NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Voclosporin with mycophenolate mofetil for treating lupus nephritis [ID3962]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Voclosporin with mycophenolate mofetil for treating lupus nephritis [ID3962]

Contents:

The following documents are made available to consultees and commentators:

1. **Response to consultee, commentator and public comments on the Appraisal Consultation Document (ACD)**

2. **Comments on the Appraisal Consultation Document from Otsuka Pharmaceuticals**

3. **Consultee and commentator comments on the Appraisal Consultation Document** from:
   a) Lupus UK
   b) UK Kidney Association
   c) UK Renal Pharmacy Group
   d) NHS England

4. **Evidence Review Group critique of company comments on the ACD**

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

Appraisal title

Single Technology Appraisal

Response to consultee, commentator and public comments on the Appraisal Consultation Document (ACD)

Type of stakeholder:

Consultees – Organisations that accept an invitation to participate in the appraisal including the companies, national professional organisations, national patient organisations, the Department of Health and Social Care and the Welsh Government and relevant NHS organisations in England. Consultees can make a submission and participate in the consultation on the appraisal consultation document (ACD; if produced). All non-company consultees can nominate clinical experts and/or patient experts to verbally present their personal views to the Appraisal Committee. Company consultees can also nominate clinical experts. Representatives from NHS England and clinical commissioning groups invited to participate in the appraisal may also attend the Appraisal Committee as NHS commissioning experts. All consultees have the opportunity to consider an appeal against the final recommendations, or report any factual errors, within the final appraisal document (FAD).

Clinical and patient experts and NHS commissioning experts – The Chair of the Appraisal Committee and the NICE project team select clinical experts and patient experts from nominations by consultees and commentators. They attend the Appraisal Committee meeting as individuals to answer questions to help clarify issues about the submitted evidence and to provide their views and experiences of the technology and/or condition. Before they attend the meeting, all experts must either submit a written statement (using a template) or indicate they agree with the submission made by their nominating organisation..

Commentators – Commentators can participate in the consultation on the ACD (if produced), but NICE does not ask them to make any submission for the appraisal. Non-company commentator organisations can nominate clinical experts and patient experts to verbally present their personal views to the Appraisal Committee. Commentator organisations representing relevant comparator technology companies can also nominate clinical experts. These organisations receive the FAD and have opportunity to report any factual errors. These organisations include comparator technology companies, Healthcare Improvement Scotland any relevant National Collaborating Centre (a group commissioned by NICE to develop clinical guidelines), other related research groups where appropriate (for example, the Medical Research Council and National Cancer Research Institute); other groups such as the NHS Confederation, the NHS Commercial Medicines Unit, the Scottish Medicines Consortium, the Medicines and Healthcare Products Regulatory Agency, the Department of Health and Social Care, Social Services and Public Safety for Northern Ireland).

Public – Members of the public have the opportunity to comment on the ACD when it is posted on the Institute's web site 5 days after it is sent to consultees and commentators. These comments are usually presented to the appraisal committee in full, but NICE reserves the right to summarise and edit comments received during consultations, or not to publish them at all, where in the reasonable opinion of NICE, the comments are voluminous, publication would be unlawful or publication would be otherwise inappropriate.

Please note: Comments received in the course of consultations carried out by NICE 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 submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
1		LUPUS UK	We are concerned that the evidence requirements set by the committee are too strict for a new treatment for lupus nephritis to be recommended. One of the most important clinical outcomes to measure efficacy of a treatment in lupus nephritis is to examine whether it slows or prevents progression to end-stage renal disease (ESRD) in the longer-term. There is limited data available relating to the time to progression to ESRD from SLE diagnosis. Mahajan et al. (**HERE**) refers to studies finding the average time ranges between 4.1 years to 7.5 years. This range is likely due to the ethnic distribution of the study cohorts, with black patients more likely to progress to ESRD. This longer-term data is not available from a Phase 3 randomised-controlled trial and to require it will prevent a potentially organ-saving and life-saving treatment from being made available for patients. Lupus nephritis is a chronic disease, with onset frequently occurring in relatively young people. Many people live with the disease over several decades, accumulating damage from disease flares and adverse effects from treatments such as corticosteroids. As such, earlier intervention with a treatment that is more effective than standard therapy could have a considerable cumulative benefit to quality of life. The clinical trial evidence indicates that voclosporin plus mycophenolate mofetil is more effective at preventing the progression of lupus nephritis than mycophenolate mofetil alone. The evidence threshold set by NICE will prevent effective new treatments for rare, life-limiting and life-threatening diseases like lupus nephritis from being available for patients who are, too frequently, poorly served by current standard therapy.	Thank you for your comment. The committee identified uncertainties with the evidence shared by the company and the company's model. However, it also acknowledged the efforts by the company to address uncertainties and amend the model. This resulted in the committee identifying a maximum acceptable ICER towards the lower end of the range normally considered a cost-effective use of NHS resources (see section 3.12 of the final draft guidance). As cost-effectiveness estimates were towards the lower end of the range considered cost effective, voclosporin was recommended.
2		LUPUS UK	We are concerned by the committee's assertion on page 3 of the draft guidance that there are several immunosuppressant options for the treatment of lupus nephritis whilst not addressing some of their significant limitations. Systematic review (**HERE**) found that the mean renal remission/response rate was less than 50% for most standard therapy. 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 (**HERE**). 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 (**HERE**). This pattern suggests limitations in the	Thank you for your comment. The nature of the condition and treatment options available are discussed separately in final draft guidance. Section 3.1 discusses the nature of the condition and

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			effectiveness of, or access to, current treatments and the need for new therapies such as voclosporin. *"[My partner] now has stage 4 kidney disease 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."* 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. Voclosporin may be a preferred alternative to cyclophosphamide because of its risk to fertility for a patient group which is predominantly young women. 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 of 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. The clinical trial for voclosporin demonstrated that it can be effective as part of a treatment regimen with a lower steroid dose. *"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."* 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*	summarises the debilitating nature of the disease. It also outlines the side effects associated with current treatments. Section 3.2 summarises the treatment options that are available.

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			myself weekly with donated antibodies and need to see an immunologist." Approximately 25% of respondents in our online survey stated that their current treatment was a "large" or "very large" interruption to work/study.	
3		LUPUS UK	We are concerned that the draft guidance will prevent a treatment with a different method of administration from being made available for people with lupus nephritis. As an oral therapy, voclosporin may have fewer barriers to access than some other current therapies used for lupus nephritis, particularly intravenous infusions such as rituximab and cyclophosphamide. Intravenous treatments such as rituximab and cyclophosphamide need to be administered at a hospital (potentially a specialist centre), which presents a barrier to access for some patients who may live a considerable distance away 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.	Thank you for your comment. The committee noted that alternative oral treatments are currently available and noted that voclosporin will be given with intravenous steroids as per the AURORA trials. Therefore, the barriers to access highlighted here will not be removed by using voclosporin. See section 3.15 of the final draft guidance for more information.
4		LUPUS UK	Aligning with our first comment, we are concerned that the evidence threshold set by NICE is unobtainable for clinical trials in rare diseases and could act as a disincentive for the development of new therapies for lupus nephritis. An inhospitable UK market could also result in new therapies not being marketed here, creating a disparity of access with the rest of Europe. Belimumab (Benlysta) was the first treatment specifically developed to treat lupus and was approved in 2011. NICE recommended belimumab for limited use by the NHS but GlaxoSmithKline subsequently withdrew marketing activity from the UK, halting technology appraisal [TA806] because they did not provide an evidence submission. No new lupus treatments have been made available in the UK outside of clinical trials since belimumab was introduced. In 2022, AstraZeneca withdrew their submission to NICE for anifrolumab, terminating the appraisal [TA793]. A concerning pattern is emerging despite lupus patients having significant unmet needs and new treatments demonstrating superior efficacy compared to current therapy.	Thank you for your comment. The committee identified uncertainties with the evidence shared by the company and the company's model. However, it also acknowledged the efforts by the company to address uncertainties and amend the model. This resultedin the committee identifying a maximum acceptable ICER towards the lower end of the range normally considered a cost-effective use of NHS resources (see section 3.12 of the final draft guidance). As cost-effectiveness estimates were towards the lower end of the range

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				considered cost effective, voclosporin was recommended.
5		NHS England	**Rheumatology Clinical Advice (first 4 responses)** We hope that there will be a further opportunity for the company to refine its model(s) so that further assessment of this can take place.	Thank you for your comment. The company made changes to its base case model which was considered by the committee. See sections 3.8 to 3.11 of the final draft guidance.
6		NHS England	Unmet need in lupus nephritis: the standard of care arm in the voclosporin studies (mycofenolate/steroids) showed only 20-30% complete response. Long term outcomes have been shown to be poorer in those with poorer initial responses (and in partial vs complete response) so the this does need to be borne in mind in analysis of a model of long term outcomes and transitions between disease states.	Thank you for your comment. The committee discussed the relationship between short term and long term outcomes, concluding that longer-term efficacy is difficult to establish and creates high uncertainty. See section 3.10 of final draft guidance.
7		NHS England	In recent years, this greater understanding of the importance of obtaining as good a response as possible at the earliest possible stage of disease or as early as possible in a flare has led to higher hurdle/tighter definitions and approach to accepting “good” outcomes. This is shown by the 2019 guideline on lupus nephritis outcomes published by the European League Against Rheumatism and European Renal Association (Fanouriakis et al, Annals Rheumatic Disease 2020). Voclosporin is the only agent showing significant benefit over the current standard of care when meeting these endpoints (Anders et al, abstract, American College of Rheumatology meeting 2022). Furthermore, these endpoints are significantly more stringent than those used in the trials that led to the approvals for mycofenolate in lupus.	Thank you for your comment. The committee discussed the relationship between short term and long term outcomes, concluding that longer-term efficacy is difficult to establish and creates high uncertainty. See section 3.10 of final draft guidance.
8		NHS England	Steroid use: there has been increasing awareness in Rheumatology clinical practice of the toxicity of steroids, including at lower doses than previously thought, to be detrimental. As a result, the direction of travel of clinical practice is to reduce steroid usage from previous dosing regimens. It has been shown that such high doses of steroids are not necessary or physiologically effective. There is significant clinical practice now using lower dose steroid regimens in lupus nephritis (eg Condon et al, Annals Rheumatic Disease 2013) so it is not quite accurate to comment that the low doses of steroids used in the voclosporin studies do not reflect UK clinical practice. Indeed, a body of opinion considers that the lower dose steroid regimens should be those that we should aim for as standard.	Thank you for your comment. The committee discussed the responses from stakeholders on the level of steroid use in the AURORA trials. The committee concluded that the AURORA trials are generalisable to the UK population but that the

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				steroid doses used may not be reflective of established NHS clinical practice. See section 3.5 of final draft guidance.
9		NHS England	**Renal clinical advice:** • has all of the relevant evidence been taken into account? Yes, we feel the relevant evidence, including the current clinical trials data and best available evidence has been taken into account which justify the recommendations made. • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? Yes, we feel these are reasonable interpretations of the evidence. Lupus nephritis is a very heterogenous condition and the different clinical presentations and treatment arms have not been considered fully by the drug company within their trial design. We agree the use of Voclosporin is not recommended based on the evidence provided. We would not use it instead of MMF or as an add on at this stage with the limited evidence for first line treatment. Consideration of its use only if patients are not responding to standard of care therapy later in their treatment course may be appropriate. We agree with the comments around proteinuria not being the best clinical end point. We agree a combination of clinical and histopathological markers would be better though acknowledging a renal biopsy at diagnosis is appropriate but repeated renal biopsy would be too high risk. We agree with the flaws in the clinical and cost effectiveness models presented by the drug company and would not feel assured by the evidence presented to justify its use without further modification to the modelling and further validated evidence. • are the provisional recommendations sound and a suitable basis for guidance to the NHS? Yes, we are happy with the provisional recommendations made and would agree with them as suitable basis for guidance for the NHS. Agree with the steroid usage doses in the trials are not reflective of those used in clinical practice.	Thank you for your comment. The committee considered the responses from stakeholders and clarified how voclosporin would be used in clinical practice, concluding that voclosporin would be used to induce remission and not as a long-term maintenance treatment (see section 3.3). The committee considered an updated model for the company base case as well as scenarios to explore uncertainty. The committee highlighted uncertainties which led it to identify a maximum acceptable ICER towards the lower end of the range normally considered a cost-effective use of NHS resources (see section 3.12 of the final draft guidance).
10		Otsuka Pharmaceuticals UK Ltd.	**<u>Executive summary</u>** Otsuka appreciate the opportunity to respond to this draft guidance document, and kindly ask the committee to consider the following comments and key points. *Revised Patient Access Scheme (PAS)*	Thank you for your comment. As this comment is a summary of other comments, please see NICE responses to comments 11, 12, 13, 14,

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			In response to the draft guidance, Otsuka has revised the PAS as outlined in Comment 2. *Updated base case following draft guidance* Revisions have been made to the base case cost-effectiveness analysis in line with the committee and the EAG's comments in the committee meeting and the draft guidance. When considering the revisions and evidence presented in Comment 3 and including the revised PAS, voclosporin + MMF is a cost-effective treatment option for adult patients with active class III, IV and V (including mixed class III/V and IV/V) LN. The ICER in the base case vs MMF is £24,267, with ICERs vs all comparators under the £30,000 per QALY threshold. *Exploring uncertainty in the model* To support the revised base case analysis, and in line with requests from the committee, we have provided additional clarity and conducted further scenario analyses (outlined in Comment 4) within the model structure and assumptions. This should help mitigate uncertainty associated with the company base case and provide further confidence that voclosporin is a cost-effective use of NHS resources. *Clarification of positioning* In response to the committee's comments regarding uncertainty on how voclosporin would be used, we have provided further clarity in Comment 5 regarding the positioning of voclosporin in UK clinical practice and the most suitable comparator (MMF). *Transparency in the model* Furthermore, in Comment 6 we acknowledge the committee's comments regarding transparency in the model and outline the processes and checks that have been undertaken to address concerns and provide more confidence in the model. *Factual inaccuracy* Finally, we note a factual inaccuracy in the draft guidance (Comment 7). **Voclosporin offers patients and the NHS an important new treatment option for LN. The demonstrated higher renal response rate and faster onset of action of voclosporin + MMF vs current standard of care (MMF) mean that patients spend less time in active disease, limiting the damage incurred to their kidneys. We hope that the revised PAS and additional analyses provided will give the committee confidence that voclosporin represents a cost-effective use of NHS resources, and that it can be recommended as a treatment option for LN, a rare disease where there is a high unmet need.**	15 and 16.
11		Otsuka Pharmaceuticals UK Ltd.	**Revised PAS** In response to the draft guidance, a revised PAS of [redacted] has been submitted to NHS England. When the PAS is applied to the list price this is equivalent to [redacted] per pack of voclosporin.	Thank you for your comment. The committee considered the revised PAS, as well as confidential prices for all other treatments in the decision making ICERs. The resulting ICERs are confidential but committee

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				concluded the most plausible ICER was likely closer to the lower end of the range normally considered a cost-effective use of NHS resources.
12		Otsuka Pharmaceuticals UK Ltd.	**<u>Updated base case following draft guidance</u>** Including the revised PAS and aligned with the discussion at the committee meeting, we present an updated base case cost-effectiveness analysis, which incorporates revisions as follows: • **Use of the random effects network meta-analysis (NMA):** In line with the committee's preference the base case has been updated to include the random effects NMA rather than the fixed effects NMA. As stated in the draft guidance, both the company and EAG agreed that the fixed and random effect analyses produced similar results. However, inclusion of this analysis provides a better approximation of relative effects, as the more credible random effects model better captures the uncertainty given the heterogenous evidence base identified for the NMA. Furthermore, we have provided an updated probabilistic sensitivity analysis (PSA) to further capture and explore any uncertainty around model inputs and the impact of the wider confidence intervals with the random effects network meta-analysis on the base case results for all comparators. • **Discontinuation for non-trial comparators:** As stated in our submission, there is a lack of published evidence available regarding the time to treatment discontinuation (TTD) for comparators not included in the clinical trials for voclosporin. In the absence of this data, it was previously assumed that there was no treatment discontinuation for non-trial comparators in the base case cost-effectiveness model. In line with requests from the EAG we provided several exploratory scenario analyses of TTD curves during clarification questions. Furthermore, our assumptions aligned with the EAG's preferred base case assumptions at technical engagement where applying TTD for non-trial comparators was presented as an exploratory rather than preferred analysis. However, we acknowledge the EAG and committee concerns and the base case has been updated to assume that in the absence of data, the TTD curve for voclosporin + MMF can be applied to the non-trial comparators to determine discontinuation and associated treatment costs. As we did at clarification questions, we also explored incorporating the TTD curve for MMF and present this scenario in Comment 4. • **Updated kidney transplant rate:** As outlined in our submission, clinical advice to the company was that 90% of patients of LN receive a transplant within two years – likely a higher rate than other CKD patients, as the average LN patient is younger and therefore more suitable for receiving a transplant. However, in line with the draft guidance, the estimated proportion of people with stage 5 CKD (ESRD) has been updated to align with the EAG's preferred assumed rate of 65% over 2 years based on clinical advice. • Long-term treatment effect assumptions in the base case remain the same as those included in the model provided at technical engagement, but we acknowledge the committee's concerns regarding uncertainty and explore this further in Comment 4. Incorporating the revisions and assumptions outlined above results in the ICERs outlined in **Table 1**.	The committee discussed the changes to the company base case following draft guidance. The committee acknowledged the efforts of the company to address its concerns and implement its preferences for some key issues. See sections 3.7, 3.8, and 3.9 of the final draft guidance for committee conclusions on each of the company base case updates. See also section 3.12 for the committee's conclusion on cost-effectiveness estimates.

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Table 1 - Revised base case results (discounted)

Technologies	Total			Incremental			ICER (£/QALY)*
	Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs	
VCS + MMF	[redacted]	[redacted]	[redacted]	-	-	-	-
MMF	[redacted]	17.40	12.90	[redacted]	[redacted]	[redacted]	£24,267
L-CYC	[redacted]	16.77	12.41	[redacted]	[redacted]	[redacted]	£6,522
H-CYC	[redacted]	16.64	12.32	[redacted]	[redacted]	[redacted]	£5,450
AZA	[redacted]	17.31	12.83	[redacted]	[redacted]	[redacted]	£20,284
RTX + MMF	[redacted]	17.79	13.20	[redacted]	[redacted]	[redacted]	£25,432
TAC + MMF	[redacted]	17.44	12.93	[redacted]	[redacted]	[redacted]	£20,541
TAC	[redacted]	17.50	12.98	[redacted]	[redacted]	[redacted]	£20,289

*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

Sensitivity analyses around revised base case

Probabilistic sensitivity analysis

Table 2 - 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]	12.90	[redacted]	£24,267	£23,575
L-CYC	[redacted]	[redacted]	12.41	[redacted]	£6,522	£6,377
H-CYC	[redacted]	[redacted]	12.32	[redacted]	£5,450	£5,430
AZA	[redacted]	[redacted]	12.83	[redacted]	£20,284	£21,724
RTX + MMF	[redacted]	[redacted]	13.20	[redacted]	£25,432	£24,248
TAC + MMF	[redacted]	[redacted]	12.93	[redacted]	£20,541	£18,925
TAC	[redacted]	[redacted]	12.98	[redacted]	£20,289	£18,668

*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

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			Figure 1 - Scatter plot of PSA results for total discounted costs and QALYs  CYC = cyclophosphamide; MMF = mycophenolate mofetil; PSA = probabilistic sensitivity analysis; QALY = quality-adjusted life year **Figure 2 - Scatter plot of PSA results for incremental discounted costs and QALYs (voclosporin + MMF vs comparators)**	

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			 CYC = cyclophosphamide; MMF = mycophenolate mofetil; PSA = probabilistic sensitivity analysis; QALY = quality-adjusted life year **Figure 3 - Cost-effectiveness acceptability curve**	

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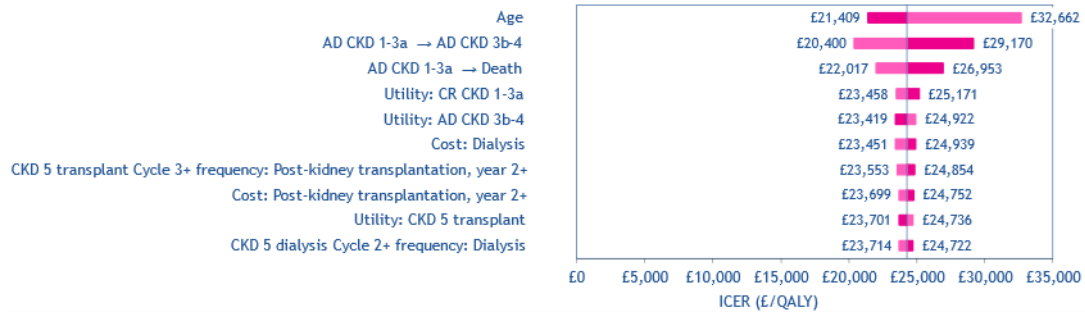
			 CYC = cyclophosphamide; MMF = mycophenolate mofetil; QALY = quality-adjusted life year *Deterministic sensitivity analysis* **Figure 4 - DSA tornado diagram - incremental costs for voclosporin + MMF vs MMF**	

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			 AD = active disease; CKD = chronic kidney disease; MMF = mycophenolate mofetil **Figure 5 - DSA tornado diagram - incremental QALYs for voclosporin + MMF vs MMF**	

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			[redacted] AD = active disease; CKD = chronic kidney disease; CR = complete response; DSA = deterministic sensitivity analysis; PR = partial response; QALY = quality-adjusted life year **Figure 6 - DSA tornado diagram – ICER (£/QALY) for voclosporin + MMF vs MMF**  AD = active disease; CKD = chronic kidney disease; CR = complete response; QALY = quality-adjusted life year	
13		Otsuka Pharmaceuticals UK Ltd.	**Exploring uncertainty in the model** We have carefully considered the comments in the draft guidance regarding uncertainties with the model structure. We would like to emphasise that when considering these uncertainties, it is important to remember that LN is a rare disease. Although there is no universally accepted definition of what constitutes a rare disease,	Thank you for your comment. The committee acknowledged the efforts of the company to address the uncertainties it raised,

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when considered separately to SLE, LN has a prevalence lower than the rare disease threshold (<5 in 10,000 people) defined by the European Medicines Agency (EMA 2022). There are inherent challenges in studying medicines for rare diseases, including small patient populations in studies and consequently, inherent limitations and uncertainties in the corresponding evidence package (Clarke 2021). This was also discussed in the original submission which highlighted that aspects of LN introduce uncertainties to the economic analysis, including the limited published clinical and economic data regarding LN and comparators, variation in clinical practice in terms of treatment duration, and uncertainty related to long-term treatment effects. However, we appreciate the committee's concerns, and to further help explore and understand uncertainty in the model and to support decision-making, we have conducted additional scenario analyses as follows:

• Discontinuation: As discussed in Comment 3, in the revised base case the TTD curve for voclosporin + MMF is applied to non-trial comparators to determine discontinuation and associated treatment costs. We have also considered and present in Table 3 the scenario of applying the TTD for MMF to non-trial comparators. We consider incorporation of TTD for voclosporin + MMF the most appropriate assumption as several of the non-trial comparators are combination therapies with MMF and discontinuation may be best captured by using the combination therapy TTD.

Table 3 – Scenario analysis with TTD for MMF used for non-trial comparators
<table>
<tr><th rowspan="2">Technologies</th><th colspan="2">Total costs (£)</th><th colspan="2">Total QALYs</th><th colspan="2">ICER (£/QALY)*</th></tr>
<tr><th>Base case</th><th>Scenario</th><th>Base case</th><th>Scenario</th><th>Base case</th><th>Scenario</th></tr>
<tr><td>VCS + MMF</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>-</td><td>-</td></tr>
<tr><td>MMF</td><td>[redacted]</td><td>[redacted]</td><td>12.90</td><td>[redacted]</td><td>£24,267</td><td>£24,267</td></tr>
<tr><td>L-CYC</td><td>[redacted]</td><td>[redacted]</td><td>12.41</td><td>[redacted]</td><td>£6,522</td><td>£6,651</td></tr>
<tr><td>H-CYC</td><td>[redacted]</td><td>[redacted]</td><td>12.32</td><td>[redacted]</td><td>£5,450</td><td>£5,566</td></tr>
<tr><td>AZA</td><td>[redacted]</td><td>[redacted]</td><td>12.83</td><td>[redacted]</td><td>£20,284</td><td>£20,294</td></tr>
<tr><td>RTX + MMF</td><td>[redacted]</td><td>[redacted]</td><td>13.20</td><td>[redacted]</td><td>£25,432</td><td>£28,397</td></tr>
<tr><td>TAC + MMF</td><td>[redacted]</td><td>[redacted]</td><td>12.93</td><td>[redacted]</td><td>£20,541</td><td>£20,796</td></tr>
<tr><td>TAC</td><td>[redacted]</td><td>[redacted]</td><td>12.98</td><td>[redacted]</td><td>£20,289</td><td>£20,650</td></tr>
</table>
*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

• Treatment duration: In line with the input from clinical experts in the draft guidance, and as requested by the committee, we have conducted additional scenario analyses to explore a range of different treatment durations for voclosporin (Tables 4 and 5). We have considered treatment durations for 12 months (in line with UK clinical expert opinion in the draft guidance), 18 months (in line with the scenario provided in our original submission) and 36 months (presented in the base case).

In the 18-month treatment duration scenario presented in Table 5, treatment duration and long-term treatment effect assumptions are aligned with the base case assumptions adjusted for the treatment duration e.g. all patients for voclosporin + MMF and all comparators receive treatment for 18 months apart from tacrolimus-containing regimens (which always have a 12-month treatment duration in line
</td><td>including the provision of multiple scenario analyses. The committee considered treatment discontinuation, treatment duration, long-term treatment effects, response for CKD states 3b-4, attrition bias in AURORA trials, and transition probabilities derived via the count method. See sections 3.6, 3.8, 3.9, 3.10 and 3.11 of final draft guidance for more information.</td></tr>
</table>

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<tr><th>Comment number</th><th>Type of stakeholder</th><th>Organisation name</th><th>Stakeholder comment
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<tr><td></td><td></td><td></td><td>
with expert clinician feedback), treatment waning effects are applied as per the base case but patient health state transition probabilities wane to the midpoint of those recorded within the AURORA trials at Months 12 and 18 (i.e. the last two periods of treatment). It is important to note that the assumptions are different for the 12-month treatment duration scenario (Table 4) as due to the limitations of the 6-month transitions (patients start in AD and are assumed not to move out of CR and PR in the first 6 months), long-term transition probabilities had to be based purely on the 12-month transitions rather than the last two periods of treatment.

Table 4 – Scenario analysis with adjustment of treatment duration to 12 months for all regimens
<table>
<tr><th rowspan="2">Technologies</th><th colspan="2">Total costs (£)</th><th colspan="2">Total QALYs</th><th colspan="2">ICER (£/QALY)*</th></tr>
<tr><th>Base case</th><th>Scenario</th><th>Base case</th><th>Scenario</th><th>Base case</th><th>Scenario</th></tr>
<tr><td>VCS + MMF</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>-</td><td>-</td></tr>
<tr><td>MMF</td><td>[redacted]</td><td>[redacted]</td><td>12.90</td><td>[redacted]</td><td>£24,267</td><td>£3,342</td></tr>
<tr><td>L-CYC</td><td>[redacted]</td><td>[redacted]</td><td>12.41</td><td>[redacted]</td><td>£6,522</td><td>Dominant</td></tr>
<tr><td>H-CYC</td><td>[redacted]</td><td>[redacted]</td><td>12.32</td><td>[redacted]</td><td>£5,450</td><td>Dominant</td></tr>
<tr><td>AZA</td><td>[redacted]</td><td>[redacted]</td><td>12.83</td><td>[redacted]</td><td>£20,284</td><td>£1,986</td></tr>
<tr><td>RTX + MMF</td><td>[redacted]</td><td>[redacted]</td><td>13.20</td><td>[redacted]</td><td>£25,432</td><td>Dominant</td></tr>
<tr><td>TAC + MMF</td><td>[redacted]</td><td>[redacted]</td><td>12.93</td><td>[redacted]</td><td>£20,541</td><td>Dominant</td></tr>
<tr><td>TAC</td><td>[redacted]</td><td>[redacted]</td><td>12.98</td><td>[redacted]</td><td>£20,289</td><td>Dominant</td></tr>
</table>
*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 5 – Scenario analysis with adjustment of treatment duration to 18 months (apart from TAC-containing regimens)
<table>
<tr><th rowspan="2">Technologies</th><th colspan="2">Total costs (£)</th><th colspan="2">Total QALYs</th><th colspan="2">ICER (£/QALY)*</th></tr>
<tr><th>Base case</th><th>Scenario</th><th>Base case</th><th>Scenario</th><th>Base case</th><th>Scenario</th></tr>
<tr><td>VCS + MMF</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>-</td><td>-</td></tr>
<tr><td>MMF</td><td>[redacted]</td><td>[redacted]</td><td>12.90</td><td>[redacted]</td><td>£24,267</td><td>£7,724</td></tr>
<tr><td>L-CYC</td><td>[redacted]</td><td>[redacted]</td><td>12.41</td><td>[redacted]</td><td>£6,522</td><td>Dominant</td></tr>
<tr><td>H-CYC</td><td>[redacted]</td><td>[redacted]</td><td>12.32</td><td>[redacted]</td><td>£5,450</td><td>Dominant</td></tr>
<tr><td>AZA</td><td>[redacted]</td><td>[redacted]</td><td>12.83</td><td>[redacted]</td><td>£20,284</td><td>£5,896</td></tr>
<tr><td>RTX + MMF</td><td>[redacted]</td><td>[redacted]</td><td>13.20</td><td>[redacted]</td><td>£25,432</td><td>Dominant</td></tr>
<tr><td>TAC + MMF</td><td>[redacted]</td><td>[redacted]</td><td>12.93</td><td>[redacted]</td><td>£20,541</td><td>£3,906</td></tr>
<tr><td>TAC</td><td>[redacted]</td><td>[redacted]</td><td>12.98</td><td>[redacted]</td><td>£20,289</td><td>£2,215</td></tr>
</table>
*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
</td><td></td></tr>
</table>

<table>
<tr><th>Comment number</th><th>Type of stakeholder</th><th>Organisation name</th><th>Stakeholder comment
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<tr><td></td><td></td><td></td><td>
Due to limitations and the associated uncertainty in the 12-month treatment duration presented above, we also explored a scenario where the 12 months of the AURORA 1 data were used to inform transition probabilities for the first 12 months, with the assumption that patients cannot respond after 12 months and can only move from response states to active disease, with no further movement between CR and PR either. In order to generate this 'AURORA 1 only' scenario, we identified and explored scenarios using the following trial and literature values for the transition from response states to AD (Table 6).

Table 6 – Sources for transition from response to AD after 12 months
<table>
<tr><th>Source</th><th>Value</th><th>Details</th></tr>
<tr><td>Input from trial transitions</td><td>[redacted]</td><td>MMF long-term trial transitions, CR to AD, in the revised base case</td></tr>
<tr><td>Nee et al. 2015</td><td>1.85%</td><td>Reported as the 6-month transition in the MMF remission arm to relapse</td></tr>
<tr><td>Yap et al. 2017</td><td>0.94%</td><td>Reports a 9% relapse over 5 years</td></tr>
</table>
Each of these values is applied in individual scenarios below (Tables 7-9). We have explored an assumption based on the AURORA 1 data (Table 7), as well as two exploratory analyses (Tables 8 and 9) based on the literature. We note that the ICERs for voclosporin + MMF remain well below the cost-effectiveness threshold of £30,000 per QALY with the assumption based on AURORA 1, and that for the two analyses based on literature values, patients transition out of response more slowly than in the clinical trial data used in the base case – voclosporin + MMF dominates all other treatments when the literature values are applied. However, we maintain that as we have clinical trial data from AURORA 2 available to support these transitions, the most robust and conservative approach is to apply the data from the clinical trials as used in our base case.

Table 7 – Scenario analysis with adjustment of treatment duration to 12 months with transition out of response as in long-term MMF transitions, CR to AD, in base case
<table>
<tr><th rowspan="2">Technologies</th><th colspan="2">Total costs (£)</th><th colspan="2">Total QALYs</th><th colspan="2">ICER (£/QALY)*</th></tr>
<tr><th>Base case</th><th>Scenario</th><th>Base case</th><th>Scenario</th><th>Base case</th><th>Scenario</th></tr>
<tr><td>VCS + MMF</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>-</td><td>-</td></tr>
<tr><td>MMF</td><td>[redacted]</td><td>[redacted]</td><td>12.90</td><td>[redacted]</td><td>£24,267</td><td>£6,219</td></tr>
<tr><td>L-CYC</td><td>[redacted]</td><td>[redacted]</td><td>12.41</td><td>[redacted]</td><td>£6,522</td><td>Dominant</td></tr>
<tr><td>H-CYC</td><td>[redacted]</td><td>[redacted]</td><td>12.32</td><td>[redacted]</td><td>£5,450</td><td>Dominant</td></tr>
<tr><td>AZA</td><td>[redacted]</td><td>[redacted]</td><td>12.83</td><td>[redacted]</td><td>£20,284</td><td>£4,894</td></tr>
<tr><td>RTX + MMF</td><td>[redacted]</td><td>[redacted]</td><td>13.20</td><td>[redacted]</td><td>£25,432</td><td>Dominant</td></tr>
<tr><td>TAC + MMF</td><td>[redacted]</td><td>[redacted]</td><td>12.93</td><td>[redacted]</td><td>£20,541</td><td>£1,813</td></tr>
<tr><td>TAC</td><td>[redacted]</td><td>[redacted]</td><td>12.98</td><td>[redacted]</td><td>£20,289</td><td>£366</td></tr>
</table>
*ICER for VCS + MMF vs comparator
</td><td></td></tr>
</table>

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment

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 8 – Scenario analysis with adjustment of treatment duration to 12 months with transition out of response as in Nee et al. 2015

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]	12.90	[redacted]	£24,267	Dominant
L-CYC	[redacted]	[redacted]	12.41	[redacted]	£6,522	Dominant
H-CYC	[redacted]	[redacted]	12.32	[redacted]	£5,450	Dominant
AZA	[redacted]	[redacted]	12.83	[redacted]	£20,284	Dominant
RTX + MMF	[redacted]	[redacted]	13.20	[redacted]	£25,432	Dominant
TAC + MMF	[redacted]	[redacted]	12.93	[redacted]	£20,541	Dominant
TAC	[redacted]	[redacted]	12.98	[redacted]	£20,289	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

Table 9 – Scenario analysis with adjustment of treatment duration to 12 months with transition out of response as in Yap et al. 2017

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]	12.90	[redacted]	£24,267	Dominant
L-CYC	[redacted]	[redacted]	12.41	[redacted]	£6,522	Dominant
H-CYC	[redacted]	[redacted]	12.32	[redacted]	£5,450	Dominant
AZA	[redacted]	[redacted]	12.83	[redacted]	£20,284	Dominant
RTX + MMF	[redacted]	[redacted]	13.20	[redacted]	£25,432	Dominant
TAC + MMF	[redacted]	[redacted]	12.93	[redacted]	£20,541	Dominant
TAC	[redacted]	[redacted]	12.98	[redacted]	£20,289	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

In summary, it is clear from the scenario analyses shown that when the treatment duration of

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voclosporin + MMF and other treatments are varied from 36 months to shorter durations such as 12 and 18 months, the ICERs for voclosporin + MMF vs all comparators become considerably more favourable than in the base case. However, we maintain that a treatment duration of a maximum of 36 months is the most appropriate for inclusion in the base case as this is in line with the availability of the AURORA trial data and the clinical advice received by the EAG and the company. It is also important to note that even with a 36-month treatment duration in the base case, not all patients receive 36 months of treatment in the model as TTD curves are applied in line with the AURORA trial data. Furthermore, these scenarios, though uncertain, suggest that the base case treatment duration is a conservative assumption and that ICERs are considerably more favourable for voclosporin + MMF at the shorter treatment durations suggested by clinical experts and noted in the draft guidance.

• Long-term treatment effect extrapolations: The committee noted that there is high uncertainty with both the company's and EAG's approaches to the long-term treatment effect extrapolations. We agree with the committee's acknowledgement that modelling repeating cycles of induction and maintenance would be difficult to construct. We also believe that this would add further uncertainty, and highlight that no precedent or approach for this has been identified in our literature reviews to inform any update to the model.

Given the inherent limitations of the available data and literature for a rare disease such as LN, there will be uncertainty in any model. However, to provide reassurance regarding output validity from our model, it should be noted that the long-term outcomes, in terms of progression to ESRD, in the MMF arm can be validated against external literature, as demonstrated in Table 10, which suggest that the long-term assumptions are appropriate for decision-making.

Table 10 - Validation of model transitions with literature sources
<table>
<tr><th>Percentage of patients in ESRD</th><th>Tektonidou 2016</th><th>Gisca 2021</th><th>Model for MMF</th></tr>
<tr><td>After 5 years</td><td>5.74%</td><td>5.02%</td><td>[redacted]</td></tr>
<tr><td>After 10 years</td><td>9.98%</td><td>10.96%</td><td>[redacted]</td></tr>
</table>
Abbreviations: ESRD = end-stage renal disease; MMF = mycophenolate mofetil.

We have also conducted additional scenarios in order to explore uncertainty in the long-term treatment effect extrapolation assumption included in the model base case. We believe that the most appropriate way to incorporate a relative effect of 0 between voclosporin + MMF and MMF after 36 months is to apply the MMF long-term transitions to both arms (as opposed to the EAG's suggestion of applying the average long-term transition probabilities from voclosporin + MMF and MMF to both arms). We therefore present a scenario (Table 11) in which the MMF long-term transitions are also applied to the voclosporin + MMF arm. We note that even in this conservative scenario voclosporin + MMF remains cost-effective vs all comparators with the exception of rituximab + MMF. We note that this is an exploratory analysis and that, as discussed in Comment 5, rituximab + MMF is unlikely to be an appropriate comparator as it is reserved for patients with non-responding/refractory disease.
</td><td></td></tr>
</table>

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Table 11 – Scenario analysis with application of the MMF long-term transitions to VCS+MMF (which assumes the relative effect after 36 months is 0)

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]	12.90	[redacted]	£24,267	£29,973
L-CYC	[redacted]	[redacted]	12.41	[redacted]	£6,522	£7,772
H-CYC	[redacted]	[redacted]	12.32	[redacted]	£5,450	£6,503
AZA	[redacted]	[redacted]	12.83	[redacted]	£20,284	£24,636
RTX + MMF	[redacted]	[redacted]	13.20	[redacted]	£25,432	£42,337
TAC + MMF	[redacted]	[redacted]	12.93	[redacted]	£20,541	£25,949
TAC	[redacted]	[redacted]	12.98	[redacted]	£20,289	£26,300

We note that there are small differences in the 'Total costs' for some of the comparators in this scenario vs. the base case. This is because the time horizon of the model is determined by the point at which <0.1% of the VCS+MMF patient population remains alive, and in the scenario the time horizon of the model is reduced by a cycle (6 months).
*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

Alongside this scenario, we restate that the faster onset of action for voclosporin + MMF vs MMF alone means that there is an earlier decrease in proteinuria and patients spend less time in active disease, therefore limiting the damage incurred to their kidneys. This is supported by several robust studies which have shown that an early decrease in proteinuria predicts good long-term renal outcomes (Parodis 2022, Tamirou 2016). We have explored an alternative way of implementing the EAG's approach of assuming voclosporin + MMF and MMF alone are equal for all health states but maintain that this assumption does not reflect the faster onset of action of voclosporin, and should therefore be considered conservative.

- **Response in CKD stages 3b-4:** As per our original submission, there is a lack of data relating to response in patients in CKD stages 3b-4. In the absence of literature values and following consultation with expert clinicians who advised that patients achieving response in this progressed stage can be as low as 2.5% it was assumed that this transition could be set to 0%. Clinical experts consulted by the EAG agreed that only a small number of patients in CKD stages 3b-4 would have a response, but that it would not be zero. The committee noted that uncertainty could be further reduced if the restriction in the model structure which stops people with CKD stages 3b to 4 from moving to response was amended, because this would better reflect clinical practice.

  In response to the comments from the EAG and committee, we have conducted further consultations with expert clinicians with the aim of further reducing uncertainty related to the response in CKD stages 3b-4. From these discussions, an assumption of 0% was stated to be reasonable (emphasising the

<table>
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uncertainty in including this transition) and it was not possible to source an estimate of the proportion of patients who would return from CR to AD in CKD stages 3b-4. Given the evident uncertainty associated with these estimates we have not included response in patients in CKD stages 3b-4 in the base case. However, we did conduct a series of scenario analyses (Tables 12-14) to explore including CKD stages 3b-4 in the model in line with the committee's comments.
We explored three scenarios with 2.5% of patients achieving response from CKD stages 3b-4 per 6-month cycle, one where 2.5% achieved CR, one where 2.5% achieved PR and one where 1.25% achieved CR and 1.25% achieved PR. As outlined above, it was not possible to source a value for patients returning from response to AD in CKD stages 3b-4 so for the purposes of these scenarios we assumed that these transitions are equal to the long-term transitions for these states for MMF.

Table 12 – Scenario analysis with assumption of 2.5% of patients achieving CR from CKD stages 3b-4
<table>
<tr><th rowspan="2">Technologies</th><th colspan="2">Total costs (£)</th><th colspan="2">Total QALYs</th><th colspan="2">ICER (£/QALY)*</th></tr>
<tr><th>Base case</th><th>Scenario</th><th>Base case</th><th>Scenario</th><th>Base case</th><th>Scenario</th></tr>
<tr><td>VCS + MMF</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>-</td><td>-</td></tr>
<tr><td>MMF</td><td>[redacted]</td><td>[redacted]</td><td>12.90</td><td>[redacted]</td><td>£24,267</td><td>£24,605</td></tr>
<tr><td>L-CYC</td><td>[redacted]</td><td>[redacted]</td><td>12.41</td><td>[redacted]</td><td>£6,522</td><td>£6,876</td></tr>
<tr><td>H-CYC</td><td>[redacted]</td><td>[redacted]</td><td>12.32</td><td>[redacted]</td><td>£5,450</td><td>£5,808</td></tr>
<tr><td>AZA</td><td>[redacted]</td><td>[redacted]</td><td>12.83</td><td>[redacted]</td><td>£20,284</td><td>£20,627</td></tr>
<tr><td>RTX + MMF</td><td>[redacted]</td><td>[redacted]</td><td>13.20</td><td>[redacted]</td><td>£25,432</td><td>£25,802</td></tr>
<tr><td>TAC + MMF</td><td>[redacted]</td><td>[redacted]</td><td>12.93</td><td>[redacted]</td><td>£20,541</td><td>£20,891</td></tr>
<tr><td>TAC</td><td>[redacted]</td><td>[redacted]</td><td>12.98</td><td>[redacted]</td><td>£20,289</td><td>£20,634</td></tr>
</table>
*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 13 –Scenario analysis with assumption of 2.5% of patients achieving PR from CKD stages 3b-4
<table>
<tr><th rowspan="2">Technologies</th><th colspan="2">Total costs (£)</th><th colspan="2">Total QALYs</th><th colspan="2">ICER (£/QALY)*</th></tr>
<tr><th>Base case</th><th>Scenario</th><th>Base case</th><th>Scenario</th><th>Base case</th><th>Scenario</th></tr>
<tr><td>VCS + MMF</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>-</td><td>-</td></tr>
<tr><td>MMF</td><td>[redacted]</td><td>[redacted]</td><td>12.90</td><td>[redacted]</td><td>£24,267</td><td>£24,385</td></tr>
<tr><td>L-CYC</td><td>[redacted]</td><td>[redacted]</td><td>12.41</td><td>[redacted]</td><td>£6,522</td><td>£6,651</td></tr>
<tr><td>H-CYC</td><td>[redacted]</td><td>[redacted]</td><td>12.32</td><td>[redacted]</td><td>£5,450</td><td>£5,581</td></tr>
<tr><td>AZA</td><td>[redacted]</td><td>[redacted]</td><td>12.83</td><td>[redacted]</td><td>£20,284</td><td>£20,405</td></tr>
<tr><td>RTX + MMF</td><td>[redacted]</td><td>[redacted]</td><td>13.20</td><td>[redacted]</td><td>£25,432</td><td>£25,567</td></tr>
<tr><td>TAC + MMF</td><td>[redacted]</td><td>[redacted]</td><td>12.93</td><td>[redacted]</td><td>£20,541</td><td>£20,667</td></tr>
<tr><td>TAC</td><td>[redacted]</td><td>[redacted]</td><td>12.98</td><td>[redacted]</td><td>£20,289</td><td>£20,413</td></tr>
</table>
*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;
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<tr><th>Comment number</th><th>Type of stakeholder</th><th>Organisation name</th><th>Stakeholder comment
Please insert each new comment in a new row</th><th>NICE Response
Please respond to each comment</th></tr>
<tr><td></td><td></td><td></td><td>
PSA = probabilistic sensitivity analysis; QALY = quality-adjusted life year; RTX = rituximab; TAC = tacrolimus; VCS = voclosporin

Table 14 – Scenario analysis with assumption of 1.25% of patients achieving CR and 1.25% of patients achieving PR from CKD stages 3b-4
<table>
<tr><th rowspan="2">Technologies</th><th colspan="2">Total costs (£)</th><th colspan="2">Total QALYs</th><th colspan="2">ICER (£/QALY)*</th></tr>
<tr><th>Base case</th><th>Scenario</th><th>Base case</th><th>Scenario</th><th>Base case</th><th>Scenario</th></tr>
<tr><td>VCS + MMF</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>-</td><td>-</td></tr>
<tr><td>MMF</td><td>[redacted]</td><td>[redacted]</td><td>12.90</td><td>[redacted]</td><td>£24,267</td><td>£24,497</td></tr>
<tr><td>L-CYC</td><td>[redacted]</td><td>[redacted]</td><td>12.41</td><td>[redacted]</td><td>£6,522</td><td>£6,766</td></tr>
<tr><td>H-CYC</td><td>[redacted]</td><td>[redacted]</td><td>12.32</td><td>[redacted]</td><td>£5,450</td><td>£5,696</td></tr>
<tr><td>AZA</td><td>[redacted]</td><td>[redacted]</td><td>12.83</td><td>[redacted]</td><td>£20,284</td><td>£20,518</td></tr>
<tr><td>RTX + MMF</td><td>[redacted]</td><td>[redacted]</td><td>13.20</td><td>[redacted]</td><td>£25,432</td><td>£25,686</td></tr>
<tr><td>TAC + MMF</td><td>[redacted]</td><td>[redacted]</td><td>12.93</td><td>[redacted]</td><td>£20,541</td><td>£20,781</td></tr>
<tr><td>TAC</td><td>[redacted]</td><td>[redacted]</td><td>12.98</td><td>[redacted]</td><td>£20,289</td><td>£20,525</td></tr>
</table>
*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

The results in Tables 12-14, though highly uncertain, suggest that incorporating these transitions do not have a large impact on the ICER and voclosporin + MMF remains a cost-effective treatment option even when response in CKD 3b-4 is approximated and included in the model.

• Attrition bias: In line with the committee's comments in the draft guidance, we have considered whether there is any possible attrition bias in the AURORA 2 data (that is, that discontinuation may not be random and there may be systematic differences between the population that discontinued AURORA 1 and the population that continued enrolment to AURORA 2). We acknowledge the attrition between the trials but note that all study personnel, site staff, monitors and patients remained blinded to study treatment for all patients in AURORA 2, which decreases the risk of any bias. It is also important to consider that AURORA 2 was an extension study, with AURORA 1 always designed with a view of allowing patients to exit in a controlled way when convenient. We also note and agree with the EAG's comments that the rate of and reasons for discontinuation were comparable across the trial arms, reducing the risk of bias.

However, in line with the committee's suggestions and requests in the draft guidance we have considered a series of approaches to understand any uncertainty associated with attrition between AURORA 1 and AURORA 2. In order to do this, we performed new analyses of the data from the AURORA clinical trials. This involved revisiting the patient-level data to understand and re-analyse the data for the 94 patients, 47 per treatment arm, who completed AURORA 1 and then did not enter AURORA 2. Transition probabilities were then adjusted and modelled in scenarios as requested in the draft guidance. The explicit number of patients used to calculate each transition is provided in the
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<tr><th>Comment number</th><th>Type of stakeholder</th><th>Organisation name</th><th>Stakeholder comment
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model to support transparency. We note that 3 patients who completed AURORA 1 were marked as ‘unknown’ at last follow up (as biomarkers required for response assessment were not recorded) and were therefore excluded from our analyses.
Three exploratory scenarios were considered as follows:
LOCF – In this scenario it was assumed that for both voclosporin + MMF and MMF groups of patients who completed AURORA 1 but did not enter AURORA 2 we could apply last observation carried forward (LOCF) from Month 12 for Months 18-36 (Table 15). We consider this the most logical of our exploratory scenarios as the same assumption is applied to both treatment groups and trial data from AURORA 1 is carried forward to inform the modelling of these patients. We note that with these assumptions, voclosporin + MMF remains cost-effective vs all comparators with the exception of rituximab + MMF, and the ICER vs MMF is actually more favourable than in the base case. As noted above and in Comment 5, rituximab + MMF is unlikely to be an appropriate comparator as it is reserved for patients with non-responding/refractory disease.

Table 15 – Scenario analysis with assumption of LOCF for patients who completed AURORA 1 but did not enter AURORA 2
<table>
<tr><th rowspan="2">Technologies</th><th colspan="2">Total costs (£)</th><th colspan="2">Total QALYs</th><th colspan="2">ICER (£/QALY)*</th></tr>
<tr><th>Base case</th><th>Scenario</th><th>Base case</th><th>Scenario</th><th>Base case</th><th>Scenario</th></tr>
<tr><td>VCS + MMF</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>-</td><td>-</td></tr>
<tr><td>MMF</td><td>[redacted]</td><td>[redacted]</td><td>12.90</td><td>[redacted]</td><td>£24,267</td><td>£21,701</td></tr>
<tr><td>L-CYC</td><td>[redacted]</td><td>[redacted]</td><td>12.41</td><td>[redacted]</td><td>£6,522</td><td>£7,199</td></tr>
<tr><td>H-CYC</td><td>[redacted]</td><td>[redacted]</td><td>12.32</td><td>[redacted]</td><td>£5,450</td><td>£5,433</td></tr>
<tr><td>AZA</td><td>[redacted]</td><td>[redacted]</td><td>12.83</td><td>[redacted]</td><td>£20,284</td><td>£18,509</td></tr>
<tr><td>RTX + MMF</td><td>[redacted]</td><td>[redacted]</td><td>13.20</td><td>[redacted]</td><td>£25,432</td><td>£31,007</td></tr>
<tr><td>TAC + MMF</td><td>[redacted]</td><td>[redacted]</td><td>12.93</td><td>[redacted]</td><td>£20,541</td><td>£18,212</td></tr>
<tr><td>TAC</td><td>[redacted]</td><td>[redacted]</td><td>12.98</td><td>[redacted]</td><td>£20,289</td><td>£18,746</td></tr>
</table>
*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

As requested by the committee, we also considered exploratory scenarios which assumed people who had voclosporin + MMF and were lost to follow-up were non-responders (i.e. moving to AD), while people who had MMF were responders (i.e. moving to CR), as well as different variations of these. We have presented these scenarios in line with the committee’s suggestion but consider them exploratory and not plausible as we apply very different assumptions to both treatment arms which is not reflective of the data captured within the AURORA 2 clinical trial.
AD for voclosporin + MMF/CR for MMF – As suggested in the draft guidance, in this scenario it was assumed that for the patients who did not enter AURORA 2 that patients in the MMF group moved to complete response and the voclosporin + MMF patients moved to active disease (Table 16). As data from the MMF group is used to inform several of the transitions for the non-trial comparators, it is clear
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Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment

that these assumptions also heavily favour the other comparators as well as MMF. We consider the results of this scenario to be highly implausible as treatments such as tacrolimus monotherapy dominate voclosporin + MMF in this scenario but were found to have significantly lower efficacy in terms of CR than voclosporin + MMF in the NMA.

Table 16 – Scenario analysis with assumption of AD for voclosporin + MMF and CR for MMF, for patients who completed AURORA 1 but did not enter AURORA 2

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]	12.90	[redacted]	£24,267	Dominated
L-CYC	[redacted]	[redacted]	12.41	[redacted]	£6,522	£1,596,495
H-CYC	[redacted]	[redacted]	12.32	[redacted]	£5,450	£294,418
AZA	[redacted]	[redacted]	12.83	[redacted]	£20,284	Dominated
RTX + MMF	[redacted]	[redacted]	13.20	[redacted]	£25,432	Dominated
TAC + MMF	[redacted]	[redacted]	12.93	[redacted]	£20,541	Dominated
TAC	[redacted]	[redacted]	12.98	[redacted]	£20,289	Dominated

*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

CR for voclosporin + MMF/AD for MMF – We also considered a scenario in which it was assumed that for the patients who did not enter AURORA 2 that patients in the MMF group moved to active disease and the voclosporin + MMF patients moved to complete response (Table 17).

Table 17 – Scenario analysis with assumption of CR for voclosporin + MMF/AD for MMF, for patients who completed AURORA 1 but did not enter AURORA 2

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]	12.90	[redacted]	£24,267	£5,644
L-CYC	[redacted]	[redacted]	12.41	[redacted]	£6,522	£1,246
H-CYC	[redacted]	[redacted]	12.32	[redacted]	£5,450	£847
AZA	[redacted]	[redacted]	12.83	[redacted]	£20,284	£4,949
RTX + MMF	[redacted]	[redacted]	13.20	[redacted]	£25,432	Dominant
TAC + MMF	[redacted]	[redacted]	12.93	[redacted]	£20,541	£3,684
TAC	[redacted]	[redacted]	12.98	[redacted]	£20,289	£2,997

*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;

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			PSA = probabilistic sensitivity analysis; QALY = quality-adjusted life year; RTX = rituximab; TAC = tacrolimus; VCS = voclosporin As discussed above, the scenarios presented in Tables 16 and 17 are not plausible and show that when vastly different assumptions are applied to the voclosporin + MMF and MMF treatment groups the ICERs, as may be expected, are shown to be considerably more or considerably less favourable for voclosporin + MMF depending on which way around the assumptions are applied. However, we have aimed to reduce the uncertainty that could be associated with any attrition between trials and in our most plausible scenario (LOCF) we note that voclosporin + MMF remains a cost-effective treatment option vs MMF and that the ICERs are similar to those in the base case. *Count method* In addition to the above points, the EAG stated that there is uncertainty in the transition probabilities for voclosporin + MMF and MMF, due to small sample sizes associated with the 'count method' used to derive transitions from the clinical trial data. We appreciate that there is uncertainty associated with this method but maintain that this is the best and most appropriate approach available and note: • Other approaches were explored during the development of the cost-effectiveness analysis. As stated in our original submission, we explored the alternative approach of calculating the transition probabilities by fitting a multinomial logit model per transition per health state. However, this was not incorporated into the model as the multinomial logit method provided unrealistic outcomes which did not align with the trial data. In response to questions from the EAG we provided further detail regarding this method in our response to clarification questions, including a table which showed the trial data, count data method and multinomial logit method side-by-side. The data presented confirmed that the multinomial logit method does not capture the observed trial data distributions as accurately as the count data method. We also presented the results of the multinomial logit method to clinicians who agreed that the results did not align with what is observed in clinical practice. • In the draft guidance, it is again acknowledged that we considered and presented alternative approaches but that they provided unrealistic outcomes, and the EAG agreed that they should be interpreted with caution. In summary, we have been transparent regarding the uncertainty associated with the 'count method' and have considered and presented alternative options where possible and aligned with EAG assumptions where possible. Given that LN is a rare disease, where population numbers and available data are limited and there will always be some uncertainty, we maintain that the count method is the most appropriate approach available. *Conclusion* As presented here, Otsuka have taken additional steps and run new analyses to explore the committee's concerns regarding the uncertainties in the model structure and assumptions. We have endeavoured to make the best use of available data where possible, and where data are absent, we have sought to make assumptions informed by expert clinician input. We conclude that these analyses provide further reassurance and confidence in our model, particular in the context of the uncertainties inherently associated with a rare disease such as LN. *References*	

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			Clarke S, et al. Orphanet J Rare Dis. 2021;16:218. Gisca E, et al. Rheumatology (Oxford). 2021;60(4):1814-22. EMA. Orphan Medicine. 2022. Available at: https://www.ema.europa.eu/en/glossary/orphan-medicine Nee R, et al. Int J Nephrol. 2015;917567. Parodis I, et al. Arch Immunol Ther Exp. 2022;70(1):8. Tamirou F, et al. Ann Rheum Dis. 2016;75(3):526-31. Tektonidou M, et al. Arthritis Rheumatol. 2016;68(6):1432-4. Yap D, et al. J Rheumatol. 2017;44(9):1375-1383	
14		Otsuka Pharmaceuticals UK Ltd.	**Clarification of positioning** Otsuka note the committee's uncertainty regarding how voclosporin would be used and welcome the opportunity to clarify the anticipated positioning of voclosporin in clinical practice. Voclosporin is expected to be used in line with the AURORA clinical trial inclusion criteria and SmPC – in combination with MMF as an **induction** treatment for the treatment of adult patients with active class III, IV or V (including mixed class III/V and IV/V) lupus nephritis (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, this would include patients with a new onset of a flare (irrespective of it being at initial diagnosis of LN or in the subsequent exacerbation of the disease after a period of remission) as well as patients with a persisting flare, not responding to another treatment. We do not agree with the committee's conclusion of 'first-line induction treatments taken with mycophenolate mofetil (methylprednisolone, rituximab and tacrolimus) and mycophenolate mofetil alone as the most likely appropriate comparators' and instead agree with the EAG that mycophenolate mofetil and tacrolimus with mycophenolate mofetil (both with corticosteroids) are the most suitable comparators. As per our original submission, and in line with expert clinician opinion, MMF is the most commonly used first-line treatment for LN in UK clinical practice and therefore the most suitable comparator; tacrolimus + MMF is also of interest as a legacy CNI combination therapy used in more severe patients. We also do not agree with the committee that rituximab + MMF is a most likely appropriate comparator as both treatment guidelines (Fanouriakis 2020, KDIGO 2021) and expert clinician opinion suggest that it is reserved for patients with non-responding/refractory disease. This is included in current NHS England guidance (NHS CCP for rituximab, 2020) which, as highlighted by the British Society for Rheumatology at technical engagement, states that rituximab should only be considered for patients who have failed to respond or have had adverse events to 2 or more immunosuppressive therapies (one of which must be either MMF or cyclophosphamide, unless contraindicated). *References* Fanouriakis A, et al. Ann Rheum Dis 2020; 79(6): 713-23. KDIGO, Kidney Int 2021; 100(4S): S1–S276 NHS Clinical Commissioning Policy: Rituximab for refractory SLE in adults and post-pubescent children. 2020. Available at: https://www.england.nhs.uk/publication/rituximab-for-refractory-systemic-lupus-erythematosus-sle-in-adults-and-post-pubescent-children/	Thank you for your comment. The committee discussed the treatment positioning of voclosporin and concluded that voclosporin would be used to induce remission and not as a long-term maintenance treatment. Based on this, it identified mycophenolate mofetil alone or with tacrolimus as the most appropriate comparators. See section 3.3 of the final draft guidance for more information.
15		Otsuka Pharmaceuticals UK Ltd.	**Transparency in the model** We acknowledge the committee's comment that it would have more confidence in a model that addresses the	Thank you for your comment. The committee discussed the efforts of the

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			EAG's concerns regarding transparency and input accuracy. We would like to highlight that several of these points were reviewed and addressed as part of our technical engagement response to Key Issue 6. We also note that the EAG emphasised that the error identified following our technical engagement response had a very minor impact on the model results and was no means a large driver of cost-effectiveness estimates. However, to further support the committee's confidence in the model, and having sought further clarification from NICE regarding transparency concerns, we have conducted further, extended quality control processes and input checks to ensure that the inputs used to inform the base case results and scenario analyses are accurate in the model. As part of this review process, we also re-reviewed and checked the model calculations and in the interests of transparency, we provide further details on the outputs from this process in Appendix A with updates included in the revised model and the revised base case in Comment 3. Furthermore, in line with the committee's statement that 'it would have more confidence in a model that had the flexibility to refer to previous treatment settings and if sources of data were clearly referenced and described' we have implemented the following processes and approach in the updated model: • Flexibility to refer to previous settings: The revised cost-effectiveness model provided with this response has been updated so that changes made to the base case (since the version provided at technical engagement) can clearly be switched on/off. • Description of data sources/referencing: As part of the review processes and input checks highlighted above, we reviewed the referencing in the model. Having taken on board the comments from the EAG and committee, we believe that these additional checks of the inputs and functional changes to support model transparency provide further confidence in the results of the model.	company to improve model transparency. It noted the EAG conclusion that issues with model inputs were resolved. However, the committee did have concerns with errors that were still present in the company's model after numerous checks and because the flexibility to refer to previous treatment settings was removed. This prevented the EAG from implementing its desired base case and cross-checking calculations in the model. The committee concluded that issues with model transparency were a considerable uncertainty, meaning it had reservations about the robustness of the model's outputs. See section 3.8 of final draft guidance for more information.
16		Otsuka Pharmaceuticals UK Ltd.	**Factual inaccuracy** We note the following factual inaccuracy in the draft guidance – • Section 3.9 (page 12 of the draft guidance) states "The company suggested this is because voclosporin has superior efficacy and safety to tacrolimus." • This was not suggested by the company, and we propose that this is changed to "The company stated this is because voclosporin has a predictable PK/PD relationship allowing for flat dosing and no therapeutic drug monitoring, whereas tacrolimus has a complex and unpredictable PK profile that requires monitoring". • This is aligned with the language used by Otsuka in the technical engagement response form and supported by the references cited in that response (Voclosporin SmPC, van Gelder 2022). *References*	Thank you for your comment. Section 3.9 has been updated in the final draft guidance as outlined in this comment.

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			van Gelder T, et al. Expert Rev Clin Pharmacol. 2022;15(5):515-529. Voclosporin (Lupkynis) SmPC. 2022	
17		The UK Kidney Association (UKKA)	Lupus nephritis predominantly affects young women and is a chronic relapsing disease requiring prolonged periods of immunosuppression for many years. Adherence can be compromised by the adverse effects of medication, with the use of steroids being particularly implicated. As identified in the expert evidence and the trials (AURORA 1 and AURORA 2), a potential use of voclosporin would enable the use of lower dose of steroids. High dose steroids have several side effects, as well as adverse effects on mental health and body image. As the treatment for lupus is for many years, it is very beneficial, with respect to both short- and long-term outcome to minimise as much as possible exposure to corticosteroids with their multiple adverse effects impacting on morbidity as well as quality of life. Additionally, there are less reported adverse effects of voclosporin compared to tacrolimus. There was also concern noted that clinicians would not use lower dose of steroids with voclosporin. However, I don't think this is a concern. Many patients with lupus nephritis are treated within specialist clinics, and access and prescribing of voclosporin will likely be limited to within this setting. Within these specialist clinics, the trial data should be appreciated and voclosporin utilised for its steroid minimising effects.	Thank you for your comment. The committee considered the stakeholder responses and concluded that the AURORA trials are generalisable to the UK population but that the steroid doses used may not be reflective of established NHS clinical practice (see section 3.5 of final draft guidance). It also considered the potential for uncaptured benefits of lower dose steroids in its discussion of the cost-effectiveness estimates (see section 3.12 of final draft guidance).
18		The UK Kidney Association (UKKA)	A significant advantage of voclosporin is the lack of drug monitoring required with a lack of blood tests to monitor levels of voclosporin needed. Kidney function needs to be monitored but this is part of the routine monitoring in lupus nephritis. The lack of monitoring has several advantages compared to tacrolimus. Blood tests do not need to be timed with the administration of the drug as they do with tacrolimus to allow accurate monitoring of levels. This is likely to be more convenient for patients. Also, the lack of monitoring blood levels may allow the drug to be more accessible within Rheumatology clinics as Rheumatologists generally do not use as much tacrolimus as Nephrologists, hence may not be as comfortable monitoring drug levels and the use of voclosporin removes the necessity for monitoring of levels	Thank you for your comment. The committee concluded that additional monitoring costs for voclosporin were not appropriate and were not included in decision-making ICERs. It also considered the equality concerns with additional monitoring for other treatments, concluding that monitoring for people with voclosporin would not be different to comparators as voclosporin is also given with mycophenolate mofetil and steroids.
19		The UK Kidney	Although there was uncertainty regarding on how voclosporin would be used in clinical practice, it can be	Thank you for your

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
		Association (UKKA)	compared to the use of tacrolimus, which is widely used in clinical practise to induce remission on a relatively short term basis (up to 12 months) as opposed to long term maintenance. Nephrologists would feel comfortable using Voclosporin in a similar manner to tacrolimus for short term treatment in which there is trial evidence (AURORA trials) to support the use with significant decreases in urine proteinuria and higher rates of response compared to standard care.	comment. The committee discussed the treatment positioning of voclosporin and concluded that voclosporin would be used to induce remission and not as a long-term maintenance treatment. Based on this, it identified mycophenolate mofetil alone or with tacrolimus as the most appropriate comparators. See section 3.3 of the final draft guidance for more information.
20	Web comment	UK Renal Pharmacy Group	Has all of the relevant evidence been taken into account? Yes - the relevant clinical trials were systematically reviewed. Expert opinions on current clinical practice were also included to help evaluate the clinical feasibility of how voclosporin would best fit in the current treatment algorithm for lupus nephritis. Most of the evidence for voclosporin appears to have been taken in to account but the natural history and poor outcomes of patients with lupus nephritis on current therapies does not appear to have been adequately considered. In particular the considerable disadvantages of having to rely on moderate and high dose steroids to induce and maintain remission or even partial response (increased risk of damage and premature death) and the likely benefits of successful regimens with low dose steroids. The markedly improved adverse event profile for voclosporin compared with tacrolimus and other calcineurin inhibitors such as ciclosporin has not been considered. Presumably as no direct evidence of comparison in trials but they have all been used in placebo controlled trials, and this reduced adverse event risk is the reason that drug levels are not required (in contrast to tacrolimus). Voclosporin has less adverse events in general as well as reduced risk of renal impairment and hypertension from calcineurin inhibitors and less risks than alternative therapies like cyclophosphamide). The fact that the baseline therapy with mycophenolate mofetil and the other comparators mentioned including cyclophosphamide, azathioprine, tacrolimus and rituximab are used based on experience and less good evidence than is provided here for voclosporin which has a clinically and statistically significant benefit in randomised controlled double blind trials is not mentioned.	Thank you for your comment. The committee considered the stakeholder responses and concluded that the AURORA trials are generalisable to the UK population but that the steroid doses used may not be reflective of established NHS clinical practice (see section 3.5 of final draft guidance). It also considered the potential for uncaptured benefits of lower dose steroids in its discussion of the cost-effectiveness estimates (see section 3.12 of final draft guidance). Final draft guidance (as well as draft guidance) also mentions that the committee concluded that the AURORA trials show clear clinical advantages of

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
				voclosporin over mycophenolate mofetil in inducing renal response when measured by protein in the urine (see section 3.4).
21	Web comment	UK Renal Pharmacy Group	Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? Yes. The summaries also allude that voclosporin does not add clear, significant benefits/changes to existing treatment algorithm. The models have not considered all the issues raised in my previous response eg benefits of lower dose steroids, reduced risk of flare, reduced risk of adverse events and their consequences. It is rare for a patient with lupus nephritis to survive 69 years, since in the UK as in other countries they have worse outcomes than patients with lupus without nephritis, although UK results are somewhat better now than those from countries where access to care may be limited by financial issues. Cost-effectiveness models for lupus are complex to generate due to the multiple risks associated with damage from persistent active disease, flares and steroid therapy over time, compounded in lupus nephritis by the frequent co-existence of hypertension as part of the consequences of renal disease due to lupus whether active or chronic and often hard to control and often made worse by steroids and tacrolimus (especially if levels not measured). The risks and costs and implications for patient well-being and lifestyle of needing regular dialysis and/or transplantation have not been adequately considered. Treatments that reduce this risk completely or delay these needs will not only reduce symptoms and costs but will impact very significantly on quality of life and both direct and indirect costs and survival.	Thank you for your comment. The committee acknowledged the difficulties in developing models for lupus nephritis, especially for long-term outcomes (see sections 3.10 and 3.11 of final draft guidance). It also considered the potential for uncaptured benefits in its discussion of the cost-effectiveness estimates (see section 3.12 of final draft guidance).
22	Web comment	UK Renal Pharmacy Group	Are the recommendations sound and a suitable basis for guidance to the NHS? Yes - whilst this guidance does not recommend voclosporin at this stage; the review has highlighted gaps in current study data and the need for long-term data. No because the drug is not recommended for use in the NHS. Voclosporin would offer a significant improvement over current therapies particularly for patients that have failed conventional therapy with mycophenolate for lupus nephritis, and even more so if they have failed other therapies currently used for refractory lupus nephritis disease (such as rituximab and as a way of avoiding need to use cyclophosphamide which has the worse adverse event profile of all the drugs used for severe lupus and lupus nephritis including considerable increased risk of infection, infertility and malignancy). So at the very least this drug should be available for patients with refractory disease that have failed at least 1 and possibly 2 drugs for lupus nephritis and they should be allowed to stay on it for at least one year (since renal response often takes at least 12 months to demonstrate and ensure that it is stable on low dose steroids). It would be preferable to keep patients on the drug for at least one year after achieving renal response before withdrawing the drug gradually to reduce the risk of renal relapse. And if patients do relapse after stopping or reducing the dose , it should be possible to give them another 12 month course before retrying withdrawal as recommended for management of lupus nephritis with other drugs. Outcomes should be determined by standard published clinical renal response criteria without the need for biopsy unless there is uncertainty whether the patient has active disease or chronic damage based on an	Thank you for your comment. This comment is no longer relevant as the final draft guidance recommendation is different to draft guidance.

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			assessment of all aspects of their lupus disease.	
23	Web comment	UK Renal Pharmacy Group	Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, sex, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity? The question was fully explored and addressed to ensure the same access to treatment for all people irrespective of various patient factors. Lupus nephritis more often affects ethnic minorities, affects them more severely and with higher risks of renal involvment. The lupus nephritis that they have is often harder to treat and these patients have higher background risk of hypertension. Lupus particularly affects women and often presents at a younger age in women from ethnic minorities (especially with African heritage). These are the patients that have the greatest risk of complications from lupus nephritis, and especially in pregnancy with inadequately treated lupus nephritis and with fertility issues if given cyclophosphamide, so not providing a drug (voclosporin) that has trial evidence of significantly improved outcomes will affect them the most . Given that the drug has been licensed for use in other countries , not allowing patients with refractory lupus nephritis in UK the opportunity to have this drug is discriminatory as the policy will reduce the chances of these ethnic minority patients achieving renal response and remission, which is particularly important before pregnancy as this would enhance their outcomes in pregnancy (as other patients may respond more often with current therapies) .	Thank you for your comment. The committee considered the equality issues as well as those raised by stakeholders in draft guidance consultation. The committee concluded that there were no relevant equality issues (see section 3.15 of final draft guidance).

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	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Appraisal Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced**.**
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.	None

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Name of commentator person completing form:	[redacted]
Comment number	**Comments** Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
1	**Executive summary** Otsuka appreciate the opportunity to respond to this draft guidance document, and kindly ask the committee to consider the following comments and key points. *Revised Patient Access Scheme (PAS)* In response to the draft guidance, Otsuka has revised the PAS as outlined in Comment 2. *Updated base case following draft guidance* Revisions have been made to the base case cost-effectiveness analysis in line with the committee and the EAG's comments in the committee meeting and the draft guidance. When considering the revisions and evidence presented in Comment 3 and including the revised PAS, voclosporin + MMF is a cost-effective treatment option for adult patients with active class III, IV and V (including mixed class III/V and IV/V) LN. The ICER in the base case vs MMF is £24,267, with ICERs vs all comparators under the £30,000 per QALY threshold. *Exploring uncertainty in the model* To support the revised base case analysis, and in line with requests from the committee, we have provided additional clarity and conducted further scenario analyses (outlined in Comment 4) within the model structure and assumptions. This should help mitigate uncertainty associated with the company base case and provide further confidence that voclosporin is a cost-effective use of NHS resources. *Clarification of positioning* In response to the committee's comments regarding uncertainty on how voclosporin would be used, we have provided further clarity in Comment 5 regarding the positioning of voclosporin in UK clinical practice and the most suitable comparator (MMF). *Transparency in the model* Furthermore, in Comment 6 we acknowledge the committee's comments regarding transparency in the model and outline the processes and checks that have been undertaken to address concerns and provide more confidence in the model. *Factual inaccuracy* Finally, we note a factual inaccuracy in the draft guidance (Comment 7).

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	Voclosporin offers patients and the NHS an important new treatment option for LN. The demonstrated higher renal response rate and faster onset of action of voclosporin + MMF vs current standard of care (MMF) mean that patients spend less time in active disease, limiting the damage incurred to their kidneys. We hope that the revised PAS and additional analyses provided will give the committee confidence that voclosporin represents a cost-effective use of NHS resources, and that it can be recommended as a treatment option for LN, a rare disease where there is a high unmet need.
2	**Revised PAS** In response to the draft guidance, a revised PAS of [redacted] has been submitted to NHS England. When the PAS is applied to the list price this is equivalent to [redacted] per pack of voclosporin.
3	**Updated base case following draft guidance** Including the revised PAS and aligned with the discussion at the committee meeting, we present an updated base case cost-effectiveness analysis, which incorporates revisions as follows: • **Use of the random effects network meta-analysis (NMA):** In line with the committee's preference the base case has been updated to include the random effects NMA rather than the fixed effects NMA. As stated in the draft guidance, both the company and EAG agreed that the fixed and random effect analyses produced similar results. However, inclusion of this analysis provides a better approximation of relative effects, as the more credible random effects model better captures the uncertainty given the heterogenous evidence base identified for the NMA. Furthermore, we have provided an updated probabilistic sensitivity analysis (PSA) to further capture and explore any uncertainty around model inputs and the impact of the wider confidence intervals with the random effects network meta-analysis on the base case results for all comparators. • **Discontinuation for non-trial comparators:** As stated in our submission, there is a lack of published evidence available regarding the time to treatment discontinuation (TTD) for comparators not included in the clinical trials for voclosporin. In the absence of this data, it was previously assumed that there was no treatment discontinuation for non-trial comparators in the base case cost-effectiveness model. In line with requests from the EAG we provided several exploratory scenario analyses of TTD curves during clarification questions. Furthermore, our assumptions aligned with the EAG's preferred base case assumptions at technical engagement where applying TTD for non-trial comparators was presented as an exploratory rather than preferred analysis. However, we acknowledge the EAG and committee concerns and the base case has been updated to assume that in the absence of data, the TTD curve for voclosporin + MMF can be applied to the non-trial comparators to determine discontinuation and associated treatment costs. As we did at clarification questions, we also explored incorporating the TTD curve for MMF and present this scenario in Comment 4.

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- **Updated kidney transplant rate:** As outlined in our submission, clinical advice to the company was that 90% of patients of LN receive a transplant within two years – likely a higher rate than other CKD patients, as the average LN patient is younger and therefore more suitable for receiving a transplant. However, in line with the draft guidance, the estimated proportion of people with stage 5 CKD (ESRD) has been updated to align with the EAG's preferred assumed rate of 65% over 2 years based on clinical advice.

- Long-term treatment effect assumptions in the base case remain the same as those included in the model provided at technical engagement, but we acknowledge the committee's concerns regarding uncertainty and explore this further in Comment 4.

Incorporating the revisions and assumptions outlined above results in the ICERs outlined in **Table 1**.

Table 1 - Revised base case results (discounted)

Technologies	Total			Incremental			ICER (£/QALY)*
	Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs	
VCS + MMF	[redacted]	[redacted]	[redacted]	-	-	-	-
MMF	[redacted]	17.40	12.90	[redacted]	[redacted]	[redacted]	£24,267
L-CYC	[redacted]	16.77	12.41	[redacted]	[redacted]	[redacted]	£6,522
H-CYC	[redacted]	16.64	12.32	[redacted]	[redacted]	[redacted]	£5,450
AZA	[redacted]	17.31	12.83	[redacted]	[redacted]	[redacted]	£20,284
RTX + MMF	[redacted]	17.79	13.20	[redacted]	[redacted]	[redacted]	£25,432
TAC + MMF	[redacted]	17.44	12.93	[redacted]	[redacted]	[redacted]	£20,541
TAC	[redacted]	17.50	12.98	[redacted]	[redacted]	[redacted]	£20,289

*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

Sensitivity analyses around revised base case

Probabilistic sensitivity analysis

Table 2 - 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]	12.90	[redacted]	£24,267	£23,575
L-CYC	[redacted]	[redacted]	12.41	[redacted]	£6,522	£6,377
H-CYC	[redacted]	[redacted]	12.32	[redacted]	£5,450	£5,430
AZA	[redacted]	[redacted]	12.83	[redacted]	£20,284	£21,724
RTX + MMF	[redacted]	[redacted]	13.20	[redacted]	£25,432	£24,248
TAC + MMF	[redacted]	[redacted]	12.93	[redacted]	£20,541	£18,925

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TAC	[redacted]	[redacted]	12.98	[redacted]	£20,289	£18,668

*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 1 - Scatter plot of PSA results for total discounted costs and QALYs

[redacted]

CYC = cyclophosphamide; MMF = mycophenolate mofetil; PSA = probabilistic sensitivity analysis; QALY = quality-adjusted life year

Figure 2 - Scatter plot of PSA results for incremental discounted costs and QALYs (voclosporin + MMF vs comparators)

[redacted]

CYC = cyclophosphamide; MMF = mycophenolate mofetil; PSA = probabilistic sensitivity analysis; QALY = quality-adjusted life year

Figure 3 - Cost-effectiveness acceptability curve

[redacted]

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[redacted]

CYC = cyclophosphamide; MMF = mycophenolate mofetil; QALY = quality-adjusted life year

Deterministic sensitivity analysis

Figure 4 - DSA tornado diagram - incremental costs for voclosporin + MMF vs MMF

AD = active disease; CKD = chronic kidney disease; MMF = mycophenolate mofetil

Figure 5 - DSA tornado diagram - incremental QALYs for voclosporin + MMF vs MMF

AD = active disease; CKD = chronic kidney disease; CR = complete response; DSA = deterministic sensitivity analysis; PR = partial response; QALY = quality-adjusted life year

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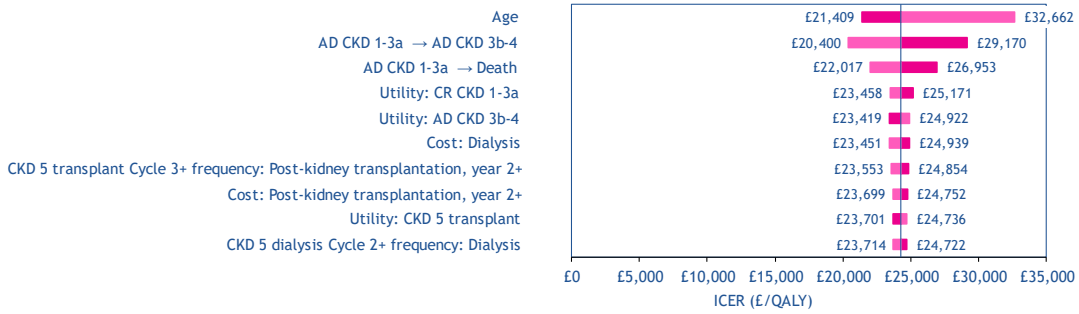
	Figure 6 - DSA tornado diagram – ICER (£/QALY) for voclosporin + MMF vs MMF  AD = active disease; CKD = chronic kidney disease; CR = complete response; QALY = quality-adjusted life year
4	**<u>Exploring uncertainty in the model</u>** We have carefully considered the comments in the draft guidance regarding uncertainties with the model structure. We would like to emphasise that when considering these uncertainties, it is important to remember that LN is a rare disease. Although there is no universally accepted definition of what constitutes a rare disease, when considered separately to SLE, LN has a prevalence lower than the rare disease threshold (<5 in 10,000 people) defined by the European Medicines Agency (EMA 2022). There are inherent challenges in studying medicines for rare diseases, including small patient populations in studies and consequently, inherent limitations and uncertainties in the corresponding evidence package (Clarke 2021). This was also discussed in the original submission which highlighted that aspects of LN introduce uncertainties to the economic analysis, including the limited published clinical and economic data regarding LN and comparators, variation in clinical practice in terms of treatment duration, and uncertainty related to long-term treatment effects. However, we appreciate the committee's concerns, and to further help explore and understand uncertainty in the model and to support decision-making, we have conducted additional scenario analyses as follows: • **Discontinuation:** As discussed in Comment 3, in the revised base case the TTD curve for voclosporin + MMF is applied to non-trial comparators to determine discontinuation and associated treatment costs. We have also considered and present in Table 3 the scenario of applying the TTD for MMF to non-trial comparators. We consider incorporation of TTD for voclosporin + MMF the most appropriate assumption as several of the non-trial comparators are combination therapies with MMF and discontinuation may be best captured by using the combination therapy TTD. **Table 3 – Scenario analysis with TTD for MMF used for non-trial comparators**

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]	12.90	[redacted]	£24,267	£24,267
L-CYC	[redacted]	[redacted]	12.41	[redacted]	£6,522	£6,651
H-CYC	[redacted]	[redacted]	12.32	[redacted]	£5,450	£5,566

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AZA	[redacted]		[redacted]		12.83	[redacted]		£20,284	£20,294
RTX + MMF	[redacted]		[redacted]		13.20	[redacted]		£25,432	£28,397
TAC + MMF	[redacted]		[redacted]		12.93	[redacted]		£20,541	£20,796
TAC	[redacted]		[redacted]		12.98	[redacted]		£20,289	£20,650

*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

- **Treatment duration:** In line with the input from clinical experts in the draft guidance, and as requested by the committee, we have conducted additional scenario analyses to explore a range of different treatment durations for voclosporin (Tables 4 and 5). We have considered treatment durations for 12 months (in line with UK clinical expert opinion in the draft guidance), 18 months (in line with the scenario provided in our original submission) and 36 months (presented in the base case).

  In the 18-month treatment duration scenario presented in Table 5, treatment duration and long-term treatment effect assumptions are aligned with the base case assumptions adjusted for the treatment duration e.g. all patients for voclosporin + MMF and all comparators receive treatment for 18 months apart from tacrolimus-containing regimens (which always have a 12-month treatment duration in line with expert clinician feedback), treatment waning effects are applied as per the base case but patient health state transition probabilities wane to the midpoint of those recorded within the AURORA trials at Months 12 and 18 (i.e. the last two periods of treatment). It is important to note that the assumptions are different for the 12-month treatment duration scenario (Table 4) as due to the limitations of the 6-month transitions (patients start in AD and are assumed not to move out of CR and PR in the first 6 months), long-term transition probabilities had to be based purely on the 12-month transitions rather than the last two periods of treatment.

Table 4 – Scenario analysis with adjustment of treatment duration to 12 months for all 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]	12.90	[redacted]	£24,267	£3,342
L-CYC	[redacted]	[redacted]	12.41	[redacted]	£6,522	Dominant
H-CYC	[redacted]	[redacted]	12.32	[redacted]	£5,450	Dominant
AZA	[redacted]	[redacted]	12.83	[redacted]	£20,284	£1,986

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RTX + MMF	[redacted]	[redacted]	13.20	[redacted]	£25,432	Dominant
TAC + MMF	[redacted]	[redacted]	12.93	[redacted]	£20,541	Dominant
TAC	[redacted]	[redacted]	12.98	[redacted]	£20,289	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

Table 5 – Scenario analysis with adjustment of treatment duration 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]	12.90	[redacted]	£24,267	£7,724
L-CYC	[redacted]	[redacted]	12.41	[redacted]	£6,522	Dominant
H-CYC	[redacted]	[redacted]	12.32	[redacted]	£5,450	Dominant
AZA	[redacted]	[redacted]	12.83	[redacted]	£20,284	£5,896
RTX + MMF	[redacted]	[redacted]	13.20	[redacted]	£25,432	Dominant
TAC + MMF	[redacted]	[redacted]	12.93	[redacted]	£20,541	£3,906
TAC	[redacted]	[redacted]	12.98	[redacted]	£20,289	£2,215

*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

Due to limitations and the associated uncertainty in the 12-month treatment duration presented above, we also explored a scenario where the 12 months of the AURORA 1 data were used to inform transition probabilities for the first 12 months, with the assumption that patients cannot respond after 12 months and can only move from response states to active disease, with no further movement between CR and PR either. In order to generate this 'AURORA 1 only' scenario, we identified and explored scenarios using the following trial and literature values for the transition from response states to AD (Table 6).

Table 6 – Sources for transition from response to AD after 12 months

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Source	Value	Details
Input from trial transitions	[redacted]	MMF long-term trial transitions, CR to AD, in the revised base case
Nee et al. 2015	1.85%	Reported as the 6-month transition in the MMF remission arm to relapse
Yap et al. 2017	0.94%	Reports a 9% relapse over 5 years

Each of these values is applied in individual scenarios below (Tables 7-9). We have explored an assumption based on the AURORA 1 data (Table 7), as well as two exploratory analyses (Tables 8 and 9) based on the literature. We note that the ICERs for voclosporin + MMF remain well below the cost-effectiveness threshold of £30,000 per QALY with the assumption based on AURORA 1, and that for the two analyses based on literature values, patients transition out of response more slowly than in the clinical trial data used in the base case – voclosporin + MMF dominates all other treatments when the literature values are applied. However, we maintain that as we have clinical trial data from AURORA 2 available to support these transitions, the most robust and conservative approach is to apply the data from the clinical trials as used in our base case.

Table 7 – Scenario analysis with adjustment of treatment duration to 12 months with transition out of response as in long-term MMF transitions, CR to AD, in base case

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]	12.90	[redacted]	£24,267	£6,219
L-CYC	[redacted]	[redacted]	12.41	[redacted]	£6,522	Dominant
H-CYC	[redacted]	[redacted]	12.32	[redacted]	£5,450	Dominant
AZA	[redacted]	[redacted]	12.83	[redacted]	£20,284	£4,894
RTX + MMF	[redacted]	[redacted]	13.20	[redacted]	£25,432	Dominant
TAC + MMF	[redacted]	[redacted]	12.93	[redacted]	£20,541	£1,813
TAC	[redacted]	[redacted]	12.98	[redacted]	£20,289	£366

*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 8 – Scenario analysis with adjustment of treatment duration to 12 months with transition out of response as in Nee et al. 2015

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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]	12.90	[redacted]	£24,267	Dominant
L-CYC	[redacted]	[redacted]	12.41	[redacted]	£6,522	Dominant
H-CYC	[redacted]	[redacted]	12.32	[redacted]	£5,450	Dominant
AZA	[redacted]	[redacted]	12.83	[redacted]	£20,284	Dominant
RTX + MMF	[redacted]	[redacted]	13.20	[redacted]	£25,432	Dominant
TAC + MMF	[redacted]	[redacted]	12.93	[redacted]	£20,541	Dominant
TAC	[redacted]	[redacted]	12.98	[redacted]	£20,289	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

Table 9 – Scenario analysis with adjustment of treatment duration to 12 months with transition out of response as in Yap et al. 2017

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]	12.90	[redacted]	£24,267	Dominant
L-CYC	[redacted]	[redacted]	12.41	[redacted]	£6,522	Dominant
H-CYC	[redacted]	[redacted]	12.32	[redacted]	£5,450	Dominant
AZA	[redacted]	[redacted]	12.83	[redacted]	£20,284	Dominant
RTX + MMF	[redacted]	[redacted]	13.20	[redacted]	£25,432	Dominant
TAC + MMF	[redacted]	[redacted]	12.93	[redacted]	£20,541	Dominant
TAC	[redacted]	[redacted]	12.98	[redacted]	£20,289	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

In summary, it is clear from the scenario analyses shown that when the treatment duration of voclosporin + MMF and other treatments are varied from 36 months to shorter durations such as 12 and 18 months, the ICERs for voclosporin + MMF vs all comparators become considerably more favourable than in the base case. However, we maintain that a treatment duration of a maximum of 36 months is the most appropriate for inclusion in the base case as this is in line with the availability of the AURORA trial data and the clinical advice received by the EAG and the

company. It is also important to note that even with a 36-month treatment duration in the base case, not all patients receive 36 months of treatment in the model as TTD curves are applied in line with the AURORA trial data. Furthermore, these scenarios, though uncertain, suggest that the base case treatment duration is a conservative assumption and that ICERs are considerably more favourable for voclosporin + MMF at the shorter treatment durations suggested by clinical experts and noted in the draft guidance.

- **Long-term treatment effect extrapolations:** The committee noted that there is high uncertainty with both the company's and EAG's approaches to the long-term treatment effect extrapolations. We agree with the committee's acknowledgement that modelling repeating cycles of induction and maintenance would be difficult to construct. We also believe that this would add further uncertainty, and highlight that no precedent or approach for this has been identified in our literature reviews to inform any update to the model.

  Given the inherent limitations of the available data and literature for a rare disease such as LN, there will be uncertainty in any model. However, to provide reassurance regarding output validity from our model, it should be noted that the long-term outcomes, in terms of progression to ESRD, in the MMF arm can be validated against external literature, as demonstrated in Table 10, which suggest that the long-term assumptions are appropriate for decision-making.

Table 10 - Validation of model transitions with literature sources

Percentage of patients in ESRD	Tektonidou 2016	Gisca 2021	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.

We have also conducted additional scenarios in order to explore uncertainty in the long-term treatment effect extrapolation assumption included in the model base case. We believe that the most appropriate way to incorporate a relative effect of 0 between voclosporin + MMF and MMF after 36 months is to apply the MMF long-term transitions to both arms (as opposed to the EAG's suggestion of applying the average long-term transition probabilities from voclosporin + MMF and MMF to both arms). We therefore present a scenario (Table 11) in which the MMF long-term transitions are also applied to the voclosporin + MMF arm. We note that even in this conservative scenario voclosporin + MMF remains cost-effective vs all comparators with the exception of rituximab + MMF. We note that this is an exploratory analysis and that, as discussed in Comment 5, rituximab + MMF is unlikely to be an appropriate comparator as it is reserved for patients with non-responding/refractory disease.

Table 11 – Scenario analysis with application of the MMF long-term transitions to VCS+MMF (which assumes the relative effect after 36 months is 0)

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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]	12.90	[redacted]	£24,267	£29,973
L-CYC	[redacted]	[redacted]	12.41	[redacted]	£6,522	£7,772
H-CYC	[redacted]	[redacted]	12.32	[redacted]	£5,450	£6,503
AZA	[redacted]	[redacted]	12.83	[redacted]	£20,284	£24,636
RTX + MMF	[redacted]	[redacted]	13.20	[redacted]	£25,432	£42,337
TAC + MMF	[redacted]	[redacted]	12.93	[redacted]	£20,541	£25,949
TAC	[redacted]	[redacted]	12.98	[redacted]	£20,289	£26,300

We note that there are small differences in the 'Total costs' for some of the comparators in this scenario vs. the base case. This is because the time horizon of the model is determined by the point at which <0.1% of the VCS+MMF patient population remains alive, and in the scenario the time horizon of the model is reduced by a cycle (6 months).
*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

Alongside this scenario, we restate that the faster onset of action for voclosporin + MMF vs MMF alone means that there is an earlier decrease in proteinuria and patients spend less time in active disease, therefore limiting the damage incurred to their kidneys. This is supported by several robust studies which have shown that an early decrease in proteinuria predicts good long-term renal outcomes (Parodis 2022, Tamirou 2016). We have explored an alternative way of implementing the EAG's approach of assuming voclosporin + MMF and MMF alone are equal for all health states but maintain that this assumption does not reflect the faster onset of action of voclosporin, and should therefore be considered conservative.

- **Response in CKD stages 3b-4:** As per our original submission, there is a lack of data relating to response in patients in CKD stages 3b-4. In the absence of literature values and following consultation with expert clinicians who advised that patients achieving response in this progressed stage can be as low as 2.5% it was assumed that this transition could be set to 0%. Clinical experts consulted by the EAG agreed that only a small number of patients in CKD stages 3b-4 would have a response, but that it would not be zero. The committee noted that uncertainty could be further reduced if the restriction in the model structure which stops people with CKD stages 3b to 4 from moving to response was amended, because this would better reflect clinical practice.

  In response to the comments from the EAG and committee, we have conducted further consultations with expert clinicians with the aim of further reducing uncertainty related to the response in CKD stages 3b-4. From these discussions, an assumption of 0% was stated to be reasonable (emphasising the uncertainty in including this transition) and it was not possible to source an estimate of the proportion of patients who would return from CR to AD in CKD stages 3b-4. Given

the evident uncertainty associated with these estimates we have not included response in patients in CKD stages 3b-4 in the base case. However, we did conduct a series of scenario analyses (Tables 12-14) to explore including CKD stages 3b-4 in the model in line with the committee's comments.

We explored three scenarios with 2.5% of patients achieving response from CKD stages 3b-4 per 6-month cycle, one where 2.5% achieved CR, one where 2.5% achieved PR and one where 1.25% achieved CR and 1.25% achieved PR. As outlined above, it was not possible to source a value for patients returning from response to AD in CKD stages 3b-4 so for the purposes of these scenarios we assumed that these transitions are equal to the long-term transitions for these states for MMF.

Table 12 – Scenario analysis with assumption of 2.5% of patients achieving CR from CKD stages 3b-4

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]	12.90	[redacted]	£24,267	£24,605
L-CYC	[redacted]	[redacted]	12.41	[redacted]	£6,522	£6,876
H-CYC	[redacted]	[redacted]	12.32	[redacted]	£5,450	£5,808
AZA	[redacted]	[redacted]	12.83	[redacted]	£20,284	£20,627
RTX + MMF	[redacted]	[redacted]	13.20	[redacted]	£25,432	£25,802
TAC + MMF	[redacted]	[redacted]	12.93	[redacted]	£20,541	£20,891
TAC	[redacted]	[redacted]	12.98	[redacted]	£20,289	£20,634

*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 13 –Scenario analysis with assumption of 2.5% of patients achieving PR from CKD stages 3b-4

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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]	12.90	[redacted]	£24,267	£24,385
L-CYC	[redacted]	[redacted]	12.41	[redacted]	£6,522	£6,651
H-CYC	[redacted]	[redacted]	12.32	[redacted]	£5,450	£5,581
AZA	[redacted]	[redacted]	12.83	[redacted]	£20,284	£20,405
RTX + MMF	[redacted]	[redacted]	13.20	[redacted]	£25,432	£25,567
TAC + MMF	[redacted]	[redacted]	12.93	[redacted]	£20,541	£20,667
TAC	[redacted]	[redacted]	12.98	[redacted]	£20,289	£20,413

*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 14 – Scenario analysis with assumption of 1.25% of patients achieving CR and 1.25% of patients achieving PR from CKD stages 3b-4

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]	12.90	[redacted]	£24,267	£24,497
L-CYC	[redacted]	[redacted]	12.41	[redacted]	£6,522	£6,766
H-CYC	[redacted]	[redacted]	12.32	[redacted]	£5,450	£5,696
AZA	[redacted]	[redacted]	12.83	[redacted]	£20,284	£20,518
RTX + MMF	[redacted]	[redacted]	13.20	[redacted]	£25,432	£25,686
TAC + MMF	[redacted]	[redacted]	12.93	[redacted]	£20,541	£20,781
TAC	[redacted]	[redacted]	12.98	[redacted]	£20,289	£20,525

*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

The results in Tables 12-14, though highly uncertain, suggest that incorporating these transitions do not have a large impact on the ICER and voclosporin + MMF remains a cost-effective treatment option even when response in CKD 3b-4 is approximated and included in the model.

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- **Attrition bias:** In line with the committee's comments in the draft guidance, we have considered whether there is any possible attrition bias in the AURORA 2 data (that is, that discontinuation may not be random and there may be systematic differences between the population that discontinued AURORA 1 and the population that continued enrolment to AURORA 2). We acknowledge the attrition between the trials but note that all study personnel, site staff, monitors and patients remained blinded to study treatment for all patients in AURORA 2, which decreases the risk of any bias. It is also important to consider that AURORA 2 was an extension study, with AURORA 1 always designed with a view of allowing patients to exit in a controlled way when convenient. We also note and agree with the EAG's comments that the rate of and reasons for discontinuation were comparable across the trial arms, reducing the risk of bias.

  However, in line with the committee's suggestions and requests in the draft guidance we have considered a series of approaches to understand any uncertainty associated with attrition between AURORA 1 and AURORA 2. In order to do this, we performed new analyses of the data from the AURORA clinical trials. This involved revisiting the patient-level data to understand and re-analyse the data for the 94 patients, 47 per treatment arm, who completed AURORA 1 and then did not enter AURORA 2. Transition probabilities were then adjusted and modelled in scenarios as requested in the draft guidance. The explicit number of patients used to calculate each transition is provided in the model to support transparency. We note that 3 patients who completed AURORA 1 were marked as 'unknown' at last follow up (as biomarkers required for response assessment were not recorded) and were therefore excluded from our analyses.

  Three exploratory scenarios were considered as follows:

  LOCF – In this scenario it was assumed that for both voclosporin + MMF and MMF groups of patients who completed AURORA 1 but did not enter AURORA 2 we could apply last observation carried forward (LOCF) from Month 12 for Months 18-36 (Table 15). We consider this the most logical of our exploratory scenarios as the same assumption is applied to both treatment groups and trial data from AURORA 1 is carried forward to inform the modelling of these patients. We note that with these assumptions, voclosporin + MMF remains cost-effective vs all comparators with the exception of rituximab + MMF, and the ICER vs MMF is actually more favourable than in the base case. As noted above and in Comment 5, rituximab + MMF is unlikely to be an appropriate comparator as it is reserved for patients with non-responding/refractory disease.

Table 15 – Scenario analysis with assumption of LOCF for patients who completed AURORA 1 but did not enter AURORA 2

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]	12.90	[redacted]	£24,267	£21,701
L-CYC	[redacted]	[redacted]	12.41	[redacted]	£6,522	£7,199

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H-CYC	[redacted]	[redacted]	12.32	[redacted]	£5,450	£5,433
AZA	[redacted]	[redacted]	12.83	[redacted]	£20,284	£18,509
RTX + MMF	[redacted]	[redacted]	13.20	[redacted]	£25,432	£31,007
TAC + MMF	[redacted]	[redacted]	12.93	[redacted]	£20,541	£18,212
TAC	[redacted]	[redacted]	12.98	[redacted]	£20,289	£18,746

*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

As requested by the committee, we also considered exploratory scenarios which assumed people who had voclosporin + MMF and were lost to follow-up were non-responders (i.e. moving to AD), while people who had MMF were responders (i.e. moving to CR), as well as different variations of these. We have presented these scenarios in line with the committee's suggestion but consider them exploratory and not plausible as we apply very different assumptions to both treatment arms which is not reflective of the data captured within the AURORA 2 clinical trial.

AD for voclosporin + MMF/CR for MMF – As suggested in the draft guidance, in this scenario it was assumed that for the patients who did not enter AURORA 2 that patients in the MMF group moved to complete response and the voclosporin + MMF patients moved to active disease (Table 16). As data from the MMF group is used to inform several of the transitions for the non-trial comparators, it is clear that these assumptions also heavily favour the other comparators as well as MMF. We consider the results of this scenario to be highly implausible as treatments such as tacrolimus monotherapy dominate voclosporin + MMF in this scenario but were found to have significantly lower efficacy in terms of CR than voclosporin + MMF in the NMA.

Table 16 – Scenario analysis with assumption of AD for voclosporin + MMF and CR for MMF, for patients who completed AURORA 1 but did not enter AURORA 2

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]	12.90	[redacted]	£24,267	Dominated
L-CYC	[redacted]	[redacted]	12.41	[redacted]	£6,522	£1,596,495
H-CYC	[redacted]	[redacted]	12.32	[redacted]	£5,450	£294,418
AZA	[redacted]	[redacted]	12.83	[redacted]	£20,284	Dominated
RTX + MMF	[redacted]	[redacted]	13.20	[redacted]	£25,432	Dominated
TAC + MMF	[redacted]	[redacted]	12.93	[redacted]	£20,541	Dominated
TAC	[redacted]	[redacted]	12.98	[redacted]	£20,289	Dominated

*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

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CR for voclosporin + MMF/AD for MMF – We also considered a scenario in which it was assumed that for the patients who did not enter AURORA 2 that patients in the MMF group moved to active disease and the voclosporin + MMF patients moved to complete response (Table 17).

Table 17 – Scenario analysis with assumption of CR for voclosporin + MMF/AD for MMF, for patients who completed AURORA 1 but did not enter AURORA 2

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]	12.90	[redacted]	£24,267	£5,644
L-CYC	[redacted]	[redacted]	12.41	[redacted]	£6,522	£1,246
H-CYC	[redacted]	[redacted]	12.32	[redacted]	£5,450	£847
AZA	[redacted]	[redacted]	12.83	[redacted]	£20,284	£4,949
RTX + MMF	[redacted]	[redacted]	13.20	[redacted]	£25,432	Dominant
TAC + MMF	[redacted]	[redacted]	12.93	[redacted]	£20,541	£3,684
TAC	[redacted]	[redacted]	12.98	[redacted]	£20,289	£2,997

*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

As discussed above, the scenarios presented in Tables 16 and 17 are not plausible and show that when vastly different assumptions are applied to the voclosporin + MMF and MMF treatment groups the ICERs, as may be expected, are shown to be considerably more or considerably less favourable for voclosporin + MMF depending on which way around the assumptions are applied. However, we have aimed to reduce the uncertainty that could be associated with any attrition between trials and in our most plausible scenario (LOCF) we note that voclosporin + MMF remains a cost-effective treatment option vs MMF and that the ICERs are similar to those in the base case.

Count method

In addition to the above points, the EAG stated that there is uncertainty in the transition probabilities for voclosporin + MMF and MMF, due to small sample sizes associated with the 'count method' used to derive transitions from the clinical trial data. We appreciate that there is uncertainty associated with this method but maintain that this is the best and most appropriate approach available and note:

- Other approaches were explored during the development of the cost-effectiveness analysis. As stated in our original submission, we explored the alternative approach of calculating the transition probabilities by fitting a multinomial logit model per transition per health state. However, this was not incorporated into the model as the multinomial logit method provided unrealistic outcomes which did not align with the trial data. In response to questions from the EAG we provided further detail regarding this method in our response to clarification questions, including a table which showed the trial data, count data method and multinomial logit method

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	side-by-side. The data presented confirmed that the multinomial logit method does not capture the observed trial data distributions as accurately as the count data method. We also presented the results of the multinomial logit method to clinicians who agreed that the results did not align with what is observed in clinical practice. • In the draft guidance, it is again acknowledged that we considered and presented alternative approaches but that they provided unrealistic outcomes, and the EAG agreed that they should be interpreted with caution. In summary, we have been transparent regarding the uncertainty associated with the 'count method' and have considered and presented alternative options where possible and aligned with EAG assumptions where possible. Given that LN is a rare disease, where population numbers and available data are limited and there will always be some uncertainty, we maintain that the count method is the most appropriate approach available. *Conclusion* As presented here, Otsuka have taken additional steps and run new analyses to explore the committee's concerns regarding the uncertainties in the model structure and assumptions. We have endeavoured to make the best use of available data where possible, and where data are absent, we have sought to make assumptions informed by expert clinician input. We conclude that these analyses provide further reassurance and confidence in our model, particular in the context of the uncertainties inherently associated with a rare disease such as LN. *References* Clarke S, et al. Orphanet J Rare Dis. 2021;16:218. Gisca E, et al. Rheumatology (Oxford). 2021;60(4):1814-22. EMA. Orphan Medicine. 2022. Available at: https://www.ema.europa.eu/en/glossary/orphan-medicine Nee R, et al. Int J Nephrol. 2015;917567. Parodis I, et al. Arch Immunol Ther Exp. 2022;70(1):8. Tamirou F, et al. Ann Rheum Dis. 2016;75(3):526-31. Tektonidou M, et al. Arthritis Rheumatol. 2016;68(6):1432-4. Yap D, et al. J Rheumatol. 2017;44(9):1375-1383
5	**Clarification of positioning** Otsuka note the committee's uncertainty regarding how voclosporin would be used and welcome the opportunity to clarify the anticipated positioning of voclosporin in clinical practice. Voclosporin is expected to be used in line with the AURORA clinical trial inclusion criteria and SmPC – in combination with MMF as an **induction** treatment for the treatment of adult patients with active class III, IV or V (including mixed class III/V and IV/V) lupus nephritis (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, this would include patients with a new onset of a flare (irrespective of it being at initial diagnosis of LN or in the subsequent

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	exacerbation of the disease after a period of remission) as well as patients with a persisting flare, not responding to another treatment. We do not agree with the committee's conclusion of 'first-line induction treatments taken with mycophenolate mofetil (methylprednisolone, rituximab and tacrolimus) and mycophenolate mofetil alone as the most likely appropriate comparators' and instead agree with the EAG that mycophenolate mofetil and tacrolimus with mycophenolate mofetil (both with corticosteroids) are the most suitable comparators. As per our original submission, and in line with expert clinician opinion, MMF is the most commonly used first-line treatment for LN in UK clinical practice and therefore the most suitable comparator; tacrolimus + MMF is also of interest as a legacy CNI combination therapy used in more severe patients. We also do not agree with the committee that rituximab + MMF is a most likely appropriate comparator as both treatment guidelines (Fanouriakis 2020, KDIGO 2021) and expert clinician opinion suggest that it is reserved for patients with non-responding/refractory disease. This is included in current NHS England guidance (NHS CCP for rituximab, 2020) which, as highlighted by the British Society for Rheumatology at technical engagement, states that rituximab should only be considered for patients who have failed to respond or have had adverse events to 2 or more immunosuppressive therapies (one of which must be either MMF or cyclophosphamide, unless contraindicated). *References* Fanouriakis A, et al. Ann Rheum Dis 2020; 79(6): 713-23. KDIGO, Kidney Int 2021; 100(4S): S1–S276 NHS Clinical Commissioning Policy: Rituximab for refractory SLE in adults and post-pubescent children. 2020. Available at: https://www.england.nhs.uk/publication/rituximab-for-refractory-systemic-lupus-erythematosus-sle-in-adults-and-post-pubescent-children/
6	**Transparency in the model** We acknowledge the committee's comment that it would have more confidence in a model that addresses the EAG's concerns regarding transparency and input accuracy. We would like to highlight that several of these points were reviewed and addressed as part of our technical engagement response to Key Issue 6. We also note that the EAG emphasised that the error identified following our technical engagement response had a very minor impact on the model results and was no means a large driver of cost-effectiveness estimates. However, to further support the committee's confidence in the model, and having sought further clarification from NICE regarding transparency concerns, we have conducted further, extended quality control processes and input checks to ensure that the inputs used to inform the base case results and scenario analyses are accurate in the model. As part of this review process, we also re-reviewed and checked the model calculations and in the interests of transparency, we provide further details on the outputs from this process in Appendix A with updates included in the revised model and the revised base case in Comment 3.

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	Furthermore, in line with the committee's statement that 'it would have more confidence in a model that had the flexibility to refer to previous treatment settings and if sources of data were clearly referenced and described' we have implemented the following processes and approach in the updated model: • Flexibility to refer to previous settings: The revised cost-effectiveness model provided with this response has been updated so that changes made to the base case (since the version provided at technical engagement) can clearly be switched on/off. • Description of data sources/referencing: As part of the review processes and input checks highlighted above, we reviewed the referencing in the model. Having taken on board the comments from the EAG and committee, we believe that these additional checks of the inputs and functional changes to support model transparency provide further confidence in the results of the model.
7	**Factual inaccuracy** We note the following factual inaccuracy in the draft guidance – • Section 3.9 (page 12 of the draft guidance) states "The company suggested this is because voclosporin has superior efficacy and safety to tacrolimus." • This was not suggested by the company, and we propose that this is changed to "The company stated this is because voclosporin has a predictable PK/PD relationship allowing for flat dosing and no therapeutic drug monitoring, whereas tacrolimus has a complex and unpredictable PK profile that requires monitoring". • This is aligned with the language used by Otsuka in the technical engagement response form and supported by the references cited in that response (Voclosporin SmPC, van Gelder 2022). *References* van Gelder T, et al. Expert Rev Clin Pharmacol. 2022;15(5):515-529. Voclosporin (Lupkynis) SmPC. 2022

Appendix A

As outlined in Comment 6, further extended quality control processes and input checks were conducted on the cost-effectiveness model. This involved review by a senior health economist who was not involved in the development of the model, who reviewed and thoroughly tested the model calculations to ensure that calculated outcomes aligned with expected outcomes when specific settings were toggled on or off, or extreme values were entered. To support transparency, all inputs used to inform the base case and scenario analyses included in this response were also checked to ensure that they were correct, aligned with reported values and appropriately referenced.

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Following this review the below updates were made and are included in the updated model and revised base case in this response. The combined impact of the updates on the ICER for voclosporin + MMF vs MMF is below £100 (-£84) and presented in Table 18 to support transparency.

Table 18 – Updates to cost-effectiveness model and impact on the ICER for voclosporin + MMF vs MMF

Update	Description	ICER vs. MMF (£/QALY)	Impact on ICER vs. MMF (£/QALY)
-	Company base case at technical engagement	£27,301	-
1	EAG fix from review of technical engagement response	£27,199	-£103
2	Update to AE costs calculation	£27,343	+£42
3	Update to transition calculations and references	£27,268	-£33
4	Adjustment to azathioprine long-term transition	N/A	N/A
5	Further alignment of inputs with EAG report	£27,311	+£10
Cumulative impact on ICER vs. MMF		**£27,217**	**-£84**

Abbreviations: AE = adverse event; ICER = incremental cost-effectiveness ratio; MMF = mycophenolate mofetil

To further support transparency each update can be toggled in the model such that the impact of the update can easily be verified, and further context is provided as follows:

1. The fix to the calculation of AE disutilities identified and included by the EAG following technical engagement has been incorporated into the revised base case model.

2. We have identified and corrected a similar inconsistency in the AE calculation on the "Costs" sheet. For an example treatment 'X' the previous formula was $INDEX(trace\_txX, \$B9, 11) * MMULT(TRANSPOSE(input\_AE\_decrement\_days/'Labels \& constants'!\$H\$7 * 6), input\_AE\_incidence\_txX * input\_AE\_cost)$ which has now been updated to $INDEX(trace\_txX, \$B9, 11) * ISUMPRODUCT(input\_AE\_incidence\_txX, input\_AE\_cost)$.

3. We have identified and corrected two transition probabilities ('CKD 5 dialysis to Death' and 'CKD 5 transplant to CKD 5 dialysis') that had not been transformed properly (i.e. were reported as probabilities but previously transformed as rates) and that the transitions were not referenced correctly to Palmer et al. 2004 and Sugrue et al. 2019.

4. An error was identified and corrected in the formula for the transition from AD to CR in the long-term transition matrix for azathioprine. The previous formula included the named value OR_CR_tx5, which has been corrected to OR_CR_tx6 in cells CD166 and CN166 on the "Transitions" sheet. This had no impact on other treatment comparisons but changes the ICER for voclosporin + MMF vs azathioprine from £14,845 to £24,299. As highlighted in our original submission and in the draft guidance, azathioprine is a maintenance therapy and not typically used as an induction therapy in UK clinical practice, we therefore consider it an unlikely appropriate comparator for voclosporin + MMF.

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5. In our extended review, we also revisited the EAG report and considered if there were any other areas where we could provide further transparency regarding inputs and where we could further align with the comments and inputs presented. This led to minor adjustments as follows:

    - Even though the inputs do not inform the base case results, we have removed any prednisone costs (i.e. for 10mg and 30mg) that could not be sourced from the EAG preferred source of eMIT

    - Furthermore, though the EAG stated that the impact on model results would be minimal, we have checked and aligned AE costs for gastroenteritis (from £2,490.47 to £2,490.30), hypertension (£640.41 to £640.22) and upper respiratory tract infection (£1,458.20 to £1,458.21) with the EAG report

    - Finally, the inflation index between 2015 to 2016 previously used the HCHS index of 2.7%, this has now been updated to reflect the 0.45% used by the EAG

To further support transparency, we have also made the following updates within the model that do not impact the model results, but we hope add further clarity and transparency regarding inputs and references:

- Where applicable, transition values on the “Clinical Inputs” sheet that were previously input directly have been updated to reflect the formula used to derive the transition probability

- Costs on the “Resource Use” and “Safety” sheets that were previously input directly have been updated to include the explicit inflation calculations to 2021 costs

- References on the “Resource Use” sheet have been updated to provide additional detail

References

Palmer A, et al. J Hum Hypertens. 2004;18(10):733-8
Sugrue D, et al. Pharmacoeconomics. 2019;37(12):1451-1468

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	**LUPUS UK**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	N/A
Name of commentator person completing form:	[redacted]

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	Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
Example 1	We are concerned that this recommendation may imply that ……..
1	We are concerned that the evidence requirements set by the committee are too strict for a new treatment for lupus nephritis to be recommended. One of the most important clinical outcomes to measure efficacy of a treatment in lupus nephritis is to examine whether it slows or prevents progression to end-stage renal disease (ESRD) in the longer-term. There is limited data available relating to the time to progression to ESRD from SLE diagnosis. Mahajan et al. (**HERE**) refers to studies finding the average time ranges between 4.1 years to 7.5 years. This range is likely due to the ethnic distribution of the study cohorts, with black patients more likely to progress to ESRD. This longer-term data is not available from a Phase 3 randomised-controlled trial and to require it will prevent a potentially organ-saving and life-saving treatment from being made available for patients. Lupus nephritis is a chronic disease, with onset frequently occurring in relatively young people. Many people live with the disease over several decades, accumulating damage from disease flares and adverse effects from treatments such as corticosteroids. As such, earlier intervention with a treatment that is more effective than standard therapy could have a considerable cumulative benefit to quality of life. The clinical trial evidence indicates that voclosporin plus mycophenolate mofetil is more effective at preventing the progression of lupus nephritis than mycophenolate mofetil alone. The evidence threshold set by NICE will prevent effective new treatments for rare, life-limiting and life-threatening diseases like lupus nephritis from being available for patients who are, too frequently, poorly served by current standard therapy.
2	We are concerned by the committee's assertion on page 3 of the draft guidance that there are several immunosuppressant options for the treatment of lupus nephritis whilst not addressing some of their significant limitations. Systematic review (**HERE**) found that the mean renal remission/response rate was less than 50% for most standard therapy. 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 (**HERE**). 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 (**HERE**). This pattern suggests limitations in the effectiveness of, or access to, current treatments and the need for new therapies such as voclosporin. *"[My partner] now has stage 4 kidney disease 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."* 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. Voclosporin may be a preferred alternative to cyclophosphamide because of its risk to fertility for a

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	patient group which is predominantly young women. 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 of 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. The clinical trial for voclosporin demonstrated that it can be effective as part of a treatment regimen with a lower steroid dose. *"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."* 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."* Approximately 25% of respondents in our online survey stated that their current treatment was a "large" or "very large" interruption to work/study.
3	We are concerned that the draft guidance will prevent a treatment with a different method of administration from being made available for people with lupus nephritis. As an oral therapy, voclosporin may have fewer barriers to access than some other current therapies used for lupus nephritis, particularly intravenous infusions such as rituximab and cyclophosphamide. Intravenous treatments such as rituximab and cyclophosphamide need to be administered at a hospital (potentially a specialist centre), which presents a barrier to access for some patients who may live a considerable distance away 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.
4	Aligning with our first comment, we are concerned that the evidence threshold set by NICE is unobtainable for clinical trials in rare diseases and could act as a disincentive for the development of

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	new therapies for lupus nephritis. An inhospitable UK market could also result in new therapies not being marketed here, creating a disparity of access with the rest of Europe. Belimumab (Benlysta) was the first treatment specifically developed to treat lupus and was approved in 2011. NICE recommended belimumab for limited use by the NHS but GlaxoSmithKline subsequently withdrew marketing activity from the UK, halting technology appraisal [TA806] because they did not provide an evidence submission. No new lupus treatments have been made available in the UK outside of clinical trials since belimumab was introduced. In 2022, AstraZeneca withdrew their submission to NICE for anifrolumab, terminating the appraisal [TA793]. A concerning pattern is emerging despite lupus patients having significant unmet needs and new treatments demonstrating superior efficacy compared to current therapy.

Insert extra rows as needed

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	The UK Kidney Association (UKKA)
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**Nil**
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1	Lupus nephritis predominantly affects young women and is a chronic relapsing disease requiring prolonged periods of immunosuppression for many years. Adherence can be compromised by the adverse effects of medication, with the use of steroids being particularly implicated. As identified in the expert evidence and the trials (AURORA 1 and AURORA 2), a potential use of voclosporin would enable the use of lower dose of steroids. High dose steroids have several side effects, as well as adverse effects on mental health and body image. As the treatment for lupus is for many years, it is very beneficial, with respect to both short- and long-term outcome to minimise as much as possible exposure to corticosteroids with their multiple adverse effects impacting on morbidity as well as quality of life. Additionally, there are less reported adverse effects of voclosporin compared to tacrolimus. There was also concern noted that clinicians would not use lower dose of steroids with voclosporin. However, I don't think this is a concern. Many patients with lupus nephritis are treated within specialist clinics, and access and prescribing of voclosporin will likely be limited to within this setting. Within these specialist clinics, the trial data should be appreciated and voclosporin utilised for its steroid minimising effects.
2	A significant advantage of voclosporin is the lack of drug monitoring required with a lack of blood tests to monitor levels of voclosporin needed. Kidney function needs to be monitored but this is part of the routine monitoring in lupus nephritis. The lack of monitoring has several advantages compared to tacrolimus. Blood tests do not need to be timed with the administration of the drug as they do with tacrolimus to allow accurate monitoring of levels. This is likely to be more convenient for patients. Also, the lack of monitoring blood levels may allow the drug to be more accessible within Rheumatology clinics as Rheumatologists generally do not use as much tacrolimus as Nephrologists, hence may not be as comfortable monitoring drug levels and the use of voclosporin removes the necessity for monitoring of levels
3	Although there was uncertainty regarding on how voclosporin would be used in clinical practice, it can be compared to the use of tacrolimus, which is widely used in clinical practise to induce remission on a relatively short term basis (up to 12 months) as opposed to long term maintenance. Nephrologists would feel comfortable using Voclosporin in a similar manner to tacrolimus for short term treatment in which there is trial evidence (AURORA trials) to support the use with significant decreases in urine proteinuria and higher rates of response compared to standard care.
4	

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Comments on the ACD submitted through the NICE Website From UK Renal Pharmacy Group

Name	[redacted]
Role	Not specified
Other role	Not specified
Organisation	UK Renal Pharmacy Group
Location	Not specified
Conflict	No
Notes	

Comments on the ACD:

- **Has all of the relevant evidence been taken into account?**

Yes - the relevant clinical trials were systematically reviewed. Expert opinions on current clinical practice were also included to help evaluate the clinical feasibility of how voclosporin would best fit in the current treatment algorithm for lupus nephritis.

Most of the evidence for voclosporin appears to have been taken in to account but the natural history and poor outcomes of patients with lupus nephritis on current therapies does not appear to have been adequately considered. In particular the considerable disadvantages of having to rely on moderate and high dose steroids to induce and maintain remission or even partial response (increased risk of damage and premature death) and the likely benefits of successful regimens with low dose steroids. The markedly improved adverse event profile for voclosporin compared with tacrolimus and other calcineurin inhibitors such as ciclosporin has not been considered. Presumably as no direct evidence of comparison in trials but they have all been used in placebo controlled trials, and this reduced adverse event risk is the reason that drug levels are not required (in contrast to tacrolimus). Voclosporin has less adverse events in general as well as reduced risk of renal impairment and hypertension from calcineurin inhibitors and less risks than alternative therapies like cyclophosphamide). The fact that the baseline therapy with mycophenolate mofetil and the other comparators mentioned including cyclophosphamide, azathioprine, tacrolimus and rituximab are used based on experience and less good evidence than is provided here for voclosporin which has a clinically and statistically significant benefit in randomised controlled double blind trials is not mentioned.

- **Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?**

Yes. The summaries also allude that voclosporin does not add clear, significant benefits/changes to existing treatment algorithm.

The models have not considered all the issues raised in my previous response eg benefits of lower dose steroids, reduced risk of flare, reduced risk of adverse events and their consequences. It is rare for a patient with lupus nephritis to survive 69 years, since in the UK as in other countries they have worse outcomes than patients with lupus without nephritis, although UK results are somewhat better now than those from countries where access to care may be limited by financial issues. Cost-effectiveness models for lupus are complex to generate due

to the multiple risks associated with damage from persistent active disease, flares and steroid therapy over time, compounded in lupus nephritis by the frequent co-existence of hypertension as part of the consequences of renal disease due to lupus whether active or chronic and often hard to control and often made worse by steroids and tacrolimus (especially if levels not measured). The risks and costs and implications for patient well-being and lifestyle of needing regular dialysis and/or transplantation have not been adequately considered. Treatments that reduce this risk completely or delay these needs will not only reduce symptoms and costs but will impact very significantly on quality of life and both direct and indirect costs and survival.

- **Are the recommendations sound and a suitable basis for guidance to the NHS?**

Yes - whilst this guidance does not recommend voclosporin at this stage; the review has highlighted gaps in current study data and the need for long-term data.

No because the drug is not recommended for use in the NHS. Voclosporin would offer a significant improvement over current therapies particularly for patients that have failed conventional therapy with mycophenolate for lupus nephritis, and even more so if they have failed other therapies currently used for refractory lupus nephritis disease (such as rituximab and as a way of avoiding need to use cyclophosphamide which has the worse adverse event profile of all the drugs used for severe lupus and lupus nephritis including considerable increased risk of infection, infertility and malignancy). So at the very least this drug should be available for patients with refractory disease that have failed at least 1 and possibly 2 drugs for lupus nephritis and they should be allowed to stay on it for at least one year (since renal response often takes at least 12 months to demonstrate and ensure that it is stable on low dose steroids). It would be preferable to keep patients on the drug for at least one year after achieving renal response before withdrawing the drug gradually to reduce the risk of renal relapse. And if patients do relapse after stopping or reducing the dose , it should be possible to give them another 12 month course before retrying withdrawal as recommended for management of lupus nephritis with other drugs. Outcomes should be determined by standard published clinical renal response criteria without the need for biopsy unless there is uncertainty whether the patient has active disease or chronic damage based on an assessment of all aspects of their lupus disease.

- **Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, sex, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?**

The question was fully explored and addressed to ensure the same access to treatment for all people irrespective of various patient factors.

Lupus nephritis more often affects ethnic minorities, affects them more severely and with higher risks of renal involvment. The lupus nephritis that they have is often harder to treat and these patients have higher background risk of hypertension. Lupus particularly affects women and often presents at a younger age in women from ethnic minorities (especially with African heritage). These are

the patients that have the greatest risk of complications from lupus nephritis, and especially in pregnancy with inadequately treated lupus nephritis and with fertility issues if given cyclophosphamide, so not providing a drug (voclosporin) that has trial evidence of significantly improved outcomes will affect them the most . Given that the drug has been licensed for use in other countries , not allowing patients with refractory lupus nephritis in UK the opportunity to have this drug is discriminatory as the policy will reduce the chances of these ethnic minority patients achieving renal response and remission, which is particularly important before pregnancy as this would enhance their outcomes in pregnancy (as other patients may respond more often with current therapies) .

NICE National Institute for Health and Care Excellence

Voclosporin with immunosuppressive therapies for treating lupus nephritis [ID3962]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on 20 December 2022. Please submit via NICE Docs.

	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Appraisal Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced.
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	NHS England
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None

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NICE National Institute for Health and Care Excellence

Voclosporin with immunosuppressive therapies for treating lupus nephritis [ID3962]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on 20 December 2022. Please submit via NICE Docs.

Name of commentator person completing form:	[redacted]

Comment number	Comments Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
Example 1	We are concerned that this recommendation may imply that ……..
1	**Rheumatology Clinical Advice (first 4 responses)** We hope that there will be a further opportunity for the company to refine its model(s) so that further assessment of this can take place.
2	Unmet need in lupus nephritis: the standard of care arm in the voclosporin studies (mycofenolate/steroids) showed only 20-30% complete response. Long term outcomes have been sown to be poorer in those with poorer initial responses (and in partial vs complete response) so the this does need to be borne in mind in analysis of a model of long term outcomes and transitions between disease states.
3	In recent years, this greater understanding of the importance of obtaining as good a response as possible at the earliest possible stage of disease or as early as possible in a flare has led to higher hurdle/tighter definitions and approach to accepting “good” outcomes. This is shown by the 2019 guideline on lupus nephritis outcomes published by the European League Against Rheumatism and European Renal Association (Fanouriakis et al, Annals Rheumatic Disease 2020). Voclosporin is the only agent showing significant benefit over the current standard of care when meeting these endpoints (Anders et al, abstract, American College of Rheumatology meeting 2022). Furthermore, these endpoints are significantly

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	more stringent than those used in the trials that led to the approvals for mycofenolate in lupus.
4	Steroid use: there has been increasing awareness in Rheumatology clinical practice of the toxicity of steroids, including at lower doses than previously thought, to be detrimental. As a result, the direction of travel of clinical practice is to reduce steroid usage from previous dosing regimens. It has been shown that such high doses of steroids are not necessary or physiologically effective. There is significant clinical practice now using lower dose steroid regimens in lupus nephritis (eg Condon et al, Annals Rheumatic Disease 2013) so it is not quite accurate to comment that the low doses of steroids used in the voclosporin studies do not reflect UK clinical practice. Indeed, a body of opinion considers that the lower dose steroid regimens should be those that we should aim for as standard.
5	**Renal clinical advice:** • has all of the relevant evidence been taken into account? Yes, we feel the relevant evidence, including the current clinical trials data and best available evidence has been taken into account which justify the recommendations made. • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? Yes, we feel these are reasonable interpretations of the evidence. Lupus nephritis is a very heterogenous condition and the different clinical presentations and treatment arms have not been considered fully by the drug company within their trial design. We agree the use of Voclosporin is not recommended based on the evidence provided. We would not use it instead of MMF or as an add on at this stage with the limited evidence for first line treatment. Consideration of its use only if patients are not responding to standard of care therapy later in their treatment course may be appropriate. We agree with the comments around proteinuria not being the best clinical end point. We agree a combination of clinical and histopathological markers would be better

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	though acknowledging a renal biopsy at diagnosis is appropriate but repeated renal biopsy would be too high risk. We agree with the flaws in the clinical and cost effectiveness models presented by the drug company and would not feel assured by the evidence presented to justify its use without further modification to the modelling and further validated evidence. • are the provisional recommendations sound and a suitable basis for guidance to the NHS? Yes, we are happy with the provisional recommendations made and would agree with them as suitable basis for guidance for the NHS. Agree with the steroid usage doses in the trials are not reflective of those used in clinical practice.

Insert extra rows as needed

Checklist for submitting comments

- Use this comment form and submit it as a Word document (not a PDF).
- Complete the disclosure about links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
- Please underline all confidential information, and separately highlight information that is 'commercial in confidence' in turquoise and information that is 'academic in confidence' in yellow. If confidential information is submitted, please submit a second version of your comments form with that information replaced with the following text: 'academic / commercial in confidence information removed'. See the NICE Health Technology Evaluation Manual (section 5.4) for more information.
- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations.
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
- If you have received agreement from NICE to submit additional evidence with your comments on the draft guidance document, please submit these separately.

Note: We reserve the right to summarise and edit comments received during consultations, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

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Voclosporin with immunosuppressive therapies for treating lupus nephritis [ID3962]

A Single Technology Appraisal

EAG appraisal of the company's response to ACD

January, 2023

Produced by	**Peninsula Technology Assessment Group (PenTAG)** **University of Exeter Medical School** **South Cloisters** **St Luke's Campus** **Heavitree Road** **Exeter** **EX1 2LU**
Authors	**Simone Critchlow**[1] **Ash Bullement**[1] **Hollie Wheat**[1] **Sophie Robinson**[2] **Dominic Taylor**[3] **Preetham Boddana**[4] **Anthony Hatswell**[1] **G.J. Melendez-Torres**[2] **Caroline Farmer**[2] [1] Delta Hat Ltd, Nottingham UK [2] Peninsula Technology Assessment Group (PenTAG), University of Exeter Medical School, Exeter [3] North Bristol NHS Trust [4] Gloucestershire Hospitals NHS Foundation Trust
Correspondence to	Caroline Farmer 3.09 South Cloisters, St Luke's Campus, Heavitree Road, Exeter, EX1 2LU; c.farmer@exeter.ac.uk
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Produced by

Peninsula Technology Assessment Group (PenTAG)
University of Exeter Medical School
South Cloisters
St Luke's Campus
Heavitree Road
Exeter
EX1 2LU

Declared competing interests of the authors

None

Rider on responsibility for document

The views expressed in this report are those of the authors and not necessarily those of the NIHR HTA Programme. Any errors are the responsibility of the authors.

This addendum is linked to EAG report

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1. INTRODUCTION

Following deliberation, the NICE committee reached a negative recommendation for voclosporin (VCS) for the treatment of lupus nephritis due to uncertainties in the evidence base, including its cost effectiveness and the way it would be used in practice. Further details concerning the NICE committee recommendation are contained within the Appraisal Consultation Document (ACD).

In this document, the external assessment group (EAG) provide an appraisal of additional evidence presented by the company to address these uncertainties. This included modifications to its base case analysis, additional scenario analyses to explore uncertainties, clarification regarding the anticipated positioning of voclosporin, and an updated patient access scheme (PAS) discount from [redacted]% to [redacted]%. In response to new evidence by the company, the EAG updated its basecase to align with amendments by the company and conducted further scenario analyses with the results of these presented herein.

2. COMPANY'S REVISED MODEL FOLLOWING ACD

2.1. Summary of the company's position and changes to the company base case

The revised base-case analysis and the results presented by the company is provided in Table 1. The revised base-case ICER for VCS plus mycophenolate mofetil (MMF) versus MMF consisted of several edits of updated inputs and calculations (following an internal quality control process) and adjustments to existing options within the model:

- Amended settings
    - Percentage reduction in transplantation rates to 65% every 2 years
        - Transplantation rates were reduced from 90% every 2 years to 65% every 2 years (equivalent to 23.08% per 6 months). This change was in line with the EAG base case settings and the ACD.
    - Updated time-to-treatment discontinuation (TTD) for non-trial comparators
        - This setting assumed equivalence between TTD for non-trial and VCS+MMF. This approach slightly deviated from the EAG's exploratory scenario that assumed that TTD for non-trial comparators was equivalent to TTD for MMF. The company considered the incorporation of TTD equivalent to VCS+MMF as *"several of the non-trial comparators are combination therapies with MMF"*
    - Implementation of random effects analysis
        - In line with the EAG preference, relevant inputs from the random-effects analysis (as opposed to the fixed-effects analysis) were included in the model and now inform the company base case
- Amended model calculations
    - Adjustments to the calculation for adverse event (AE) costs and utilities
        - Following an error identified during technical engagement
    - Amendments to transition calculations
        - Chronic kidney disease (CKD) stage 5 dialysis -> CKD 5 transplant transition probability corrected to align with the referenced publication

- CKD stage 5 dialysis -> Death transition probability corrected to align with the referenced publication
- CKD stage 5 transplant -> CKD 5 dialysis transition probability corrected to align with the referenced publication
- Update to the post-follow-up azathioprine to amend error identified

- Updated costs
  - Alignment with EAG costs and inflation indices

Table 1 - Revised company base case results

Technologies	Total			Incremental			ICER (£/QALY)*
	Costs	LYG	QALYs	Costs	LYG	QALYs	
VCS + MMF	[redacted]	[redacted]	[redacted]	-	-	-	-
MMF	[redacted]	17.40	12.90	[redacted]	[redacted]	[redacted]	£24,267
L-CYC	[redacted]	16.77	12.41	[redacted]	[redacted]	[redacted]	£6,522
H-CYC	[redacted]	16.64	12.32	[redacted]	[redacted]	[redacted]	£5,450
AZA	[redacted]	17.31	12.83	[redacted]	[redacted]	[redacted]	£20,284
RTX + MMF	[redacted]	17.79	13.20	[redacted]	[redacted]	[redacted]	£25,432
TAC + MMF	[redacted]	17.44	12.93	[redacted]	[redacted]	[redacted]	£20,541
TAC	[redacted]	17.50	12.98	[redacted]	[redacted]	[redacted]	£20,289

*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; QALY(s) = quality-adjusted life year(s); RTX = rituximab; TAC = tacrolimus; VCS = voclosporin

Although not presented within the company response, the deterministic incremental results of the company base case are provided in Table 2.

Table 2 - Revised company incremental base case results

Treatment	Costs	QALYs	Incremental Cost	Incremental QALY	ICER
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Excluded treatments					
[redacted]	[redacted]				
[redacted]	[redacted]				
[redacted]	[redacted]				
[redacted]	[redacted]				
[redacted]	[redacted]				

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; QALY(s) = quality-adjusted life year(s); RTX = rituximab; TAC = tacrolimus; VCS = voclosporin

The net health benefit (NHB) and net monetary benefit (NMB) are presented in Table 3.

Table 3: Company 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 company base case							
VCS + MMF							
MMF	[redacted]	[redacted]	£24,267	[redacted]	[redacted]	[redacted]	[redacted]
L-CYC	[redacted]	[redacted]	£6,522	[redacted]	[redacted]	[redacted]	[redacted]
H-CYC	[redacted]	[redacted]	£5,450	[redacted]	[redacted]	[redacted]	[redacted]
AZA	[redacted]	[redacted]	£20,284	[redacted]	[redacted]	[redacted]	[redacted]
RTX + MMF	[redacted]	[redacted]	£25,432	[redacted]	[redacted]	[redacted]	[redacted]
TAC + MMF	[redacted]	[redacted]	£20,541	[redacted]	[redacted]	[redacted]	[redacted]
TAC	[redacted]	[redacted]	£20,289	[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

The EAG noted that the company's model provided in response to the draft guidance removed functionality introduced as part of the EAG's original critique, including switches implemented by the EAG to investigate alternative settings and assumptions that inform the EAG base case and technical engagement analyses. As such, the EAG were unable re-produce all of its previous analyses.

The EAG further identified an error on the 'NMA' sheet of the company's revised model that resulted in some outputs from the random effects analysis not being included within the company base case. These related to the following cells:

- Sheet 'NMA' cells E53:E55
- Sheet 'NMA' cells G53:G55

Amendments to this setting did not appear to influence the company base case and instead informed the lower and upper bounds influencing the one-way (deterministic) sensitivity analysis.

2.2. Summary of scenario analyses provided by the company

The company provided several scenario analyses to explore uncertainty associated with VCS+MMF. These scenarios fell into five overarching categories:

1. Discontinuation of non-trial comparators
2. Treatment duration of VCS+MMF
3. Long-term treatment effect extrapolations for VCS+MMF
4. Response for patients in CKD stages 3b-4
5. The potential impact of attrition bias

Each of these categories are discussed in Section 3.3.

3. EAG APPRAISAL OF THE COMPANY RESPONSE

3.1. Revised PAS

The company provided an updated PAS discount for voclosporin (█%).

3.2. Company revised base case

3.2.1. Use of the random effects NMA

In line with the EAG and NICE committee's preference, the company updated their base case to include outputs from the random-effects NMA. The EAG updated its base case to include this setting.

3.2.2. Discontinuation for non-trial comparators

The company updated its base case for non-trial comparators (all comparators except for MMF) to have TTD based on the TTD curve for VCS+MMF. This deviated from the EAG's exploratory scenario, which assumed non-trial comparators had equivalent TTD to MMF, which the company argued was the most 'appropriate assumption' as several of the non-trial comparators were combination therapies with MMF. The company explored the discontinuation for non-trial comparators set to MMF only in scenario analysis. The EAG disagreed with this justification, as of the six comparators, only two are in combination with MMF (rituximab with MMF and tacrolimus with MMF). Further to this, in their response, the company considered that rituximab + MMF was only an appropriate comparator when considering patients who had not responded (or experienced AEs) to two or more immunosuppressive therapies. The EAG therefore specified TTD for non-trial comparators equivalent to MMF into its revised base case.

3.2.3. Updated kidney transplant rates

In line with the draft guidance, the company amended kidney transplantation rates from 90% over two years to 65% over two years (equivalent to 23.08% every 6 months). This was aligned with the EAG's preferred assumptions.

3.2.4. Updated modelling inputs/calculations following errors identified

Several updates to the company calculations were made. These were implemented to address prior concerns or to fix modelling errors.

- Fixes applied to AEs: In line with the error in AE disutilities identified by the EAG at technical engagement, the company further discovered that this error also related to AE costs. A fix was applied which was accepted by the EAG and incorporated into the EAG revised base case.

- Amendments to azathioprine long-term transitions: The company updated the azathioprine post follow-up transition probabilities as previously the transition from AD CKD1-3a to CR CKD 1-3a was informed by the odds ratio for high-dose cyclophosphamide. The EAG agreed with this fix and accepted it as part of the revised EAG base case.

- Amendments to transition calculations and references: The company identified that two transition probabilities (CKD 5 transplant to CKD 5 dialysis and CKD 5 dialysis to Death) were not transformed properly and used incorrect references. These were updated. A summary of these differences is illustrated in Table 4**Error! Reference source not found.** below. The EAG traced the calculations to their original source, and implemented the changes within its revised base case.

Table 4: Updated transition probabilities and references informing the revised company base case

Transition probability	Company original value in company submission	Original reference	Company updated value at draft ACD response	Updated reference
CKD stage 5 dialysis → Death	7.47%	Sugrue *et al.*, 2019	8.10%	Palmer *et al.*, 2004(1)
CKD stage 5 transplant → CKD stage dialysis	2.96%	Palmer *et al.*, 2004	3.05%	Palmer *et al.*, 2004(1)
CKD stage 5 transplant→ Death	2.62%	Palmer *et al.*, 2004	2.62%	Sugrue *et al.*, 2019(2)

Abbreviations: ACD, appraisal consultation document; appraisal CKD, chronic kidney disease; CS, company submission

- Alignment and update of resource and safety costs: The company provided more details on how costs were included within the model and updated specific values to align with prior EAG comments (costs for gastroenteritis, hypertension and upper respiratory tract infection). Costs for prednisone at 10mg and 30mg were removed as these were not available from eMIT. Within the new version of the model, the EAG traced costs back to their sources and interpreted the process for uplifting costs for current prices. The EAG confirmed alignment across most costs with one discrepancy and one cost that could not be found. The former

related to the cost for kidney transplantation, where the value in the model of £14,530.50 was referenced as the weighted average of LA01A, LA02A and LA03A for kidney transplant, LA12A and LA11Z for pre-transplant, and LA13A and LA14Z for post-transplant. Using this approach, the EAG derived a slightly different estimate of £14,350.79 This discrepancy was minor and was expected to have a minimal impact on cost-effectiveness, however the EAG explored this for completeness (see Table 5). The latter was the AE cost for herpes zoster inputted as £8,868.09 and referenced as Gauthier et al. 2019.(3) This cost could not be found within the cited reference, but the EAG considered this also to have a minimal impact on the cost-effectiveness results. Updates to cost inflation indices and alignment with EAG costs: The company updated the inflation index between 2015 to 2016 to use the values aligned with the EAG. The EAG accepted this.

Table 5: Cost discrepancy in kidney transplantation cost (from NHS cost collection)(4, 5)

<table>
<tr><th>Cost component</th><th>NHS reference cost cited</th><th>Estimate</th><th></th></tr>
<tr><td></td><td></td><td>Company</td><td>EAG</td></tr>
<tr><td>Kidney transplant</td><td>Weighted average LA01A LA02A & LA03A<table><tr><th>Code</th><th>Activity</th><th>Cost</th></tr><tr><td>LA01A</td><td>673</td><td>£14,448</td></tr><tr><td>LA02A</td><td>1165</td><td>£13,774</td></tr><tr><td>LA03A</td><td>684</td><td>£12,837</td></tr><tr><td>Total</td><td colspan="2">£13,699.77</td></tr></table></td><td>£13,699.77</td><td>£13,699.77</td></tr>
<tr><td>Pre-transplant</td><td>Weighted average LA12A & LA11Z<table><tr><th>Code</th><th>Activity</th><th>Cost</th></tr><tr><td>LA11Z</td><td>2,973</td><td>£363</td></tr><tr><td>LA12A</td><td>9,317</td><td>£387</td></tr><tr><td>Total</td><td colspan="2">£381.22</td></tr></table></td><td>£485.51</td><td>£381.22</td></tr>
<tr><td>Post-transplant</td><td>Weighted average LA13A and LA14Z<table><tr><th>Code</th><th>Activity</th><th>Cost</th></tr><tr><td>LA13A</td><td>89,099</td><td>£269</td></tr><tr><td>LA14Z</td><td>3,577</td><td>£280</td></tr><tr><td>Total</td><td colspan="2">£269.80</td></tr></table></td><td>£345.23</td><td>£269.80</td></tr>
<tr><td>Total</td><td></td><td>£14,530.50</td><td>£14,350.79</td></tr>
</table>

Abbreviations: EAG, external assessment group; NHS, national health service

3.3. Company analyses to explore uncertainty in the model

The company provided a multitude of scenario analyses to explore uncertainty within the model. These are discussed in turn throughout this section.

3.3.1. Discontinuation

As well as updating the company base case to consider VCS+MMF TTD for non-trial comparators, the company also explored setting TTD for non-trial comparators equal to MMF alone. As previously outlined, the EAG was unconvinced by the justification provided by the company for the use of VCS+MMF to inform TTD for non-trial comparators that several treatments were in combination with MMF. The EAG noted that this was only two treatments (tacrolimus+MMF and rituximab+MMF), one of which the company stated was unlikely to be an appropriate comparator to voclosporin. Given that the majority of the comparators were monotherapies, the EAG considered it more appropriate to assumed that TTD for non-trial comparators were equivalent to MMF alone. This was incorporated into the EAG revised base case (see Section 3.6), however, the EAG noted that this was still a simplifying assumption and this remained an area of uncertainty in the absence of treatment-specific TTD data.

3.3.2. Treatment duration

The company's model assumed that treatment stopped at 36 months, in line with the availability of AURORA trial data. Clinical advice to the company supported a stopping rule of 36 months, however the draft guidance noted that assuming that treatment stopped at 36 months was arbitrary, and there was uncertainty in the treatment duration dependent on whether VCS was used to induce or maintain remission. In response to the draft guidance, the company conducted two scenario analyses to explore the impact of stopping treatment with VCS at either 12-months or 18-months. In addition, the company conducted 3 scenario analyses using three different evidence sources to inform transition probabilities when stopping treatment at 12-months.

In the analyses, treatment with VCS stopped at either 12- or 18-months. Further to this, three scenarios were considered where VCS was stopped at 12 months with corresponding transition probabilities adjusted to reflect a halt in treatment. Within these scenarios, it was assumed that patients receiving VCS+MMF could not respond after 12 months and could only move from response states back to active disease (with no further movement between CR and PR). Separate analyses were conducted according to the three different evidence sources for transitions from response back to AD after 12 months: an input from the AURORA 2 trial data (5.95% per cycle on the MMF arm); an input from Nee *et al.,* 2015 (1.85% reported as the 6-month transition in the MMF remission arm to relapse(6)); and an input from Yap *et al.,* 2017 (0.94% reported as a 9% relapse rate over 5 years(7)). The company stated that the clinical

data from AURORA 2 were the most robust given these constituted clinical trial data and were aligned with the data used within the company base case. Whilst the EAG agreed with this comment, the EAG disagreed that this was a conservative approach. Rather the EAG considered that the large difference seen between the AURORA trial estimates (5.95%) and the literature values (1.85% and 0.94%) could question the validity of the transitions estimated from AURORA data. The comparability between these rates was questionable, and without further detail it was unclear to the EAG why the transitions from CR to AD in the AURORA trial data were higher than the literature, bringing into question the durability of response achieved within the trial.

Whilst the company explored several scenarios shortening the duration of treatment for VCS, the EAG was tentative about the extent to which these fully addressed the uncertainty raised by the committee. None of the scenarios explored a longer duration of treatment, and more importantly, in line with comments from the draft guidance consultation document, no scenarios were presented which considered re-treatment with VCS over time. As highlighted in the consultation document, re-treatment with VCS to induce response would be both expected and desirable in the future and was not considered within the model. The use of VCS within an induction and maintenance treatment framework was not feasibly explored within the current economic model and the trial was not designed to capture the efficacy of a treatment regime that considered re-treatment. The EAG therefore still considered treatment duration (and corresponding efficacy) an area of uncertainty.

3.3.3. Long-term treatment effect extrapolations

The company provided validation of the model transition probabilities against two sources available within the literature (Tektonidou *et al*., 2016(8) and Gisca *et al*., 2021(9)). The company presented the percentage of patients in end-stage renal disease (ESRD) at 5-years and 10-years. The EAG noted that the values from Gisca *et al.,* 2021 were traceable, however the values from the Tektonidou *et al*., 2016 study were not. Despite this, there were several figures from Tektonidou *et al.*, 2016 where percentages presented by the company appeared similar, and hence, although not explicitly stated how the numbers were determined, the EAG were satisfied that these studies provided a reasonable comparison to validate the model. However, it was unclear to the EAG why the number of patients in ESRD at 15 years presented in the studies (such as those in Tektonidou *et al.*, 2016) were not also used as validation. Further to this, the EAG noted that whilst the final movements to ESRD was a relevant validation approach, the health state occupancy prior to CKD stage 5 was not validated against

any alternative literature, and therefore whilst the values appeared comparable, there was still considerable uncertainty in the time spent in various health states prior to ESRD (further emphasised by the AURORA trial data being limited to 3-years).

Within the company base case, the long-term transition probabilities for VCS+MMF for the CKD stage 1-3a PR and CKD stage 1-3a AD states were assumed equivalent to the data obtained from the AURORA trials for MMF. For the CKD stage 1-3a CR state, the model assumed an average of the VCS+MMF AURORA data and the MMF AURORA data. As a scenario analysis, the company explored the impact of equivalent long-term transition probabilities with all of the CKD stage 1-3a probabilities for VCS+MMF assumed equivalent to the MMF data (from the AURORA trials). The EAG here noted that the prior functionality (and what informed the EAG base case) to consider the application of long-term transition probabilities for both VCS+MMF and MMF arms to be equivalent to the average data from the AURORA study for both arms was not considered and was not included within the model provided by the company. This limited the extent to which a) the uncertainty was explored by the company and b) the EAG was able to independently explore uncertainty and run its technical engagement stage preferred base case settings.

The EAG considered that though scenarios had been explored, there were two types of uncertainty related to the long-term extrapolations. The first related to the duration of the treatment effect, which was explored within the current model framework and was tested by the EAG at previous stages of the appraisal process, and by the company in their response to the draft guidance consultation document. The second related to the uncertainty associated with using short-term data (on both the VCS+MMF and the MMF arm) to inform long-term transitions. This uncertainty could not be addressed within the current model and with the current data available concerning the efficacy of voclosporin. As highlighted in the draft guidance, the long-term efficacy was difficult to establish and extrapolate from the short-term data and as such, there was high uncertainty with both the company's and EAG's approaches to the long-term treatment effect extrapolations.

3.3.4. Response in CKD stages 3b-4

In the absence of literature values, the company consulted with expert clinicians who advised that ~2.5% of patients would achieve some level of response. The company implemented three exploratory scenarios to explore response rate in CKD stages 3b-4. These are:

- Assuming 2.5% of patients per year in CKD stage 3b-4 in AD achieved CR
- Assuming 2.5% of patients per year in CKD stage 3b-4 in AD achieved PR
- Assuming 1.25% of patients per year in CKD stage 3-4 in AD achieve PR and 1.25% achieve CR

The EAG noted that although the description from the company implied that only these transitions were edited, the inclusion of these scenarios relied on several other transitions being populated, and as such, further assumptions were made by the company. The transition probabilities informing the scenarios presented are summarised in Table 6 with the corresponding source/assumption.

Table 6: Transition probabilities from CKD stage 3b-4 PR and CR states

Transition probability	CR = 2.5%	PR = 2.5%	CR = 1.25% PR = 1.25%	Source
CKD stage 3b-4 AD → CKD stage 3b-4 CR	2.50%	N/A	1.25%	KOL assumption explored
CKD stage 3b-4 AD → CKD stage 3b-4 PR	0.00%	N/A	1.25%	KOL assumption explored
CKD stage 3b-4 CR → CKD stage 3b-4 AD	5.95%	N/A	5.95%	AURORA post-follow up transition for CKD stage 1-3a CR – CKD stage 1-3a AD
CKD stage 3b-4 CR → CKD stage 3b-4 PR	0.00%	0.00%	0.00%	Assumption
CKD stage 3b-4 CR → CKD stage 3b-4 Death	3.92%	3.92%	3.92%	Sugrue *et al.*, 2019
CKD stage 3b-4 PR → CKD stage 3b-4 AD	N/A	25.00%	25.00%	AURORA post follow up transition for CKD stage 1-3a CR – CKD stage 1-3a AD
CKD stage 3b-4 PR → CKD stage 3b-4 CR	N/A	0.00%	0.00%	Assumption
CKD stage 3b-4 PR → CKD 3b-4 Death	N/A	3.92%	3.92%	Sugrue *et al.*, 2019

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

As the company outlined in their response, these scenarios were highly uncertain but indicated that the change in response rates had a small impact on the deterministic results. Given the probabilities are non-zero, the EAG would have preferred this setting to have been implemented in the company base case (with corresponding uncertainty captured within sensitivity analysis).

3.3.5. Attrition bias

In line with the committee's suggestions and requests in the draft guidance, the company provided exploratory scenarios to assess the potential directional impact of attrition bias which may have arisen as a result of the discontinuation rates from AURORA 1 (39.5% of people discontinued AURORA 1 and did not enter the AURORA 2 study). The company provided three scenarios:

1. Last observation carried forward (LOCF)
2. Assuming people who had VCS+MMF that were lost to follow-up were non-responders (i.e., moving to AD) while people who had MMF were responders (i.e., moving to CR)

3. Assuming people who had VCS+MMF that were lost to follow-up were responders (i.e., moving to CR) and while people receiving MMF were non-responders (i.e., moving to AD).

The results from the three methods are summarised in Table 7. The results illustrated the uncertainty range and impact of various assumptions for the patients who were lost to follow-up. Although extreme scenarios, scenarios 2 and 3 (labelled as scenario 3b and 3c in the company model) highlighted the extent to which the missing patients may influence the cost-effectiveness of VCS+MMF. Further discussion of the scenarios is provided in the following sections.

Table 7: Company scenario analysis to explore potential impact of attrition bias

Technologies	Pairwise ICERs vs VCS+MMF			
	Company revised base case (no adjustment for attrition)	**Scenario 1 (LOCF)**	**Scenario 2 (VCS+MMF patients move to AD and MMF patients move to CR)**	**Scenario 3 (VCS+MMF patients move to CR and MMF patients move to AD)**
MMF	£24,267	£21,701	Dominated	£5,644
L-CYC	£6,522	£7,199	£1,596,495	£1,246
H-CYC	£5,450	£5,433	£294,418	£847
AZA	£20,284	£18,509	Dominated	£4,949
RTX + MMF	£25,432	£31,007	Dominated	Dominant
TAC + MMF	£20,541	£18,212	Dominated	£3,684
TAC	£20,289	£18,746	Dominated	£2,997

Abbreviations: AZA = azathioprine; CYC = cyclophosphamide; ICER = incremental cost-effectiveness ratio; LOCF, last observation carried forward; L-CYC = low-dose cyclophosphamide; H-CYC = high-dose cyclophosphamide; MMF = mycophenolate mofetil; QALY = quality-adjusted life year; RTX = rituximab; TAC = tacrolimus; VCS = voclosporin

3.3.5.1. Last observation carried forward (LOCF)

The EAG noted that the consideration of the LOCF method resulted in similar results to the company base case approach, with the pairwise ICER vs MMF reducing from £24,267 to £21,707 (results are summarised in Table 7). In some instances, within this scenario the ICER increased (compared to L-CYC the ICER increased from £6,522 to £7,199 and compared to rituximab+MMF the ICER increased from £25,432 to £31,007 (above the willingness to pay threshold). Though the EAG noted that this method seemed broadly appropriate, the EAG queried the implementation of the patient numbers used to inform this scenario. This is with regard to the 18-month transition probability for VCS+MMF from CKD stage 1-3a CR transition to CKD stage 1-3a AD where the base case input indicated that two patients were observed

however the LOCF method indicated only 1 patient was observed. The EAG was unclear as to why the patient number would be less in the LOCF methodology.

3.3.5.2. Assuming VCS+MMF patients lost to follow-up were non-responders and MMF patients were responders

This scenario presented by the company assumed a pessimistic outcome of VCS from AURORA, in that all patients lost to follow-up moved to active disease while all MMF patients lost to follow-up achieved a complete response. This scenario was requested by the committee.

While this is an unlikely scenario, the results of this analysis indicated that VCS+MMF was dominated by all of its comparators (except L-CYC and H-CYC, which had ICERs far above the range that would be considered cost-effective). Results are summarised in Table 7.

3.3.5.3. Assuming VCS+MMF patients lost to follow-up were responders and MMF patients were non-responders

This scenario presented by the company assumed a favourable outcome of VCA from AURORA, in that all patients lost to follow-up achieved CR while all MMF patients lost to follow-up were assumed to move to active disease. As expected, the results of this scenario were more favourable than the base case and all ICERs were less than £20,000 per QALY. Results are summarised in Table 7.

3.4. Transparency in the company model

Following the draft guidance document, the company provided a revised model with clearer illustration and referencing to how literature was used to inform model inputs. This was notably clearer with regard to both transition probabilities estimates and costing inputs (which had later been uplifted). The company also stated that a re-review of the model had been undertaken, although the EAG nevertheless found further errors (see Section 3.2.4).

Overall, the EAG believed that this concern was now addressed and most model inputs were traced to the original source (see Section 3.2 for further details). However, the removal of functionality to return to prior settings and notably the EAG base case heavily limited the EAG's ability to explore previous scenarios and crosscheck against prior model calculations (outside of the company technical engagement [TE] base case).

3.5. Clarification about the positioning of VCS

In its response, the company stated that it considered VCS would be used in clinical practice consistent with the AURORA clinical trial inclusion criteria: i.e., in combination with MMF and corticosteroids as an induction treatment for active LN as either a first-line or subsequent line therapy. This statement clarified that VCS was not intended to be used as a maintenance therapy for LN, though it allowed variation in the line of treatment for induction according to clinician judgement.

Although the company stated that VCS would not be used as a maintenance therapy (i.e. to maintain a CR over time), the EAG considered that the company's anticipated duration of treatment with VCS (36-months) and its explored scenarios (12- and 18-months) were be beyond the typical length of time an induction treatment for LN would be administered. The EAG were therefore of the view that VCS would be used according to the need of the person with LN and clinician preference, which may include both shorter and longer treatment durations. The company conducted scenario analyses to explore the effect of shorter treatment durations on the ICER (12- and 18-months; see Section 3.3.2), though no scenario for a longer treatment duration was feasible due to the lack of longer follow-up data from AURORA to inform transitions in the mode. The company's scenario analyses at 12- and 18-months appeared to show that VCS was within the WTP threshold compared to key comparators, though the implementation of these analyses means that these results were uncertain (see Section 3.3.2).

The license for VCS permits flexibility in the line at which VCS would be used in practice, which the EAG considered may be appropriate given the heterogeneous nature of the condition, and where choice of treatment is informed by both clinicians' and patients' preferences and patient needs. However, the EAG noted that there was no certain evidence for the efficacy of VCS for each individual treatment line. The AURORA clinical trial sample included approximately equal proportions of people who were receiving and not receiving MMF at baseline, and subgroup analyses across the AURORA and AURA-LV trials showed inconsistent but large and statistically significant differences in treatment effect according to its use. The EAG considered that this increased uncertainty about the effect of treatment line of the effectiveness of VCS. The company's model structure also did not allow for exploration of cost effectiveness according to variations in treatment order. The EAG therefore considered the effect of treatment order to be an uncertainty in this appraisal and considered that the way in which VCS would be used in practice to potentially affect its clinical and cost effectiveness. Moreover, as noted in Section

3.3.1, the company did not address the expectation that VCS would be used more than once to re-treat LN during a person's lifetime.

With regard to specific comparators, clinical advice to the EAG was consistent with the response from the company: i.e., that in general, the main comparators for VCS would be MMF in the first line and mycophenolate with tacrolimus in a subsequent line. The EAG was also advised that rituximab would generally not be a comparator to VCS as this is typically used late on the treatment pathway for people who have become unresponsive to multiple lines of treatment. However, the EAG was also advised that alterative treatment ordering may be used in accordance with clinician and patient needs and preferences, and that alternative comparators may nevertheless be appropriate for consideration.

3.6. Factual inaccuracy

In its response, the company suggested that there was a factual inaccuracy in the draft guidance concerning the company's view on the positioning of VCS with tacrolimus. The EAG agreed with the company that the statement was inaccurate. In its submission, the company claimed that voclosporin had a more predictable pharmacokinetic and pharmacodynamic profile than tacrolimus, which would reduce the need for regular monitoring. The company's claim about monitoring has been addressed in earlier EAG responses.

4. EAG UPDATED BASE CASE

As noted within Section 2, the company's model provided in response to the ACD removed functionality introduced as part of the EAG's original critique, including switches implemented by the EAG to investigate alternative settings and assumptions to inform the EAG base case and TE. As such, the EAG were unable to re-produce previous analyses and instead had to adapt its preferred settings. The EAG revised base case is in line with the revised company model, with the exception of the following:

- TTD for all non-trial comparators was assumed to be equivalent to MMF
- For long-term treatment extrapolations, VCS+MMF was assumed to be equivalent to the MMF transitions

The EAG revised base case is presented in Table 8, and the incremental results are shown in Table 9.

Table 8 - Revised EAG base case results

Technologies	Total			Incremental			ICER (£/QALY)*
	Costs	LYG	QALYs	Costs	LYG	QALYs	
VCS + MMF	[redacted]	[redacted]	[redacted]				
MMF	[redacted]	17.40	12.90	[redacted]	[redacted]	[redacted]	£29,973
L-CYC	[redacted]	16.77	12.41	[redacted]	[redacted]	[redacted]	£7,912
H-CYC	[redacted]	16.64	12.32	[redacted]	[redacted]	[redacted]	£6,628
AZA	[redacted]	17.31	12.83	[redacted]	[redacted]	[redacted]	£24,647
RTX + MMF	[redacted]	17.79	13.20	[redacted]	[redacted]	[redacted]	£46,794
TAC + MMF	[redacted]	17.44	12.93	[redacted]	[redacted]	[redacted]	£26,252
TAC	[redacted]	17.50	12.98	[redacted]	[redacted]	[redacted]	£26,738

*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; QALY(s) = quality-adjusted life year(s); RTX = rituximab; TAC = tacrolimus; VCS = voclosporin.

Table 9 - Revised EAG incremental base case results

Treatment	Costs	QALYs	Incremental Cost	Incremental QALY	ICER
MMF	[redacted]	[redacted]			
RTX + MMF	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

VCS + MMF	[redacted]
Excluded treatments	
L-CYC	[redacted]
H-CYC	[redacted]
AZA	[redacted]
TAC + MMF	[redacted]
TAC	[redacted]

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; QALY(s) = quality-adjusted life year(s); RTX = rituximab; TAC = tacrolimus; VCS = voclosporin.

The net health benefit (NHB) and net monetary benefit (NMB) are presented in Table 10.

Table 10: EAG 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 company base case							
VCS + MMF				[redacted]	[redacted]	[redacted]	[redacted]
MMF	[redacted]	[redacted]	£29,973	[redacted]	[redacted]	[redacted]	[redacted]
L-CYC	[redacted]	[redacted]	£7,912	[redacted]	[redacted]	[redacted]	[redacted]
H-CYC	[redacted]	[redacted]	£6,628	[redacted]	[redacted]	[redacted]	[redacted]
AZA	[redacted]	[redacted]	£24,647	[redacted]	[redacted]	[redacted]	[redacted]
RTX + MMF	[redacted]	[redacted]	£46,794	[redacted]	[redacted]	[redacted]	[redacted]
TAC + MMF	[redacted]	[redacted]	£26,252	[redacted]	[redacted]	[redacted]	[redacted]
TAC	[redacted]	[redacted]	£26,738	[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

Results of the one-way sensitivity analysis and probabilistic sensitive analysis are presented in Figure 1 and Figure 2, respectively.

Figure 1: EAG 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

Figure 2: EAG 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

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