National Institute for Health and Care Excellence

Single Technology Appraisal (STA)

Voclosporin with immunosuppressive therapies for treating lupus nephritis [ID3962]

Response to consultee and commentator comments on the draft remit and draft scope (pre-referral)

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Comment 1: the draft remit

Section	Consultee/ Commentator	Comments [sic]	Action
Appropriateness	Otsuka Pharmaceuticals	Yes, it is appropriate to refer this topic to NICE. Lupus nephritis (LN) is an incurable, debilitating and potentially life-threatening disease that can cause permanent kidney damage and develop into chronic kidney disease (CKD) and even end-stage renal disease (ESRD) (Almaani et al. 2017, Fanouriakis et al. 2020). In addition, almost all treatments currently used for LN are prescribed off-label, and there is yet to be any published NICE guidance for the management of LN. References: Almaani S, et al. Clin J Am Soc Nephrol 2017; 12(5): 825-35. Fanouriakis A, et al. Ann Rheum Dis 2020; 79(6): 713-23.	Thank you for your comment. No action needed.
	Novartis Pharmaceuticals	Novartis considers it appropriate to refer this topic to NICE for appraisal.	Thank you for your comment. No action needed.

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	LUPUS UK	Yes, it is appropriate for NICE to appraise the use of voclosporin in treating lupus nephritis. Voclosporin is a new treatment which could be added to the currently very limited range available for managing lupus nephritis. The new therapy could improve health outcomes and quality of life for patients. In a British cohort (HERE), 5-year mortality decreased by 60% during the 30 years between 1975 and 2005, but in the last decade of the study, there was still a substantial (about 5%) 5-year mortality rate, and the rate of end-stage renal disease (ESRD) remained constant (7-8% at 5 years). This suggests that the efficacy of the current therapies is limited and further improvement will not be possible without new, more effective therapeutic approaches, such as voclosporin. The Draft Scope lists the Population(s) as “Adults with active lupus nephritis”. Will this appraisal consider the technology’s use in children and adolescents?	Thank you for your comment. Voclosporin. has been trialled in a population >18 years. However final guidance will be issued in accordance with the marketing authorisation. No action needed.
	UK Renal Pharmacy Group	Nil to comment	Thank you no action needed.
Wording	Otsuka Pharmaceuticals	Yes, the wording is appropriate.	Thank you for your comment. No action needed.
	Novartis Pharmaceuticals	In line with the population suggested for the appraisal, the term “active” [lupus nephritis] could be added to the remit.	Thank you for your comment. Remits are kept reasonably broad, however the population specified in the scope

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			states ‘adults with active lupus nephritis’.
	LUPUS UK	The current wording refers to the Population(s) as: “Adults with active lupus nephritis”. However, there is no indication within the scoping for how disease activity will be measured or whether there is a threshold of disease activity level for eligibility.	Thank you for your comment. The technology section of the scope has been updated to reflect the inclusion criteria of the relevant clinical trial. This specifies adults with class III, IV or V (including mixed class III/V and IV/V) active lupus nephritis.
	UK Renal Pharmacy Group	Nil to comment	Thank you no action needed.
Timing Issues	Otsuka Pharmaceuticals	Otsuka considers this appraisal to be urgent as despite current treatment options, a substantial proportion of patients with LN go on to develop ESRD within 15 years (~10–30%); a highly lethal and debilitating disease which may require kidney dialysis or transplant (Mahajan et al. 2020). In particular, the efficacy and tolerability of immunosuppressant treatment remains suboptimal (e.g. mycophenolate mofetil [MMF] or cyclophosphamide). Although current generation calcineurin inhibitors (CNIs; tacrolimus and ciclosporin A) have shown efficacy in combination with	Thank you for your comment. NICE aims to provide draft guidance to the NHS within 6 months from the date when the marketing authorisation for a technology is granted. NICE has scheduled this topic into its work

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		traditional immunosuppressant treatment, they are otherwise associated with safety limitations and require regular drug monitoring (Peleg et al. 2020). Voclosporin is a novel and innovative next-generation CNI with a consistent pharmacokinetic/pharmacodynamic profile that retains the efficacy benefits associated with CNI treatment and eliminates the need for regular therapeutic drug monitoring associated with current CNIs (Rovin et al. 2021). Voclosporin offers patients and the NHS an important new option in the treatment of patients with LN and can contribute to addressing the unmet need for treatments which are effective in achieving renal response, to preserve kidney function, and minimise the risk of progression to ESRD. References: Mahajan A, et al. Lupus 2020; 29(9): 1011-1020. Peleg Y, et al. Clin J Am Soc Nephrol 2020; 15(7): 1066-72. Rovin BH, et al. Lancet 2021; 397(10289): 2070-80.	programme. For more information please see https://www.nice.org.uk/guidance/awaiting-development/gid-ta10878
	Novartis Pharmaceuticals	No comments	Thank you no action needed.
	LUPUS UK	-	Thank you no action needed.
	UK Renal Pharmacy Group	Nil to comment	Thank you no action needed.

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Additional comments on the draft remit	Otsuka Pharmaceuticals	No additional comments	Thank you no action needed.
	Novartis Pharmaceuticals	No comments	Thank you no action needed.
	LUPUS UK	-	Thank you no action needed..
	UK Renal Pharmacy Group	No comment	Thank you no action needed.

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments [sic]	Action
Background information	Otsuka Pharmaceuticals	The information is an accurate summary of the recommendations published within the 2018 British Society for Rheumatology (BSR) clinical guideline for the management of systemic lupus erythematosus (SLE) (Gordon et al. 2018). Within this guideline, the BSR recommend that patients with LN are managed according to 2012 recommendations by the European League Against Rheumatism and European Renal Association–European Dialysis and Transplant Association (EULAR/ERA-EDTA) (Bertsias et al. 2012, Gordon et al. 2018). However, please note that EULAR have since published updated guidance for the management of SLE and LN (2019 and 2021) which	Thank you for your comments. The background section of the scope has been updated accordingly.

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		contradict some treatment-related information within the background section (Fanouriakis et al. 2020, Fanouriakis et al. 2021). In particular: • The latest EULAR guidance (2019/2021) recommends azathioprine as a maintenance treatment only. • The latest EULAR guidance (2019/2021) recommends rituximab for patients with non-responding/relapsing/refractory disease only. Beyond BSR/EULAR recommendations, the most up-to-date guidelines for the treatment of LN have recently been published by the Kidney Disease: Improving Global Outcomes (KDIGO) Glomerular Diseases Work Group (October 2021). KDIGO 2021 guidelines have an international perspective, but largely reflect the EULAR/ERA-EDTA guidelines (KDIGO, 2021) bar the following key differences: • KDIGO refer to azathioprine as an add-on treatment option for class V active LN only. • KDIGO refer to rituximab as an add-on treatment option for class III–V active LN, but only for the purpose of corticosteroid minimisation. • KDIGO refer to voclosporin in combination with MMF/mycophenolic acid as a treatment option for the initial treatment of class III-V active LN. References: Gordon C, et al. Rheumatology (Oxford) 2018; 57(1): e1-e45. Bertsias GK, et al. Ann Rheum Dis 2012; 71(11): 1771-82. Fanouriakis A, et al. Ann Rheum Dis 2020; 79(6): 713-23. Fanouriakis A, et al. Ann Rheum Dis 2021; 80(1): 14-25. KDIGO. Kidney Int 2021; 100(4S): S1–S276.	

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	Novartis Pharmaceuticals	No comments	Thank you no action needed.
	LUPUS UK	The background information states, “Rituximab may also be considered as initial treatment for people with pure Class V (membranous) lupus nephritis.” However, this is not reflected in the current Clinical Commissioning Policy (HERE). The current Policy indicates that only patients who have failed to respond or have had adverse events to 2 or more immunosuppressive therapies (one of which must be either mycophenolate or cyclophosphamide, unless contraindicated) may be commenced on rituximab. The background information mentions how much more prevalent lupus nephritis is in people from Indo-Asian, Afro-Caribbean and Chinese family backgrounds. However, it does not discuss important differences in disease severity or prognosis. The background information also excludes any mention of the increased prevalence and severity of lupus nephritis in juvenile-onset SLE. We would recommend that you include additional background information in the Scope. Below is some reference material for your use. • The severity of disease and progression to renal failure in patients with lupus nephritis is significantly greater in black and Chinese patients. Neuman et al. (HERE) found the 5-yr renal survival was 72% for black patients with lupus nephritis compared with 91% for white patients (P = 0.001). Renal outcome and the level of immunosuppressant use in Asians were comparable to Afro-American black patients in some studies. Asian patients were also found to have higher overall damage scores compared with white patients. (HERE)	Thank you for your comment. The background section has been updated to reflect the clinical commissioning policy for Rituximab. The background section is intended to provide a brief summary of the condition. The appraisal committee will consider subgroups based on differences in baseline risk of specific health outcomes and where there is evidence that suggests differential cost effectiveness. No action needed. With regard to juvenile-onset SLE: the scope is focused on the adult population only at this stage since the relevant clinical trials were

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		• Contreras *et al.* (HERE) found that black patients were almost twice as likely to have WHO class IV lesions as white patients (51 *versus* 30%). In addition, black patients were three times more likely to double their serum creatinine or reach ESRD (31 *versus* 10%; *P* < 0.05) than white patients. • Austin et al. (HERE) suggested that the poorer renal prognosis in black patients with severe lupus nephritis resulted from the fact that they were more than twice as likely to have "high risk" histology, that is the presence of cellular crescents and interstitial fibrosis, as white patients (29 versus 13%; P < 0.05). • Patients with HLA-DRB1*15, uniquely found in black patients, have a greater likelihood of renal disease. In addition, the presence of FcγRIIA-R131, an allelic variant of the IgG receptor FcγRIIA that results in decreased ability to clear immune complexes, is significantly more frequent among black patients with lupus nephritis. • Juvenile-onset SLE (JSLE) is recognised to have a more active disease course when compared with adult-onset disease and patients have a worse long-term survival. Kidney involvement occurs in over 50% of children. Kidney remission remains suboptimal with only 40–60% of patients achieving complete remission. Kidney flares are seen in over a third of patients. The rate of chronic kidney disease (CKD) 5 is reported to be up to 15% and the presence of lupus nephritis has an established link with an associated increase in mortality. Findings show that current treatment regimens are unable to completely halt the kidney inflammatory process in the majority of patients and this contributes to damage accumulation. (HERE)	restricted to people over 18 years old. The appraisal will appraise the clinical and cost effectiveness of the treatment within its marketing authorisation, which has not been granted at this time.

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	UK Renal Pharmacy Group	Nil to comment	Thank you, no action needed.
The technology/ intervention	Otsuka Pharmaceuticals	The description of the technology is accurate, other than: • The first paragraph should be updated with the following text (**bold** font represents updated text): o "Voclosporin (Lupkynis™; Otsuka Pharmaceuticals) is a calcineurin-inhibitor immunosuppressant that **suppresses** lymphocyte proliferation, T-cell cytokine production, and expression of T-cell activation surface antigens. **In addition, voclosporin is associated with the stabilisation of the renal podocyte actin cytoskeleton.**" • The second paragraph should be updated as follows: o "Voclosporin does not currently have a marketing authorisation in the UK for treating lupus nephritis. It has been studied in a **randomised, placebo-controlled Phase 3** clinical trial in combination with mycophenolate mofetil and **low-dose oral corticosteroids** in people with active lupus nephritis."	Thank you for your comment. The description of the technology and clinical trial has been updated.
	Novartis Pharmaceuticals	No comments	Thank you no action needed
	LUPUS UK	-	Thank you no action needed.
	UK Renal Pharmacy Group	Nil to comment	Thank you no action needed.

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Population	Otsuka Pharmaceuticals	Voclosporin is [redacted] Patients with low severity disease (class I and class II) do not usually require specific immunosuppressive treatment (Fanouriakis et al. 2020, Fanouriakis et al. 2021). The population should be amended to: •"Adults with class III, IV or V (including mixed class III/V and IV/V) active lupus nephritis" There are no subgroups within this population that should be considered separately. References: Fanouriakis A, et al. Ann Rheum Dis 2020; 79(6): 713-23. Fanouriakis A, et al. Ann Rheum Dis 2021; 80(1): 14-25.	Thank you for your comment. The population has not been updated to keep it broad. However, the "the technology" section has been updated to include the inclusion criteria of the relevant clinical trial.
	Novartis Pharmaceuticals	No comments	Thank you no action needed.
	LUPUS UK	The Population has been defined as "Adults with active lupus nephritis". It is not clear from the current definition how disease activity will be measured or what the threshold (eligibility criteria) for access to this treatment may be. The appraisal may need to consider different classes of lupus nephritis as specific subgroups. Existing treatment pathways vary based on the presenting class of lupus nephritis (i.e. patients must be pure class V to have calcineurin inhibitors or rituximab recommended).	Thank you for your comments. Voclosporin has been trialled in a population >18 years with class III, IV or V (including mixed class III/V and IV/V) active lupus nephritis. Although the scope has

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		The Population in the Draft Scope is only adults. Will the appraisal consider the technology's use in children and adolescents? Due to the increased prevalence, severity and morbidity associated with lupus nephritis in juvenile-SLE (see references in our comments about Background Information), we would request that the population is extended to include all people aged 5 and over.	not specified potential subgroups (e.g classification of lupus) the appraisal committee can consider, during its deliberations, whether there are subgroups of individuals for whom the effectiveness evidence suggests differential cost effectiveness. However final guidance will be issued in accordance with the marketing authorisation.
	UK Renal Pharmacy Group	Nil to comment	Thank you no action needed.
Comparators	Otsuka Pharmaceuticals	Included comparators are consistent with those outlined within EULAR guidelines (Fanouriakis et al. 2020, Fanouriakis et al. 2021). • In particular, EULAR recommend MMF/mycophenolic acid [MPA] or intravenous cyclophosphamide in combination with glucocorticoids as standard treatments of active LN; while a CNI (tacrolimus or ciclosporin A) may be used either in combination with MMF or MPA or as monotherapy as a best alternative for the treatment of active LN.	Thank you for your comment. No action needed.

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		• Once patients achieve response, EULAR recommend subsequent maintenance treatment with MMF/MPA, a CNI, or azathioprine (if pregnancy is contemplated). • Non-responding/refractory patients may also receive rituximab (as monotherapy or as add-on therapy to MMF/MPA or cyclophosphamide), or belimumab as an add-on treatment to MMF/MPA or cyclophosphamide. References: Fanouriakis A, et al. Ann Rheum Dis 2020; 79(6): 713-23. Fanouriakis A, et al. Ann Rheum Dis 2021; 80(1): 14-25.	
	Novartis Pharmaceuticals	All the treatments listed in the draft scope are used in the UK for the treatment of lupus nephritis. However, not all of them would be considered standard care. Feedback during the scoping workshop for the proposed technology appraisal of belimumab for treating lupus nephritis [ID2722] seemed to suggest that currently mycophenolate plus corticosteroids is used the most. Azathioprine would not tend to be used as a first-line treatment and rituximab use varies across the UK, with most centres only prescribing it after failure of other treatments. Depending on the timing and outcome of proposed technology appraisal ID2722, belimumab could also be a relevant comparator in an appraisal of voclosporin, if established NHS practice in England by then. We therefore suggest adding “belimumab (subject to ongoing NICE appraisal)” to the list of comparators.	NICE does not routinely include technologies under appraisal as comparators unless final guidance is due to be published imminently. No action needed. Technologies do not need to have a marketing authorisation

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		Several of the comparators listed in the draft scope (mycophenolate, azathioprine, rituximab) do not currently have a marketing authorisation in the UK for this indication. This information could be added.	to be considered a comparator. No action needed
	LUPUS UK	The Comparators listed within the Draft Scope are currently used in the NHS for the treatment of lupus nephritis. According to the BSR Guidelines for the Management of Lupus in Adults, calcineurin inhibitors (ciclosporin, tacrolimus) or rituximab are recommended for pure class V nephritis as alternative options or for non-responders to other treatments. This means that the population who have received these treatments may potentially have more severe and/or refractory disease than the trial population for voclosporin. It is worth noting that rituximab is currently not licensed for the treatment of SLE (BNF 2021) but is available as a treatment option through routine commissioning for refractory SLE in adults and post-pubescent children. A comparison with rituximab will be difficult because of weak evidence for the efficacy of rituximab. Those of black African/Caribbean ethnicity may be a predictor of poor response to rituximab (HERE). A relatively large proportion of black patients (26%) may partly explain the negative results of the LUNAR randomised controlled trial with rituximab compared to the positive data reported in observational studies mostly in European white patients.	Thank you for your comment. They have been noted. The appraisal committee will normally be guided by established practice in the NHS when considering the appropriate comparators. The appraisal committee can consider as comparators technologies that do not have a marketing authorisation for the indication defined in the scope when they are considered to be part of established clinical practice for the indication in the NHS.

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		Due to the heterogeneity and sometimes refractory nature of SLE, it is not possible to describe any of the currently available treatments as 'best alternative care'.	Comment noted. This can be considered by the appraisal committee in its deliberations. Comment noted. The committee can explore the heterogeneity using subgroups potentially, but could depend on the wording specified in the marketing authorisation.
	UK Renal Pharmacy Group	Nil to comment	Thank you no action needed.
Outcomes	Otsuka Pharmaceuticals	The outcome measures defined in the scope are appropriate and should capture the most important health-related benefits of voclosporin. However, we note that any potential effect of voclosporin on the incidence of ESRD may be demonstrated as an indirect effect (e.g. through economic modelling) since it was not feasible to accurately measure the impact of voclosporin on ESRD incidence within the timeframe of the Phase 2 and Phase 3 trials.	Comment noted. No action needed.
	Novartis Pharmaceuticals	We agree that the listed outcomes are relevant. In addition to the incidence of end-stage renal disease, we suggest also adding time to end-stage renal disease, as a delay in kidney failure and consequently in the need for dialysis or a kidney transplant would be considered of value to patients and carers, as	Thank you for your comment. The list of outcomes in the scope is not intended to be

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		well as the NHS. A potential benefit in terms of reducing risk of organ damage would also be a relevant outcome and we propose to add this.	exhaustive, the appraisal committee can consider other outcomes if appropriate. No action needed
	LUPUS UK	An outcome measure that is not currently included is 'access to treatment'. It is worth noting that some currently used therapies, such as rituximab, can present significant barriers to access. Rituximab can only be administered intravenously at hospital infusion clinics. This can have geographical and financial barriers associated with it, resulting in those from poorer socioeconomic groups being unable to accept the treatment if offered. As an oral therapy, voclosporin does not present these same barriers to access. "Adverse effects of treatment" is listed as an outcome measure, which we would expect to include rates of infection due to immunosuppressive qualities of treatments. We believe that this should be expanded to include reports of vaccine-preventable infections. Early findings from studies examining efficacy of COVID-19 vaccination in immunosuppressed groups have indicated that rituximab and cyclophosphamide may be attributed with lower vaccine efficacy. As an immune-suppressing therapy, we would expect voclosporin to potentially reduce the protection offered by vaccination. However, the degree to which it does this is important. If patients taking voclosporin have reasonable vaccine responses, it should be considered favourably for this patient group – especially due to kidney disease being recognised as a significant risk factor for serious disease from COVID-19 infection. "Health-related quality of life" is listed as an outcome measure. It is very important that this is measured appropriately for a fair comparison of outcome	Thank you for your comment. The outcome measures in the scope describe the principal health outcome measures appropriate for the analysis; access to treatment is not a health outcome measure and so it not relevant. No action needed. The list of outcomes provides a summary of main outcomes and is not intended to be an exhaustive list. The appraisal committee can consider other outcomes if appropriate. The EQ-5D is the preferred measure of health-related quality of

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		measures to be made. EQ-5D has been reported to "lack sensitivity or fail to capture important aspects of health in SLE" (HERE).	life. If an alternative measure is used evidence must be provided that shows why EQ-5D is not appropriate. A detailed account of how the alternative measure was generated, its validity and how it affects utility values should also be provided.
	UK Renal Pharmacy Group	Nil to comment	Thank you no action needed.
Economic analysis	Otsuka Pharmaceuticals	The economic analysis suggested is appropriate. LN is a progressive disease with potential life-long implications, particularly with respect to ESRD. In line with the reference case, the appropriate time horizon for estimating clinical and cost-effectiveness in this appraisal is lifetime.	Thank you for your comment. No action needed.
	Novartis Pharmaceuticals	No comments	Thank you no action needed.

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	LUPUS UK	See above comments (under Outcomes) concerning appropriate methods for measuring quality of life in SLE patients.	Thank you for your comment. No action needed.
	UK Renal Pharmacy Group	Nil to comment	Thank you no action needed.
Equality and Diversity	Otsuka Pharmaceuticals	No equality issues identified.	Thank you for your comment. No action needed.
	Novartis Pharmaceuticals	No comments	Thank you no action needed.
	LUPUS UK	As mentioned in our comments under 'Background Information' lupus nephritis affects people of all ethnic groups but is more prevalent and has poorer outcomes in people of African, Caribbean, and Chinese heritage. People of black African/Caribbean heritage are also at a higher risk of developing diabetes and hypertension. It should be considered whether steroid-sparing treatments such as voclosporin could have additional advantages over standard treatments by reducing some adverse effects and risks of comorbidities – especially considering the high dependence on corticosteroids in current standard therapy. SLE disproportionately affects women and commonly presents in those of childbearing age. Lupus nephritis is also much more prevalent in juvenile-SLE. Cyclophosphamide is still used to treat lupus nephritis despite presenting a risk of infertility. The role of voclosporin in the treatment of young	Thank you for your comment. It has been noted in the equality impact assessment form that lupus nephritis is more common among people with Indo-Asian, African, Caribbean and Chinese family backgrounds and women. The committee will consider these factors during the appraisal.

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		patients should be carefully considered to reduce this adverse treatment effect.	
	UK Renal Pharmacy Group	Nil to comment	Thank you, no action needed.
Other considerations	Otsuka Pharmaceuticals	No further considerations are requested.	Thank you for your comment. No action needed
	Novartis Pharmaceuticals	No comments	Thank you, no action needed.
	LUPUS UK	-	Thank you no action needed.
	UK Renal Pharmacy Group	1. Therapeutic drug monitoring is not required for voclosporin compared to other CNIs, such as tacrolimus and ciclosporin. However, regular eGFR assessment is still necessary according to the product literature (e.g., every 2 weeks for the first month, and every 4 weeks thereafter). 2. Voclosporin should be avoided in pregnancy due to the alcohol content contained within the drug formulation. 3. High pill burden as voclopospin is only available in 7.9mg capsule and the starting dose is 23.7mg twice daily. Therefore, total quantity required per day is 6 capsules. 4. Voclosporin capsules can only be swallowed whole. Oral administration may be challenging in those with nil oral route or swallowing difficulties. Other comparators such as tacrolimus can be given in an alternative route, such as sublingually or intravenously. And ciclosporin (Neoral) is available	Thank you for your comment. These aspects (points 1-6) should be included in evidence submissions will be considered by Evidence Review Group and the appraisal committee. The committee can consider the issues with any requirements for alternatives in people

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		in oral solution, therefore dose can be administered via enteral feeding tube if required. 5. In the US, the cost per patient per year is estimated to be around $92,000. The cost of voclosporin is significantly higher compared to other existing CNIs, such as ciclosporin (Vanquoral) which is estimated to be around £500 - £800. Cost implication would be further complicated by the duration of treatment. 6. Blueteq should be considered to ensure the appropriateness of its prescribing.	who cannot swallow. This has been highlighted in the equality impact assessment form. No changes to the scope are needed.
Innovation	Otsuka Pharmaceuticals	Yes, voclosporin is innovative in its potential to make a significant and substantial impact. Episodes of active LN cause the irreversible loss of kidney nephrons, resulting in an earlier onset of ESRD and a reduction in the overall lifespan of the kidney (Anders et al. 2020). For this reason, EULAR guidelines highlight the need to control LN in a timely manner (i.e. target a reduction in proteinuria within 3 months, and achieve a target urine protein creatinine ratio [UPCR] of ≤0.5 mg/mg within 12 months) (Fanouriakis et al. 2020, Fanouriakis et al. 2021). Standard of care (SoC) treatment with traditional immunosuppressants (MMF or cyclophosphamide) is associated with sub-optimal clinical response rates and a slow treatment response, thereby extending the length of time that a patient is exposed to active LN and nephron damage (Rovin et al. 2021). CNIs have demonstrated greater clinical response rates and a shorter time to response when used in combination with an SoC immunosuppressant (Liu et al. 2015). However, currently available CNIs are also associated with key safety limitations; including hypertension, kidney dysfunction/nephrotoxicity, and several metabolic disorders such as glucose intolerance, diabetes, and dyslipidaemia (Peleg et al. 2020). In addition, they are associated with a narrow therapeutic index (i.e. the level of exposure required for efficacy is	Thank you for your comment. During the development of the appraisal, the committee will consider the degree to which voclosporin is an innovative technology when making its recommendations. No action needed.

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		similar to that associated with toxicity), and so they require monthly therapeutic drug monitoring (Schiff et al. 2007). Voclosporin is an effective next-generation CNI which incorporates a modification to a functional group of ciclosporin A; leading to a four-fold increase in immunosuppressive potency, faster metabolite elimination, and fewer CNI-associated side effects (Mayo et al. 2013, Rovin et al. 2019). Critically, Phase 3 data indicates that the addition of voclosporin to SoC immunosuppressant therapy leads to improved renal response rates compared to immunosuppressant therapy alone (complete renal response: 41% vs 23% [p<0.001], respectively) (Rovin et al. 2021). Furthermore, patients in the voclosporin arm responded far more rapidly (median time to UPCR ≤0.5 mg/mg: 169 days vs 372 days [p<0.001], respectively) (Rovin et al. 2021). Moreover, voclosporin has fewer safety limitations than currently available CNIs. Voclosporin is associated with a lower magnitude of CNI-associated adverse events, a lower risk of metabolic disorders such as hypertriglyceridemia and diabetes, and does not appear to cause nephrotoxicity (Mayo et al. 2013, Rovin et al. 2021). Increased potency, and decreased metabolite exposure also means that voclosporin has a predictable pharmacokinetic and pharmacodynamic profile, which is associated with a broader safety margin/therapeutic index relative to currently available CNIs. Therefore, unlike other CNIs, therapeutic monitoring of drug levels is not required for voclosporin (Rovin et al. 2019). For the above reasons, voclosporin offers the NHS an alternative to currently available CNIs, and the opportunity to achieve renal remission in more patients, and more rapidly compared to current SoC. In turn, voclosporin will help to delay irreversible kidney damage associated with active LN.	

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		Voclosporin is expected to be the first and only CNI to be indicated for patients with LN specifically. References: Anders H, et al. Nature Reviews Disease Primers 2020; 6(1): 1-25. Fanouriakis A, et al. Ann Rheum Dis 2020; 79(6): 713-23. Fanouriakis A, et al. Ann Rheum Dis 2021; 80(1): 14-25. Liu Z, et al. Annals of internal medicine 2015; 162(1): 18-26. Schiff J, et al. Clin J Am Soc Nephrol 2007; 2(2): 374-84. Peleg Y, et al. Clin J Am Soc Nephrol 2020; 15(7): 1066-72. Rovin BH, et al. Kidney Int 2019; 95(1): 219-31. Mayo PR, et al. J Clin Pharmacol 2013; 53(8): 819-26. Rovin BH, et al. Lancet 2021; 397(10289): 2070-80.	
	Novartis Pharmaceuticals	No comments	Thank you no action needed.
	LUPUS UK	-	Thank you no action needed.
	UK Renal Pharmacy Group	Nil to comment	Thank you no action needed.

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Questions for consultation	Otsuka Pharmaceuticals	**Have all relevant comparators for voclosporin with immunosuppressives been included in the scope?** • **Which treatments are considered to be established clinical practice in the NHS for lupus nephritis?** Yes – all relevant comparators have been included in the scope. The BSR have published the only national guideline for the management of mild, moderate, and severe SLE in adults (2018). Within this guideline, the BSR recommended that patients with LN should be managed according to European guidance developed by the EULAR/ERA-EDTA (described above within the 'Comparators' section). Clinical practice within the NHS is generally aligned with BSR/EULAR guidelines and international guidelines published by KDIGO. However, LN treatment selection is driven by patient-related factors (e.g. treatment response, side effects, and pregnancy-planning) and clinicians may therefore deviate from recommendations contained within each guideline. **Are the outcomes listed appropriate?** Yes. The outcomes listed are appropriate. **Are there any subgroups of people in whom voclosporin with immunosuppressives is expected to be more clinically effective and cost effective or other groups that should be examined separately?** • **Should different classes of lupus nephritis be considered as specific subgroups?** No. different classes of LN should not be considered as specific subgroups. Otsuka are not aware of any particular subgroups of interest.	Please refer to responses above relating to these points.

Section	Consultee/ Commentator	Comments [sic]	Action
		Where do you consider voclosporin with immunosuppressives will fit into the existing NICE pathway? Otsuka expect voclosporin in combination with immunosuppressive therapies (MMF and corticosteroids) to be an additional treatment option for patients with LN alongside MMF/MPA and cyclophosphamide-based treatments for the treatment of class III, IV or V (including mixed class III/V and IV/V) LN. In particular, voclosporin should be used ahead of other CNI-based treatment due to its improved immunosuppressive potency, tolerable safety profile, and broader therapeutic index which eliminates the need for regular therapeutic drug monitoring. **Do you consider voclosporin with immunosuppressives to be innovative in its potential to make a significant and substantial impact on health-related benefits and how it might improve the way that current need is met (is this a 'step-change' in the management of the condition)?** Yes, please refer to above 'Innovation' section. **Do you consider that the use of voclosporin with immunosuppressives can result in any potential significant and substantial health-related benefits that are unlikely to be included in the QALY calculation?** Yes, the benefits of voclosporin are likely to extend beyond the domains considered within the QALY calculation. • LN typically arises during a patient's prime working years and is associated with considerable carer burden and societal impact (Aghdassi et al. 2011). The debilitating nature of LN means that the majority of patients are not employed, while many who are employed regularly miss days of work (Aghdassi et al. 2011). Similarly, carers of patients with LN have reported time off work to provide care, and a negative impact on financial status and social activity (Kent et al. 2017). The disease is particularly impactful for	

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		patients who progress to ESRD, a disease that qualifies as a disability and requires dialysis or transplant. As such, it may affect a patient's ability to gain or stay in employment and families/carers may experience additional quality of life impairment. • Many patients with LN are women of childbearing age. Pregnancy associated with LN is often a major cause for concern among patients, as active LN is associated with poor maternal and foetal outcomes (Lightstone and Hladunewich 2017). References: Anders H, et al. Nature Reviews Disease Primers 2020; 6(1): 1-25. Aghdassi E, et al. J Rheumatol 2011; 38(4): 658-66. Kent T, et al. Lupus 2017; 26(10): 1095-100. Lightstone L, Hladunewich MA. Seminars in nephrology; 2017: Elsevier; 2017. p. 347-53. **To help NICE prioritise topics for additional adoption support, do you consider that there will be any barriers to adoption of this technology into practice? If yes, please describe briefly.** No. Otsuka are not aware of any barriers to the adoption of voclosporin.	
	Novartis Pharmaceuticals	*Have all relevant comparators for voclosporin with immunosuppressives been included in the scope?* Belimumab (subject to ongoing NICE appraisal) could be added to the list of comparators. Please also see above comments to the 'Comparators' section. *Which treatments are considered to be established clinical practice in the NHS for lupus nephritis?*	Please refer to responses above relating to these points.

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		Feedback during the scoping workshop for the proposed technology appraisal of belimumab for treating lupus nephritis [ID2722] seemed to suggest that currently mycophenolate plus corticosteroids is used the most. Please also see above comments to the 'Comparators' section. *Are the outcomes listed appropriate?* We consider the listed outcomes appropriate, with the potential to add further relevant outcomes. Please see above comments to the 'Outcomes' section. *Where do you consider voclosporin with immunosuppressives will fit into the existing NICE pathway?* We expect that voclosporin, if recommended by NICE for the full population under assessment, would be used for biopsy-proven active lupus nephritis class III, IV, and/or V in addition to immunosuppressive standard therapies, in line with the inclusion criteria of the relevant clinical trial.1 1 A Randomized, Controlled Double-blind Study Comparing the Efficacy and Safety of Orelvo (voclosporin) (23.7 mg Twice Daily) with Placebo in Achieving Renal Response in Subjects with Active Lupus Nephritis. Study protocol version 2.0. Available at: https://clinicaltrials.gov/ProvidedDocs/99/NCT03021499/Prot_002.pdf [Date accessed: 30 Nov 2021] *NICE intends to appraise this technology through its Single Technology Appraisal (STA) Process. We welcome comments on the appropriateness of appraising this topic through this process.* We agree that the STA process is appropriate for this appraisal.	
	LUPUS UK	Any questions we feel able to comment on have been addressed in appropriate sections above.	Thank you no action needed.

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	UK Renal Pharmacy Group	Nil to comment	Thank you no action needed.
Additional comments on the draft scope	Otsuka Pharmaceuticals	No additional comments.	Thank you no action needed.
	Novartis Pharmaceuticals	Where applicable, consistency with the final scope of the proposed appraisal of belimumab for treating lupus nephritis [ID2722] should be ensured.	Thank you for your comment. NICE recognises the importance of adopting a consistent approach to appraisals. No action needed
	LUPUS UK	Voclosporin should not only be appraised on the basis of cost effectiveness related to comparator treatments. As a heterogeneous disease with varied treatment responses, there is an unmet need for patients who are refractory to other available treatments. If voclosporin was not found to be more cost effective than comparators, it should still be made available through the NHS, at the very least, for those patients with no other feasible treatment options.	Thank you for your comment. The appraisal committee will considered whether there are subgroups of individuals for whom the effectiveness evidence suggests differential cost effectiveness. No action needed.

Section	Consultee/ Commentator	Comments [sic]	Action
	UK Renal Pharmacy Group	N/A	Thank you no action needed.

The following consultees/commentators indicated that they had no comments on the draft remit and/or the draft scope

n/a