURORA 2 study to both arms within the model (VCS+MMF and MMF). The EAG's understanding based on expert advice is that achieving and maintaining response is what is

important for patients, and response is what primarily drives progression through the model. As such pooling of the transition probabilities allows utilisation of the trial data in this way inherently assumes that the transition probabilities applied at 36-months are driven by health state occupancy rather than the individual treatment arms. Similar to scenario 12A, the impact of this scenario has a marked increase on the company base case ICER (increasing by £25,549 from £19,897 to £45,446), indicating just how sensitive the cost-effectiveness estimates are to the assumption that there is a long-term difference in the expected transitions for VCS+MMF versus MMF alone (which is not driven by the proportion of patients that achieved response).

6.2.13. Impact on the ICER of additional clinical and economic analyses undertaken by the EAG

The EAG made the changes described in Sections 6.2.1 to 6.2.12. Each change was made individually. The results of the EAG's exploratory analyses are provided in Table 31 for voclosporin+MMF versus MMF.

Table 31: EAG's exploratory analyses of voclosporin+MMF versus MMF

EAG assumption	Section in EAG report	Incremental costs	Incremental QALYs	ICER £/QALY	+/- company base case
EAG corrected company base-case	*6.1*	[redacted]	[redacted]	[redacted]	
Scenario 1: Utility values - use weighted average of Table B.3.10 (observed in AURORA 1 and 2) - EQ-5D by visit and status	*6.2.1*	[redacted]	[redacted]	[redacted]	*+£1,504*
Scenario 2A: Transplant utility - taken from Li et al. 2017	*6.2.2.1*	[redacted]	[redacted]	[redacted]	*+£255*
Scenario 2B: Dialysis utility - taken from meta-analysed dialysis values presented in Cooper 2020	*6.2.2.2*	[redacted]	[redacted]	[redacted]	*+£87*
Scenario 2C: Dialysis utility - Briggs et al. 2016 (presented in Cooper 2020) with the transplant increment from Li et al. 2017	*6.2.2.3*	[redacted]	[redacted]	[redacted]	*+£334*
Scenario 3: 1/2 additional pack of VCS for wastage	*6.2.3*	[redacted]	[redacted]	[redacted]	*+£516*
Scenario 4:2g dose of MMF applied to VCS+MMF and	*6.2.4*	[redacted]	[redacted]	[redacted]	*-£13*

EAG assumption	Section in EAG report	Incremental costs	Incremental QALYs	ICER £/QALY	+/- company base case
MMF (MMF for other regimens and subsequent treatments remain the same)					
Scenario 5 Additional monitoring for all CNI treatments	*6.2.5*	[redacted]	[redacted]	[redacted]	*+£965*
Scenario 6: Amend treatment, resource use and EOL costs within the model to match original source	*6.2.6*	[redacted]	[redacted]	[redacted]	*+£217*
Scenario 7A: Application of 95% RDI to treatments	*6.2.7.1*	[redacted]	[redacted]	[redacted]	*-£1,198*
Scenario 7B: Application of MMF TTD to other comparator treatments	*6.2.7.2*	[redacted]	[redacted]	[redacted]	*N/A**
Scenario 8: Restricted movement from transplant to dialysis: set to 0%	*6.2.8*	[redacted]	[redacted]	[redacted]	*+£460*
Scenario 9: Percentage reduction in transplantation rates from current value (43.77% per 6 months) – reduction to 23.08%	*6.2.9*	[redacted]	[redacted]	[redacted]	*-£371*
Scenario 10A: Removal of LN related death in CKD stage 1-3a from count method	*6.2.10*	[redacted]	[redacted]	[redacted]	*+£3,600*
Scenario 10B: Removal of LN related death in CKD stage 1-3a (CR, PR and AD removal from count method and additional model input capturing AD -> death in CKD stage 1-3a)	*6.2.6*	[redacted]	[redacted]	[redacted]	+£18,228
Scenario 11: Company setting: Model transitions: allow transitions to CKD 3b-5 in the first 36 months	*6.2.11*	[redacted]	[redacted]	[redacted]	*-£5,086*
Scenario 12A: Removal of long-term treatment effect for VCS+MMF (set transitions from 36 months equal to placebo)	*6.2.12.1*	[redacted]	[redacted]	[redacted]	*+£26,515*
Scenario 12B: Application of average transition probabilities from 36-months applied to both arms	*6.2.12.2*	[redacted]	[redacted]	[redacted]	*+£25,549*

Abbreviations: CKD, chronic kidney disease; CR, complete response; EAG, Evidence Assessment Group; EOL, end-of-life; ICER, incremental cost-effectiveness ratio; LN, lupus nephritis; MMF, mycophenolate mofetil; PR, partial response; QALY, quality adjusted life year; TTD, time-to-treatment discontinuation; VCS, voclosporin

Notes: * this does not affect the main comparison of voclosporin+MMF versus MMF but results have been presented within section 6.2.7 to understand the impact on the results of voclosporin+MMF versus other model comparators (and results are presented as part of the EAG preferred assumptions in a fully incremental format within section 6.3)

6.3. EAG's preferred assumptions

The EAG did not consider it possible to provide a preferred ICER that was able to address all of the described limitations/uncertainties inherent within the company's submitted model. This is largely because limitations pertinent to the model structure and uncertainty in the long-term transition probabilities could not be resolved. Despite this, the EAG has identified several alternative assumptions that are considered to represent a more suitable basis from which to understand the likely cost-effectiveness of voclosporin+MMF.

The tentative preferred base case ICER is £40,029 as shown in Table 32 below for voclosporin+MMF versus MMF. This table shows the cumulative change on the ICER for each change made within the model. The increase in the ICER is mostly driven by the removal of any long-term treatment differences associated with voclosporin+MMF and MMF alone.

Pairwise results of voclosporin+MMF versus all comparators when applying the EAG base case are presented in Table 33 with a full incremental provided in Table 34.

Table 32: EAG's preferred model assumptions

Preferred assumption	Section in EAG report	Cumulative ICER £/QALY
Company base-case		*£19,876*
Company base-case with fix applied		*£19,897*
Align resource use, AE, EOL and drug costs	*4.2.8*	*£20,114*
Add in ½ pack wastage for voclosporin	*4.2.8*	*£20,631*
Update trial utilities to weighted average from AURORA 1 and AURORA 2 observations	*4.2.7*	*£22,190*
Update literature-based utilities for transplant from Li et al.2017	*4.2.7*	*£22,496*
Update literature-based utilities for dialysis from meta-analysis of Cooper et al. 2020	*4.2.7*	*£22,603*
Apply 95% RDI to all treatments	*4.2.8*	*£21,291*
Stop LN death in CKD stage 1-3a	*4.2.6*	*£25,605*

Preferred assumption	Section in EAG report	Cumulative ICER £/QALY
Allow transitions CKD stage 3b-4 in first 36 months	*4.2.6*	*£18,488*
Use average long-term transition probabilities from VCS+MMF and MMF applied to both arms	*4.2.6*	*£40,029*

Abbreviations: EAG, Evidence Assessment Group; ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life year

Note: *The EAG prefers the incorporation of Scenario 12B (average across arms) over Scenario 12A (same as MMF); however, due to the need for additional functionality in the company's model to allow this scenario to be included, the EAG was unable to implement equivalent functionality to apply to the indirect comparators that feature in the fully-incremental analysis within the timeframe for preparing the EAG's report.

Table 33: EAG preferred analysis: pairwise comparison

	Total discounted costs	Total discounted QALYs	Incremental discounted costs versus VCS + MMF	Incremental discounted QALYs versus VCS + MMF	ICER versus VCS + MMF
EAG base case pairwise incremental results					
VCS + MMF	[redacted]	[redacted]	-	-	-
MMF	[redacted]	[redacted]	[redacted]	[redacted]	£40,029
L-CYC	[redacted]	[redacted]	[redacted]	[redacted]	£8,743
H-CYC	[redacted]	[redacted]	[redacted]	[redacted]	£8,038
AZA	[redacted]	[redacted]	[redacted]	[redacted]	£14,555
RTX + MMF	[redacted]	[redacted]	[redacted]	[redacted]	£29,958
TAC + MMF	[redacted]	[redacted]	[redacted]	[redacted]	£16,550
TAC	[redacted]	[redacted]	[redacted]	[redacted]	£17,895

Abbreviations: AZA = azathioprine; CEM, cost-effectiveness model; CYC, cyclophosphamide; H-CYC, high-dose CYC; L-CYC, low-dose CYC; MMF, mycophenolate mofetil; QALYs, quality adjusted life years; RTX, rituximab; TAC, tacrolimus; VCS, voclosporin

Note: *The EAG prefers the incorporation of Scenario 12B (average across arms) over Scenario 12A (same as MMF); however, due to the need for additional functionality in the company's model to allow this scenario to be included, the EAG was unable to implement equivalent functionality to apply to the indirect comparators that feature in the fully-incremental analysis within the timeframe for preparing the EAG's report.

Table 34: Full incremental analysis of voclosporin+MMF versus comparators: EAG preferred assumptions

Treatment	Total discounted costs	Total discounted QALYs	Incremental discounted costs	Incremental discounted QALYs	ICERs (following re-baseline)
Company incremental base case (results taken by EAG from updated company CEM provided at clarification stage)					

Treatment	Total discounted costs	Total discounted QALYs	Incremental discounted costs	Incremental discounted QALYs	ICERs (following re-baseline)
MMF	[redacted]	[redacted]	[redacted]	[redacted]	
AZA	[redacted]	[redacted]	[redacted]	[redacted]	Extendedly dominated
TAC + MMF	[redacted]	[redacted]	[redacted]	[redacted]	Extendedly dominated
TAC	[redacted]	[redacted]	[redacted]	[redacted]	Extendedly dominated
L-CYC	[redacted]	[redacted]	[redacted]	[redacted]	Extendedly dominated
H-CYC	[redacted]	[redacted]	[redacted]	[redacted]	Extendedly dominated
RTX + MMF	[redacted]	[redacted]	[redacted]	[redacted]	Extendedly dominated
VCS + MMF	[redacted]	[redacted]	[redacted]	[redacted]	£40,029.31

Abbreviations: AZA = azathioprine; CEM, cost-effectiveness model; CYC, cyclophosphamide; H-CYC, high-dose CYC; L-CYC, low-dose CYC; MMF, mycophenolate mofetil; QALY, quality adjusted life year; RTX, rituximab; TAC, tacrolimus; VCS, voclosporin

Note: *The EAG prefers the incorporation of Scenario 12B (average across arms) over Scenario 12A (same as MMF); however, due to the need for additional functionality in the company's model to allow this scenario to be included, the EAG was unable to implement equivalent functionality to apply to the indirect comparators that feature in this analysis within the timeframe for preparing the EAG's report.

6.4. Conclusions of the cost-effectiveness section

6.4.1. The company's choice of model structure and approach to informing transition probabilities is subject to substantial uncertainty

Whilst the company's model broadly reflects the progression nature of CKD in an LN population, it is subject to several important structural limitations which restrict the ability to fully understand and interpret the uncertainty associated with the cost-effectiveness of voclosporin+MMF as a treatment for LN. These issues include the derivation of transition probabilities, the rigid model structure which forces patients to follow a certain trajectory (examples here include no CKD progression within 3 years, inability to achieve response in CKD stages 3b-4, inability to progress CKD stage for patients in CR and PR with earlier CKD stage 1-3a), the application of health state utility values and the long-term treatment effect assumptions associated. The EAG was only able to partially address some of the limitations in the company's model framework based on the information available

6.4.2. Several of the company's model inputs lacked transparency

As highlighted throughout the report, the EAG raised a number of concerns with respect to the transparency of model inputs, notable the cost inputs incorporated within the model. Owing to the fact that costs (whether uplifted or not), were included as inputs with limited description of their original source, the EAG has had to make assumptions when crosschecking the company's model with the referenced inputs.

6.4.3. The company's approach to analysing trial utilities was inappropriate and not fit for decision making

Importantly, the EAG considered that the company's approach to analysing trial utilities was wholly inappropriate and should not be used to inform decision making. Although the company used data collected from the AURORA trial programme to populate the utility values within the model, the approach used was considered to be methodologically wrong, with an assumption made which negated several months of informative HRQoL data. The EAG has substantial reservations in relation to the conduct of the utility analysis and recommends that a regression model should have been used to derive health state utility values.

6.4.4. The company's sensitivity analyses were subject to a number of limitations

Though the company provided scenario analysis associated with cost-effectiveness results, the EAG considered the analyses presented (CS Table B.3-25) to be uninformative and surface level, without inclusion of the larger more important structural issues within the model and hence preventing a clearer picture of true uncertainty associated with the decision problem under consideration. To illustrate this, only ten scenario analyses were presented, of which four related to adjusting the time horizons and varying the discount rates. No scenarios were presented which explored the impact of structural assumptions on the model such as allowing specific movements between health states, or alterations to the approaches taken to estimate transition probabilities. While utilities values were tested, only two scenarios were presented, a literature based analysis, and the exclusion of age-adjustment.

6.4.5. The EAGs tentative preferred base-case analysis yields an ICER in excess of £20,000 per QALY gained and is subject to substantial

structural uncertainty owing to limitations of the company's economic model that were not possible for the EAG to address

The EAG's preferred base-case analysis included several changes to the company's analysis in attempt to address limitations highlighted throughout the report. It should be emphasised that the EAG was not able to illustrate all uncertainty and limitations associated with the company's analysis and this was a result of the company's selected model structure alongside data availability. When considering the EAG's preferred settings, the changes resulting in slightly smaller total costs and fewer projected incremental QALYs gains. This resulted in an increase in the ICER by over 100% (from £19,876 estimated by the company to an EAG preferred base case of £40,029).

7. DISEASE SEVERITY

The company considered that the condition does not meet the criteria associated with a severity modifier and therefore did not present the calculation of the QALY shortfall in line with the new methods and processes. [9]

For completeness the EAG have assessed the appropriateness of a severity modifier by calculating the QALY shortfall using the Schneider et al. (2021) estimator tool. [38] This tool uses data from the Office of National Statistics (ONS) for England[39] to generate general population survival with various sources of data to inform utility estimates. The two are combined to estimate anticipated QALYs based on user inputted age of the patient population (assumed to be 33 from the company model) and percentage female in the patient population (assumed 87% rounded to the nearest integer from the company model). Using the company's modelled deterministic QALYs on the MMF arm (13.08) the QALY shortfall was estimated and is presented in Table 35. For further description of the methods used to estimate the QALY shortfall, the EAG refer to the NICE new methods manual[1] and the description of the references provided in Schneider et al. 2021. [2] The EAG are aligned with the company that the population does not meet the criteria associated with a severity modifier.

Table 35: Assessment of severity modifier by EAG

Alternative HRQoL norms provided in the Schneider et al. estimator tool	Absolute shortfall	Proportional shortfall	Corresponding QALY weight
Reference case: Hernandez Alava et al., EQ-5D-5L to 3L mapping + HSE 2017-2018	6.32	32.59%	x 1
Alternative A: van Hout et al., EQ-5D-5L to 4L mapping + HSE 2017-2018	6.45	33.02%	x 1
Alternative B: MVH, EQ-5D-3L value set + health state profiles	7.20	35.52%	x 1
Alternative C: MVH, EQ-5D-3L value set + HSE 2012+14	7.12	32.25%	x 1

Abbreviations: HRQoL, health-related quality of life; QALY, quality adjusted life-year.

References

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Appendix A: PSA output: cost-effectiveness planes voclosporin+MMF versus individual comparators

Figure 13: Cost-effectiveness plane for voclosporin+MMF vs. low dose CYC

Abbreviations: CYC, cyclophosphamide; MMF, mycophenolate mofetil, QALY, quality-adjusted life-year; vs, versus.

Figure 14: Cost-effectiveness plane for voclosporin+MMF vs. high dose CYC

Abbreviations: CYC, cyclophosphamide; MMF, mycophenolate mofetil, QALY, quality-adjusted life-year; vs, versus.

Figure 15: Cost-effectiveness plane for voclosporin+MMF vs. azathioprine

Abbreviations: MMF, mycophenolate mofetil, QALY, quality-adjusted life-year; vs, versus.

Figure 16: Cost-effectiveness plane for voclosporin+MMF vs. rituximab+MMF

Abbreviations: MMF, mycophenolate mofetil, QALY, quality-adjusted life-year; vs, versus.

Figure 17: Cost-effectiveness plane for voclosporin+MMF vs. tacrolimus+MMF

Abbreviations: MMF, mycophenolate mofetil, QALY, quality-adjusted life-year; vs, versus.

Figure 18: Cost-effectiveness plane for voclosporin+MMF vs. tacrolimus

Abbreviations: MMF, mycophenolate mofetil, QALY, quality-adjusted life-year; vs, versus.

Single Technology Appraisal

Voclosporin with immunosuppressive therapies for treating lupus nephritis [ID3962]

EAG report – factual accuracy check and confidential information check

"Data owners may be asked to check that confidential information is correctly marked in documents created by others in the evaluation before release." (Section 5.4.9, NICE health technology evaluations: the manual).

You are asked to check the EAG report to ensure there are no factual inaccuracies or errors in the marking of confidential information contained within it. The document should act as a method of detailing any inaccuracies found and how they should be corrected.

If you do identify any factual inaccuracies or errors in the marking of confidential information, you must inform NICE by **5pm on 1 August 2022** using the below comments table.

All factual errors will be highlighted in a report and presented to the Appraisal Committee and will subsequently be published on the NICE website with the committee papers.

Please underline all confidential information, and separately highlight information that is submitted as '[redacted]' in turquoise, all information submitted as '[redacted]' in yellow, and all information submitted as '[redacted]' in pink.

Issue 1 Disease Background

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 2.1 Introduction: page 23*:* 'The overall incidence of LN is between 1 and 8.7 cases per 100,000 person years, and with a prevalence of 8 – 180 cases per 100,000 people. 4,5'	'Data describing the prevalence and incidence of LN in the UK are currently limited. Among publicly available data, the most recent UK-specific study was a 2001 retrospective analysis conducted in England, which reported overall LN prevalence and incidence rates of 4.4 and 0.4 per 100,000 of the population, respectively.28 '	The references to substantiate the incidence and prevalence in the EAG report, are for SLE. Suggest aligning with the incidence and prevalence figures for LN, presented in the CS	Many thanks for raising this error, we have accepted the suggested text in the revised report (EAG report, p. 24).
Section 2.1 Introduction: page 23*:* 'While SLE is generally more common amongst females, LN is more common amongst males'	LN occurs more commonly in females 'Both SLE and LN is more common amongst females'	The available literature notes higher prevalence of both SLE and LN in females. Wang H et al. Arch Rheumatol 2018; 33:17–25;	Thank you for this comment. Our research indicates that prevalence of LN has generally been found to be higher amongst males than females with SLE. A recent review (Anders H-J, Saxena R, Zhao M-h, Parodis I, Salmon JE, Mohan C. Lupus nephritis. Nature reviews Disease primers. 2020;6(1):1-25) notes this, although the authors noted that not all studies have shown this consistently, likely due to variation in study

			methods. Given the inconsistency of the literature and the potential for confusion between risk and absolute numbers of people with LN, the EAG has re-worded the original sentence in the EAG report (p.24).
Section 2.1 Introduction: page 23*:* 'In general, 5-yr risk of ESRD in people in LN is 11% (95% CI 10–12%), 10-yr is 17% (95% CI 16–18%), and 15-yr is 22% (95% CI 20–23%). The risk is higher in developed nations, particularly for 15-yr risk.'	In general, 5-yr risk of ESRD in people in LN is 11% (95% CI 10–12%), 10-yr is 17% (95% CI 16–18%), and 15-yr is 22% (95% CI 20–23%). The risk is higher in developing nations, particularly for 15-yr risk.	Reference states: ESRD risks at 5 years were only slightly higher in developing countries than in developed countries during the 2000s but 15 year risks were 10 perc points higher in developing countries	Thank you for highlighting this typo, we have amended the sentence as suggested (p.24).

Issue 2 Alignment with Marketing Authorisation

Description of problem	**Description of proposed amendment**	**Justification for amendment**	**EAG response**
Section 2.1 Introduction: page 23*:* 'In this report, the Evidence Assessment Group (EAG) provides a review of the evidence	Suggest maintaining consistency with anticipated license and amending this sentence to 'In this report, the Evidence Assessment Group (EAG)	Change proposed to be consistent with the most up-to-date draft SmPC and as outlined in the response to the clarification questions.	This is not a factual inaccuracy. This statement in the EAG report is consistent with the NICE scope for the appraisal. The EAG noted on page 26 of its report that the company provided an update at

submitted by Otsuka Pharmaceuticals in support of voclosporin (Lupkynis) in combination with immunosuppression therapy for the treatment of lupus nephritis.'	provides a review of the evidence submitted by Otsuka Pharmaceuticals in support of voclosporin (Lupkynis) in combination with immunosuppression therapy for the treatment of lupus nephritis. The Company provided an update in the Clarification Question stage regarding the expected indication being Voclosporin (Lupkynis) in combination with Mycophenolate Mofetil for the treatment of lupus nephritis.'		clarification with regard to the anticipated license for voclosporin.
Section 2.1 Introduction: page 24*:* 'Voclosporin does not currently have a license for use in the UK; in November 2021 the European Medicines Agency (EMA) requested further information from the company, to which it is still preparing its response (as of January 2022). 7 If the company receive a positive decision for voclosporin from the EMA, [redacted]	'Otsuka received a positive CHMP opinion for Lupkynis on the 21st of July 2022, [redacted].'	Voclosporin has received CHMP positive opinion [redacted]	This is not a factual inaccuracy. The EAG thank the company for highlighting that a license has now been received for voclosporin, though note that the Committee for Medicinal Products for Human Use (CHMP) reached this decision on the date the EAG report was submitted. The statement in the EAG report was therefore correct at the time of writing.

[redacted].			
4.2.8.5.2. Additional monitoring for CNI-based treatments, first paragraph. *6.2.5. Scenario 5: Additional monitoring for CNI treatment applied to voclosporin,* whole section The EAG has explored a scenario analysis where this cost is also applied to the VCS+MMF treatment arm (given that VCS is also a CNI treatment), which is described further in Section 6.2.	The company challenge the inclusion of this scenario as therapeutic drug monitoring is not required in the latest draft SmPC and therefore it is not in line with anticipated SmPC. If the EAG disagree to remove the reference to the scenario, Otsuka's alternative wording is below: 'The EAG has explored a scenario analysis, despite the lack of therapeutic drug monitoring being required in the provided draft SmPC, where this cost is also applied to the VCS+MMF treatment arm (given that VCS is also a CNI treatment), which is described further in Section 6.2.'	According to our draft SmPC, no therapeutic drug monitoring is required.	This is not a factual inaccuracy. As stated above, the CHMP reached a positive decision for voclosporin on the date the EAG submitted its report, and therefore this was not considered in its appraisal. To date, the summary of product characteristics (SmPC) for voclosporin has not yet been published, and the EAG is unable to review the guidance that has been provided by the committee. On the basis of the evidence presented to the EAG, clinical advice was that monitoring for people with LN receiving voclosporin should (at least initially) be comparable to treatment with tacrolimus, due to the known risks of CNIs. The EAG therefore considered this scenario analysis to be pertinent to the NICE committee.

Issue 3 Comparator

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 2.1, page 23*:* 'Sometimes additional treatment with a calcineurin inhibitor (CNI; such as tacrolimus), an anti-malarial (hydroxychloroquine), or with rituximab is indicated.'	'Sometimes additional treatment with a calcineurin inhibitor (CNI; such as tacrolimus) or with rituximab is indicated.'	Hydroxychloroquine is considered a background treatment as per guidelines whereas the current wording implies that hydroxychloroquine could have been considered as a comparator, which is not in line with the scope. Therefore, Otsuka provided an alternative wording	This is not a factual inaccuracy and the EAG disagree with the company that the wording implies that hydroxychloroquine would be a comparator to voclosporin. The paragraph highlighted by the company is describing current care for people with LN, which typically includes treatment with hydroxychloroquine.
Section 2.4. Critique of company's definition of decision problem, page 25: 'Treatment with a CNI would typically be administered after patients had not responded to treatment with MMF/MPA alone, or if first-line treatment with MMF/MPA was contraindicated. In this case, the main comparators for voclosporin would be azathioprine, rituximab, or tacrolimus'	'Treatment with a CNI would typically be administered after patients had not responded to treatment with MMF/MPA alone, or if first-line treatment with MMF/MPA was contraindicated. In this case, the main comparators for voclosporin would be rituximab, or tacrolimus'	Otsuka request to remove azathioprine as it is only used for maintenance, and voclosporin's SmPC is anticipated to be for management of active disease. Sources: Voclosporin's draft SmPC and EULAR/ERA-EDTA and KDIGO guidelines	The EAG thank the company for this comment, although disagree that this is a factual inaccuracy. The inclusion of azathioprine in this statement was based on clinical advice to the EAG that azathioprine would be one of the options considered if treatment with MMF/MPA was contraindicated. The EAG understands that while azathioprine may be most frequently used as a maintenance therapy, there may be people in the NHS who receive azathioprine as a treatment for active LN. Throughout the EAG report, the

			EAG noted that treatment for LN is often highly variable across settings, and therefore the EAG consider it appropriate to be inclusive in its description of currently used treatments.

Issue 4 Clinical effectiveness

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
3.2.2.1. Design of the studies, page 34 first paragraph 'None of the trial sites were based in the UK, which at clarification the company stated was due to an understanding that uptake of voclosporin in the UK would be less than in Europe'	'None of the trial sites were based in the UK, which at clarification the company stated was due to an understanding during the feasibility assessment of the trial that interest in the clinical trial of voclosporin in the UK would be less than in Europe.'	Otsuka request an alternative wording to be used due to an omission of additional relevant detail by Otsuka during the clarification question stage. Specifically, that UK was included in the scoping process for the clinical studies, but interest in conducting the clinical studies was considered to be higher elsewhere in Europe following a feasibility assessment.Therefore, our response to the clairifaction questions did not refer to the update/interest in the product itself, rather the study.	The EAG thanks the company for this clarification, and has amended the text accordingly (p.36).

3.2.2.5. Critical appraisal of the design of the studies, page 49 second paragraph 'AURORA 2 included only those participants who chose to continue from AURORA 1, and due to a high level of attrition at this time, AURORA 2 was under-powered for all its analyses.'	'AURORA 2 included only those participants who chose to continue from AURORA 1 with a primary outcome of demonstrating safety. Despite not all patients entering the study, due to sufficient number of patients entering the AURORA 2 study a number of analyses achieved statistical significance '	Otsuka would like to contest the statement that AURORA 2 was under-powered in all of its analyses as a number of analyses, as demonstrated, achieved statistical significance.	This is not a factual inaccuracy. Due to a significant reduction in the sample size entering AURORA 2 from AURORA 1, AURORA 2 was under-powered based on the company's planned power calculations. These calculations are based on hypotheses generated from multiple sources of evidence, and are unaffected by obtained results (post hoc calculations are also not advisable). The EAG further notes that under-powered trials can both under- and over-estimate treatment effects. The EAG has highlighted concerns with the quality of the AURORA 2 trial and consider all results – irrespective of their statistical significance – to be at risk of bias (EAG report Section 3.2.2.5).

In section 3.4.1, on page 66 & 67, the EAG notes: 'The company did not present random effects models for base case NMAs, asserting that this was due to lack of convergence. However, this claim was not substantiated with respect to specific model diagnostics, and the EAG could not trace where and to what degree the company detected evidence of non-convergence. Thus, the EAG presents random effects estimates alongside fixed effects estimates below. This is important as well because the heterogeneity in both NMAs suggests that a random effects model more appropriately reflects the included data.'	Otsuka suggests amending the whole section to not include random effects model. 'The company did not present random effects models for base case NMAs, asserting that this was due to lack of convergence.'	Otsuka notes, that current wording implies that random effects is the preferred route. Although Otsuka agree a random effects NMA may be more appropriate due to the observed heterogeneity between studies in the network, we would propose to reconsider presenting the outcomes of the random effect model given that Stan produces error warnings under the current model parameters, which has driven our approach. Therefore, Otsuka believe there is reason to declare the random effects model, with a half normal (0,5) prior for the between study heterogeneity, as not suitable for complete reliable inference. This is because of the divergent transition warnings produced for the random effects base case NMAs. This is further substantianted by the guidance for Stan declares that "Even a small number of divergences after warmup cannot be safely ignored if completely reliable inference is required".	This is not a factual inaccuracy. The company did not substantiate their claim of a lack of convergence for random effects analyses, and the EAG statement is therefore correct.

		Although the posterior may be declared good enough to move forward with when few divergences and good diagnostics are observed, in the context of decision making we think this would be unreliable.	

Issue 5 Cost-effectiveness

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
4.2.2.2. Health states within CKD stages 1-3a and 3b-4, last paragraph of page 28. 'With respect to achieving PR or CR from AD in the CKD stage 3b-4 state, justification for this aspect of the model was provided by the company as to implement a "conservative approach" (CS Section B.3.2.2, p.112).'	''With respect to achieving PR or CR from AD in the CKD stage 3b-4 state, justification for this aspect of the model was provided by the company as due to a lack of available data and in line with KOL feedback that indicated response to be rare in patients that reach CKD 3b-4, and therefore, the company stated a 'conservative approach' was taken.'	Taking a conservative approach was not the reason for removal of the noted transitions. This was instead driven by the lack of available data and in line with KOL feedback. As a result, Otsuka consider the ommission of additional rationale in the current wording to innacurately imply our position.	Many thanks for raising this clarification. We accept that adding the company's rationale for this decision is appropriate, though have re-worded the suggested text (EAG report, p. 80).
4.2.8.4. Background therapy (BT) costs, first paragraph page 107	'Glucocorticoids were dosed differently within the model, with a higher dose of up to 2,500 mg	Otsuka challenge the wording as justification was provided to be in line with AURORA protocols in	The EAG do not consider this to be a factual inaccuracy. The company did not justify the rationale for assuming

'The EAG's main concern regarding BT is the difference between tapered glucocorticoids from either the AURORA trials or the literature. These were dosed differently within the model, with a higher dose of up to 2,500 mg used outside of the AURORA 1 and AURORA 2 trials, with no justification for the differences provided in the CS.'	used outside of the AURORA 1 and AURORA 2 trials. This discrepancy is driven by rapid glucocorticoid tapering as per AURORA protocols to 2.5 mg/day at week 16.'	the CS (Sections B.2.3.1.3.2. and B.2.3.2.1) Further detail was not requested during the Clarification Question stage, however Otsuka would be more than happy to elaborate if required.	differences in the use of glucorticoids between the treatments in the model. The CS stated *"Background therapy costs are also incorporated into the model to account for the co-administration of tapered corticosteroids and hydroxychloroquine (**Error! Reference source not found.**)."* and provided a table of costs. However, based on the description provided and to align with the CS (Sections B.2.3.1.3.2 and B.2.3.2.1), we have updated wording within the EAG report in section 4.2.8.4 (page 110) to state: *"The EAG's main concern regarding BT is the difference between tapered glucocorticoids from either the AURORA trials or the literature. These were dosed differently within the model, with a higher dose of up to 2,500 mg used outside of the AURORA 1 and AURORA 2 trials. The AURORA trial protocols outlined rapid glucocorticoid tapering to 2.5mg/day at week 16. No justification was provided in the*

			CS as to why glucocorticoid tapering would not be considered for the alternative comparators."
6.1. EAG corrections and adjustments to the company's base case model, last bullet point, page 127. 'Error in NMA application for PRR and CRR'	'Error in NMA application for PRR.'	The error was only in PRR, not both PRR and CRR as outlined in company's clarification responses	Many thanks for raising this typo. We have updated the wording as suggested (Section 6.1 page 129).
Table 31: EAG's exploratory analyses of voclosporin+MMF versus MM, table 31 page 142. 'Scenario 7A: Application of 95% RDI to treatments, -£1,198 from company's base case.'	'Scenario 7A: Application of 95% RDI to treatments, -£197.99 from company's base case.'	The company note a calculation error in table 31 for completeness: [redacted] = -£197.99	Many thanks to the company for raising this. This is a typo in the ICER and not the difference between the ICER and the company's base case. This ICER should state [redacted] and not [redacted].; therefore [redacted] - [redacted] = £1,197.99 (£1,198 to 2.d.p). This ICER has been updated in Table 31 (page 144).

Issue 6 Typographical errors of importance (please note, smaller typographical errors not highlighted)

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Table 1: Clinical trials included in the CS; page 33, Section 3.2.1:	'Voclosporin 39.5mg'	Rovin BH, Solomons N, Pendergraft WF, 3rd, et al. A randomized, controlled double-	Thank you for highlighting this typo. We have corrected the text as suggested (p.35).

AURA-LV, intervention column*:* 'Voclosporin 39.55mg'		blind study comparing the efficacy and safety of dose-ranging voclosporin with placebo in achieving remission in patients with active lupus nephritis. Kidney Int 2019; 95(1): 219-31.	

Location of incorrect marking	**Description of incorrect marking**	**Amended marking**
Give full details of inaccurate marking - document title and page number	Give details of incorrect confidential marking	Please copy the impacted section here, with your amended marking.

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Single Technology Appraisal

Voclosporin with immunosuppressive therapies for treating lupus nephritis [ID3962]

Technical engagement response form

As a stakeholder you have been invited to comment on the External Assessment Report (EAR) for this evaluation.

Your comments and feedback on the key issues below are really valued. The EAR and stakeholders' responses are used by the committee to help it make decisions at the committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form

We are asking for your views on key issues in the EAR that are likely to be discussed by the committee. The key issues in the EAR reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the EAR.

You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise.

If you would like to comment on issues in the EAR that have not been identified as key issues, you can do so in the 'Additional issues' section.

If you are the company involved in this evaluation, please complete the 'Summary of changes to the company's cost-effectiveness estimates(s)' section if your response includes changes to your cost-effectiveness evidence.

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Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.

Do not include medical information about yourself or another person that could identify you or the other person.

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Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information redacted. See the NICE health technology evaluation guidance development manual (sections 5.4.1 to 5.4.10) for more information.

The deadline for comments is **5pm** on **9 September 2022**. Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

Technical engagement response form

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About you

Table 1 About you

Your name	Lucia Gallego
Organisation name: stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder, please leave blank)	Otsuka Pharmaceuticals UK Ltd.
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**N/A**

Key issues for engagement

All: Please use the table below to respond to the key issues raised in the EAR.

Table 2 Key issues

Key issue	Does this response contain new evidence, data or analyses?	Response
Key issue 1: Network meta-analysis (NMA) estimates may not be reliable and should better account for heterogeneity.	Yes	**Summary of the issue** Otsuka presented fixed effects NMAs on the basis that random effects NMAs were judged as not converging. The EAG regarded that this claim had not been sustained and recommended the use of appropriate informative priors, or otherwise clear evidence that no plausible random effects model would lead to convergent estimates in the base case. **Otsuka's response** Otsuka has followed the EAG's advice and undertaken an analysis to better account for heterogeneity within the random effects NMA model. The following analysis makes use of informative priors for the between-study heterogeneity parameter, as per Turner et al. (2015). Two choices of priors have been selected for the analysis, the first being the overall 'average' distribution for a general healthcare setting, represented by a log-normal distribution with mean of -2.56 and standard deviation of 1.74. The second prior used for the analysis is obtained from Table IV in Turner et al. (2015), this prior represents a log-normal distribution with a mean of -2.93 and a standard deviation of 1.58 LN (-2.93, 1.582). The setting for the second prior is based on a subjective outcome, as renal response is subject to meeting certain criteria. Under the first informative prior, 95% of the prior density lies between 0 and 2.34. Under the second informative prior, 95% of the prior density lies between 0 and 1.18

Complete Renal Response (CRR)

The below table presents the results for the base case CRR network. Applying the average predictive distribution in a general healthcare setting, log-normal (-2.93, 1.582), divergent transitions were still discovered in the random effects model, however, with good general MCMC diagnostics the posterior would be appropriate for inference. Under the second, more specific prior, no divergent transitions were discovered and therefore complete inference could be made from the posterior. In comparison to the fixed effect model the estimates from the random effects models are indifferent in terms of the point estimates, with slightly greater uncertainty observed in the random effect models, as expected.

Odds ratios vs. MMF for CRR NMA with Turner Priors

	Fixed effects OR (95% CrI)	Random effects OR (95% CrI) τ = log-normal (-2.56, 1.74^2)	Random effects OR (95% CrI) τ = log-normal (-2.93, 1.58^2)
VCS+MMF	[redacted]	[redacted]	[redacted]
AZA			
H-CYC			
L-CYC			
RTX+MMF			
TAC			
TAC+MMF			
Tau	NA	0.11	0.09
Model fit	Residual deviance 41.8, pD 24.3, DIC 66.1	Residual deviance 41.1, pD 25.1, DIC 66.2	Residual deviance 41.2, pD 25.0, DIC 66.2

Abbreviations: AZA = azathioprine; CrI = credible Interval; DIC = deviance information criterion; H-CYC = high-dose cyclophosphamide; L-CYC = low-dose cyclophosphamide; MMF = mycophenolate mofetil; OR = odds ratio; pD = parameters; PRR: Partial renal response; RTX = rituximab; TAC = tacrolimus; VCS = voclosporin

Partial Renal Response (PRR)

The table below presents the results for the base case PRR network. By applying informative prior distributions for the between-study heterogeneity parameter, both random effect models converge with no divergent transitions produced in Stan. The estimates from the random effects models are comparable with the fixed effect model, however, as with the CRR network, there is more uncertainty as represented by the wider credible intervals (CrIs) in the random effects models.

Odds ratios vs MMF for PRR NMA with Turner Priors

	Fixed effects OR (95% CrI)	Random effects OR (95% CrI) τ = log-normal (-2.56, 1.74^2)	Random effects OR (95% CrI) τ = log-normal (-2.93, 1.58^2)
VCS+MMF	[redacted]	[redacted]	[redacted]
H-CYC			
L-CYC			
RTX+MMF			
TAC			
Tau	NA	0.09	0.07
Model fit	Residual deviance 17.9, pD 15.2, DIC 32.3	Residual deviance 17.3, pD 15.5, DIC 32.7	Residual deviance 17.2, pD 15.4, DIC 32.6

Abbreviations: AZA = azathioprine; CrI = credible Interval; DIC = deviance information criterion; H-CYC = high-dose cyclophosphamide; L-CYC = low-dose cyclophosphamide; MMF = mycophenolate mofetil; OR = odds ratio; pD = parameters; PRR: Partial renal response; RTX = rituximab; TAC = tacrolimus; VCS = voclosporin

Employing relevant priors as provided by Turner et al (2015) led to convergence in the random effects models for CRR and PRR, respectively. This provides a better approximation of the relative effects, as the more credible random effects model captures the uncertainty amongst the heterogenous evidence base identified for the NMA. Two informative priors were used for the analysis. The outcomes from the analyses are indifferent to the point estimates from the

		fixed effects used in the company base case (with no change or +/- 0.01 change in the odds ratio observed in most cases) but there will be an increase in uncertainty in the probabilistic analyses due to the wider CrIs from the random effects NMAs. However, as per the EAG report, the differences observed in the point estimates are not expected to substantially impact the cost-effectiveness results. **References** Turner R, et al. Stat Med. 2015;34(6):984-98.
Key issue 2: The company's model structure is subject to a number of structural limitations.	Yes	**Summary of the issue** The company's model is associated with a number of restrictive settings and assumptions. **Otsuka's response** An economic SLR was conducted to find relevant cost-effectiveness models (CEMs) which highlighted that data in the field of LN is limited. Since, there are no licensed products for LN in the UK that have been subject to HTA, the number of models identified was also limited. Out of all the models identified, a CEM assessed by the Institute for Clinical and Economic Review (ICER) in the US in 2021 was thought to be the most representative of LN and its clinical pathway. ICER's model does not openly refer to chronic kidney disease (CKD) stages as such, but the structure implies two CKD levels: pre-ESRD (CKD1-4), which in their model is covered by CR, PR and AD; and ESRD (CKD5). Upon clinicians' feedback, Otsuka considered that ICER's model could be enhanced by splitting CKD into three groups: CKD1-3a, CKD3b-4 and CKD5. Clinical advice indicated that substantial changes in symptoms, QoL, management, mortality and costs are seen once patients reach CKD3b/4 due to the progressive damage to their kidneys and increased risk of cardiovascular events due to CKD. As patients' kidneys have incurred moderate to severe loss of function when they reach CKD3b/4 (eGFR< 45), achieving a response to treatment is very rare, and therefore, that functionality was switched off in the model. Once a patient reaches CKD3b, they

		cannot achieve a response, they can only remain in active disease (AD), transition to CKD5 or die. This assumption is mentioned by the EAG as a source of uncertainty. As there is a lack of data relating to response in this specific cohort (CKD3b/4), Otsuka sought clinical advice to meet this gap and the feedback was that there are ~2.5% of patients who would respond. Otsuka therefore felt that including this in the model would lead to a major source of uncertainty and the better option was to switch off this functionality. The EAG highlighted that there is some lack of clarity on how flares are captured in the model. A flare means that the disease is active, and activity drives damage, which causes patients to progress through the CKD stages. Even though Otsuka's model does not record flares as such, they are predominantly reflected by patients being in the active disease state, which is a state linked to a lower QoL and higher costs due to the use of more aggressive therapies and their associated side effects. A breakdown of the key issues regarding the model structure as reported by the EAG and Otsuka's response is provided below: <u>CKD progression is only possible from AD</u>: This assumption was validated by three independent clinicians based on the pathology of the disease: Progression through the different stages of CKD occurs as damage accumulates in the kidneys. Damage accumulates during periods of active disease and this kidney damage is irreversible. For the purposes of the model, Otsuka's assumption is that patients must spend a period of time in active disease for the disease to progress. Whereas this might represent a slight simplification of the disease, as some patients may only get diagnosed with later CKD stages when their activity has somewhat stabilised; clinicians confirmed that activity does lead to the damage, and there would be no data to inform any additional transition. Therefore, only patients that are in active disease are allowed to progress through the stages of CKD in the model, and this assumption has been kept in the revised base case.

		No CKD progression in the first 36 months of the model: The CEM is reflective of the AURORA clinical trials for the first 36 months, and as no CKD progression was observed in AURORA 1 or AURORA 2, no progression occurs in the original base case model. However, functionality was included to explore a scenario of patients progressing within the first 36 months. Upon reflection, Otsuka agrees with the EAG in that this is unlikely to be reflective of clinical practice and have changed their model base case to allow patients to transition across the CKD stages at any point in the model. Transitions in the first 3 years are based on the 'count method': As outlined in the company submission, a different method to calculate transitions probabilities was explored during the development of the CEM. However, this alternative method (multinomial logit) provided unrealistic outcomes that did not match the trial data. Moreover, clinical opinion confirmed that the transition probabilities obtained with the multinomial logit were not reflective of clinical practice, and therefore, Otsuka discarded this method. Although the count method poses some limitations (as any other method would do), it is widely used to calculate transition probabilities, and some of the uncertainty generated due to sample size has been addressed elsewhere (i.e., mortality). Very few within-trial deaths, and cause of death is not explicitly captured: LN is a manifestation of systemic lupus erythematosus (SLE), and patients with SLE are subjected to higher mortality rates than the wider population. Patients with SLE show increased mortality rates when compared to age- and sex-matched controls in the general population. Infections, CV complications, and CKD, especially kidney failure, are major causes of death. Early deaths are related to infections or lupus activity, while CV and malignant complications and deaths related to kidney failure account for late mortalities. Infection is a leading cause of death in patients with LN, and infection-related deaths are more common during the initial phase of management following exposure to intensive immunosuppressive therapy (KDIGO 2021).

Technical engagement response form

In AURORA 1, a total of six deaths were reported, five in the placebo arm and one in the intervention arm (AURORA 1 CSR 2020). In AURORA 2, four deaths were reported in the placebo arm and none in the intervention arm (AURORA 2 CSR 2022):

AURORA 1 – Summary of AEs resulting in death

Adverse event	Related to treatment	Related to LN
Placebo		
Pneumonia	No	No
Lupus nephritis	No	Yes
Pulmonary embolism	No	Yes
Pneumonia/ septic shock	No	Yes
Acute respiratory failure	No	Yes
Voclosporin		
Pneumonia	No	Yes

AURORA 2 – Summary AEs resulting in death

Adverse event	Related to treatment	Related to LN
Placebo		
Pulmonary embolism	No	Yes
Coronavirus infection	No	No
Coronavirus infection	No	No
Coronavirus infection	No	No

In the original base case, Otsuka calculated mortality in CR and PR in CKD1-3a from AURORA 1 and 2, for both VCS+MMF and MMF, using the count method. As no deaths were observed in AD in the VCS+MMF arm, Otsuka took a conservative approach and applied a constant mortality rate to AD in both arms based on the deaths in the MMF arm. These deaths observed in AURORA 1 and 2 are linked to complications related to SLE, or infections that patients with LN are at increased risk of contracting. Clinical advice was that the original mortality estimates

		in CKD1-3a in AD were slightly low (likely due to the more controlled environment found in a clinical trial versus a real clinical setting). These deaths had originally been defined as LN deaths and incurred the corresponding LN death cost. However, upon considering the EAG's feedback, Otsuka agrees that patients should not incur LN-related death costs, which are associated with kidney failure, in CKD stages 1-4, and instead these deaths have been costed the same as background mortality. Even though deaths were observed in the clinical trial in complete and partial response patients, they have been removed from CR and PR in the revised base case to account for some of the uncertainty that the count method could have generated. As highlighted in the EAG's report, due to the nature of the count method, the number of deaths could have been overestimated. For example, in the MMF arm n=1 patient with PR CKD stage 1-3a died between 24- and 30-months, and because n=22 patients were still at risk at this time, this ultimately translated to a 4.5% probability of death in this cycle specifically, versus 0.0% for the VCS+MMF arm as no patients died during this time period. Although the number of deaths was lower in the VCS+MMF arm than the MMF arm, Otsuka applied the MMF mortality constants to AD to the VCS+MMF arm also, as in clinical practice it is expected that a patient in active disease would have the same mortality outcome, no matter what treatment is provided (since we are considering only deaths not linked to kidney failure). This constant is included in the revised base case. Deaths occurring in CKD5 are classified as LN deaths, as these are linked to kidney failure, and incur a LN death cost. **References** AURORA 1 CSR. 2020. AURORA 2 CSR. 2022. KDIGO. Kidney Int. 2021;100(4S): S1-S276.

Key Issue 3: The long-term treatment effect of voclosporin + MMF and its comparators is unknown.	Yes	**Summary of the issue** Uncertainty related to sustained efficacy within the model was captured by applying a long-term waning effect for VCS+MMF. The model assumes that when all patients permanently discontinue VCS + MMF (assumed to be 36 months in the base-case analysis), transition probabilities 'wane' to reflect an average of the estimated probabilities for the last two model cycles across both treatment arms from AURORA 2 (i.e., VCS + MMF versus MMF). **Otsuka's response** The overarching goal of LN treatment is to rapidly reduce proteinuria and inflammation, to prevent; further kidney damage, progression to and through the stages of CKD, and the development of ESRD (CKD5) (Anders et al. 2020; Dall'Era et al. 2015; KDIGO 2021). Evidence suggests that early reduction in proteinuria, particularly within 6–12 months from the start of treatment, is the single best predictor of improved long-term renal outcomes, including reduced risk of disease flares, ESRD (CKD5), and death (Rovin et al. 2021). EULAR/ERA-EDTA clinical guidelines state that treatments should aim for optimisation (preservation or improvement) of kidney function, accompanied by a reduction in proteinuria of at least 25% by 3 months, 50% by 6 months, and a UPCR target <500–700mg/g by 12 months (complete clinical response) (Fanouriakis et al. 2020). These time-dependent goals highlight the importance of achieving an early response to treatment. Immunosuppressive treatment targets the active inflammatory lesions in kidney histopathology, the extent of which portend CKD and long-term kidney prognosis (KDIGO 2021). The longer a patient spends in active disease, the more damage can accumulate in their kidneys. VCS+MMF has been shown to have a faster onset of action versus MMF alone (169 vs 372 days) (AURORA 1 CSR 2020). A faster onset of action means that patients spend less time in active disease, therefore, limiting the damage incurred to their kidneys. Progression across the CKD stages could also be expected to be slower. Furthermore, patients' response is maintained via maintenance treatment, and therefore the transition probabilities associated with VCS+MMF at 36 months are unlikely to immediately equal MMF at 36 months.

		In the original model base case it was assumed that when all patients permanently discontinue VCS + MMF at 36 months, all transition probabilities wane to reflect an average of the estimated probabilities for the last two model cycles across both treatment arms from AURORA 2. Transition probabilities for patients in the MMF arm remain the same as they were in the last cycle of the MMF arm. The EAG carried out two different scenarios in which the long-term transition probabilities for VCS+MMF are the same as the long-term transition probabilities for MMF, and these are only applied to patients in CR (long-term benefit is associated with state occupancy at the end of the model). The first scenario derives these transition probabilities from the MMF arm of the AURORA 2 data, while the second scenario averages them from the VCS+MMF and MMF arms from AURORA 2 data. Otsuka acknowledges there is a level of uncertainty when extrapolating short-term data to inform long-term outcomes and as such, has explored a number of scenarios that aim to reduce the uncertainty. Otsuka agrees with the EAG assumption, where the long-term benefit is associated with state occupancy at the end of the trial period of the model, and as such, it has revised the base case as follows: <u>VCS+MMF</u> At discontinuation: *Patients in AD and PR:* The transition probabilities in the revised base case are set to match those of MMF. This assumption is supported by MMF being the most used maintenance therapy: most patients are likely to be put on MMF once they have stopped their induction/ active disease treatments (if they were taking MMF alone, they are likely to be switched to a lower MMF dose) (Fanouriakis et al. 2020), and therefore, it is reasonable to assume that those patients who have not achieved a response will have similar transition probabilities to those observed in the MMF arm. *Patients in CR:* It is assumed that patients wane to an average (i.e., midpoint) of the estimated probabilities from the AURORA 2 trial at Months 30 and 36 for the VCS + MMF arm, and those recorded at Months 30 and 36 months for the MMF alone arm (i.e., 50% VCS+MMF, 50%

		MMF). This assumption is based on voclosporin's faster onset of action: patients' kidneys are likely to have incurred less damage as they achieved a complete response faster than patients that were taking MMF alone. Otsuka has also explored scenarios in which the waning for patients in CR is varied from 30% (i.e., 30% VCS+MMF, 70% MMF) to 100% of the VCS+MMF arm transition probability, and in all of them voclosporin has been shown to be cost-effective. This % can be adjusted in cell G59 in the clinical input sheet, and it will change the % of the VCS+MMF arm included in the transition probabilities, with the remaining % from the MMF arm. Exploration of these different levels of waning has shown that despite the uncertainty surrounding the long-term effects of treatment, voclosporin still remains a cost-effective option. <u>MMF</u> Long-term transition probabilities for MMF remain the same as they were before discontinuation – a conservative assumption considering no waning of effect is assumed for MMF, whereas waning is assumed for VCS+MMF. <u>The other comparators</u> The only data available for the comparators was the transition probabilities for patients in the AD health state (derived from the NMA). At discontinuation: *Patients in AD*: The waning assumptions have been updated depending on the probability of staying in the AD health state for the comparator and MMF at 36 months. This means that for each comparator: • If the probability of staying in the AD health state at 36 months is lower than for MMF (i.e. as for RTX+MMF, TAC+MMF, TAC), the comparator moves to the same transition probabilities as MMF • If the probability of staying in the AD health state at 36 months is greater than for MMF (i.e. as for low-dose CYC, high-dose CYC, AZA), then the comparator long-term

		transition probability is left unchanged from the transitions derived from the NMA, to avoid inflating the efficacy of the comparator after discontinuation *Patients in PR and CR*: The transition probabilities in the revised base case are set to match those of MMF (as it was done in the original base case). It was not possible to derive data to support these transitions from the NMA as individual patient data for PR and CR was not available for comparators other than MMF (which was included in the AURORA trials), so it was assumed that all other comparators have the same transition probabilities as MMF. **References** Anders H, et al. Nat Rev Dis Primers. 2020;6(1):7. Dall'Era M, et al. Arthritis Rheumatol. 2015;67(5):1305-13. KDIGO. Kidney Int. 2021;100(4S):S1-S276. Rovin B, et al. Lancet. 2021;397(10289):2070-80. Fanouriakis A, et al. Ann Rheum Dis. 2020;79(6):713-23. AURORA 1 CSR. 2020.
Key Issue 4: The utility estimates used in the company's model are inappropriate.	Yes	**Summary of the issue** Lack of appropriate analysis methods to derive utility values from the AURORA 1 and AURORA 2 studies, omission of a large quantity of data from AURORA 1 and AURORA 2 from the estimation of utility values, and use of literature-based utility values for later states that reflect a different group of patients. **Otsuka's response** As suggested by the EAG, Otsuka has carried out a regression analysis on the utilities in AURORA 1 and AURORA 2. These utilities have been incorporated into the revised base case for patients in CKD1-3a in CR, PR and AD. Results are based on a mixed effect model repeated measures analysis, with EQ-5D at each visit used as the response variable and patient ID as the random effect. As is standard for utility analyses for HTA, and based on the assumptions of the randomised trial, no individual-level covariates were included in this model.

Overview of utilities including regression analysis

Health state	Old utilities (submission)	Old utilities SE	Weighted utilities (EAG scenario)	Regression utilities	Regression utilities SE
CR	[redacted]	[redacted]	0.814	[redacted]	[redacted]
PR	[redacted]	[redacted]	0.800	[redacted]	[redacted]
AD	[redacted]	[redacted]	0.727	[redacted]	[redacted]

Although the regression analysis has been included within the revised base case, the differences between health state utility values for CR, PR and AD, do not reflect in the differences seen in the literature, nor in other models in LN. Therefore, inclusion of the regression analysis is viewed as a conservative approach, as use of literature values would result in a greater QALY gain for voclosporin.

Overview of all identified utility estimates by health state

Health state	Utilities for CKD1-3a	Source
CR	0.800 (SE: 0.160) EQ-5D, Sweden	Bexelius et al. 2013 / Institute for Clinical and Economic Review 2021
	0.820 (SE: 0.180) Time trade off UK SLE population reporting on mild, moderate, severe SLR flares, and severe renal flares	Pollard et al., 2015
	0.750 (SE: 0.180) EQ-5D, US Corresponds to a SLEDAI score < 5	Aggarwal et al. 2009

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<tr><td>PR</td><td>Decrement: -0.090 (SE: -0.018)</td><td>Mohara et al. 2014 / Institute for Clinical and Economic Review 2021</td></tr>
<tr><td rowspan="2">AD</td><td>-0.176 (SE: -0.035)</td><td>Mohara et al. 2014</td></tr>
<tr><td>0.450 (SE: NR)</td><td>Pollard et al. 2015</td></tr>
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Otsuka has also considered the papers from which the EAG's preferred utilities for transplant and dialysis and has incorporated these utilities as part of the revised base case.

<u>References</u>
Bexelius C, et al. Lupus. 2013;22(8)793-801
ICER. Lupus Nephritis - An Assessment of Voclosporin and Belimumab. 2021.
Pollard C, et al. Health Qual Life Outcomes. 2015;13(1):66
Aggarwal R, et al. J Rheumatol. 2009;36(6):1209-16
Mohara A, et al. Rheumatology. 2014;53(1):138-44
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<td>Key Issue 5: The company has not appropriately calculated the costs of treatment in the model.</td>
<td>Yes</td>
<td><u>Summary of the issue</u>
The company's model includes a number of assumptions made with respect to costing voclosporin, MMF, and other comparators included via the indirect comparison.
A number of different issues were identified in this section and different scenarios were explored by EAG, which are covered below.

<u>Otsuka's response</u>

<u>Wastage for voclosporin</u>
Otsuka agrees that patients might discontinue treatment before finishing their voclosporin pack, hence a half-pack worth of wastage has been applied in the revised base case, in line with EAG's scenario.</td>
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MMF dose of 2.5g

MMF dose was assumed to be 2.5g per day in the model, as it is the average dose of that recommended in clinical guidelines (2-3g/ day). However, as highlighted by the EAG, the standard dose used in the AURORA trials was of 2g, and therefore the dose and corresponding cost have been adjusted in the revised base case to 2g.

Therapeutic drug monitoring

Otsuka's base case included therapeutic drug monitoring costs for tacrolimus regimens as tacrolimus has a complex and unpredictable PK profile that requires monitoring (van Golder). This cost was not applied to voclosporin, as voclosporin has a predictable PK/PD relationship allowing for flat dosing and no requirement for regular therapeutic drug monitoring (Voclosporin SmPC 2022).

The EAG conducted a scenario to explore the cost of additional therapeutic drug monitoring for CNI treatment including voclosporin. Otsuka disagrees with this scenario and has therefore not included therapeutic drug monitoring as part of the revised base case.

Relative dose intensity (RDI)

An RDI of 100% was applied to all treatments but tacrolimus due to a lack of data. However, Otsuka agrees with the EAG that in clinical practice dose adjustments are likely to occur and has incorporated the EAG's suggestion of a 95% RDI for all treatments but for MMF and VCS+MMF. Otsuka has analysed the trial data to derive the exact values (see tables below), based on daily doses of 47.4mg for voclosporin and 2g for MMF, when patients were on treatment (before discontinuation).

AURORA 1- Summary of Dose Intensity for Voclosporin/placebo and MMF

Parameter	Category	Placebo (N=178)	23.7mg BID (N=178)	Overall (N=356)
Voclosporin/ placebo dose intensity	n	178	178	356
	Mean (SD)	96.04 (10,104)	87.08 (20,392)	91.56 (16,684)
	Median	100.00	99.18	100.00
	Min: Max	44.9; 100.00	12.6; 100	12.6; 100
	(IQR)	(99.13; 100.00)	(79.45; 100)	(91,06; 100,00)

		MMF Dose intensity: n 178 178 356; Mean (SD) 98.0 (18.89) 93.6 (20.35) 95.8 (19.73); Median 99.1 99.0 99.1; Min: Max 29; 150 11; 150 11; 150; (IQR) (97.7; 100.0) (93.8; 100.0) (96.1; 100.0) **AURORA 2- Summary of Dose Intensity for Voclosporin/placebo and MMF** Parameter / Category / Placebo (N=100) / 23.7mg BID (N=116) / Overall (N=216) Voclosporin/ placebo dose intensity: n 100 116 216; Mean (SD) 94.62 (12.038) 85.65 (20.486) 89.80 (17.644); Median 100 97.79 99.91; Min: Max 42.3; 100.0 31.1; 100.0 31.1; 100.0; (IQR) (97.33; 100.00) (74.59; 100.00) (88.93; 100.00) MMF Dose intensity: n 100 116 216; Mean (SD) 95.2 (18.16) 95.2 (17.67) 95.2 (17.86); Median 99.7 99.5 99.6; Min: Max 43; 150 42; 150 42; 150; (IQR) (95.4; 100.0) (95.1; 100.0) (95.2; 100.0) **References** Voclosporin (Lupkynis) SmPC. 2022.
Key Issue 6: There is a lack of transparency around the inputs used in the company's model.	Yes	**Summary of the issue** The EAG identified a number of issues with respect to transparency of reporting in both the CS and the company's model, which impacted its ability to verify a variety of aspects of the CS. **Otsuka's response** Disutilities

		A coding error in the application of disutilities was identified by the EAG and it has been corrected in the EAG report ("Company base-case with fix applied") and in the revised base case. The disutilities associated with AEs affected the "QALYs" sheet, on rows 5:6 columns Q, AB, CP, DA. This error only affected MMF containing regimens, and since VCS+MMF contains MMF, the base case results were slightly affected (the change was <1%). Deaths Otsuka has reviewed the cost-effective model parameters. On review of the LN deaths an error was corrected in the model (if a death is present in the AURORA data, the transitions to CR, PR and AD had not been re-weighted to account for the death transition of 1.73% overriding the observed transition to death). This has been corrected on the worksheet 'Input conversion' cells D65:I66. Misalignment of costs and reference source Some of the costs used in the model did not seem to align with the reference source. As such, the EAG conducted a scenario that aligned the costs to the original sources, applied cheaper drug cost prices were available, and inflated costs to current prices where relevant. The EAG also adjusted the LN-related mortality cost to be aligned with 'any diagnosis' end of life cost. Upon revision, Otsuka agrees with all changes mentioned above and has incorporated them as part of the revised base case except for the LN-related mortality cost. As explained in key issue number 2, Otsuka agrees that deaths in CKD1-4 should not incur an LN death cost, which is associated with kidney failure. However, Otsuka believes that a LN-related death cost should still be applicable to deaths occurring in CKD5 (ESRD). As such, the revised base case has an "any diagnosis" end of life cost applied to all deaths in CKD1-4 and LN-related death cost applied to deaths in CKD5. Otsuka can confirm that it has verified the model input parameters referred to throughout this report and that the values used are accurate and appropriate to inform decision making.

Key Issue 7: Uncertainty in how voclosporin will be used in practice.	No	**Summary of the issue** The EAG considered it uncertain but plausible that the effect of voclosporin may vary according to the way it is used. **Otsuka's response** Voclosporin's anticipated marketing authorisation is in combination with MMF for the treatment of adult patients with active class III, IV or V (including mixed class III/V and IV/V) lupus nephritis. This includes patients at initial diagnosis of LN, those with newly flaring disease (previously in remission), and those previously diagnosed but inadequately treated for LN. Guidelines recommend the use of MMF and cyclophosphamide as initial therapies while multiple other therapeutic options are available depending on individual patients' response and needs. In the UK, RTX+MMF and TAC+MMF are typically reserved for patients who are refractory to other treatment options. The AURORA trials provide direct evidence of a significant benefit to active LN patients treated with VCS+MMF versus MMF alone: more patients in the VCS+MMF arm achieved a complete response than patients in the MMF arm (40.8% vs 22.5% at 52 weeks), and patients on VCS+MMF achieved a complete response earlier (169 vs 372 days). The evidence for VCS+MMF supports use in line with the anticipated marketing authorisation.

Additional issues

All: Please use the table below to respond to additional issues in the EAR that have not been identified as key issues. Please do **not** use this table to repeat issues or comments that have been raised at an earlier point in this evaluation (for example, at the clarification stage).

Table 3 Additional issues from the EAR

Issue from the EAR	Relevant section(s) and/or page(s)	Does this response contain new evidence, data or analyses?	Response

Summary of changes to the company's cost-effectiveness estimate(s)

Company only: If you have made changes to the base-case cost-effectiveness estimate(s) in response to technical engagement, please complete the table below to summarise these changes. Please also provide sensitivity analyses around the revised base case. If there are sensitivity analyses around the original base case which remain relevant, please re-run these around the revised base case.

Table 4 Changes to the company's cost-effectiveness estimate

The company's base case ICER following EAG clarification questions (i.e. including correction of the coding error in the application of disutilities identified by the EAG) was **£19,897/QALY** versus MMF. The impact of each change on this ICER (versus MMF) is presented in the table below with results versus all comparators, with all changes implemented, presented in the revised base case.

[redacted]

Key issue(s) in the EAR that the change relates to	Company's base case before technical engagement	Change(s) made in response to technical engagement	Impact on the company's base-case incremental cost-effectiveness ratio (ICER)
Key Issue 2: The company's model structure is subject to a number of structural limitations	1. In line with the AURORA clinical trials, no movement from CKD 1-3a to CKD 3b-4 in the first 36 months 2. Deaths observed within the AURORA clinical trials are assumed to inform LN related death in CKD stages 1-3a	1. Inclusion of transitions to CKD 3b-4 and 5 in the first 36 months (as EAG scenario 11) 2. a) Removal of LN deaths for CR and PR, CKD stages 1-3a using count method (as EAG scenario 10A) with the additional change of removal of LN-related death costs for CKD stages 1-4 (updated	*Following change 1:* ICER vs MMF: [redacted] Change in ICER: [redacted] *Following change 2:* ICER vs MMF: [redacted] Change in ICER: [redacted] **Following these changes combined:** **ICER vs MMF:** [redacted]

Technical engagement response form

		calculations on 'Costs' worksheet for 'Death, LN related' for all treatments). Deaths occurring in CKD5 are classified as LN deaths, as these are linked to kidney failure, and incur a LN death cost b) On review of the LN deaths an error was corrected in the model (if a death is present in the AURORA data, the transitions to CR, PR and AD had not been re-weighted to account for the death transition of 1.73% overriding the observed transition to death. (This has been corrected on the worksheet 'Input conversion' cells D65:I66)	**Change in ICER:** [redacted]
Key Issue 3: The long-term treatment effect of voclosporin + MMF and its comparators is unknown	Application of 'treatment waning' using average of VCS+MMF transitions with MMF transitions applied to VCS+MMF arm	Updated 'treatment waning' for long-term transition probabilities: For VCS+MMF: • Patients in the AD and PR health states – set to MMF transitions (rather than average of VCS+MMF and MMF transitions)	Following this change: ICER vs MMF: [redacted] Change in ICER: [redacted]

		• Patients in the CR health state – set to average of VCS+MMF and MMF transitions
		
		For MMF: No change in transition probabilities
		
		For comparators:
		• Patients in the CR and PR health states – set to MMF transitions
		• Patients in the AD health state – dependent on probability of staying in the AD health state for the comparator and MMF
		  ○ If the probability is lower for the comparator than MMF, set to MMF transitions
		  ○ If the probability is greater for the comparator than MMF, set to transitions derived from ITC data for comparator	

Key Issue 4: The utility estimates used in the company's model are inappropriate	1. Utility values from AURORA 2 observed in Month 36 2. Utility values for dialysis and transplant from Lee et al. (2005)	1. Utility values from regression analysis of AURORA 1 and AURORA 2 (worksheet 'Utilities' G11) 2. Utility values for dialysis and transplant from Li et al. (2017) and Cooper et al. (2020) (as EAG scenarios 2A and 2B)	*Following change 1:* ICER vs MMF: [redacted] Change in ICER: [redacted] *Following change 2:* ICER vs MMF: [redacted] Change in ICER: [redacted] **Following these changes combined:** **ICER vs MMF:** [redacted] **Change in ICER:** [redacted]
Key Issue 5: The company has not appropriately calculated the costs of treatment in the model	1. No wastage associated with discontinuation of VCS 2. MMF dose assumed to be 2.5g/day (averaged based on guidelines) 3. RDI of 100% applied to all treatments (except TAC) due to lack of data	1. Half-pack wastage applied for VCS (as EAG scenario 3) 2. MMF dose and costs set to 2g/day – in line with target dose in AURORA trial (as EAG scenario 4) 3. RDI of 95% for all treatment except for MMF and VCS+MMF which are based on a new analysis of trial data (worksheet 'Treatment costs' E14)	*Following change 1:* ICER vs MMF: [redacted] Change in ICER: [redacted] *Following change 2:* ICER vs MMF: [redacted] Change in ICER: [redacted] *Following change 3:* ICER vs MMF: [redacted] Change in ICER: [redacted] **Following these changes combined:** **ICER vs MMF:** [redacted] **Change in ICER:** [redacted]

<table>
<tr>
<td>Key Issue 6: There is a lack of transparency around the inputs used in the company's model</td>
<td>Lack of transparency regarding inputs used in the model</td>
<td>Verified and included EAG's updated treatment and resource costs (as EAG Scenario 6) but with "any diagnosis" end of life cost applied to all deaths in CKD1-4 and LN-related death cost applied to deaths in CKD5</td>
<td>Following this change:
ICER vs MMF: [redacted]
Change in ICER: [redacted]</td>
</tr>
<tr>
<td>Company's base case following technical engagement (or revised base case)</td>
<td colspan="3">[redacted]

The company's revised base case, inclusive of the updated PAS, is presented below.

Revised base case results (discounted)
<table>
<tr><th rowspan="2">Technologies</th><th colspan="3">Total</th><th colspan="3">Incremental</th><th rowspan="2">ICER (£/QALY)*</th></tr>
<tr><th>Costs (£)</th><th>LYG</th><th>QALYs</th><th>Costs (£)</th><th>LYG</th><th>QALYs</th></tr>
<tr><td>VCS + MMF</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>-</td><td>-</td><td>-</td><td>-</td></tr>
<tr><td>MMF</td><td>[redacted]</td><td>17.57</td><td>13.03</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>£27,301</td></tr>
<tr><td>L-CYC</td><td>[redacted]</td><td>16.96</td><td>12.57</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>£7,870</td></tr>
<tr><td>H-CYC</td><td>[redacted]</td><td>16.83</td><td>12.48</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>£6,704</td></tr>
<tr><td>AZA</td><td>[redacted]</td><td>17.20</td><td>12.76</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>£14,825</td></tr>
<tr><td>RTX + MMF</td><td>[redacted]</td><td>17.95</td><td>13.32</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>£22,722</td></tr>
<tr><td>TAC + MMF</td><td>[redacted]</td><td>17.62</td><td>13.07</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>£23,345</td></tr>
<tr><td>TAC</td><td>[redacted]</td><td>17.68</td><td>13.12</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>£23,849</td></tr>
</table>
*ICER for VCS + MMF vs comparator

Abbreviations: AZA = azathioprine; CYC = cyclophosphamide; ICER = incremental cost-effectiveness ratio; L-CYC = low-dose CYC; H-CYC = high-dose CYC; LYG = life years gained; MMF = mycophenolate mofetil; QALYs = quality-adjusted life years; RTX = rituximab; TAC = tacrolimus; VCS = voclosporin</td>
</tr>
</table>

Sensitivity analyses around revised base case

Probabilistic sensitivity analysis

Mean results of PSA (1000 simulations) and comparison with revised base case results

Technologies	Total costs (£)		Total QALYs		ICER (£/QALY)*	
	Revised base case	PSA	Revised base case	PSA	Revised base case	PSA
VCS + MMF	[redacted]	[redacted]	[redacted]	[redacted]	-	-
MMF	[redacted]	[redacted]	13.03	[redacted]	£27,301	£28,169
L-CYC	[redacted]	[redacted]	12.57	[redacted]	£7,870	£7,566
H-CYC	[redacted]	[redacted]	12.48	[redacted]	£6,704	£6,538
AZA	[redacted]	[redacted]	12.76	[redacted]	£14,825	£15,389
RTX + MMF	[redacted]	[redacted]	13.32	[redacted]	£22,722	£24,977
TAC + MMF	[redacted]	[redacted]	13.07	[redacted]	£23,345	£22,122
TAC	[redacted]	[redacted]	13.12	[redacted]	£23,849	£23,499

*ICER for VCS + MMF vs comparator

Abbreviations: AZA = azathioprine; CYC = cyclophosphamide; ICER = incremental cost-effectiveness ratio; L-CYC = low-dose cyclophosphamide; H-CYC = high-dose cyclophosphamide; MMF = mycophenolate mofetil; PSA = probabilistic sensitivity analysis; QALY = quality-adjusted life year; RTX = rituximab; TAC = tacrolimus; VCS = voclosporin

Scatter plot of PSA results for total discounted costs and QALYs

Abbreviations: CYC = cyclophosphamide; MMF = mycophenolate mofetil; PSA = probabilistic sensitivity analysis; QALY = quality-adjusted life year

Scatter plot of PSA results for incremental discounted costs and QALYs (voclosporin + MMF vs comparators)

Abbreviations: CYC = cyclophosphamide; MMF = mycophenolate mofetil; PSA = probabilistic sensitivity analysis; QALY = quality-adjusted life year

Cost-effectiveness acceptability curve

Abbreviations: CYC = cyclophosphamide; MMF = mycophenolate mofetil; QALY = quality-adjusted life year

Deterministic sensitivity analysis

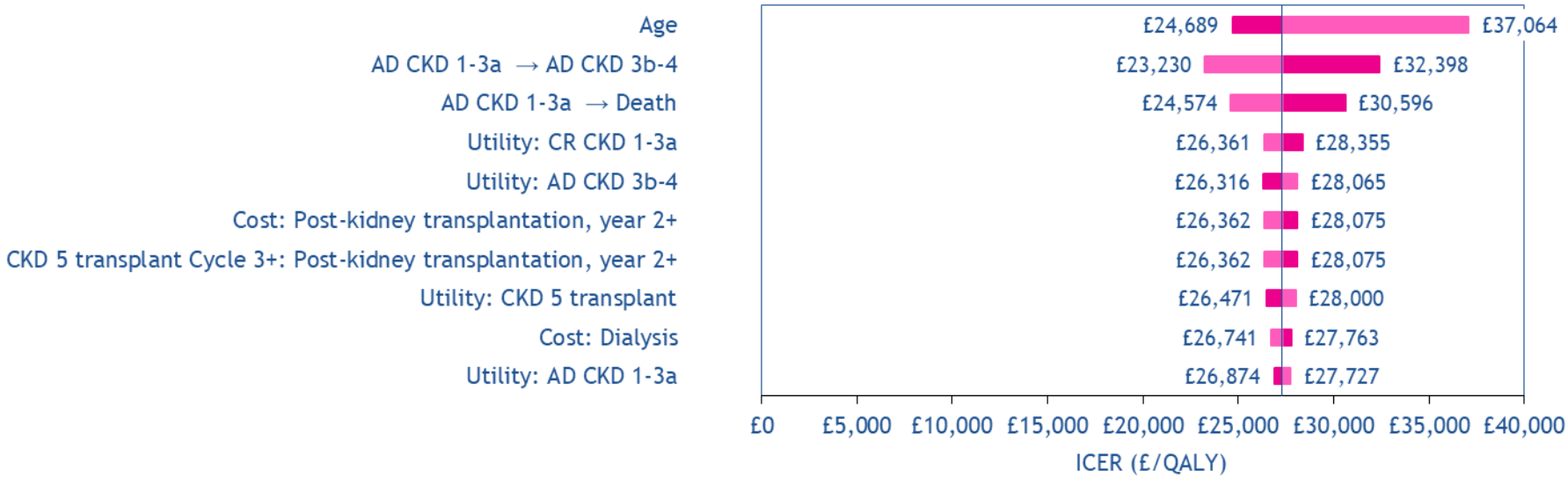
DSA tornado diagram - incremental costs for voclosporin + MMF vs MMF

Abbreviations: AD = active disease; CKD = chronic kidney disease; DSA = deterministic sensitivity analysis; MMF = mycophenolate mofetil

DSA tornado diagram - incremental QALYs for voclosporin + MMF vs MMF

Abbreviations: AD = active disease; CKD = chronic kidney disease; CR = complete response; DSA = deterministic sensitivity analysis; PR = partial response; QALY = quality-adjusted life year

DSA tornado diagram – ICER (£/QALY) for voclosporin + MMF vs MMF



Abbreviations: AD = active disease; CKD = chronic kidney disease; CR = complete response; DSA = deterministic sensitivity analysis; QALY = quality-adjusted life year

NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Voclosporin with immunosuppressive therapies for treating lupus nephritis [ID3962]

Patient expert statement and technical engagement response form

Thank you for agreeing to give us your views on this treatment and its possible use in the NHS.

Your comments and feedback on the key issues below are really valued. You can provide a unique perspective on conditions and their treatment that is not typically available from other sources. The external assessment report (EAR) and stakeholder responses are used by the committee to help it make decisions at the committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form

In part 1 we are asking you about living with lupus nephritis or caring for a patient with lupus nephritis. The text boxes will expand as you type.

In part 2 we are asking for your views on key issues in the EAR that are likely to be discussed by the committee. The key issues in the EAR reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the EAR (section 1).

A patient perspective could help either:

- resolve any uncertainty that has been identified OR
- provide missing or additional information that could help committee reach a collaborative decision in the face of uncertainty that cannot be resolved.

Patient expert statement

You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise. We have given guidance on the issues in which we expect this to be the case and advice on what you could consider when giving your response.

In part 3 we are asking you to provide 5 summary sentences on the main points contained in this document.

Help with completing this form

If you have any questions or need help with completing this form please email the public involvement (PIP) team at pip@nice.org.uk (please include the ID number of your appraisal in any correspondence to the PIP team).

Please use this questionnaire with our hints and tips for patient experts. You can also refer to the Patient Organisation submission guide. **You do not have to answer every question** – they are prompts to guide you. There is also an opportunity to raise issues that are important to patients that you think have been missed and want to bring to the attention of the committee.

Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable. Please type information directly into the form.

We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Your response should not be longer than 15 pages.

Please note, **part 1** can be completed at any time. We advise that **part 2** is completed after the expert engagement teleconference (if you are attending or have attended). At this teleconference we will discuss some of the key issues, answer any specific questions you may have about the form, and explain the type of information the committee would find useful.

Patient expert statement

The deadline for your response is **5pm** on **9 September 2022.** Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

Patient expert statement

Part 1: Living with this condition or caring for a patient with lupus nephritis

Table 1 About you, lupus nephritis, current treatments and equality

1. Your name	Sian Brennan
2. Are you (please tick all that apply)	☒ A patient with lupus nephritis? ☐ A patient with experience of the treatment being evaluated? ☐ A carer of a patient with lupus nephritis? ☐ A patient organisation employee or volunteer? ☐ Other (please specify):
3. Name of your nominating organisation	Lupus UK
4. Has your nominating organisation provided a submission? (please tick all options that apply)	☐ No (please review all the questions and provide answers when possible) ☐ Yes, my nominating organisation has provided a submission ☐ I agree with it and **do not wish to** complete a patient expert statement ☒ Yes, I authored / was a contributor to my nominating organisations submission ☐ I agree with it and **do not wish to** complete this statement ☐ I agree with it and **will be** completing
5. How did you gather the information included in your statement? (please tick all that apply)	☒ I am drawing from personal experience ☐ I have other relevant knowledge or experience (for example, I am drawing on others' experiences). Please specify what other experience: ☐ I have completed part 2 of the statement **after attending** the expert engagement teleconference

	☒ I have completed part 2 of the statement **but was not able to attend** the expert engagement teleconference ☐ I have not completed part 2 of the statement
6. What is your experience of living with lupus nephritis? **If you are a carer (for someone with lupus nephritis) please share your experience of caring for them**	I have suffered from Lupus Nephritis since I was 13 years old, I am now 31, I ended up in ICU when I was 18 and on dialysis, it's been quite a rollercoaster ride! My school attendance was terrible due hospital appointments and day admissions for treatment, meaning my education was of course impacted. Whilst I am fortunate to work for very understanding employers, my absence record is unsurprisingly far higher than the average employee for the same reasons. The greatest symptoms I have are lethargy, high blood pressure and then general Lupus symptoms, arthritic issues etc. Because of my previous Lupus nephritis treatments, I also now have secondary immune deficiency, which means I must inject myself weekly with donated antibodies, leading up to the treatment, I was constantly on antibiotics and had to be so cautious in crowds and refrain from public transport due to the threat of infection. It also now means I need to see an immunologist. This is all because of my lupus nephritis treatments, there were no other options and I understand that, from my Dr's perspective, my care has always been great but it was trying to choose the lesser evil and the only available treatments have now led to further illnesses and burdens on me as a patient - they've completely destroyed my immune system which poses new risks to me. A recent biopsy did confirm I will eventually go into renal failure and so I attend hospital appointments very regularly, I tend to sit around stage 4 CKD. I can't remember the last time I woke up and felt like I had enough energy for the day, living with Lupus Nephritis, in my experience, is constantly running on empty.
7a. What do you think of the current treatments and care available for lupus nephritis on the NHS? **7b. How do your views on these current treatments compare to those of other people that you may be aware of?**	7.a) In my personal experience, there was nothing that worked effectively enough. I tried, steroids, MMF, cyclophosphamide, Rituximab, azathioprine. Rituximab did work, it was probably the first treatment that I physically felt improvement on but not effectively enough, meaning I had to have it regularly to manage my Lupus Nephritis which has ultimately caused the destruction of my immune system and posed a whole new set of issues for me. Also, I'm a woman and I no longer get periods which is attributed to my treatments but not enough is known or explained

	to females at time of treatment and the truth is, even if it was, the alternative option is kidney failure as that's what will happen if they can't get your Lupus under control so you still would have no option but to proceed with the treatment. That was difficult for me to come to terms with as a young female. In conclusion, I don't feel there is any real effective treatment currently available for all individuals. I appreciate the treatments available will have worked for some but for me, they didn't. 7b) Anybody close to me as they have seen the challenges, I have endured would agree with my opinions above.
8. If there are disadvantages for patients of current NHS treatments for lupus nephritis (for example, how they are given or taken, side effects of treatment, and any others) please describe these	Rituximab must be given in hospital, which involves time off school/work, same with Cyclophosphamide. It's not nice to constantly have to ask for time off, even with understanding employers, it can be frustrating and it impacts your ability to lead a normal life with your illness, my education was impacted. The treatments also have strong side effects, particularly cyclophosphamide, I'd be really sick after it. Also, the serious implications on your immune system as I have detailed above and your ability to have children, as I've also mentioned above. These are huge sacrifices to make as a patient. Being on steroids since I was 10, means I unsurprisingly means I have osteopenia and in my hip I'm on the cusp of osteoporosis as confirmed on my recent Dexa scan. There is also the bloating which is really difficult to deal with as a young adult and undoubtedly has implications on mental health. Azathioprine is better as it is a tablet you can take at home, but I wasn't able to get to the recommended dose as it started to impact my red blood cells and when in a serious flare, it doesn't control the Lupus.
9a. If there are advantages of voclosporin over current treatments on the NHS please describe these. For example, the effect on your quality of life, your ability to continue work, education, self-care, and care for others? **9b. If you have stated more than one advantage, which one(s) do you consider to be the most important, and why?**	9a) The fact you can manage your treatment at home is a huge benefit, it reduces the impact on quality of life and work/life commitments. It's also designed for Lupus nephritis with proven better results than the alternatives currently available. It doesn't have the awful side effects of the likes of Cyclophosphamide and Rituximab (fertility, sickness, hair loss, loss of immune system etc.) I think it would have a massive positive impact on day to day life with Lupus nephritis, for the individual but also for their family, not having to take time off for hospital trips or to care for the patient post-treatment.

9c. Does voclosporin help to overcome or address any of the listed disadvantages of current treatment that you have described in question 8? If so, please describe these	9b) That is designed specifically for Lupus Nephritis. For me, this massively increases the likelihood of the treatment targeting the problem areas more effectively and efficiently, which would then reduce the likelihood of the patient developing the secondary issues, like fertility and immune-deficiency problems I have experienced and reduce the time they need to spend in hospital. 9c) I think it would help to overcome most of them, you don't need to go to hospital, there is no evidence that you will be sick after like cyclophosphamide, it shouldn't completely destroy your immune system as there is no evidence to suggest it will affect fertility.
10. If there are disadvantages of voclosporin over current treatments on the NHS please describe these. For example, are there any risks with voclosporin? If you are concerned about any potential side effects you have heard about, please describe them and explain why	I have no concerns; I think any progression in treatment advancement is positive and should be explored and trailed. I appreciate the treatment would be too late to heal my current issues, but it could prevent somebody else ending up in my position.
11. Are there any groups of patients who might benefit more from voclosporin or any who may benefit less? If so, please describe them and explain why Consider, for example, if patients also have other health conditions (for example difficulties with mobility, dexterity or cognitive impairments) that affect the suitability of different treatments	11. Those who's Lupus Nephritis hasn't responded as well to traditional medications. Those who struggle to get to hospital. If the likes of calcort or aziathioprine is controlling an individual's diseases, they mightn't yield the same benefit from voclosporin
12. Are there any potential equality issues that should be taken into account when considering lupus nephritis and voclosporin? Please explain if you think any groups of people with this condition are particularly disadvantaged Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or	12. I don't have any opinion on this

belief, sex, and sexual orientation or people with any other shared characteristics More information on how NICE deals with equalities issues can be found in the NICE equality scheme Find more general information about the Equality Act and equalities issues here.	
13. Are there any other issues that you would like the committee to consider?	I know I have previously mentioned it but I do think it is important that the committee does consider individuals like myself, who now have secondary immune deficiency and can't have children because of existing treatments. We do need to consider the impact this has on patient quality of life and mental health and support any progression on treatment that could avoid these situations.

Part 2: Technical engagement questions for patient experts

Issues arising from technical engagement

The issues raised in the EAR are listed in table 2. We welcome your comments on the issues, but you do not have to provide a response to every issue, such as the ones that are technical, that is, cost effectiveness-related issues. We have added a comment to the issues where we consider a patient perspective would be most relevant and valuable. If you think an issue that is important to patients has been missed in the EAR, please let us know in the space provided at the end of this section.

For information: the patient organisation that nominated you has also been sent a technical engagement response form (a separate document) which asks for comments on each of the key issues that have been raised in the EAR, the patient organisation responses will also be considered by the committee.

Table 2 Issues arising from technical engagement

Key issue 1: Network meta-analysis (NMA) estimates may not be reliable and should better account for heterogeneity. • **Does the company's NMA sufficiently account for heterogeneity?** • **Is a fixed effects or random effects NMA more appropriate?**	Not in a position to comment on this
Key issue 2: The company's model structure is subject to a number of structural limitations. • **Are the restrictive settings and assumptions in the model**	Not in a position to comment on this

Patient expert statement

identified by the EAG significant and should they be adjusted? • **What percentage of patients with lupus nephritis who enter end stage renal disease are expected to receive a kidney transplant?**	
Key Issue 3: The long-term treatment effect of voclosporin + MMF and its comparators is unknown. • **Are the short-term data for voclosporin + MMF sufficient to generalise to the longer term?** • **Are the short-term data while patients are on treatment reflective of longer-term outcomes when patients are no longer receiving the same treatment up until 3 years?** • **The company assumes the treatment effect of voclosporin + MMF wanes indefinitely based on the average effect of voclosporin + MMF and MMF alone. Do you consider this approach to be appropriate?**	I believe when it comes to medical treatment we have to make assumptions, to expect to wait to obtain life or long term data, in my opinion, is unreasonable and doing so means delaying patient benefits and increasing the likelihood of patient deterioration due to ineffective treatments currently available. As a patient, I would be more than happy to start taking voclosporin based on the evidence provided in current trials.
Key Issue 4: The utility estimates used in the company's model are inappropriate.	

Patient expert statement

• **Are the utility values used by the company reflective of the expected utility of patients with lupus nephritis?** • **Are the literature-based utility values for later states reflective of the utility of patients with lupus nephritis in later states?** **We consider patient perspectives may particularly help to address this issue.**	
Key Issue 5: The company has not appropriately calculated the costs of treatment in the model. • **Is it appropriate to assume 95% relative dosing intensity for all treatments?** • **Is it appropriate to assume no treatment discontinuation for comparator treatments?**	N/A
Key Issue 6: There is a lack of transparency around the inputs used in the company's model.	N/A
Key Issue 7: Uncertainty in how voclosporin will be used in practice. • **Where would voclosporin be used in the treatment pathway?**	I think voclosporin should be used at a Dr's discretion, he knows his patients and the drugs available but understanding the cost elements, at a minimum, it should be used when less evasive, traditional treatments have failed to yield the required results. For e.g. I was needing Rituximab every 4/5months which is what caused the destruction of my immune system, in a situation like that, before it gets to that point, another treatment option, like

Patient expert statement

• **Would voclosporin be used as a first-line treatment?** • **How long would patients be expected to receive voclosporin?** • **What factors would influence the decision to stop treatment?** • **Would the treatment effect of voclosporin vary based on how it is used (i.e., earlier or later treatment lines, shorter or longer treatment durations, new onset or relapsed lupus nephritis)? If so, what magnitude would the variation be?** **We consider patient perspectives may particularly help to address this issue.**	voclosporin should be explored and offered. At the time I had exhausted all available treatment options so I had no choice but to continue with the evasive Rituximab but we need more options for Dr's to avoid situations like mine occurring. In terms of duration, I think it should be until there is satisfactory control of the Lupus nephritis and if stopping the medication causes a relapse, treatment should be continued.
Are there any important issues that have been missed in EAR?	

Part 3: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

- We need more effective treatment options to help reduce patient deterioration cause through an inability to effectively control Lupus nephritis
- Voclosporin provides an alternative treatment option, with positive results that is already being used in other markets, this could dramatically help to improve disease management and patient quality of life
- Current treatments are evasive and can cause additional issues for patients, like in my case where I have now developed another condition, namely secondary immune deficiency, requiring new treatment and posing greater risks to my life.
- Click or tap here to enter text.
- Click or tap here to enter text.

Thank you for your time.

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

☒ **Please tick this box** if you would like to receive information about other NICE topics.

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Patient expert statement

NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Voclosporin with immunosuppressive therapies for treating lupus nephritis [ID3962]

Clinical expert statement and technical engagement response form

Thank you for agreeing to comment on the external assessment report (EAR) for this evaluation, and for providing your views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature. The EAR and stakeholder responses are used by the committee to help it make decisions at the committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form

In part 1 we are asking for your views on this technology. The text boxes will expand as you type.

In part 2 we are asking for your views on key issues in the EAR that are likely to be discussed by the committee. The key issues in the EAR reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the EAR (section 1). You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise.

A clinical perspective could help either:

- resolve any uncertainty that has been identified OR
- provide missing or additional information that could help committee reach a collaborative decision in the face of uncertainty that cannot be resolved.

In part 3 we are asking you to provide 5 summary sentences on the main points contained in this document.

Clinical expert statement

Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable. Please type information directly into the form.

Do not include medical information about yourself or another person that could identify you or the other person.

We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information redacted. See the NICE health technology evaluation guidance development manual (sections 5.4.1 to 5.4.10) for more information.

Please note, part 1 can be completed at any time. We advise that **part 2** is completed after the expert engagement teleconference (if you are attending or have attended). At this teleconference we will discuss some of the key issues, answer any specific questions you may have about the form, and explain the type of information the committee would find useful.

The deadline for your response is **5pm** on **9 September 2022.** Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Clinical expert statement

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

Part 1: Treating lupus nephritis and current treatment options

Table 1 About you, aim of treatment, place and use of technology, sources of evidence and equality

1. Your name	Alan Salama
2. Name of organisation	Lupus UK
3. Job title or position	Professor of Nephrology
4. Are you (please tick all that apply)	☐ An employee or representative of a healthcare professional organisation that represents clinicians? ☒ A specialist in the treatment of people with lupus nephritis? ☐ A specialist in the clinical evidence base for lupus nephritis or voclosporin? ☐ Other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☐ Yes, I agree with it ☐ No, I disagree with it ☐ I agree with some of it, but disagree with some of it ☒ Other (they did not submit one, I do not know if they submitted one etc.)
6. If you wrote the organisation submission and/or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission)	☐ Yes
7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
8. What is the main aim of treatment for lupus nephritis? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability)	The condition is not curable at the moment but rather has a tendency to repeatedly relapse and remit. Therefore, treatment is aimed at: Minimising organ damage

	Improving symptoms and quality of life, while minimising adverse drug related effects In the context of lupus nephritis this means reducing renal dysfunction and proteinuria while dealing with the systemic features of the disease if they are present. Treatment is generally thought of in two blocks- induction of remission therapy and maintenance therapy, aimed at consolidating remission and minimising the chances of relapse. It has become obvious that while there are clear benefits of therapy, there are also short and long term adverse effects and treatment is therefore tapered in an attempt to minimise the likelihood and severity of adverse events. More recently steroids have been highlighted as the perceived cause of many of the infectious and long term side effects- so many attempts at finding new ways of reducing steroid therapy have been taken. It should be emphasised that a proper dose response trial of steroids has never been carried out and so the optimal dosing of steroids is uncertain and has evolved from older data which was imperfect and not well controlled, dating back to the 1960s.
9. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount)	With regards lupus nephritis there are kidney related outcomes that are important (see below). In addition, it is common for patients with active lupus nephritis to have other organ or system involvement, though this is not universal. In the cases of more extensive systemic disease- other outcome measures or scoring systems provide important information on the success of therapy. However, in all of these cases kidney disease severity is a critical factor in predicting overall patient survival and morbidity. Although not a perfect measure- as it can reflect both active disease and disease damage, urine protein reduction is a key outcome measure. It is slow to achieve nadir levels, which can take a year (or more) but it is a valuable marker of disease and predictor of long term kidney dysfunction. Similarly, serum creatinine is a useful marker, although many patients with lupus nephritis can still have significant disease – on biopsy, yet not show marked changes in serum creatinine. Finally, there is the histological assessment which is prone to sampling bias but provides important information on the state of disease activity and chronic damage.

10. In your view, is there an unmet need for patients and healthcare professionals in lupus nephritis?	Yes, there are problems with adverse effects of current therapies which have direct morbidities and also contribute to non-compliance. In addition, there is still a percentage of patients who do not respond well to therapy , and progress to end stage kidney disease – necessitating dialysis or transplantation. Currently we are limited by the number of available drugs and drug combinations that we can offer- more therapeutic options allow for customisation of therapy for the individual to maximise response and minimise toxicity.
11. How is lupus nephritis currently treated in the NHS? • Are any clinical guidelines used in the treatment of the condition, and if so, which? • Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.) • What impact would the technology have on the current pathway of care?	There are numerous recommendations that exist – including KDIO, EULAR, and the America college of rheumatology lupus nephritis guidelines. They are broadly similar as there are limited options for therapeutic variations. They essentially all suggest the use of background hydroxychloroquine in addition to a regimen of steroids and mycophenolate mofetil with or with addition of a CNI, or the use of low dose cyclophosphamide. Addition of B cell depletion is generally reserved for non-responders. This is in the form of rituximab and or belimumab or alternatives if allergic (such as obinutuzimab). There are generally variations in dosing of steroids used, whether pulsed steroids are included, the speed of taper and the maintenance doses used. This is true between sites and even within a series of hospital specialists. MMF is generally given at 2-3g a day for induction if tolerated based on trial data. Cyclophosphamide is generally given as a EUROLUPUS regimen 500 mg every two weeks The technology is reported to be a better version of the current CNIs that are available and that are currently added in, especially in the far east and in those patients who are nephrotic. The benefits include more predictable absorption and less hypertension and hyperglycaemia. Monitoring is generally required with CNI and the monitoring here uses the changes in creatinine rather than drug levels- however strategy can also be used with more conventional CNI. It would be used as apart of a triple therapy regimen- which is generally not the first regimen used in the UK, but if used according to the trial would allow for use of significantly lower doses of steroid than are currently used. This I do see as being of benefit.

12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice? • How does healthcare resource use differ between the technology and current care? • In what clinical setting should the technology be used? (for example, primary or secondary care, specialist clinic) • What investment is needed to introduce the technology? (for example, for facilities, equipment, or training)	No, it would make people use a triple therapy regimen possibly as a starting point rather than MMF/steroids dual therapy or cyclophhosphamide The Aurora trial essentially compared standard of care with MMF but with LOWER dose steroid to the triple therapy of low dose steroid, MMF and voclosporin. So, if trial was followed, we would introduce a triple therapy regimen but would be confident that outcomes are as good- or possibly better than those with high dose steroid and MMF only. The real benefit of steroid minimisation may not be apparent for a prolonged period. The technology would be used in the same settings as now so no special changes/investments are needed.
13. Do you expect the technology to provide clinically meaningful benefits compared with current care? • Do you expect the technology to increase length of life more than current care? • Do you expect the technology to increase health-related quality of life more than current care?	Lower dose steroids are beneficial- however, we do not know what would happen at the end of the 52 week period if we stopped voclosporin. Mainteneance at that stage would be with MMF and likely without steroids- while this is a reasonable strategy we don't know the relapse rate of these patients. If more people are in remission then we would predict better long term kidney function, less progression to ESKD and need for transplantation or dialysis. In addition, reducing proteinuria will have a likely benefit on cardiovascular morbidity and mortality which is significantly augmented in this population. I expect lower steroid doses to be associated with better quality of life.
14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	No it appears to work across all subgroups tested. It is appealing for patients with nephrotic syndrome especially, but we already often use other CNIs in this scenario.
15. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use? (For example, any concomitant treatments needed, additional clinical requirements, factors affecting patient	No different, I think. There will be an increase in pill burden. Compliance may be poorer if more drugs are needed to be taken . Monitoring: although drug levels are not routinely measured a close eye will need to be kept on kidney function and there may be greater need to recall patients for blood results review.

acceptability or ease of use or additional tests or monitoring needed)	
16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	There appears to be no addition burden of hyperglycaemia or hypertension. No additional testing is routinely warranted. Use of the technology will be dependent on the severity of the lupus nephritis
17. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation? • Do the instruments that measure quality of life fully capture all the benefits of the technology or have some been missed? For example, the treatment regimen may be more easily administered (such as an oral tablet or home treatment) than current standard of care	Steroid related adverse effects are important and many are dose dependent , so using lower doses will benefit patients. The longer term outcomes related to steroid toxicity may not be picked up in a Quality of life assessment done at the time. However, it is worth remembering that this treatment will be for a time limited period and the patients will likely need maintenance therapy to stop disease flares.
18. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met? • Is the technology a 'step-change' in the management of the condition? • Does the use of the technology address any particular unmet need of the patient population?	It is not revolutionary, but evolutionary, in that it is a better version of the current drugs available. It is likely to be more expensive but offers an alternative induction strategy that would mean physicians are more comfortable minimising steroids, which I see as being of benefit.
19. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	These appear to be no worse than the standard of care. There will be increased pill burden however.
20. Do the clinical trials on the technology reflect current UK clinical practice? • If not, how could the results be extrapolated to the UK setting?	Yes and no. The steroid doses used in the Aurora trial were significantly lower than those generally used as standard of care in the UK. This therefore made it favourable in the trial for the voclosporin arm. The benefit of the voclosporin may be not fully realised if physicians use standard(ie higher) doses of steroids along with MMF and voclosporin- especially in using pulsed methylprednisolone and starting doses and duration of oral prednisolone. So, its benefit will require a

• What, in your view, are the most important outcomes, and were they measured in the trials? • If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes? • Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	change in how steroids are used- which I believe is timely and achievable. There are no trials of steroid dosing to define the ideal steroid regime, so this is the most variable part of treatment in the UK. The outcomes are hard renal endpoints which were used in the trial- proteinuria of less than 0.5mg/g and a GFR >60 – although this is somewhat artificial in that all of the participants had a GFR > 60 to start with – this group often has persevered renal function. A better outcome would have been a delta GFR from entry to trial end. Proteinuria is a hard and important outcome however. No additional adverse effects as far as I know.
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
22. How do data on real-world experience compare with the trial data?	Not used in the UK
23. NICE considers whether there are any equalities issues at each stage of an evaluation. Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged. Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics. Please state if you think this evaluation could	The condition disproportionally affects women, especially from Black and Asian ethnicities. However, there is no reason to think this technology would be either advantageous or disadvantageous to these particular groups. So no real difference to standard of care.

• exclude any people for which this treatment is or will be licensed but who are protected by the equality legislation • lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population • lead to recommendations that have an adverse impact on disabled people. Please consider whether these issues are different from issues with current care and why. More information on how NICE deals with equalities issues can be found in the NICE equality scheme. Find more general information about the Equality Act and equalities issues here.	

Part 2: Technical engagement questions for clinical experts

We welcome your comments on the key issues below, but you may want to concentrate on issues that are in your field of expertise. If you think an issue that is important to clinicians or patients has been missed in the EAR, please also advise on this in the space provided at the end of this section.

The text boxes will expand as you type. Your responses to the following issues will be considered by the committee and may be summarised and presented in slides at the committee meeting.

For information: the professional organisation that nominated you has also been sent a technical engagement response form (a separate document) which asks for comments on each of the key issues that have been raised in the EAR. These will also be considered by the committee.

Table 2 Issues arising from technical engagement

Key issue 1: Network meta-analysis (NMA) estimates may not be reliable and should better account for heterogeneity. • **Does the company's NMA sufficiently account for heterogeneity?** • **Is a fixed effects or random effects NMA more appropriate?**	There are issues with trials on lupus nephritis which have used different definitions for primary endpoints and definitions for renal remission. I am not sure I completely understand the statistical arguments that are made and so cannot really comment, however, I think they used MMF as a comparator to MMF and voclosporin- without taking into account steroid dosing which is critical to the outcome.
Key issue 2: The company's model structure is subject to a number of structural limitations. • **Are the restrictive settings and assumptions in the model**	"Since there was no CKD progression in the trial this has been disabled in their model". This is an issue as patients with lupus nephritis may have repeated episodes of nephritis and may not all start with normal renal function as they did in the trial. In addition other factors need to be considered which impact on progression outside of trial settings- such as delays in diagnosis, and compliance with drug which can lead to some irreversible kidney damage. In aurora 12 % were enrolled but did not complete for one reason or another. In

identified by the EAG significant and should they be adjusted? • **What percentage of patients with lupus nephritis who enter end stage renal disease are expected to receive a kidney transplant?**	fact ESRD has remained fairly constant as a percentage of patients with lupus nephritis in a number of trials and databases over the last twenty years. As lupus nephritis affects younger populations the majority of patients with ESRD caused by SLE would be eligible for kidney transplantation – unless they have significant other comorbidities. In my experience most would be transplanted although they may wait longer than average – due to ethnicity and immunological barriers.
Key Issue 3: The long-term treatment effect of voclosporin + MMF and its comparators is unknown. • **Are the short-term data for voclosporin + MMF sufficient to generalise to the longer term?** • **Are the short-term data while patients are on treatment reflective of longer-term outcomes when patients are no longer receiving the same treatment up until 3 years?** • **The company assumes the treatment effect of voclosporin + MMF wanes indefinitely based on the average effect of voclosporin + MMF and MMF alone. Do you consider this approach to be appropriate?**	The short term data are good, and the speed of onset of remission is better with voclosporin. Although Proteinuria is a good long term predictor of renal outcome, the persistence of low level proteinuria would be important to quantify , and this is not obtained in a one year trial. The issue with CNI's is that when they are stopped- there is often a subsequent increase in proteinuira- in part due to the effect the CNIs have on stabilising the podocyte. So the follow up of proteinuria in those patients when voclosporin is stopped is important and may suggest that the short term benefit may not persist in all patients beyond the use of drug. So I agree that three years after stopping the voclosporin the short term data my no longer be applicable. In addition there are relapses which can be frequent and will be dependent not just on the induction therapy but the duration, dose and type of maintenance therapy. The long term effect of voclosporin addition to standard of care may therefore not be so simple to predict and I cannot understand how this could be considered to be fixed for the next 70 years. See above regarding hangover effect of voclosporin- the drug has two effects, the immunosuppressive effect which can switch off the autoimmune process and the kidney inflammation – but which takes time, and a more immediate effect on stabiliisng of the podocytes which means a more rapid reduction in proteinuria. The first effect may indeed last for a longer period of time beyond the use of the drug, but the latter may not. So the effect of induction with voclosporin and MMF which is then converted to MMF maintenance is not readily predicted form the short term trial data

Key Issue 4: The utility estimates used in the company's model are inappropriate. • **Are the utility values used by the company reflective of the expected utility of patients with lupus nephritis?** • **Are the literature-based utility values for later states reflective of the utility of patients with lupus nephritis in later states?**	With regards the utility assessments: It is not correct to assume a 50% splt between haemo- and peritoneal dialysis It is true that those having a transplant are likely to be younger and generally fitter than those who remain on haemodialysis I agree that using only the 36 month QoL data does not make much sense and would have missed a significant signal during the earlier course of treatment
Key Issue 5: The company has not appropriately calculated the costs of treatment in the model. • **Is it appropriate to assume 95% relative dosing intensity for all treatments?** • **Is it appropriate to assume no treatment discontinuation for comparator treatments?**	No- there will be discontinuations in comparators- due to adverse effects, non compliance and non responsiveness
Key Issue 6: There is a lack of transparency around the inputs used in the company's model.	I cannot speak to this
Key Issue 7: Uncertainty in how voclosporin will be used in practice. • **Where would voclosporin be used in the treatment pathway?** • **Would voclosporin be used as a first-line treatment?**	It would be used as induction therapy with MMF and low dose steroids Especially important in those where steroid dose limitations is critical- those overweight, diabetic or borderline, steroid adverse effects, bone disease etc It would be in my mind represent an option of a lower steroid regimen Yes it could be a first line treatment

• **How long would patients be expected to receive voclosporin?** • **What factors would influence the decision to stop treatment?** • **Would the treatment effect of voclosporin vary based on how it is used (i.e., earlier or later treatment lines, shorter or longer treatment durations, new onset or relapsed lupus nephritis)? If so, what magnitude would the variation be?**	I expect that two years would be enough for the voclosporin- perhaps even less if the patients have gone into early complete remission Reduction in proteinuria would allow withdrawal of voclosporin and maintenance with MMF There are likely to be impediments to use of voclosporin in patients with existing CKD – as there is more likely a greater toxicity in this cohort with possible decline in renal function- so relapsing patients with a history of lupus nephritis and CKD may need a shorter course
Are there any important issues that have been missed in EAR?	

Part 3: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

Voclopsorin is a slightly better drug than the currently available CNI's
It would allow a lower steroid dose to be mandated which will be a good thing
The maximal benefit of voclosporin will only be realised if the low steroid dosing is adhered to. If more pulsed steroids and higher doses of oral steroids are used its likely that more side effects will be realised and long term benefits attenuated
The long term benefits of adding in a CNI and reducing steroids are not known
Click or tap here to enter text.

Thank you for your time.

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

☐ x **Please tick this box** if you would like to receive information about other NICE topics.

For more information about how we process your personal data please see our privacy notice.

NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Voclosporin with immunosuppressive therapies for treating lupus nephritis [ID3962]

Patient expert statement and technical engagement response form

Thank you for agreeing to give us your views on this treatment and its possible use in the NHS.

Your comments and feedback on the key issues below are really valued. You can provide a unique perspective on conditions and their treatment that is not typically available from other sources. The external assessment report (EAR) and stakeholder responses are used by the committee to help it make decisions at the committee meeting. Usually, only unresolved, or uncertain key issues will be discussed at the meeting.

Information on completing this form

In part 1 we are asking you about living with lupus nephritis or caring for a patient with lupus nephritis. The text boxes will expand as you type.

In part 2 we are asking for your views on key issues in the EAR that are likely to be discussed by the committee. The key issues in the EAR reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the EAR (section 1).

A patient perspective could help either:

- resolve any uncertainty that has been identified OR
- provide missing or additional information that could help committee reach a collaborative decision in the face of uncertainty that cannot be resolved.

Patient expert statement

You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise. We have given guidance on the issues in which we expect this to be the case and advice on what you could consider when giving your response.

In part 3 we are asking you to provide 5 summary sentences on the main points contained in this document.

Help with completing this form

If you have any questions or need help with completing this form, please email the public involvement (PIP) team at pip@nice.org.uk (please include the ID number of your appraisal in any correspondence to the PIP team).

Please use this questionnaire with our hints and tips for patient experts. You can also refer to the Patient Organisation submission guide. **You do not have to answer every question** – they are prompts to guide you. There is also an opportunity to raise issues that are important to patients that you think have been missed and want to bring to the attention of the committee.

Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable. Please type information directly into the form.

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Your response should not be longer than 15 pages.

Please note, **part 1** can be completed at any time. We advise that **part 2** is completed after the expert engagement teleconference (if you are attending or have attended). At this teleconference we will discuss some of the key issues, answer any specific questions you may have about the form, and explain the type of information the committee would find useful.

Patient expert statement

The deadline for your response is **5pm** on **9 September 2022.** Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

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Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

Patient expert statement

Part 1: Living with this condition or caring for a patient with lupus nephritis

Table 1 About you, lupus nephritis, current treatments, and equality

1. Your name	Amy Somers
2. Are you (please tick all that apply)	☒ A patient with lupus nephritis? ☐ A patient with experience of the treatment being evaluated. ☐ A carer of a patient with lupus nephritis? ☒ A patient organisation employee or volunteer? ☐ Other (please specify):
3. Name of your nominating organisation	Lupus UK
4. Has your nominating organisation provided a submission? (Please tick all options that apply)	☐ No (please review all the questions and provide answers when possible) ☒ Yes, my nominating organisation has provided a submission ☐ I agree with it and **do not wish to** complete a patient expert statement ☐ Yes, I authored / was a contributor to my nominating organisations submission ☐ I agree with it and **do not wish to** complete this statement ☒ I agree with it and **will be** completing this statement
5. How did you gather the information included in your statement? (Please tick all that apply)	☒ I am drawing from personal experience ☐ I have other relevant knowledge or experience (for example, I am drawing on others' experiences). Please specify what other experience: ☒ I have completed part 2 of the statement **after attending** the expert engagement teleconference

	☐ I have completed part 2 of the statement **but was not able to attend** the expert engagement teleconference ☐ I have not completed part 2 of the statement
6. What is your experience of living with lupus nephritis? **If you are a carer (for someone with lupus nephritis) please share your experience of caring for them**	My experience of living with Lupus nephritis has been challenging in every sense. Lupus has impacted every aspect of my life. Initially, pre diagnosis I was working full time (60+ hour weeks) as a camera assistant in film and television. My symptoms started as oedema in my legs and my diagnosis was fast (within two weeks I had blood tests and a kidney biopsy) I was very much in the 'denial phase' so I continued my intensive work schedule post diagnosis, the only change was to take medication. It was very challenging to schedule clinic appointments and blood monitoring whilst continuing my TV career. I had a painful reality check of what it meant to be immune suppressed when I got shingles a month after diagnosis. It became difficult to maintain my social life and friendships. I also found it very difficult to do my intensive all hours/ locations (often outside in the rain and cold) job to full capacity whilst anxious of avoiding infection. The swelling in my legs was uncomfortable and meant I had to raise them when possible. This led me to make the discission to retrain in a more sustainable (indoor) profession. I completed a patisserie course and started working for a local café, baking and as a barista. This reduced the infection risk and intensive hours but after a few years the debilitating and painful fatigue, brain fog and join pain symptoms of Lupus manifested so I had to leave employment all together as my energy was so unpredictable. I can wake up and not be able get out of bed, let alone shower because of the pain and exhaustion. I often struggle to drive as my concentration cannot be sustained and physically holding the wheel is painful. Most days I need to sleep (mostly in the early afternoon) for 2-3 hrs to be able to function. I have struggled to maintain a healthy weight whilst on steroids and due to the chronic fatigue. The implications were and are physical, emotional, and financial. My self-esteem and sense of self-worth was non-existent. In applying for benefits, you are asked to highlight the worst aspects of your life and condition which at my most vulnerable point was near unbearable. I struggled to be an advocate for myself, I was very angry and frustrated. Subsequently my 6-year relationship with

	my partner fell apart, the multifaceted stresses of a chronic condition were too much to handle. I relied heavily on my family for financial, emotional, and physical support, living with my sister for 6 months. As a previously independent woman in my 30's, the resulting dependence caused me to suffer with depression. Through this time, I also started chemotherapy which was intensive and physically debilitating followed by a second painful kidney biopsy causing bleeding and requiring oral morphine and bed rest. This was to determine if scarring of my kidneys was the reason my proteinuria would not decrease with medication. In 2018 I joined Lupus Europe as a volunteer, this gave me a sense of worth that I had lost and allowed me to return to 'work' with a community who could understand and respect my limitations without judgement or the fear of letting people down. I began to engage with the patient community and learn about Lupus, to educate myself and meet likeminded passionate patients helped me to redirect a lot of the frustration and anger into something positive. I am now a member of the Lupus Europe board, a EUPATI fellow and committee member of Lupus UK's Northwest group. These roles allow me the space and flexibility to allocate the energy I have productively. I have lived with Lupus nephritis for over 10 years. I am now in a new relationship, which is only possible due to my understanding of my condition and implementing strategies so we can maintain a partnership rather than a carer dynamic which is very important to me. This also hinges on the financial support of ESA and PIP so I can keep some autonomy and reduce the burden on my partner (such as employing a cleaner, paying for medication, physical aids, mental health support.) I now have the flexibility and support to rest when I need to and have learnt to adapt, my initial reaction was to push against the fatigue, but this just prolongs and worsens it. A lack of understanding of Lupus is also significant in the burden on patients to explain the severity of their condition, unlike other more well know diseases (i.e., cancer) which society implicitly understands. Throughout my treatment journey I have been acutely aware of preventing possible damage to my kidneys and the risk of ESRD. There have been times when no one

	can ascertain if the symptoms I suffer are Lupus related or drug related, this is very difficult to wrap your head around whilst continuing to adhere to medication when it could be the cause of your suffering. My clinical team (Rheumatology and Nephrology) and I are working together to find a combination of treatment which can achieve remission in my kidney disease and preferably eradicate the other debilitating symptoms if not significantly reduce them. My goal is to feel and to be healthy and ultimately able to return to work and have financial independence and a good quality of life.
7a. What do you think of the current treatments and care available for lupus nephritis on the NHS? **7b. How do your views on these current treatments compare to those of other people that you may be aware of?**	The heterogenous nature of Lupus has meant that my treatment journey has consisted of 8 different immune suppressive medications over a 10-year period to get my disease to be 'stable'. With each new medication comes a new set of side effects to identify, counter medicate if necessary and adjust to. There are also increased visits to clinic for monitoring bloods and a renewed expectation of success. I had an anaphylactic reaction to two different biologic medications (Rituximab and Ofatumumab). New medications can also include needing to have a kidney biopsy (I have had 2) or intravenous delivery which is painful and logistical I am encouraged that new medications are being approved and used for treating LN. It is a complex heterogeneous disease and by having more treatment options, hopefully that will deliver a personalised approach to reach remission sooner for better long-term outcomes. Clinicians are also demonstrating a less 'steroid centric' approach to LN treatment on diagnosis, while I appreciate the need for corticoids, they have such a detrimental effect on the patient physically and mentally in high doses that if other medications can control their disease this could be preferable for the patient. Also, the long-term effects of steroids and difficulty reducing dosage could be avoided. I am fortunate to be treated at a Lupus centre of excellence, but this is not the case for all patients nationally. Access should not be limited by region. It has been shown in other disease areas, such as cancer, the effectiveness of multi-disciplinary support for patients and their care givers on diagnosis. I would like to see this approach implemented in Lupus care.

8. If there are disadvantages for patients of current NHS treatments for lupus nephritis (for example, how they are given or taken, side effects of treatment, and any others) please describe these	Tablet medications are the standard, but they come with a monitory cost to the patient and consumption is a daily reminder of your chronic condition. Sub cutaneous delivery can be painful and cause bruising. Intravenous medications require regular clinic visits which can be difficult to coordinate as you most likely need a care giver to assist at these visits and time off work or childcare etc. All new medications need monitoring, usually with bloods and regularly at the start, this is often difficult for a patient to coordinate, especially if they do not live close to their clinic. Steroids are still a first line treatment in LN, their impact and side effects are significant, weight gain, mood changes, long term osteoporosis etc. MMF is a 'standard of care' medication for LN, quite often used as a first response to disease activity (It was my first treatment). This medication is unsafe for Men and women if you want to conceive. It also cannot be taken if you are pregnant. As the majority of LN patients are women in their 20's and 30's this is a significant QoL side effect. Biologic medication, which has been shown to be effective in LN also has pregnancy implications. There is a challenging contraction in LN and pregnancy as you need your kidneys to be stable to carry a baby but also need effective treatment to achieve stability which would be a medication counter indicated in pregnancy. This all takes time which impacts family planning and can have a negative impact on the patient and their partner. Medications used for LN such as Cyclophosphamide impact fertility, I went through egg retrieval prior to treatment to preserve my fertility. This change in hormones had a significant negative effect on my LN disease activity resulting in painful mouth ulcers and severe fatigue. The overriding effect of immune suppression in LN treatment is very challenging for a patient. Limiting your exposure to infection can also limit your QoL.
9a. If there are advantages of Voclosporin over current treatments on the NHS, please describe these. For example, the effect on your quality of life, your ability to continue work, education, self-care, and care for others?	Patients need options, Voclosporin provides an alternative treatment that could prove invaluable to LN patients that have not responded positively to existing treatments or have had a severe reaction to other medications.

9b. If you have stated more than one advantage, which one(s) do you consider to be the most important, and why? **9c. Does voclosporin help to overcome or address any of the listed disadvantages of current treatment that you have described in question 8? If so, please describe these**	It is one of only a few non-biologic medications approved specifically for Lupus. I believe this would give it some protection in prescribing laws for Lupus, whereas existing medications that are used in Lupus treatment could be withdrawn. This could have an impact on Lupus research in the future. If Voclosporin can reduce the need for steroids this would be very significant for patients. If Voclosporin proves safe for pregnancy it could give patients more options. A targeted therapy like Voclosporin should reduce the risk of infection that is associated with high dose steroids and other 'broader' treatments like cyclophosphamide, thus enabling a better quality of life and hopefully less disruption for the patient.
10. If there are disadvantages of Voclosporin over current treatments on the NHS please describe these. For example, are there any risks with Voclosporin? If you are concerned about any potential side effects you have heard about, please describe them, and explain why	I do not have any first-hand knowledge or experience of this.
11. Are there any groups of patients who might benefit more from voclosporin or any who may benefit less? If so, please describe them and explain why Consider, for example, if patients also have other health conditions (for example difficulties with mobility, dexterity, or cognitive impairments) that affect the suitability of different treatments	Patients that have had no success or adverse reactions with existing medication could find that Voclosporin is their last option of medication to prevent kidney damage. Existing comorbidities, which is common for Lupus patients could present an interaction with Voclosporin (such as blood pressure issues) As it is a self-administered oral medication, cognitive impairments could affect adherence. This could be managed with doctor monitoring. Dexterity issues in dispensing pills could also present an issue, this could be supported by an occupational therapist with patient aids.
12. Are there any potential equality issues that should be taken into account when considering lupus nephritis and voclosporin? Please explain if you think	If Voclosporin (as other CNI's) is safe in pregnancy, its use would help patients to manage their Lupus without having to postpone family planning. In a community of patients which are predominantly women of childbearing age this is very significant.

any groups of people with this condition are particularly disadvantaged Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics More information on how NICE deals with equalities issues can be found in the NICE equality scheme Find more general information about the Equality Act and equalities issues here.	It could also take the burden off the patients to have to discuss fertility Some existing medications can affect fertility, leading to fertility preservation measures. I have undergone egg harvesting/freezing in which I had to self-administer hormones. This process is not only costly to the NHS but also an extra ordeal for an already chronically ill person to endure. A highly emotive process.
13. Are there any other issues that you would like the committee to consider?	Not at this time

Part 2: Technical engagement questions for patient experts

Issues arising from technical engagement

The issues raised in the EAR are listed in table 2. We welcome your comments on the issues, but you do not have to provide a response to every issue, such as the ones that are technical, that is, cost effectiveness-related issues. We have added a comment to the issues where we consider a patient perspective would be most relevant and valuable. If you think an issue that is important to patients has been missed in the EAR, please let us know in the space provided at the end of this section.

For information: the patient organisation that nominated you has also been sent a technical engagement response form (a separate document) which asks for comments on each of the key issues that have been raised in the EAR, the patient organisation responses will also be considered by the committee.

Table 2 Issues arising from technical engagement

Key issue 1: Network meta-analysis (NMA) estimates may not be reliable and should better account for heterogeneity. • **Does the company's NMA sufficiently account for heterogeneity?** • **Is a fixed effects or random effects NMA more appropriate?**	
Key issue 2: The company's model structure is subject to a number of structural limitations. • **Are the restrictive settings and assumptions in the model**	

Patient expert statement

identified by the EAG significant and should they be adjusted? • **What percentage of patients with lupus nephritis who enter end stage renal disease are expected to receive a kidney transplant?**	
Key Issue 3: The long-term treatment effect of voclosporin + MMF and its comparators is unknown. • **Are the short-term data for voclosporin + MMF sufficient to generalise to the longer term?** • **Are the short-term data while patients are on treatment reflective of longer-term outcomes when patients are no longer receiving the same treatment up until 3 years?** • **The company assumes the treatment effect of voclosporin + MMF wanes indefinitely based on the average effect of voclosporin + MMF and MMF alone. Do you consider this approach to be appropriate?**	
Key Issue 4: The utility estimates used in the company's model are inappropriate.	

Patient expert statement

• **Are the utility values used by the company reflective of the expected utility of patients with lupus nephritis?** • **Are the literature-based utility values for later states reflective of the utility of patients with lupus nephritis in later states?** **We consider patient perspectives may particularly help to address this issue.**	
Key Issue 5: The company has not appropriately calculated the costs of treatment in the model. • **Is it appropriate to assume 95% relative dosing intensity for all treatments?** • **Is it appropriate to assume no treatment discontinuation for comparator treatments?**	
Key Issue 6: There is a lack of transparency around the inputs used in the company's model.	
Key Issue 7: Uncertainty in how voclosporin will be used in practice. • **Where would voclosporin be used in the treatment pathway?**	

Patient expert statement

• **Would voclosporin be used as a first-line treatment?** • **How long would patients be expected to receive voclosporin?** • **What factors would influence the decision to stop treatment?** • **Would the treatment effect of voclosporin vary based on how it is used (i.e., earlier, or later treatment lines, shorter or longer treatment durations, new onset, or relapsed lupus nephritis)? If so, what magnitude would the variation be?** **We consider patient perspectives may particularly help to address this issue.**	
Are there any important issues that have been missed in EAR?	

Part 3: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

- My Lupus patient journey has had significant negative impact on my physical and mental health and that of my care givers.
- Empowering the patient ultimately benefits all parties.
- Multidisciplined ‘wrap around’ approach to patient care on diagnosis for better long-term outcomes.
- New medications give clinicians and patients options, in a currently incurable chronic condition.
- Pregnancy and preserving fertility should be at the forefront when considering treatment options. (Even if the patient is not currently planning a family)

Thank you for your time.

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

☐ **Please tick this box** if you would like to receive information about other NICE topics.

For more information about how we process your personal data please see NICE's privacy notice.

NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Voclosporin with immunosuppressive therapies for treating lupus nephritis [ID3962]

Technical engagement response form

As a stakeholder you have been invited to comment on the External Assessment Report (EAR) for this evaluation.

Your comments and feedback on the key issues below are really valued. The EAR and stakeholders' responses are used by the committee to help it make decisions at the committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form

We are asking for your views on key issues in the EAR that are likely to be discussed by the committee. The key issues in the EAR reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the EAR.

You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise.

If you would like to comment on issues in the EAR that have not been identified as key issues, you can do so in the 'Additional issues' section.

If you are the company involved in this evaluation, please complete the 'Summary of changes to the company's cost-effectiveness estimates(s)' section if your response includes changes to your cost-effectiveness evidence.

Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.

Do not include medical information about yourself or another person that could identify you or the other person.

We are committed to meeting the requirements of copyright legislation. If you want to include journal articles in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information redacted. See the NICE health technology evaluation guidance development manual (sections 5.4.1 to 5.4.10) for more information.

The deadline for comments is **5pm** on **9 September 2022**. Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

Technical engagement response form

About you

Table 1 About you

Your name	British Society for Rheumatology
Organisation name: stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder, please leave blank)	[redacted] (The BSR have consulted with the BILAG group, which is a UK wide network of research active clinicians with a specialist interest in Lupus, who also form the steering committee of the national Lupus Registry.)
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	

Key issues for engagement

All: Please use the table below to respond to the key issues raised in the EAR.

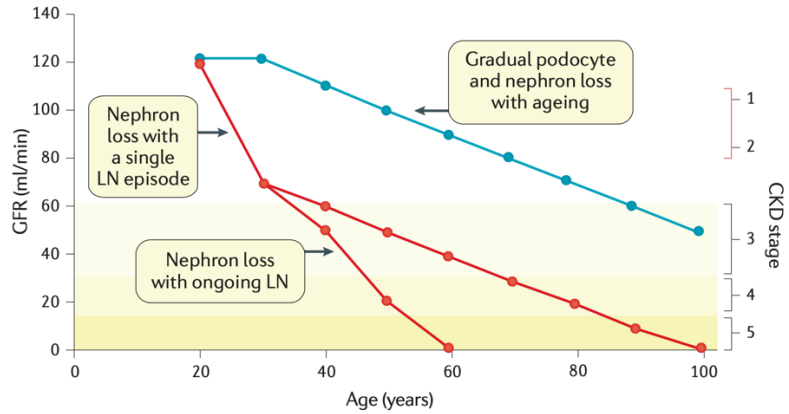
Table 2 Key issues

Key issue	Does this response contain new evidence, data or analyses?	Response
Key issue 1: Network meta-analysis (NMA) estimates may not be reliable and should better account for heterogeneity.	No	There is heterogeneity between available lupus nephritis studies, both in terms of defined end-points but also study methodology, notably steroid-taper regimens. No studies directly compare treatment regimes so comparisons have to be achieved through modelling. Differences in racial subgroups and proportions of the difference renal classes are known to be important stratifiers of outcome. The difference in end-point definitions between studies are relatively subtle and perhaps of limited clinical relevance. The endpoint employed in AURORA1 seems pragmatic and clinically relevant and of course the study met this endpoint. Our main concern would be around variation in the use of concomitant corticosteroids in these different studies (beyond that required to meet endpoints). The clinical value of steroid minimisation has been increasingly recognised as studies have evolved. High concomitant steroid use has been argued as a key reason why previous Rituximab RCTs failed to meet endpoints (LUNAR). The low steroid regimen employed in the AURORA1 protocol seems to offer significant clinical benefits over and above the primary trial outcomes and this is perhaps not captured in the current NMA model. In other words, a certain renal outcome with

		the lower steroid dose in AURORA would be preferable to the same renal outcome with a high steroid dose in another study. Mycophenolate monotherapy and mycophenolate + rituximab would be the most widely employed direct comparators in UK practice. However, under current NHSE guidance, rituximab cannot be added until mycophenolate is already trialled and response is found to be inadequate (which is likely a significant disadvantage since significant damage may have occurred by the time rituximab is added). Mycophenolic acid is commonly used in patients with toxicity to mycophenolate mofetil. This is more expensive. We are unable to comment on model results as they are fully redacted.
Key issue 2: The company's model structure is subject to a number of structural limitations.	No	We have included a number of observations about the cost effectiveness model in this section: We agree is seems over-optimistic to expect 90% of patients with end-stage kidney disease due to lupus nephritis will receive a transplant within 2 years – perhaps 60% in our experience. We believe that the development of CKD can occur within 36 months of treatment onset, particularly when new nephritis is accompanied by significant acute kidney injury. In fact the clinicians contributing to this review have examples of this from their own practice. Evaluating serum creatinine or eGFR may significantly underestimate renal damage. Biopsies often indicate permanent damage to nephrons in lupus nephritis patients with normal creatinine and eGFR. Since renal function gradually deteriorates in all people over life, such damage may become clinically significant later in life. This is especially important if repeat episodes of nephritis occur, each adding to cumulative damage. Hence prevention of damage observed within 36

		months of treatment will not capture the benefit of all interventions. Improvements in parameters such as proteinurea are likely to predict better results for these later unmeasured outcomes. CKD progression will be more likely in patients with active disease, but progression can occur due to other factors. In particular the progression from CKD stages 3b/4 to stage V may be dependant on factors such as hypertension or heavy proteinuria. It is correct that it would be unlikely for patients with CKD stage 3b/4 to achieve complete renal response definitions, but this does not mean treatment would be unsuccessful at controlling renal inflammation as would be judged by the gold standard of a renal biopsy (and hence reduce the risk of further progression to end-stage) It is difficult to make assumptions about the duration of therapy. We agree it is unlikely the specific voclosporin/MMF combination would persist beyond 36 months in the face of either complete remission or progressive disease, however it clear from AURORA1 that complete remission is still only achieved in a minority of patients and these patients will inevitably be continuing immunosuppressive therapy in one form or another, often for years. There is an existing literature drawing on previous trials that examines the link between shorter-terms trial outcomes with longer-term disease progression (12 month proteinuria being a key factor). We are not sure this has been referenced e.g. Tamirou et al Lupus Sci Mrd 2015:2:e000123.doi:10.1002/art.39026 and Dall'Era et al Arthritis Rheumatol 2015:67:1305-13
Key Issue 3: The long-term treatment effect of voclosporin +	No	This is not entirely true. It is also by no means a unique issue in lupus nephritis (for example biologic trials in rheumatoid arthritis evaluate control of joint inflammation

MMF and its comparators is unknown.		over a year or two but do not evaluate joint damage occurring over many years of disease and the lack of these long-term damage data were not considered a barrier to approval by NICE). The 36 months of data offered by AURORA2 is good in terms of evidence offered from previous nephritis trials. Although it is arguable to what extent the benefits of 36 months voclosporin would be fixed over the remaining life-span of the patient, we would emphasise that short term benefit in rates of renal remission and prevention of CKD on any therapy do predict better long term outcomes. Lupus nephritis in many patients will go through cycles of remission and flare. Subsequent flare history and treatments will also be important factors here, although it remains the case that evidence suggests achievement of low-levels of proteinuria at 12 months is associated with good long-term renal outcome. However, since significant renal damage often occurs during a first episode of lupus nephritis, it is likely that benefit in 36 months of voclosporin does predict better long term outcomes. Hence it is reasonable that the benefits seen over 36 months may be an underestimate of the totality of lifetime benefit. The lifetime trajectory changes as a result of the initial therapy. We just don't know how long therapies must be continued to realise those lifetime benefits. This concept is illustrated in this figure from Anders, HJ., Saxena, R., Zhao, Mh. et al. Lupus nephritis. Nat Rev Dis Primers 6, 7 (2020).

		https://doi.org/10.1038/s41572-019-0141-9 
Key Issue 4: The utility estimates used in the company's model are inappropriate.	No	No comment
Key Issue 5: The company has not appropriately calculated the costs of treatment in the model.	No	Comments made in our answer to Key Issue 2 are relevant here. We noticed the Rituximab comparator had factored 4 infusions in 12 months. This is commonly used in routine NHS prescribing but a specific interval is not recommended and some clinicians may choose to use rituximab less frequently. 4 infusions in 12 months was the dose used in the LUNAR trial. Lower frequency of rituximab without specialised monitoring will lead to more frequent relapses. Modelling based on 4 infusions in 12 months is therefore appropriate. Again, it is important to note that current NHSE guidance only allows the use of rituximab in disease that is refractory to either mycophenolate or cyclophosphamide. Most patients on Mycophenolate monotherapy will be on 2g a day, with some on 3g a day for an initial period of a few months. We are unclear if the long-term economic cost of corticosteroid-induced damage (diabetes/osteoporosis etc.) have been factored in.

		Lupus nephritis non-response is typically associated with higher use of corticosteroid and a greater risk of these issues.
Key Issue 6: There is a lack of transparency around the inputs used in the company's model.	No	Much of this seems to be redacted.
Key Issue 7: Uncertainty in how voclosporin will be used in practice.	No	We are surprised there seems to be uncertainty about this. We assume that clinicians would wish to use this as per the clinical trial inclusion criteria as an up-front treatment for newly diagnosed nephritis, in combination with mycophenolate, or possibly as an early add-on treatment for patients failing on mycophenolate mofetil if for some reason it hadn't been used initially. It is clear that outcomes with current standard therapy (MMF and prednisolone) are far from acceptable, with approximately half of patients not achieving remission and therefore being at risk of renal failure immediately or in subsequent years of life, as well as ongoing high dose glucocorticoids, both of which shorten life substantially. There are now multiple phase II and phase III trials that demonstrate that combination of MMF/Pred with new agents such as voclosporin, belimumab or Obinutuzumab can improve these outcomes. As a result, we believe that combination therapies should be offered to all patients with class III, IV and V lupus nephritis. We would develop new BSR guidelines to emphasise this and work in our networks to disseminate this in practice. We point out that current NICE guidance does not allow comparator treatments such as Rituximab or Belimumab to be used in this way as 1st line therapy.

Additional issues

All: Please use the table below to respond to additional issues in the EAR that have not been identified as key issues. Please do **not** use this table to repeat issues or comments that have been raised at an earlier point in this evaluation (for example, at the clarification stage).

Table 3 Additional issues from the EAR

Issue from the EAR	Relevant section(s) and/or page(s)	Does this response contain new evidence, data or analyses?	Response
Additional issue 1: Insert additional issue	Please indicate the section(s) of the EAR that discuss this issue	Yes/No	Please include your response, including any new evidence, data or analyses, and a description of why you think this is an important issue for decision making
Additional issue 2: Insert additional issue	Please indicate the section(s) of the EAR that discuss this issue	Yes/No	Please include your response, including any new evidence, data or analyses, and a description of why you think this is an important issue for decision making

Summary of changes to the company's cost-effectiveness estimate(s)

Company only: If you have made changes to the base-case cost-effectiveness estimate(s) in response to technical engagement, please complete the table below to summarise these changes. Please also provide sensitivity analyses around the revised base case. If there are sensitivity analyses around the original base case which remain relevant, please re-run these around the revised base case.

Table 4 Changes to the company's cost-effectiveness estimate

Key issue(s) in the EAR that the change relates to	Company's base case before technical engagement	Change(s) made in response to technical engagement	Impact on the company's base-case incremental cost-effectiveness ratio (ICER)
Insert key issue number and title as described in the EAR	Briefly describe the company's original preferred assumption or analysis	Briefly describe the change(s) made in response to the EAR	Please provide the ICER resulting from the change described (on its own), and the change from the company's original base-case ICER.
Company's base case following technical engagement (or revised base case)	Incremental QALYs: [QQQ]	Incremental costs: [£££]	Please provide company revised base-case ICER

Sensitivity analyses around revised base case
PLEASE DESCRIBE HERE

NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Voclosporin with immunosuppressive therapies for treating lupus nephritis [ID3962]

Technical engagement response form

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You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise.

If you would like to comment on issues in the EAR that have not been identified as key issues, you can do so in the 'Additional issues' section.

If you are the company involved in this evaluation, please complete the 'Summary of changes to the company's cost-effectiveness estimates(s)' section if your response includes changes to your cost-effectiveness evidence.

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Thank you for your time.

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Technical engagement response form

About you

Table 1 About you

Your name	[redacted]
Organisation name: stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder, please leave blank)	On behalf of NHS England
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**I have nothing to disclose**

Key issues for engagement

All: Please use the table below to respond to the key issues raised in the EAR.

Table 2 Key issues

Key issue	Does this response contain new evidence, data or analyses?	Response
Key issue 1: Network meta-analysis (NMA) estimates may not be reliable and should better account for heterogeneity.	**Yes**/No	I agree with this and agree with the comments made in the EAR response. My main concern here would be the varying outcome definitions, follow up times and population descriptions. There needs to be consistency around how this is measured and accounted for.
Key issue 2: The company's model structure is subject to a number of structural limitations.	**Yes**/No	I fully agree with this and agree with the comments made in the EAR response. In particular the application of CKD progression is incorrect, and the study does not reflect or capture CKD disease progression from a chronic state which as clinicians we see frequently and is a significant concern. They don't account for patients with renal impairment and CKD progression data is disabled within the AURORA studies which is completely not aligned with clinical practice and would not give me confidence to use this in my patients.
Key Issue 3: The long-term treatment effect of voclosporin + MMF and its comparators is unknown.	**Yes**/No	This is a significant concern both from a clinician and patient perspective. The data presented in the EAR reflects early data from use of volclosporin and MMF and its comparators. The longer-term data is not available and would be necessary when explaining the rationale for its usage. From the AURORA 1 and 2 studies a number of assumptions are made which from my experience and understating are incorrect. The short term data cannot generalise for the longer term and that it cannot be assumed that the short-term data while patients are on treatment are reflective of longer-term outcomes when patients are no longer receiving the same

		treatment up until 3 years. The waning effect is not proven. I agree this approach is inappropriate and unjustified. This will be difficult to explain to patients when clinicians would not feel this is justified as an assumption/argument.
Key Issue 4: The utility estimates used in the company's model are inappropriate.	**Yes**/No	Fully agree with the EAR response. The utility models used in both AURORA 1 and 2 studies are inappropriate and do not follow standard convention. I would support using multiple regression analyses taking into account confounding factors. I agree a lot of the data collected from both studies have not been used effectively. I would ask for an explanation why this is the case and for more effective use of the data.
Key Issue 5: The company has not appropriately calculated the costs of treatment in the model.	**Yes**/No	I agree with the response provided in the EAR and agree the company has not appropriately calculated the costs of treatment in the model. The treatment course of LN patients is complex and as a clinician you would individualise the treatment for maximal effectiveness for your patient as well as minimising the side effects. The dose adjustment and this variation in practice has not been considered and accounted for by the company and therefore many of the calculations are baseless and not consistent with clinical practice.
Key Issue 6: There is a lack of transparency around the inputs used in the company's model.	**Yes**/No	A agree with this and agree with the comments made in the EAR response. This is not my area of expertise and hence my comments are limited for this.
Key Issue 7: Uncertainty in how voclosporin will be used in practice.	**Yes**/No	This is a valid concern. From my experience in managing many lupus and vasculitis patients, this is the case for many new medications which are currently under trial and with limited long-term data. There will some hesitation to changing current best practice without further evidence for first line usage. Clinicians may be more willing to use this in patients who have refractory disease rather than as first line. From my current clinical experience we used CNI's such as Tacrolimus in patients with relapsing disease or "grumbling" disease where patients do not achieve full remission with ongoing proteinuria and disease parameters reflecting ongoing activity. We have used MMF, Tacrolimus and low dose Pred in these patients with some success but these are for refractory patients rather than first line.

Additional issues

All: Please use the table below to respond to additional issues in the EAR that have not been identified as key issues. Please do **not** use this table to repeat issues or comments that have been raised at an earlier point in this evaluation (for example, at the clarification stage).

Table 3 Additional issues from the EAR

Issue from the EAR	Relevant section(s) and/or page(s)	Does this response contain new evidence, data or analyses?	Response
Additional issue 1: Insert additional issue	Please indicate the section(s) of the EAR that discuss this issue	Yes/No	Please include your response, including any new evidence, data or analyses, and a description of why you think this is an important issue for decision making
Additional issue 2: Insert additional issue	Please indicate the section(s) of the EAR that discuss this issue	Yes/No	Please include your response, including any new evidence, data or analyses, and a description of why you think this is an important issue for decision making

Summary of changes to the company's cost-effectiveness estimate(s)

Company only: If you have made changes to the base-case cost-effectiveness estimate(s) in response to technical engagement, please complete the table below to summarise these changes. Please also provide sensitivity analyses around the revised base case. If there are sensitivity analyses around the original base case which remain relevant, please re-run these around the revised base case.

Table 4 Changes to the company's cost-effectiveness estimate

Key issue(s) in the EAR that the change relates to	Company's base case before technical engagement	Change(s) made in response to technical engagement	Impact on the company's base-case incremental cost-effectiveness ratio (ICER)
Insert key issue number and title as described in the EAR	Briefly describe the company's original preferred assumption or analysis	Briefly describe the change(s) made in response to the EAR	Please provide the ICER resulting from the change described (on its own), and the change from the company's original base-case ICER.
Company's base case following technical engagement (or revised base case)	Incremental QALYs: [QQQ]	Incremental costs: [£££]	Please provide company revised base-case ICER

Sensitivity analyses around revised base case
PLEASE DESCRIBE HERE

NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Voclosporin with immunosuppressive therapies for treating lupus nephritis [ID3962]

Technical engagement response form

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If you would like to comment on issues in the EAR that have not been identified as key issues, you can do so in the 'Additional issues' section.

If you are the company involved in this evaluation, please complete the 'Summary of changes to the company's cost-effectiveness estimates(s)' section if your response includes changes to your cost-effectiveness evidence.

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Do not include medical information about yourself or another person that could identify you or the other person.

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Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information redacted. See the NICE health technology evaluation guidance development manual (sections 5.4.1 to 5.4.10) for more information.

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Thank you for your time.

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Technical engagement response form

About you

Table 1 About you

Your name	
Organisation name: stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder, please leave blank)	NHS England – Specialised rheumatology clinical reference group
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	

Key issues for engagement

All: Please use the table below to respond to the key issues raised in the EAR.

Table 2 Key issues

Key issue	Does this response contain new evidence, data or analyses?	Response
Key issue 1: Network meta-analysis (NMA) estimates may not be reliable and should better account for heterogeneity.	No	No head to head data are available so the submitting company needs to account for this. Study design for trials in SLE has evolved over the years. e.g. the rate of steroid reduction has been very different in studies; if there is too much corticosteroid in active treatment and placebo arms then no treatment effect can be seen (this was an issue in some of the rituximab RCTs). Definitions of CRR varied and again has evolved over time. The AURORA1 phase 3 met its primary endpoint namely a clinical meaningful and statistically higher CRR rate compared to placebo at week 52 40.8% vs 22.5%) in combination with MMF and oral steroids. Cannot comment on model as results from primary analysis are redacted (table B.2-30). Makes sense that voclosporin and MMF and also MMF with RTX are the most effective options. Appendix D was not available/included in the papers for stakeholder comment.
Key issue 2: The company's model structure is subject to a number of structural limitations.	No	It is correct to separate CKD stages 1-3a and stages 3b-4 and subsequent stages as per B.3.2.2 We agree that CKD progression will need coexisting disease activity which does not respond to treatment and so causes damage which means that the patient moves from one CKD stage to a more severe one.

		We agree with the EAG that on occasions a patient is likely to progress to 3b or beyond within the first 36 months of treatment. We do not think it should be assumed that MMF would be stopped in all patients after 3 years but the combination would be discontinued at this 36 month time point (Table B.3.2 line 3). B.3.3.2.4 states that 90% patients with ESRD receive a transplant within 2 years – may be fewer getting the transplant.
Key Issue 3: The long-term treatment effect of voclosporin + MMF and its comparators is unknown.	No	It is not unusual to not know the longterm effect of a new treatment when phase 3 trials have only recently concluded. AURORA 2 does provide data for the clinical effectiveness up to 36 months so an additional 2 years compared with the 12 months reported in the AURORA 1 phase 3 study; this is therefore very helpful. One would anticipate that some patients will start to flare on discontinuing treatment (a third of patients can relapse even after a complete response). Some patients will certainly continue treatment with MMF beyond 3 years. Flares will need to be treated with an escalation in treatment.
Key Issue 4: The utility estimates used in the company's model are inappropriate.	Yes/No	Please provide your response to this key issue, including any new evidence, data or analyses
Key Issue 5: The company has not appropriately calculated the costs of treatment in the model.	Yes/No	We agree with the EAG that some patients are likely to discontinue treatment (voclosporin and/ or MMF) because of side effects but they will then move on to try another therapy to either suppress active disease inflammation or maintain control of disease as the aim is to prevent damage and ESRF.. We agree that patients will be on 2g per day of MMF and a smaller percentage who have more active/refractory disease will require a higher dose of 2.5g/ day or 3g/day.
Key Issue 6: There is a lack of transparency around the inputs used in the company's model.	Yes/No	Difficult to comment due to redacted data. We believe the cost for RTX is lower than quoted in the CS; the costs reduced considerably when rituximab biosimilars became available.

Key Issue 7: Uncertainty in how voclosporin will be used in practice.	Yes/No	Voclosporin could be used as per clinical trial entry criteria or in a smaller cohort of patients with early refractory disease i.e. inadequate response to MMF and steroids. However, it is always better to start any treatment early and switch off disease activity and so prevent renal damage and thus reducing the risk of progressive CKD/end stage renal failure which has a significant morbidity for patients and cost to the NHS. The exact positioning of voclosporin in the treatment pathway will affect its cost-effectiveness. It should be noted that access to RTX in combination with MMF is reserved for patients with more refractory disease as per NHS England clinical commissioning policy (see clinical commissioning policy: NHS England » Rituximab for refractory Systemic Lupus Erythematosus (SLE) in adults and post-pubescent children) but it can be argued, from the clinical perspective, that this relatively cheap treatment could be positioned earlier in the treatment pathway.

Additional issues

All: Please use the table below to respond to additional issues in the EAR that have not been identified as key issues. Please do **not** use this table to repeat issues or comments that have been raised at an earlier point in this evaluation (for example, at the clarification stage).

Table 3 Additional issues from the EAR

Issue from the EAR	Relevant section(s) and/or page(s)	Does this response contain new evidence, data or analyses?	Response
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Additional issue N: Insert additional issue			[INSERT / DELETE ROWS AS REQUIRED]

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Technical engagement response form

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Your name	[redacted]
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Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	Since April 2005 Novartis has exclusively licensed glycopyrronium bromide and certain intellectual property relating to its use and formulation from Vectura and its co-development partner, Sosei Heptares. The following inhaled medications are comprised of, or contain glycopyrronium bromide: • Seebri® Breezhaler® (glycopyrronium bromide) (used as a maintenance treatment for Chronic Obstructive Pulmonary Disease (COPD)) • Ultibro® Breezhaler® (indacaterol/glycopyrronium bromide) is used as a maintenance treatment for COPD • Enerzair® Breezhaler® (indacaterol/glycopyrronium bromide/mometasone furoate) is used as a maintenance treatment for asthma uncontrolled with LABA/ICS. Phillip Morris International (a tobacco company) has acquired Vectura Group Limited (formerly Vectura Group plc).

Key issues for engagement

All: Please use the table below to respond to the key issues raised in the EAR.

Table 2 Key issues

Key issue	Does this response contain new evidence, data or analyses?	Response
Key issue 1: Network meta-analysis (NMA) estimates may not be reliable and should better account for heterogeneity.	No	Given the presence of substantial heterogeneity across trials included in the NMA networks, for example with regard to study methodology or definition of complete/ partial renal response, we agree with the EAG that random effects NMAs would generally be considered more suitable than fixed effect NMAs. The use of treatment effect estimates generated in fixed effect NMAs despite the presence of substantial heterogeneity should be appropriately justified, as in probabilistic analyses this might lead to underrepresentation of uncertainty due to narrower confidence intervals compared to random effects NMAs.
Key issue 2: The company's model structure is subject to a number of structural limitations.	No	We agree with the EAG that disabling transitions from CKD stages 1-3a to CKD stages 3b-4 for the first 3 years of the model is inappropriate. Even if such transitions were not observed in the trial, they are certainly possible. The AURORA trial included patients with baseline eGFR >45 ml/min/1.73 m^2. Any confirmed eGFR deterioration compared to baseline could therefore result in a patient moving to CKD stage 3b (defined as eGFR 30 to <45 ml/min/1.73 m^2). The model should hence allow consideration of the possibility of such transitions in the probabilistic analyses. We also agree that a direct transition from a CKD stage 1-3a / 'Partial response' health state to CKD stage 3b-4 (without first going through an 'Active disease' health state within CKD stage 1-3a) appears possible, since the company's

		definition of partial response relates exclusively to a reduction in UPCR. Therefore, a patient could still experience a decline in eGFR while technically being considered a partial responder. Under these circumstances, the possibility to transition to CKD stages 3b-4 should thus not be disabled in the model.
Key Issue 3: The long-term treatment effect of voclosporin + MMF and its comparators is unknown.	No	No comments.
Key Issue 4: The utility estimates used in the company's model are inappropriate.	No	We share the EAG's concerns regarding the trial data utility analyses carried out by the company. In addition to the multiple issues raised by the EAG, we are wondering whether in deriving CKD stage 3b-4 utility values from trial-based CKD stage 1-3a values, it would have been more appropriate to apply literature-based utility decrements (from Jesky et al 2016) in a multiplicative, rather than an additive manner. A proportionate reduction, instead of applying an absolute decrement to all values of 0.055, may better account for the facts that absolute utility values for CKD stages 1-3a differ between AURORA trial data and Jesky et al 2016, and that utilities were generated through different measures in these two sources (SF-36 mapped to EQ-5D in AURORA vs EQ-5D in Jesky et al 2016).
Key Issue 5: The company has not appropriately calculated the costs of treatment in the model.	No	The company assumes that all comparators except for MMF have no discontinuations in the economic model. We agree with the EAG that this assumption is implausible as some patients would always be expected to discontinue treatment for a number of reasons, such as adverse events or insufficient efficacy.
Key Issue 6: There is a lack of transparency around the inputs used in the company's model.	No	No comments.
Key Issue 7: Uncertainty in how voclosporin will be used in practice.	No	We agree with the EAG that the treatment pathway and the way in which voclosporin will be used in clinical practice is highly variable across the population.

		Patients with lupus nephritis have complex needs and the choice of treatment should be tailored to patients' needs.

Additional issues

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Issue from the EAR	Relevant section(s) and/or page(s)	Does this response contain new evidence, data or analyses?	Response
Additional issue 1: Implicit incorporation of trial-based early stopping rule in the model	EAR section 4.2.6.5; Company submission section B.3.3.4 (page 120)	No	EAR section 4.2.6.5 describes how treatment discontinuation rates in the economic model are informed by time to treatment discontinuation analyses from the AURORA trials, and that the model base case includes a stopping rule at 36 months. As detailed in section B.3.3.4 of the company submission (page 120), the AURORA-1 trial included protocol-defined early stopping rules for suboptimal responders after 8 weeks (for patients with confirmed reduction of UPCR of ≤25%) and after 12 weeks (for patients with confirmed >30% decrease from baseline eGFR). From the information provided in the company submission it was not clear how many

			patients in either arm of the trial discontinued treatment under these early stopping rules. Since discontinuation rates in the economic model are based on discontinuation rates observed in the AURORA trials, it is our understanding that the model therefore implicitly incorporates above early stopping rules for suboptimal responders. If the same stopping rules were not applied in UK clinical practice, there may be a risk that the model underestimates drug acquisition costs. Therefore, we suggest that stopping rules for voclosporin may warrant further discussion with the clinical experts, as well as consideration of how such stopping rules could impact cost-effectiveness.

Voclosporin with immunosuppressive therapies for treating lupus nephritis: A Single Technology Appraisal [ID3962]

ERG Review of Company's Response to Technical Engagement Response

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Produced by

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This TE response is linked to ERG report	Critchlow, Bullement, Wheat, Robinson, Taylor, Boddana, Hatswell, Melendez-Torres, Farmer. Voclosporin with immunosuppressive therapies for treating lupus nephritis [ID3962]: A Single Technology Appraisal. Peninsula Technology Assessment Group (PenTAG), 2022.

1. INTRODUCTION

This document provides the Evidence Review Group's (ERG's) critique of the company's response to the technical engagement report produced by the National Institute for Health and Care Excellence (NICE) for the appraisal of voclosporin with immunosuppressive therapies for treating lupus nephritis (ID3962). The company response to each of the issues outlined in the technical report are discussed in further detail in Section 3.

The company has made a series of changes to its economic model and has also provided a revised patient access scheme (PAS) discount of [redacted]% (though at the time of submission the company noted this had not yet been accepted by NHS England). The company produced additional data relating to utility derived from a regression analysis of health-related quality of life (HRQoL) data obtained in AURORA 1 and AURORA 2, which have been incorporated within the cost-effectiveness model. The company also updated their network meta-analyses (NMAs) in response to the ERG appraisal, but the updated data were not incorporated in their updated model.

The ERG critique of the new company analysis is presented in Section 2. During the appraisal the ERG noted an error in the original company model that was not corrected in the version provided at technical engagement (detailed in Section 4.1), and so updated results are provided following correction of this error.

Following evidence from stakeholders provided during technical engagement, the ERG have updated their base case and also present updated results in Section 2.

Please note that all results presented in this document do not include confidential prices for comparator treatments to voclosporin. Analyses incorporating these prices are provided in an appendix to this document.

2. UPDATED COMPANY AND ERG BASE CASE ANALYSES

2.1. Overview of changes to the company base case

In response to the ERG report, the company present a revised base case more closely aligned with the ERG preferred assumptions. The changes to the company base case and their relation to the ERG report are summarised below. A discussion of the company amendments and the extent to which they address issues raised by the ERG in their appraisal is provided in Section 3.

- Amendments to the health state utility values for CKD stage 1-3a (key issue 4 in the ERG report)
- Amendments to the health state utility values for CKD stage 5 (ERG report scenario 2)
- Consideration of ½ pack cost applied to VCS (ERG report scenario 3)
- Application of a 2g dose of MMF applied to VCS+MMF and MMF arms (ERG report scenario 4)
- Amendments to the cost inputs to align with referenced sources (ERG report scenario 6)
- Adaptation of LN related death costs from CKD stages 1-4 (key issue 5 in the ERG report)
- Removal of LN related deaths from CKD stages 1-3a (ERG report scenario 10)
- Inclusion of transitions into CKD stages 3b-4 in the first 36 months (ERG report scenario 11)
- The application of RDI based on data from AURORA 1 and AURORA 2 for voclosporin+MMF and MMF (key issue 5 in the ERG report)
- Amendments to the treatment waning effect applied to the VCS+MMF arm (key issue 3 in the ERG report).

An updated model was provided by the company during technical engagement (TE), however rather than apply switches to implement changes, the company amended model formulae and overrode model functions. It was therefore not possible for the ERG to compare the impact of each of the revisions made by the company on the results. Instead, the ERG has compared

results between model versions and aligned settings where possible i.e., applying the same settings in the ERG basecase presented in the ERG report and the version provided by the company at TE. This process did not find perfect alignment between ICERs, however results were relatively close.

2.2. Revised results of the company base case

Revised results as presented by the company are provided in Table 1.

Table 1: Revised base case results provided by the company

Technologies	Total			Incremental			ICER (£/QALY)*
	Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs	
VCS + MMF	[redacted]	[redacted]	[redacted]	-	-	-	-
MMF	[redacted]	17.57	13.03	[redacted]	[redacted]	[redacted]	£27,301
L-CYC	[redacted]	16.96	12.57	[redacted]	[redacted]	[redacted]	£7,870
H-CYC	[redacted]	16.83	12.48	[redacted]	[redacted]	[redacted]	£6,704
AZA	[redacted]	17.20	12.76	[redacted]	[redacted]	[redacted]	£14,825
RTX + MMF	[redacted]	17.95	13.32	[redacted]	[redacted]	[redacted]	£22,722
TAC + MMF	[redacted]	17.62	13.07	[redacted]	[redacted]	[redacted]	£23,345
TAC	[redacted]	17.68	13.12	[redacted]	[redacted]	[redacted]	£23,849

*ICER for VCS + MMF vs comparator

Abbreviations: AZA = azathioprine; CYC = cyclophosphamide; ICER = incremental cost-effectiveness ratio; L-CYC = low-dose CYC; H-CYC = high-dose CYC; LYG = life years gained; MMF = mycophenolate mofetil; QALYs = quality-adjusted life years; RTX = rituximab; TAC = tacrolimus; VCS = voclosporin

As part of the critique, the ERG noted an error in the calculation of adverse event disutilities, which overestimates the disutilities included within the model across all arms which include MMF. More details on this have been provided in Section 4.1. Although this has minimal impact on the cost-effectiveness results, a revised company base case including the ERG AE disutility fix is provided in Table 2 for transparency and has been included as part of the ERG revised base case also. Incremental results are presented in Table 3. Net monetary-benefit (NMB) and Net health benefit (NHB) are provided in Table 4.

Results from the one-way sensitivity analysis (OWSA) are provided in Figure 1 while the results from the probabilistic sensitivity analysis (PSA) are presented in Figure 2 and Table 5.

Table 2: Company revised base case pairwise ICERs with AE disutility fix applied

Technologies	Total			Incremental			ICER (£/QALY)*
	Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs	
VCS + MMF	[redacted]	[redacted]	[redacted]	-	-	-	-
MMF	[redacted]	17.57	13.04	[redacted]	[redacted]	[redacted]	£27,199
L-CYC	[redacted]	16.96	12.57	[redacted]	[redacted]	[redacted]	£7,770
H-CYC	[redacted]	16.83	12.48	[redacted]	[redacted]	[redacted]	£6,625
AZA	[redacted]	17.20	12.76	[redacted]	[redacted]	[redacted]	£14,591
RTX + MMF	[redacted]	17.95	13.33	[redacted]	[redacted]	[redacted]	£22,532
TAC + MMF	[redacted]	17.62	13.08	[redacted]	[redacted]	[redacted]	£23,251
TAC	[redacted]	17.68	13.12	[redacted]	[redacted]	[redacted]	£23,169

*ICER for VCS + MMF vs comparator

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Table 3: Company revised base case incremental analysis with AE disutility fix applied

Technologies	Total		Incremental		ICER (£/QALY)*
	Costs (£)	QALYs	Costs (£)	QALYs	
MMF	[redacted]	[redacted]			
AZA	[redacted]	12.76	[redacted]	[redacted]	Extendedly dominated
TAC + MMF	[redacted]	13.08	[redacted]	[redacted]	Extendedly dominated
TAC	[redacted]	13.12	[redacted]	[redacted]	Extendedly dominated
L-CYC	[redacted]	12.57	[redacted]	[redacted]	Extendedly dominated
H-CYC	[redacted]	12.48	[redacted]	[redacted]	Extendedly dominated
RTX + MMF	[redacted]	13.33	[redacted]	[redacted]	Extendedly dominated
VCS + MMF	[redacted]	[redacted]	[redacted]	[redacted]	£27,199

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Table 4: Company revised base case with AE disutility fix applied: NHB and NMB pairwise analyses of voclosporin+MMF versus comparators

Treatment	Incremental results		ICER	NHB		NMB	
	Incremental discounted costs	Incremental discounted QALYs	Pairwise cost per QALY gained	£20,000 WTP threshold	£30,000 WTP threshold	£20,000 WTP threshold	£30,000 WTP threshold
Revised company base case							
VCS + MMF							
MMF	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
L-CYC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
H-CYC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
AZA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
RTX + MMF	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TAC + MMF	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TAC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: AZA, azathioprine; CEM, cost-effectiveness model; CYC, cyclophosphamide; H-CYC, high-dose CYC; ICER, incremental cost-effectiveness ratio; L-CYC, low-dose CYC; MMF, mycophenolate mofetil; NHB, net health benefit; NMB, net-monetary benefit; QALY, quality adjusted life year; RTX, rituximab; TAC, tacrolimus; VCS, voclosporin; WTP, willingness-to-pay

Figure 1: One-way sensitivity analysis company revised base case with AE disutility fix applied

Abbreviations: AD = active disease; CKD = chronic kidney disease; ICER = incremental cos—effectiveness ratio; ICUR = incremental cost-utility ratio; MMF = mycophenolate mofetil; QALYs = quality-adjusted life years; VCS = voclosporin

Figure 2: Company revised base case – Incremental PSA for costs and QALYs of VCS+MMF vs. comparators with AE disutility fix applied

Abbreviations: AZA = azathioprine; CYC = cyclophosphamide; ICER = incremental cost-effectiveness ratio; L-CYC = low-dose CYC; H-CYC = high-dose CYC; MMF = mycophenolate mofetil; QALYs = quality-adjusted life years; RTX = rituximab; TAC = tacrolimus; VCS = voclosporin

Table 5: Company revised base case probabilistic ICERs with AE disutility fix applied

Technologies	Total		Incremental		ICER (£/QALY)*
	Costs (£)	QALYs	Costs (£)	QALYs	
VCS + MMF	[redacted]	[redacted]			
MMF	[redacted]	[redacted]	[redacted]	[redacted]	£27,780
L-CYC	[redacted]	[redacted]	[redacted]	[redacted]	£7,776
H-CYC	[redacted]	[redacted]	[redacted]	[redacted]	£6,337
AZA	[redacted]	[redacted]	[redacted]	[redacted]	£15,720
RTX + MMF	[redacted]	[redacted]	[redacted]	[redacted]	£29,659
TAC + MMF	[redacted]	[redacted]	[redacted]	[redacted]	£21,852
TAC	[redacted]	[redacted]	[redacted]	[redacted]	£23,179

Abbreviations: AZA = azathioprine; CYC = cyclophosphamide; ICER = incremental cost-effectiveness ratio; L-CYC = low-dose CYC; H-CYC = high-dose CYC; MMF = mycophenolate mofetil; QALYs = quality-adjusted life years; RTX = rituximab; TAC = tacrolimus; VCS = voclosporin

2.3. Updated ERG base case

Based on the company response and submissions received by the various stakeholders the ERG has opted to also revise its base case cost-effectiveness assumptions. Settings have been amended as follows:

- Alignment with company on 2g dosing of MMF for VCS+MMF and MMF in line with AURORA 1 trial (ERG report scenario 4)
- Alignment with the company on inclusion of RDI for VCS+MMF and MMF
- Alignment with company on adaptation to LN-related death costs for CKD stage 1-4
- Alignment with the company's utility values for CKD stage 1-3a based on the newly presented regression analysis (key issue 4 in the ERG report).
- Consider revised transplantation rates at 65% over 2 years (scenario 9 in ERG report) in line with further feedback received from stakeholder submissions
- Correction applied to company model error on AE disutilities

All other settings remain the same as that presented within the ERG report. The pairwise results for the ERG's revised base case are provided in Table 6 with fully incremental results provided in Table 7. The isolated impact on the ERG's original base case submitted as part of the report

are not possible due to the amendment to the company's model calculations i.e., fixing of LN deaths and adaptations to other model calculations including ERG settings.

Table 6: ERG revised base case pairwise ICERs

Technologies	Total			Incremental			ICER (£/QALY)*
	Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs	
VCS + MMF	[redacted]	[redacted]	[redacted]				
MMF	[redacted]	17.54	13.00	[redacted]	[redacted]	[redacted]	£31,654
L-CYC	[redacted]	16.81	12.44	[redacted]	[redacted]	[redacted]	£7,243
H-CYC	[redacted]	16.68	12.35	[redacted]	[redacted]	[redacted]	£6,120
AZA	[redacted]	17.06	12.64	[redacted]	[redacted]	[redacted]	£13,887
RTX + MMF	[redacted]	17.83	13.22	[redacted]	[redacted]	[redacted]	£21,665
TAC + MMF	[redacted]	17.49	12.96	[redacted]	[redacted]	[redacted]	£22,380
TAC	[redacted]	17.55	13.01	[redacted]	[redacted]	[redacted]	£22,302

*ICER for VCS + MMF vs comparator

Abbreviations: AZA = azathioprine; CYC = cyclophosphamide; ICER = incremental cost-effectiveness ratio; L-CYC = low-dose CYC; H-CYC = high-dose CYC; LYG = life years gained; MMF = mycophenolate mofetil; QALYs = quality-adjusted life years; RTX = rituximab; TAC = tacrolimus; VCS = voclosporin

Table 7: ERG revised base case incremental analysis

Technologies	Total		Incremental		ICER (£/QALY)*
	Costs (£)	QALYs	Costs (£)	QALYs	
MMF	[redacted]	13.00			
AZA	[redacted]	12.64	[redacted]	[redacted]	Extendedly dominated
TAC + MMF	[redacted]	12.96	[redacted]	[redacted]	Extendedly dominated
TAC	[redacted]	13.01	[redacted]	[redacted]	Extendedly dominated
L-CYC	[redacted]	12.44	[redacted]	[redacted]	Extendedly dominated
H-CYC	[redacted]	12.35	[redacted]	[redacted]	Extendedly dominated
RTX + MMF	[redacted]	13.22	[redacted]	[redacted]	Extendedly dominated
VCS + MMF	[redacted]	[redacted]	[redacted]	[redacted]	£31,654

Abbreviations: AZA, azathioprine; CEM, cost-effectiveness model; CYC, cyclophosphamide; H-CYC, high-dose CYC; ICER, incremental cost-effectiveness ratio; L-CYC, low-dose CYC; MMF, mycophenolate mofetil; QALY, quality adjusted life year; RTX, rituximab; TAC, tacrolimus; VCS, voclosporin; WTP, willingness-to-pay

Table 8: ERG revised base case: NHB and NMB pairwise analyses of voclosporin+MMF versus comparators

Treatment	Incremental results		ICER	NHB		NMB	
	Incremental discounted costs	Incremental discounted QALYs	Pairwise cost per QALY gained	£20,000 WTP threshold	£30,000 WTP threshold	£20,000 WTP threshold	£30,000 WTP threshold
Revised ERG base case							
VCS + MMF							
MMF	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
L-CYC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
H-CYC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
AZA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
RTX + MMF	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TAC + MMF	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TAC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: AZA, azathioprine; CEM, cost-effectiveness model; CYC, cyclophosphamide; H-CYC, high-dose CYC; ICER, incremental cost-effectiveness ratio; L-CYC, low-dose CYC; MMF, mycophenolate mofetil; NHB, net health benefit; NMB, net-monetary benefit; QALY, quality adjusted life year; RTX, rituximab; TAC, tacrolimus; VCS, voclosporin; WTP, willingness-to-pay

Figure 3: ERG revised base case - One-way sensitivity analysis

Abbreviations: AD = active disease; CKD = chronic kidney disease; ICER = incremental cos—effectiveness ratio; ICUR = incremental cost-utility ratio; MMF = mycophenolate mofetil; QALYs = quality-adjusted life years; VCS = voclosporin

Note: This analysis was conducted by the EAG using the company model

Figure 4: ERG revised base case – Incremental PSA for costs and QALYs of VCS+MMF vs. comparators

Abbreviations: AZA = azathioprine; CYC = cyclophosphamide; ICER = incremental cost-effectiveness ratio; L-CYC = low-dose CYC; H-CYC = high-dose CYC; MMF = mycophenolate mofetil; QALYs = quality-adjusted life years; RTX = rituximab; TAC = tacrolimus; VCS = voclosporin

Note: This analysis was conducted by the EAG using the company model

Table 9: ERG revied base case probabilistic ICERs

Technologies	Total		Incremental		ICER (£/QALY)*
	Costs (£)	QALYs	Costs (£)	QALYs	
VCS + MMF	[redacted]	[redacted]			
MMF	[redacted]	12.89	[redacted]	[redacted]	£29,767
L-CYC	[redacted]	12.39	[redacted]	[redacted]	£7,092
H-CYC	[redacted]	12.31	[redacted]	[redacted]	£6,055
AZA	[redacted]	12.59	[redacted]	[redacted]	£14,445
RTX + MMF	[redacted]	13.12	[redacted]	[redacted]	£21,989
TAC + MMF	[redacted]	12.88	[redacted]	[redacted]	£20,526
TAC	[redacted]	12.91	[redacted]	[redacted]	£21,208

Abbreviations: AZA = azathioprine; CYC = cyclophosphamide; ICER = incremental cost-effectiveness ratio; L-CYC = low-dose CYC; H-CYC = high-dose CYC; MMF = mycophenolate mofetil; QALYs = quality-adjusted life years; RTX = rituximab; TAC = tacrolimus; VCS = voclosporin

Table 10: ERG revised base case – cumulative impact

Preferred assumption	Incremental cost	Incremental QALYs	Cumulative ICER £/QALY
Company revised base-case at TE stage	[redacted]	[redacted]	£27,301
Company base-case with Fix 2 applied	[redacted]	[redacted]	**£27,199 (-£103)**
Average transition probabilities from 36-months applied to both arms	[redacted]	[redacted]	£32,713 (+£5,515)
Update percentage reduction in transplantation rates from current value (23.08% per 6 months)	[redacted]	[redacted]	*£31,654* (-£1,059)
ERG preferred base case at TE stage	[redacted]	[redacted]	*£31,654*
ERG preferred base case at TE stage plus additional CNI monitoring cost for voclosporin	[redacted]	[redacted]	*£33,697 (+£2,043)*

Abbreviations: CKD, chronic kidney disease; ERG, Evidence Assessment Group; ICER, incremental cost-effectiveness ratio; LN, lupus nephritis; MMF, mycophenolate mofetil; QALY, quality adjusted life year; RDI, relative dosing intensity, TE, technical engagement; VCS, voclosporin

3. ERG REVIEW OF KEY ISSUES

Key Issue 1: Network meta-analysis (NMA) estimates may not be reliable and should better account for heterogeneity.

Summary of the key issue

The company presented fixed effects NMAs on the basis that random effects NMAs were judged as not converging. The ERG regarded that this claim had not been sustained and recommended the use of appropriate informative priors, or otherwise clear evidence that no plausible random effects model would lead to convergent estimates in the base case.

Summary of the company response

In their response, the company acknowledged the value of informative priors and estimated random effects models for complete renal response (CRR) and partial renal response (PRR) outcomes using informative priors derived from Turner (2015). The priors they used corresponded to the 'average' distribution for an average healthcare setting, and the 'average' distribution for subjective outcomes. The resultant analyses reflected generally similar point estimates, but wider credible intervals. The company indicated a preference for the CRR NMA based on a subjective outcomes prior due to stability of inference, and no specific preference between informative priors for the PRR NMA.

ERG response

The ERG agrees that the implementation of the informative priors has generated more credible NMAs, and for consistency takes up both CRR and PRR NMAs using the subjective outcomes prior. This is especially important because stakeholder comments consistently agreed with the ERG that population characteristics, including treatment histories, and trial characteristics, including outcome definitions and steroid dosing, generated heterogeneity in the NMAs.

However, this issue is only partially resolved as the resultant random effects point estimates and corresponding CODA traces for probabilistic sensitivity analyses were not implemented in the company's model. The ERG regards that its 'preferred' base case would include random effects NMAs.

Key Issue 2: The company's model structure is subject to a number of structural limitations.

Summary of the key issue

The company's model is associated with a number of restrictive settings and assumptions which preclude in-depth investigation of the impacts these aspects of the model have on cost-effectiveness results. These features include:

- CKD progression is only possible from an 'active disease' sub-state (and so patients with renal response are not subjected to a risk of CKD progression)
- No CKD progression events in AURORA 1 or AURORA 2, and so CKD progression is disabled in the company's base-case analysis for the first 3 years, but this is not expected to align with clinical practice
- Transitions in the first 3 years are based on the 'count method', which is subject to limitations mostly due to sample size
- Very few within-trial deaths, and cause of death is not explicitly captured but is modelled to incur differential costs

Summary of the company response

As part of their response to TE, the company provided justification for the model structure selected and discussed limitations in turn. In brief:

- The company highlighted that clinical advice suggested that a minority of patients (~2.5%) would achieve response (CR or PR) in the later CKD stages (CKD stage 3b-4) and therefore transitions into response states for these later CKD stages were not considered part of the base-case model structure.
- Within the company's model, CKD progression is only possible from active disease (AD). Whilst the company acknowledges that this may represent a simplification of the disease process, clinical advice highlighted that there would be a lack of data to inform additional transitions, so modelled patients must spend time in AD before progression.

- CKD progression from stage 1-3a to stage 3b-4 has been altered in the company's revised base case and can now occur at any point in the initial 36-month period (previously this could only occur after 36 months and as such the revised base case is now aligned with the ERG analysis).

- The company has maintained the previously used count method to inform model transitions. LN-related death costs were updated to align with an ERG suggestion that patients in CKD stages 1-3a should incur background mortality costs instead. LN related deaths from CR and PR health states have been removed with the count method adjusted accordingly (in line with the ERG analyses).

ERG response

The ERG acknowledges the changes the company has made to their base case. The first change relates to allowing CKD progression prior to 36 months. This change is aligned with Scenario 11 explored by the ERG in its report and is also in line with submissions received from stakeholders during TE.

The second change to the company base case relates to removing LN death from CR and PR health states. As part of its original report, the ERG explored two scenarios where LN deaths were removed from the model, in one instance this was removed from the count method calculations, and in the second method, deaths were removed from the count method and the user input, acknowledging that both were required to remove the LN deaths entirely. The company highlighted within its response to TE that an error has been corrected in its revised base case related to LN deaths where transitions to CR, PR and AD had not been re-weighted to account for the parameter inputs overriding the observed transition to death. The revised company base case applies a fix to this error but also removes LN related death from the PR and CR health states from CKD stage 1-3a.The costs associated with LN death have also been amended so that deaths from any health state in CKD stage 1-4 are costed as background mortality and only costs from CKD stage 5 are costed as LN deaths. The ERG are satisfied with this revision and has incorporated the amend as part of it's base case also (extending the removal of LN death costs from CKD stage 1-3 to CKD stage 1-4).

Despite the changes made, the ERG considers that the model structure still remains a key issue and area of uncertainty with regard to decision making for multiple reasons:

- Firstly, though the company provide justification of the approach taken to conceptualise the cost-effectiveness model, submissions from stakeholders indicate uncertainty in the model structure and the approach taken (including application of CKD progression, appropriate alignment with clinical practice, and in one instance, questioning whether the full value of treatment was captured within the model structure when considering the impact on the immune system and impacts on fertility which may have considerable impact on health outcomes and quality of life).

- Secondly, clinical feedback obtained by the company suggested that ~2.5% of patients are expected to achieve response after state CKD 3b-4; the ERG believe that this should be implemented within the model to align with clinical expectations, since the predicted patient response will always exhibit uncertainty (can be non-zero). The company has not amended the restriction in the model structure which inhibits movement to response (CR or PR) from CKD stage 3b-4. The ERG note that this still creates a discrepancy in the model structure diagram provided by the company but more importantly, is at odds with expectation, as submissions from stakeholders indicated that whilst response was unlikely, it is possible for patients in CKD stages 3b-4 to achieve, and possibly maintain, stable disease.

- Thirdly, although the ERG acknowledges the limited alternative options for exploring transition probabilities, shortcomings still remain in implementing the count method to derive transition probabilities.

- Fourthly, advice from experts to the ERG indicated that transplant rates included within the model (90% across two years) may be too high and the ERG therefore considered further analyses related to this in the ERG report (Scenario 9). Submissions from stakeholders also suggested that transplant rates as high as 90% across 2 years may be too high.. A transplantation of 60% was considered a more appropriate value by one stakeholder submission (note that the ERG explored 65% within 2 years in the aforementioned ERG Scenario). As such the ERG has revised its base case settings to align with a lower transplantation rate (65% within 2 years, based on clinical advice to the ERG). Nevertheless, the ERG accepts that the most appropriate transplantation rate remains an area of uncertainty within the model.

Key Issue 3: The long-term treatment effect of voclosporin + MMF and its comparators is unknown.

Summary of the key issue

There is uncertainty in the long-term effect of VCS+MMF and how this compares to the long-term effect of MMF alone, as well as other comparators. The company's model requires extrapolation of transition matrices over a lifetime horizon (equivalent to 69 years beyond the initial 3 years of follow-up data available from the AURORA 1 and AURORA 2 studies). The company's application of independent transition matrices from the trial data makes two important assumptions: (1) that short-term data are sufficient to generalise to the longer term, and (2) that the short-term data while patients are on treatment are reflective of longer-term outcomes when patients are no longer receiving the same treatment up until 3 years. The company has assumed a 'waning' effect which takes the average effects across both arms and applied this to the VCS+MMF arm indefinitely. The ERG considered this approach to be inappropriate and unjustified in the absence of long-term data and clear justification within the CS.

Summary of the company response

The company agreed that there is a level of uncertainty when extrapolating the short-term data to inform long-term outcomes. The company present a revised base case as follows:

- Patients in the AD and PR states at 36-months on the VCS+MMF arm are assumed to match those of MMF, since MMF is the most frequently used maintenance therapy
- Patients in the CR states at 36-months are assumed to be an average between the VCS+MMF and MMF probabilities from AURORA 2 trial at 30- and 36-months.
- Other comparators' long-term outcomes are informed by the transition probabilities for patients in the AD health state from the NMA, dependent on whether each transition probability is less than, or greater than, the equivalent probability in the MMF state transition matrix.

ERG response

The ERG acknowledges that the company agrees with interpretation of this as a key issue for consideration, and further acknowledges the alternative scenario prepared by the company.

Overall, the ERG does not consider this key issue to have been resolved by the new evidence or rationale presented in the company's response. However, as noted in the ERG report, the ERG considered it unlikely that this key issue would be resolved without further data related to the long-term treatment effects and/or input from clinical expert opinion. This uncertainty was emphasised by submissions from stakeholders who too raised concerns around the generalisability and appropriateness of using short-term data to inform long-term transition probabilities, and lack of evidence concerning disease progression following cessation of treatment with voclosporin.

Further to this, whilst some stakeholders considered the short-term benefits of treatment to be predictive of longer-term outcomes, there was acknowledgement that this is dependent on the duration of treatment, which is a further component of uncertainty (for both VCS + MMF and MMF alone, see Key Issue 7). Some stakeholder submissions highlighted the usefulness of the AURORA 2 study yet commented some patients may start to flare on discontinuation of treatment, and for other patients, treatment beyond 3 years is expected. This also links closely with the stopping rules assumed within the company model alongside Key Issue 5 (the appropriateness of calculating drug costs within the model).

Key Issue 4: The utility estimates used in the company's model are inappropriate.

Summary of the key issue

The ERG considered that there was a lack of appropriate analysis methods to derive utility values used within the cost-effectiveness model with data omitted from both the AURORA 1 and AURORA 2 studies. The ERG also considered limitations in the use of literature-based utility values for later states that reflect a different group of patients.

Summary of the company response

The company has carried out a regression analysis of the utility data collected in AURORA 1 and AURORA 2 as recommended by the ERG. The company response presented these utilities and incorporated them as part of the company's revised base case to inform utility values in CKD states 1-3a (for CR, PR and AD). The company also presented further data identified from the literature that could have been used to inform health states CKD 1-3a and suggested that, as these utilities result in a higher QALY gain for voclosporin+MMF, the regression analysis may be considered a conservative approach. In addition to this, the company agreed with the ERG's

assumptions relating to alternative utility values for the CKD 5 transplant and dialysis health states, and as such, has incorporated these into its revised base case.

ERG response

The ERG considers this issue resolved as a regression analysis has been completed and implemented within the company model using all relevant data from within the AURORA 1 and AURORA 2 trials. Based on the new information presented, the ERG has revised its base case assumptions to include the updated utility values for CKD stage 1-3a. The ERG would however highlight that there is still uncertainty present in the utility values used within the model and notably those obtained from the wider literature. The ERG does not agree with the statement from the company in its response that the inclusion of the regression analysis is conservative as the regression analysis is a more methodologically appropriate way of utilising data collected from their clinical trial instead of the incorporation of external literature outside of the clinical trial (which could be subject to a number of limitations).

Key Issue 5: The company has not appropriately calculated the costs of treatment in the model.

Summary of the key issue

The company's model includes a number of assumptions made with respect to costing voclosporin, MMF, and other comparators included via the indirect comparison. The ERG considered there to have been a fundamental misinterpretation by the company with respect to the difference between RDI and TTD, which means that while premature discontinuation is captured within the model (through TTD), any dose adjustments are not reflected (through RDI, or an equivalent measure). The company costed MMF assuming a dose of 2.5 g/day, whereas in AURORA 1 and AURORA 2 this was dosed at 2 g/day. Moreover, in AURORA 2, MMF dose reductions were permitted per protocol, and this is not reflected within the company's model. For other comparators, TTD is assumed to be 100% which the company justified based on a lack of data to quantify premature treatment discontinuation. The ERG considered this to be inappropriate given that some patients are expected to discontinue treatment due to lack of efficacy or occurrence of AEs.

Summary of the company response

The ERG acknowledges several amendments to the company's revised base case, which are now more closely aligned with the ERG's preferred assumptions and exploratory scenarios. Firstly, the company added an additional cost for half a pack of voclosporin to the drug

acquisition costs to account for potential wastage. Additionally, the standard 2g per day dosing regimen of MMF within the AURORA trials is now represented within the model, previously assumed to be 2.5g per day. Therapeutic drug monitoring costs for the voclosporin arm were excluded from the revised company base case, as per the initial company submission. No amendments were outlined relating to the stopping rules for the treatments within the model or the assumptions relating to time to treatment discontinuation.

ERG response

The ERG acknowledges the application of some of their proposed changes within the company's base case including those for wastage costs, application of RDI and amending the MMF dose to 2g in line with the AURORA trials.

Therapeutic drug monitoring costs were included within the company submission for the CNI comparator tacrolimus, however the company did not consider these for voclosporin (also a CNI). Following clinical advice, the ERG was recommended to include drug monitoring costs for all CNI inhibitors, thus these costs were applied to voclosporin in an additional scenario. This assumption was also in line with submissions received by stakeholders during TE that suggested that monitoring of kidney function and blood results would be anticipated for patients treated with voclosporin. The company disagreed with this additional cost applied to the voclosporin arm, and as such the ERG considers this a point for discussion by the appraisal committee with appropriate consideration needed to ensure costs are adequately captured within the cost-effectiveness model.

The ERG also highlights that there has yet been no change to comparator TTD, with no discontinuation included within the company's base case for treatments included from the indirect treatment comparison. As current, the company has included TTD such that 100% of patients receive each comparator therapy during each model cycle whilst the ERG, as an exploratory scenario, set TTD for each indirectly-estimated comparator equal to the MMF arm due to a lack of data for these other treatments. An assumption of no discontinuation is not reflective of UK clinical practice, and feedback as part of the NICE process has indicated that treatment discontinuation for the comparators outside of the trial should also be considered, and that the company's assumption (of no discontinuation) is implausible. ~~Similarly, the company's revised base case still incorporates 100% RDI for all other non-trial comparator arms except tacrolimus (which applies 95%). As a result, it is likely that the model calculations overestimate the total drug costs for all comparators except MMF. Incremental costs between comparators~~

~~and the VCS+MMF arm are therefore likely biased in favour of VCS+MMF, alongside the resulting ICER. The ERG does not consider this issue resolved.~~[1] Further to this, additional issues were raised by stakeholders with regard to the stopping rules included within the model for both the intervention and comparators. This is an additional point of uncertainty which may affect the total drug costs considered on all arms within the cost-effectiveness model.

Key Issue 6: There is a lack of transparency around the inputs used in the company's model.

Summary of the key issue

The ERG identified a number of issues with respect to transparency of reporting in both the CS and the company's model, which impacted its ability to verify a variety of aspects of the CS. Issues included hardcoded values which did not match source material (due to inflation and/or converting outputs for use within the model), misalignment in source costs with those used in the model, inconsistencies in apparent inflation indices used to adjust costs, and non-systematic identification of drug costs leading to some costs that were higher than other available sources (e.g., prednisolone sourced from BNF and not eMIT).

Summary of the company response

The company has amended its base case with regard to the coding error identified by the ERG. In addition to this, the analyses conducted by the ERG highlighted a further error related to the inclusion of LN deaths within the model transition probabilities. The company highlighted that this error has now been addressed as part of its revised base case analysis. With regard to the misalignment of costs and reference sources, the company has aligned with the ERG's cost amendments and has stated that model input parameters have been checked and values incorporated within the model are verified and accurate to inform decision making.

ERG response

Given the number of inputs and calculations within the model, alongside the limited description of calculations against the sources, it was not possible for the ERG to perform a complete check of inputs against their reference sources and as such the ERG would like to thank the company for crosschecking all inputs within the model and for confirming that the correct values are used throughout the model. However, during its appraisal at TE, the ERG found an additional error

[1] This text has been removed after a factual inaccuracy was identified.

that impacted model results (the AE disutility error highlighted in Section Additional error in the company model4.1), and further to this found issues related to transparency within the model (including the addition of new parameters without removal of the original estimates). In addition, the lack of flexibility within the model to refer to prior settings (and cost-effectiveness estimates) has limited the ability of the ERG to crosscheck model ICERs and calculations throughout the process. As a consequence, the ERG cannot confidently conclude that there are no further edits in the model, and the ERG consider this to issue around transparency to be unresolved.

Key Issue 7: Uncertainty in how voclosporin will be used in practice.

Summary of the key issue

LN is a highly heterogeneous condition and the way in which people with LN receive treatment in NHS practice also varies significantly. There is also wide variation in practice between treating centres and clinicians in the ordering and longevity of treatment. Broadly, there is uncertainty in the clinical community about the optimum duration of immunosuppression treatment, which needs to balance a desire for shorter treatment courses with the need to establish a stable CR. The ERG considered it uncertain but plausible that the effect of voclosporin may vary according to the way it is used. In particular, the ERG noted that the line of treatment where voclosporin is used and its duration of administration may impact its clinical and cost effectiveness.

Summary of the company response

The company noted that the anticipated marketing authorisation for voclosporin does not specify a line of treatment for administrating voclosporin. The company reiterated the rate of CR in the AURORA trial, which includes participants at differing treatment lines.

ERG response

The company has not presented new evidence or further rationale that resolves this key issue though as noted in the ERG report, within the timeframe of technical engagement the ERG considered it unlikely that the company would be able to provide new evidence that would reduce uncertainties that the effect of voclosporin may vary according to its use (e.g., duration and line of treatment). Submissions from stakeholders during technical engagement agreed that there is variation in current care of LN across patients and treating clinicians, with particular uncertainty related to the optimum duration of treatment needed to achieve a renal response and benefit long-term health outcomes. Stakeholders considered that both shorter and longer

durations of treatment than used in the clinical trials may be used in practice, with this adapted according to clinician judgement about the stability of renal response. Longer durations of treatment may particularly be used for those who were slower to achieve a response and those with existing organ damage. There was disagreement amongst stakeholders about whether voclosporin would primarily be used as a first- or second-line treatment: several stakeholders highlighted the potential benefits of early control of disease progression and therefore considered that voclosporin should primarily be used as a first-line treatment, while others noted uncertainty in the clinical and cost effectiveness of voclosporin and suggested it should be used in those refractory to existing treatments. Additional issues related to the real-world use of voclosporin mentioned by stakeholders included likely compliance with oral treatment and variation in the dose of steroids (see also Section 4.2). Several stakeholders agreed with the ERG that variation in the use of voclosporin (and its comparators) would affect clinical and cost effectiveness estimates.

4. ERG CRITIQUE OF ADDITIONAL EVIDENCE

4.1. Additional error in the company model

The ERG highlights an additional error noted in the company's calculation of the disutility values associated with adverse events which was not identified at the ERG report stage. The company error arises in the QALYs sheet in the calculation of AE disutility column for each treatment including MMF (cells Q9, AB9, AX9, CP9, and DA9). An example formula from cell Q9 is presented below:

*=-INDEX(trace_tx1, $B9, 11)*MMULT(TRANSPOSE[redacted],input_AE_disutility*input_AE_incidence_tx1)*

The formula incorrectly divides the total duration of the AE Inputs!$M$1778:$M$1797) by the number of days in the cycle ('Labels & constants'!$H$7*6). Given the positioning of the brackets in this formula this results in the duration being divided by the number of days in a month (*'Labels & constants'!$H$7)* to estimate the disutility and then incorrectly multiplies the disutility by 6. This error in brackets results in an overestimate of AE disutilities. Instead, the formula should read as follows:

*=-INDEX(trace_tx1, $B9, 11)*MMULT(TRANSPOSE[redacted],input_AE_disutility*input_AE_incidence_tx1)*

This divides the total duration of the AE by the number of days in 6 months which is aligned with the cycle length and aligns with the rest of the model calculation for the disutilities.

The difference in this highlight section of the formula is also illustrated as follows:

Company model:

$$\frac{AE\ duration}{days\ in\ a\ month} \times 6\ months$$

Correction made:

$$\frac{AE\ duration}{days\ in\ a\ month\ \times 6}$$

It should be noted that amending this error has a very minor impact on the model results and is by no means a large driver of cost-effectiveness estimates. However, for completeness this has

been raised and amended across all relevant cells as part of the ERG revised base case. A summary of the impact on the company's revised base case is shown in Table 11 below.

Table 11: Company revised base case (pairwise ICERs)

Technologies	Total			Incremental			ICER (£/QALY)*
	Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs	
VCS + MMF	[redacted]	[redacted]	[redacted]	-	-	-	-
MMF	[redacted]	17.57	13.03	[redacted]	[redacted]	[redacted]	£27,301
L-CYC	[redacted]	16.96	12.57	[redacted]	[redacted]	[redacted]	£7,870
H-CYC	[redacted]	16.83	12.48	[redacted]	[redacted]	[redacted]	£6,704
AZA	[redacted]	17.20	12.76	[redacted]	[redacted]	[redacted]	£14,825
RTX + MMF	[redacted]	17.95	13.32	[redacted]	[redacted]	[redacted]	£22,722
TAC + MMF	[redacted]	17.62	13.07	[redacted]	[redacted]	[redacted]	£23,345
TAC	[redacted]	17.68	13.12	[redacted]	[redacted]	[redacted]	£23,849

*ICER for VCS + MMF vs comparator

Abbreviations: AZA = azathioprine; CYC = cyclophosphamide; ICER = incremental cost-effectiveness ratio; L-CYC = low-dose CYC; H-CYC = high-dose CYC; LYG = life years gained; MMF = mycophenolate mofetil; QALYs = quality-adjusted life years; RTX = rituximab; TAC = tacrolimus; VCS = voclosporin

Table 12: Company revised base case with AE fix applied (pairwise ICERs)

Technologies	Total			Incremental			ICER (£/QALY)*
	Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs	
VCS + MMF	[redacted]	[redacted]	[redacted]	-	-	-	-
MMF	[redacted]	17.57	13.04	[redacted]	[redacted]	[redacted]	£27,199 (-£103)
L-CYC	[redacted]	16.96	12.57	[redacted]	[redacted]	[redacted]	£7,770 (-£100)
H-CYC	[redacted]	16.83	12.48	[redacted]	[redacted]	[redacted]	£6,625 (-£78)
AZA	[redacted]	17.20	12.76	[redacted]	[redacted]	[redacted]	£14,591 (-£233)
RTX + MMF	[redacted]	17.95	13.33	[redacted]	[redacted]	[redacted]	£22,532 (-£190)
TAC + MMF	[redacted]	17.62	13.08	[redacted]	[redacted]	[redacted]	£23,251 (--£94)
TAC	[redacted]	17.68	13.12	[redacted]	[redacted]	[redacted]	£23,169 (-£680)

*ICER for VCS + MMF vs comparator

Abbreviations: AZA = azathioprine; CYC = cyclophosphamide; ICER = incremental cost-effectiveness ratio; L-CYC = low-dose CYC; H-CYC = high-dose CYC; LYG = life years gained; MMF = mycophenolate mofetil; QALYs = quality-adjusted life years; RTX = rituximab; TAC = tacrolimus; VCS = voclosporin

4.2. Steroids administered in the included trials

Stakeholder submissions to technical engagement noted that the dose of steroids used in the trials of voclosporin were lower than would be used in clinical practice in the NHS. This was considered to potentially affect the generalisability of the evidence from the clinical trials to clinical practice, but one stakeholder further suggested that this would disadvantage the comparator to voclosporin as steroids would be administered at a sub-optimal dose that would not typically be used. This was not consistent with clinical advice to the ERG, as while it was agreed that the dose used in the trials is lower than typical clinical practice the advice was that the lower dose would be efficacious and is consistent with guidelines for reducing the dose of steroids administered to people with LN so as to reduce AEs. It was noted by stakeholders that there is no high-quality evidence for the effectiveness of the dose of steroids used in the trials, however if voclosporin was able to deliver clinical benefits with a lower dose of steroids this may be beneficial for reducing AEs of steroids. Overall, the ERG was unable to resolve the discrepancy between clinical experts about whether the dose of steroids used in the clinical trials, particularly in the comparator arm, were sufficiently efficacious.