# Voclosporin: a novel calcineurin inhibitor for the treatment of lupus nephritis

Gelder, T. van; Lerma, E.; Engelke, K.; Huizinga, R.B.

EXPERT REVIEW OF CLINICAL PHARMACOLOGY
2022, VOL. 15, NO. 5, 515–529
https://doi.org/10.1080/17512433.2022.2092470

Taylor & Francis
Taylor & Francis Group

DRUG PROFILE

OPEN ACCESS Check for updates

# Voclosporin: a novel calcineurin inhibitor for the treatment of lupus nephritis

Teun van Gelder[a], Edgar Lerma [b], Kory Engelke[c] and Robert B. Huizinga[c]

[a]Department of Clinical Pharmacy & Toxicology, Leiden University Medical Center, Leiden, The Netherlands; [b]Section of Nephrology, University of Illinois at Chicago College of Medicine/Advocate Christ Medical Center, Chicago, IL, USA; [c]Department of Research, Aurinia Pharmaceuticals Inc, Victoria, British Columbia, Canada

**ABSTRACT**

**Introduction:** Lupus nephritis (LN) is a severe manifestation of systemic lupus erythematosus. Standard-of-care immunosuppressive therapies achieve poor complete renal response (CRR) rates, with considerable toxicity. This article reviews voclosporin, a novel oral calcineurin inhibitor (CNI) approved for treatment in adults with active LN by the US Food and Drug Administration (the FDA) in January 2021.

**Areas covered:** This review summarizes the chemical properties, pharmacokinetics, and pharmacodynamics of voclosporin, and its efficacy and safety in LN, based on literature review covering PubMed searches, manufacturers' websites, and documents produced by the FDA.

**Expert opinion:** Voclosporin is a CNI with a consistent pharmacokinetic–pharmacodynamic relationship resulting from enhanced calcineurin binding and reduced drug and metabolite load. This profile permits therapeutic efficacy in LN at a dose associated with relatively low calcineurin inhibition, and therefore a potentially improved safety profile. Pivotal trials demonstrated a significant benefit of adding voclosporin to standard therapy, with rapid reduction in proteinuria, and a clinically meaningful and significantly higher CRR rate at 1 year. At approved doses for LN, potential advantages of voclosporin versus historical experience with CNIs include lack of need for therapeutic drug monitoring, benign metabolic, lipid and electrolyte profile, and no impact on mycophenolate mofetil levels.

**ARTICLE HISTORY**
Received 20 December 2021
Accepted 8 June 2022

**KEYWORDS**
Calcineurin inhibitor; lupus nephritis; mycophenolate mofetil; proteinuria; systemic lupus erythematosus; voclosporin

## 1. Introduction

Systemic lupus erythematosus (SLE) is a chronic inflammatory disease that can affect any organ, but often injures the kidney [1]. Lupus nephritis (LN) occurs in around 40% of patients with SLE, though incidence varies between different regions of the world and between different races and ethnicities, with Asian, Black, and Hispanic patients at higher risk than Whites [1,2]. In the USA, an estimated 50–60% of adults with SLE will develop LN during the first 10 years of disease [3]. Lupus nephritis is a major risk factor for morbidity and mortality in SLE; 10–30% of patients with LN develop end-stage kidney disease (ESKD), and presence of LN in patients with SLE reduces 10-year survival from 92% to 88% [2–4].

Clinical presentation of LN may be silent, characterized by urinary abnormalities (e.g. hematuria, mild proteinuria), or more overt, with nephrotic syndrome (heavy proteinuria [>3.5 g/24 h] and hypoalbuminemia [<3 g/dL], with edema and hyperlipidemia in most cases), acute nephritic syndrome, or progressive renal insufficiency [5–7]. Renal biopsy is important in the diagnosis of LN as it enables the histological classification (class I–VI) and evaluation of disease activity and chronicity that form the basis for treatment decisions [3,8].

The European League Against Rheumatism/European Renal Association–European Dialysis and Transplant Association (EULAR/ERA–EDTA) recommendations published in 2019 advocate immunosuppressive treatment in active class III (with or without class V) or IV (with or without class V) LN, with or without coexisting histological chronicity; for pure class V LN, immunosuppression is recommended for patients with nephrotic-range proteinuria (>3.5 g/24 h) and in those with proteinuria >1 g/24 h despite the use of renin–angiotensin–aldosterone system blockers [6,9]. Treatment goals set by EULAR/ERA-EDTA are based on proteinuria, the best single predictor of long-term renal outcome, with goals of ≥25% reduction in proteinuria by 3 months, ≥50% reduction by 6 months, and a target of complete renal response (CRR), defined as proteinuria <0.5–0.7 g/24 h with near-normal glomerular filtration rate (GFR), by 12 months [9,10]. Treatment agents covered in the EULAR/ERA-EDTA recommendations include mycophenolate mofetil (MMF), cyclophosphamide (CY), azathioprine (AZA), and glucocorticoids (GC), though their use is off-label [9].

Guidelines for management of glomerular disease published in 2021 by Kidney Disease Improving Global Outcomes (KDIGO) include the management of LN; many of the recommendations are similar to the EULAR recommendations [11–13]. The KDIGO guidelines define CRR as proteinuria <0.5 g/g measured as urine protein-to-creatinine ratio (UPCR) from a 24-h urine collection and stabilization of estimated GFR (eGFR) to within 10–15% of baseline; the guidelines point out that the common criteria of response in LN are based on clinical thresholds and timelines that may be optimistic and suggest clinicians can reasonably allow 18–24 months to achieve CRR if patients are improving. Recommended initial

**CONTACT** Edgar Lerma nephron0@gmail.com

This article has been republished with minor changes. These changes do not impact the academic content of the article.

**Article highlights**

- Voclosporin is a novel calcineurin inhibitor (CNI), the first CNI to be approved in the USA for the treatment of adults with active lupus nephritis (LN).
- Voclosporin has a dual mechanism of action in LN: immunosuppressive, via inhibition of T-cell activation, and antiproteinuric, via stabilization of kidney podocytes.
- Potential advantages of voclosporin over traditional CNIs include a consistent, predictable pharmacokinetic–pharmacodynamic relationship that eliminates the need for therapeutic drug monitoring, and an improved lipid, glucose, and metabolic profile.
- The absence of pharmacokinetic interaction between voclosporin and mycophenolate mofetil (MMF) means they can be administered concomitantly, without MMF dosage adjustment and with no risk of mycophenolic acid analog-related side effects after voclosporin discontinuation.
- In clinical trials, addition of voclosporin to standard-of-care therapy (MMF plus glucocorticoids) improved complete renal response rate (CRR), with a rapid reduction in proteinuria (an outcome known to be associated with improved long-term outcomes).
- An adverse event associated with voclosporin is reduction in estimated glomerular filtration rate, a known effect of CNIs that may be managed with dose modification.

treatment for proliferative LN is GC plus low-dose intravenous CY or mycophenolic acid (MPA) analogs (MPAA); in patients with baseline eGFR ≥45 mL/min/1.73 $m^2$, voclosporin can be added to MPAA and GC as initial therapy for 1 year [12].

The Asia-Pacific League of Associations for Rheumatology (APLAR) consensus statements on the management of SLE, published in 2021, were developed to guide health-care professionals in the Asia-Pacific region, where factors such as infection risk and reduced tolerance of immunosuppressive medications influence therapeutic decisions among Asian patients [14]. Recommended initial treatment for class III, IV or class V (with significant proteinuria) LN is GC plus standard dose intravenous CY or MMF (with dose adjusted for body weight); low-dose intravenous CY or tacrolimus, in combination with GC, are second-line therapies.

Only 10–40% of patients achieve CRR with previously available standard-of-care therapeutic options (MMF or CY, both in combination with GC) [1,15–17]. Although risk of ESKD in patients with LN in developed countries declined from the 1970s to the mid-1990s, at least in part due to the increased use of immunosuppressive treatments, the risk then plateaued, before increasing in the late 2000s; 22% of contemporary patients with LN will develop ESKD within 15 years of diagnosis, with the rate rising to 44% in those with class IV LN [4]. In addition to the poor response rates, standard-of-care therapy, particularly the use of high-dose GC, is associated with high rates of adverse events (AEs) [18,19].

## 2. Overview of treatment options

With the limitations of previously available standard-of-care therapies, more recent approaches in LN have focused on combining new immunosuppressive agents with standard regimens and reducing GC exposure to reduce toxicity [12,19]. Two therapies have been approved for LN in the USA: belimumab, which is also approved in Europe, was approved by the US Food and Drug Administration (the FDA) in 2020 for patients with active LN receiving standard therapy; voclosporin was approved by the FDA in January 2021 for adults with active LN in combination with a background immunosuppressive regimen [20–23].

Belimumab is a human monoclonal antibody specific for B lymphocyte stimulator protein (also known as B-cell activating factor) [16]. Belimumab is indicated in the USA and Europe as add-on therapy for the treatment of adult patients with active LN [21,22]. Obinutuzumab is an investigational B-cell-targeting agent, a Type II anti-CD20 monoclonal antibody. Obinutuzumab showed activity in a Phase II study in proliferative LN when added to standard therapies and is now in Phase III development (NCT04221477) [24].

The calcineurin inhibitors (CNIs) cyclosporine and tacrolimus have long been used in patients receiving organ transplants and in autoimmune diseases despite a well-characterized safety profile that includes acute and chronic nephrotoxicity, hypertension, electrolyte disturbances (including hyperkalemia and hypomagnesemia), dyslipidemia (particularly cyclosporine) and hyperglycemia/diabetes (tacrolimus). These toxicities relate to the effects of calcineurin inhibition outside of immunosuppression and may necessitate dosage reduction [25–31]. Cyclosporine and tacrolimus have been investigated as therapy in LN, mainly in Asian populations, in short-term studies with higher steroid doses [1,32–36]. A systematic review has found higher CRR rates with tacrolimus plus GC than CY plus GC, but no difference between tacrolimus plus GC and MMF plus GC; multitarget therapy with tacrolimus, MMF and GC was associated with higher CRR rate than CY plus GC [37]. The EULAR/ERA-EDTA 2019 recommendations cite MMF plus CNI (tacrolimus) as a therapeutic option, but tacrolimus was not recommended at that time as a first-line treatment because of the lack of controlled data in non-Asian populations, and the need for longer-term studies [9]. The more recently published KDIGO guidelines reserve triple therapy with reduced-dose MPA, GC, and tacrolimus/cyclosporine for patients who cannot tolerate standard-dose MPA or are unfit for or will not use CY-based regimens [12]. Another limitation of tacrolimus and cyclosporine (which require therapeutic drug monitoring) is that the optimal blood trough concentration in LN has not been established; target tacrolimus concentrations used in studies in Asian populations have largely been chosen to avoid toxic effects and are based upon transplant literature [11,38].

Voclosporin is a novel CNI, approved by the US FDA for the treatment of adults with active LN in combination with background immunosuppressive therapy on the basis of large, global, multiethnic trials in which it was given in combination with MMF and low dose GC (Table 1) [18,20,39].

## 3. Introduction to voclosporin

### 3.1. Chemistry

The two legacy CNIs, cyclosporine and tacrolimus, have different chemical structures, and their pharmacological effect, although similar, is mediated via different cytoplasmic receptors: cyclosporine is a cyclic peptide that binds to cyclophilin,

Table 1. Clinical trials of voclosporin in lupus nephritis.

| Study | Design | Cohort | *N* | Treatment | Primary endpoint | Outcome |
|---|---|---|---|---|---|---|
| AUVCS-2018-01 | Phase I, open-label, multicenter | Adults with SLE ± history of LN; on MMF 2 g/day for ≥28 days | 24 (8 with history of LN) | Voclosporin 23.7 mg BID for 7 days + 2 g/day MMF | Effect of voclosporin on PK of MPA | No effect of voclosporin on MPA plasma concentration–time profile; no effect on MPA $C_{max}$, $AUC_{0-12}$ or $T_{max}$ |
| NCT02141672 (AURA-LV) | Phase II, double-blind, placebo-controlled; 79 centers in 20 countries across North and Latin America, Europe, and Asia | Adults with SLE and Class III, IV or V LN as evidenced by kidney biopsy within 6 months of screening, proteinuria ≥1.5 mg/mg (≥2 mg/mg for Class V), and eGFR >45 mL/min/1.73 $m^2$ | 265 | Voclosporin 23.7 mg or 39.5 mg BID or placebo, + MMF 2 g/day and rapidly tapered low-dose corticosteroid | CRR at 24 weeks | 13% increase in CRR rate at 24 weeks voclosporin 23.7 mg BID (32.6%) vs placebo (19.3%) ($P = 0.046$); CRR at 24 weeks maintained at 48 weeks in 100% patients 26%; increase in CRR at 48 weeks (49.4% vs 23.9%) ($P < 0.001$) |
| NCT03021499 (AURORA 1) | Phase III, double-blind, placebo-controlled; 142 centers in 27 countries across North and Latin America, Europe, South Africa, and Asia | Adults with SLE and Class III, IV or V LN with kidney biopsy within 6 months of screening or within 2 years of screening + at least a doubling of UPCR in the 6 months before screening, proteinuria ≥1.5 mg/mg (≥2 mg/mg for Class V), and eGFR >45 mL/min/1.73 $m^2$ | 357 | Voclosporin 23.7 mg BID or placebo, + MMF 2 g/day and rapidly tapered low-dose corticosteroids | CRR at 52 weeks | 18% increase in CRR rate at 52 weeks with voclosporin (40.8%) vs placebo (22.5%) ($P < 0.0001$) |
| NCT03597464 (AURORA 2) | Phase III, double-blind, placebo-controlled continuation study | Subjects who have completed 52 weeks in AURORA 1 continue the same randomized treatment in AURORA 2 for 2 additional years | 216 | Voclosporin 23.7 mg BID or placebo, + MMF and low-dose corticosteroids starting at the same dose as at the end of AURORA 1 | Long-term safety | Study ongoing. Interim analysis: reductions in proteinuria maintained with no change in mean eGFR at 30 months |

AUC, area under the concentration–time curve; BID, twice daily; $C_{max}$, maximum serum concentration; CRR, complete renal response; eGFR, estimated glomerular filtration rate; LN, lupus nephritis; MMF, mycophenolate mofetil; MPA, mycophenolic acid; *P*, probability value; PK, pharmacokinetics; SLE systemic lupus erythematosus; $T_{max}$, time to maximum serum concentration; UPCR, urine protein-to-creatinine ratio.

whereas tacrolimus is a macrocyclic lactone that binds to FK-binding protein 12 [27,40]. Voclosporin is an oral CNI with a cyclic undecapeptide structure that was developed through modification of cyclosporine, in an attempt to identify a compound with improved efficacy, metabolic stability, and safety [31,41]. The structural modification (addition of a single carbon extension to the amino acid-1 position) produces a molecule with high potency and a favorable metabolic profile [31], without the need for therapeutic drug monitoring. Voclosporin forms a heterodimeric complex with cyclophilin A, which binds to and inhibits calcineurin, a calcium-dependent phosphatase involved in cytokine production and activation of T-cells (Figure 1) [41]. X-ray crystallography suggests the side-chain modification at amino acid-1 in voclosporin alters the way in which the cyclophilin–voclosporin complex binds to a composite surface of catalytic and regulatory subunits in calcineurin (the 'latch region'); this change in binding confers potent inhibition of calcineurin [41,42]. In addition, this modification on amino acid-1 shifts the primary site for voclosporin metabolism to the amino acid-9 position; the resulting IM9 metabolite, which is about eightfold less potent than voclosporin, represents 16.7% of total drug-related exposure [43,44]. In contrast, cyclosporine is extensively metabolized to a variety of metabolites, notably AM1, which is produced in large amounts relative to IM9, and AM19; in transplant patients, concentrations of and total exposure to AM1 exceed or approximate to cyclosporine concentrations, and both AM1 and AM19 have been associated with nephropathy (nephrotoxicity) [44–49]. The low metabolite load associated with voclosporin would be expected to result in a low degree of competitive inhibition of the parent molecule by its less active metabolite [31].

### 3.2. Pharmacodynamics

Voclosporin is a CNI immunosuppressant. By inhibiting the activity of calcineurin, CNIs have two distinct activities in LN: immunomodulatory effects on T-cells and stabilization of the podocyte (Figure 1). In the T-cell, inhibition of calcineurin prevents the translocation of nuclear factor of activated T-cells (NFAT) to the nucleus with the subsequent reduction in the transcription of genes encoding inflammatory cytokines, resulting in the reduction of lymphocyte proliferation and T-cell mediated responses [27,40]. In the podocyte, the inhibition of calcineurin prevents the dephosphorylation of synaptopodin, therefore maintaining the stabilizing function of the cytoskeleton and reducing proteinuria [40,50–53].

Voclosporin inhibits calcineurin in a dose-dependent manner up to 1 mg/kg with little or no lag time between the time to maximum drug concentration and time to maximum calcineurin inhibition [20,54]. *In vitro* studies using blood from non-human primates have shown voclosporin to be a potent inhibitor of diverse immune functions, including lymphocyte proliferation, T-cell cytokine production, and T-cell surface antigen expression [55]. Similarly, voclosporin suppressed a range of T-cell functions *in vivo* in non-human primates [56]. Voclosporin was more potent than cyclosporine in these nonclinical studies [55,56].

In healthy human subjects, single ascending doses of voclosporin were associated with dose-dependent calcineurin inhibition, with maximal inhibition peaking at 3.0 mg/kg; time to peak inhibition corresponded with $T_{max}$ (time to peak concentration) for whole blood concentration, with 1.5 and 3.0 mg/kg doses achieving 80% and 90% calcineurin inhibition, respectively [54]. Based on population pharmacokinetic-pharmacodynamic modeling, a strong correlation was observed between voclosporin blood concentration and estimated calcineurin inhibition up to a maximum of 64 mg twice daily (BID) [57]. The therapeutic dose used in LN was selected on the basis of an integrated safety analysis of voclosporin in healthy subjects and patients with other conditions (psoriasis, uveitis, and renal transplant) at doses of 0.2–0.6 mg/kg BID. The linear pharmacokinetic profile in this dosing range demonstrated that weight-based dosing was not necessary, and there was a dose-dependent increase in the number and severity of AEs and serious AEs [43]. The therapeutic dose in LN, 23.7 mg BID, corresponds to a dose of 0.4 mg/kg for a 70 kg individual [43]. At this dose, estimated calcineurin inhibition was 15.7% at trough voclosporin blood concentration and 58.1% at maximal concentration [57]. This degree of calcineurin inhibition at the therapeutic voclosporin dose in LN (mean ~30%) is far lower than the ~60% target calcineurin inhibition with cyclosporine during the first-year post-renal transplantation [42,54,57,58].

### 3.3. Pharmacokinetics and metabolism

In healthy human subjects, following single oral doses of voclosporin (0.25–4.5 mg/kg), systemic exposure increased in a linear manner, with 1:1 dose-proportional, first-order linear pharmacokinetics at doses greater than 1.5 mg/kg [54]. At lower doses, systemic exposure increased in a linear but slightly greater than 1:1 dose-proportional manner [54]. To ensure adequate absorption, voclosporin is to be taken on an empty stomach [20,54]. Voclosporin is the major circulating component, with pharmacologic activity mainly attributed to the parent compound [20]. Over 99% of the drug is eliminated as metabolite, mainly via the cytochrome P450 3A4 (CYP3A4) isoform, via feces [20,44]. Exposure is increased in individuals with severe renal impairment (creatinine clearance [CrCL] <30 mL/min) and in those with mild or moderate hepatic impairment [20,42]. Clinical studies of voclosporin did not include sufficient numbers of patients aged 65 years and over to determine whether they respond differently from younger patients, but clinical experience has not identified concerns; in general, dose selection should begin at the low end of the dosing range in elderly patients, reflecting the greater frequency of decreased hepatic, renal or cardiac function, and of concomitant disease or other drug therapy [20].

The pharmacokinetics of other legacy CNIs used (off-label) in the treatment of LN (cyclosporine, tacrolimus) are complex and unpredictable because of characteristics such as a narrow therapeutic index and variable absorption, distribution, and elimination, together with pharmacogenetic factors; the resulting intra-individual and inter-individual pharmacokinetic variability means that therapeutic drug monitoring is required to optimize

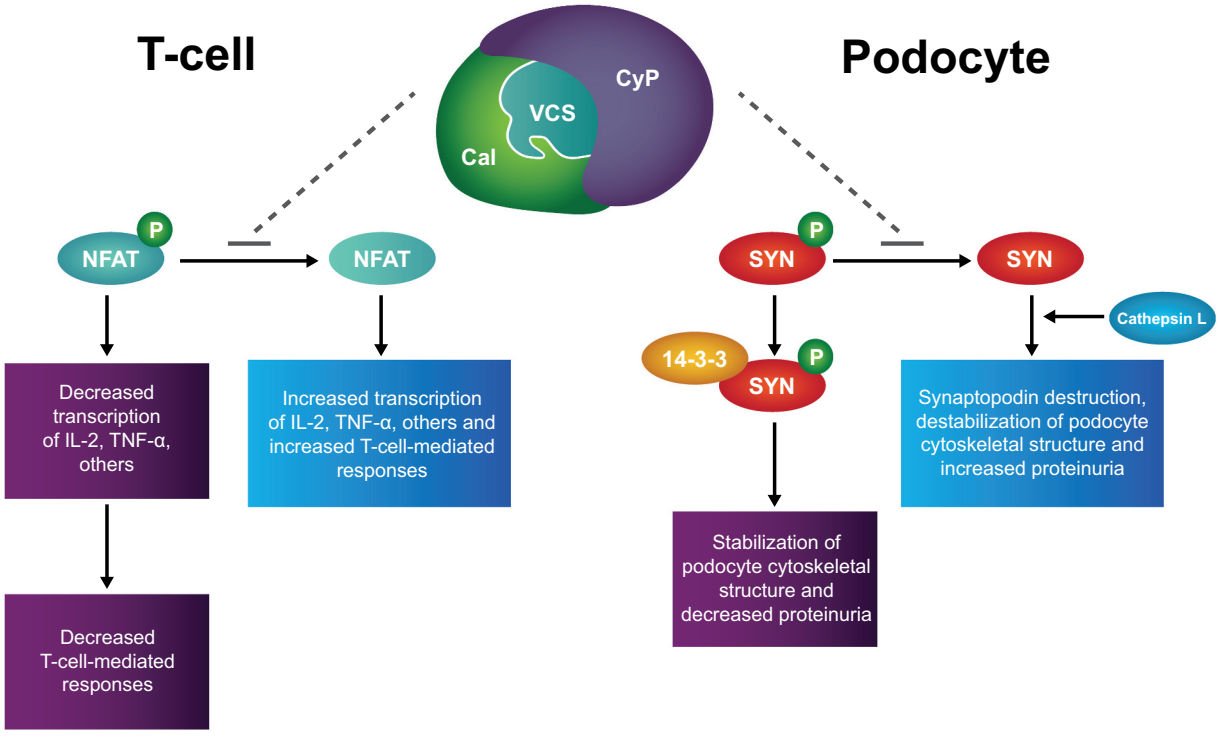


**Figure 1.** In T-cells, voclosporin (VCS) binds cyclophilin A (CyP), and the resulting complex (VCS–CyP) binds and competitively inhibits calcineurin (Cal) from dephosphorylating phosphorylated nuclear factor of activated T-cells (NFAT-P) to nuclear factor of activated T-cells (NFAT) [46]. When dephosphorylated, NFAT activates translation and transcription of various cytokines (IL-2, TNF-α, others), which promotes T-cell proliferation [40]. In podocytes, calcineurin activity is involved in destabilization of the podocyte actin cytoskeleton. Phosphorylated synaptopodin (SYN-P) binds with 14-3-3 protein, which stabilizes the actin cytoskeleton of the podocyte. When activated, calcineurin dephosphorylates synaptopodin, which marks it for destruction by cathepsin L, subsequently leading to podocyte cytoskeleton destabilization and increased proteinuria. By inhibiting this dephosphorylation pathway, VCS maintains SYN-P, which protects synaptopodin from destruction and thus promotes actin cytoskeleton stabilization [50,53].

treatment with these agents, to ensure adequate dosing and minimize toxicity [26,29,30,59,60]. In contrast, population pharmacokinetic analysis in patients with LN showed voclosporin to have predictable pharmacokinetics, with no clinically meaningful influence of sex, body weight, age, serum albumin, total bilirubin or eGFR (>45 mL/min/1.73 $m^2$; patients with eGFR ≤45 mL/min/1.73 $m^2$ were excluded from voclosporin clinical trials) [57]. Dose adjustment is not required based on these covariates [57]. Likewise, age (18–66 years), race (White, Black, Asian, other), and body weight (32–133 kg) had no clinically significant impact on voclosporin pharmacokinetics [20]. The predictable pharmacokinetic profile of voclosporin in patients with LN, together with the strong correlation between voclosporin whole blood concentration and calcineurin inhibition, eliminates the need for therapeutic drug monitoring, and enables a pharmacodynamic rather than pharmacokinetic approach to dosing, with dose adjusted in response to decreases in eGFR [20,57]. Therapeutic drug monitoring of voclosporin is unlikely to be of added benefit to patient management [57].

Calcineurin inhibitors can induce acute renal dysfunction as a result of vasoconstriction of the afferent arteriole leading to a decrease in GFR; this is a dose-dependent effect that occurs early in the treatment timeline and is usually reversible via dose reduction [61]. Baseline eGFR should be established before initiating voclosporin treatment at a starting dose of 23.7 mg BID (or 15.8 mg BID in patients with severe renal impairment or mild/moderate hepatic impairment); voclosporin is not recommended in patients with baseline eGFR ≤45 mL/min/1.73 $m^2$, unless the benefit exceeds the risk [20]. Estimated GFR is assessed every 2 weeks for the first month, and every 4 weeks thereafter. If eGFR is reduced by 20–30% from baseline, dosage should be reduced, initially by 7.9 mg BID; if eGFR is ≥30% reduced versus baseline and <60 mL/min/1.73 $m^2$, the drug should be discontinued, and possibly reinitiated at a lower dose when eGFR has returned to ≥80% of baseline [20].

Cyclosporine (but not tacrolimus) reduces exposure to MPA, the active metabolite of the pro-drug MMF, via inhibition of its enterohepatic recirculation; increasing doses of cyclosporine are associated with lower MPA concentrations, and discontinuation of cyclosporine leads to a rise in MPA trough concentrations that may be associated with MPA-related side effects such as leukopenia [62,63]. In an open-label Phase I study in adults (18–65 years) with stable SLE from multiple ethnic groups ($N$ = 25, including 8 with a history of LN) (Table 1), at the therapeutic dose of 23.7 mg BID, voclosporin had no clinically relevant effect on MPA exposure; voclosporin and MMF can be given concomitantly without need for MMF dosage adjustment, and there is no risk of emergence of MPA-related side effects after voclosporin discontinuation [63,64].

As with other CNIs, co-administration with CYP3A4 inhibitors increases voclosporin exposure while CYP3A4 inducers decrease blood concentrations; co-administration with strong CYP3A4 inhibitors (e.g. ketoconazole, itraconazole,

clarithromycin) should be avoided as these medications increase the risk of nephrotoxicity, dosage adjustment is recommended with moderate CYP3A4 inhibitors (e.g. fluconazole, verapamil, diltiazem, erythromycin), and moderate-to-strong inducers (e.g. carbamazepine, efavirenz, rifampin, rifabutin) should be avoided [20,44]. Like cyclosporine and tacrolimus, voclosporin is a P-glycoprotein inhibitor, such that caution is required when coadministering with other P-glycoprotein inhibitors (e.g. verapamil, erythromycin, sertraline, reserpine); dose reduction of some P-glycoprotein substrates (e.g. digoxin) may be needed [20,45].

## 4. Clinical efficacy

The efficacy of voclosporin in LN has not been compared in clinical trials with other CNIs [65]. The efficacy and safety of voclosporin in combination with MMF and strict steroid tapers for the treatment of adults with active LN was shown in two pivotal double-blind, placebo-controlled, multicenter, multiethnic studies, AURA-LV (NCT02141672, Phase II, $N$ = 265) and AURORA 1 (NCT03021499, Phase III, $N$ = 357) (Table 1, Table 2) [18,39]. Notably, these trials enrolled racially diverse patients from centers across the Americas, Europe, Asia, and South Africa. AURA-LV and AURORA 1 had similar design and endpoints, enrolling adult patients (18–75 years) with a diagnosis of SLE and biopsy-proven active LN, UPCR ≥1.5 mg/mg (or ≥2 mg/mg if pure class V), and eGFR >45 mL/min/1.73 $m^2$. Key demographic characteristics at baseline were similar between voclosporin and control arms in both trials, and representative of patients with LN (>83% female). Subjects were treated with voclosporin (23.7 mg BID or 39.5 mg BID in AURA-LV; 23.7 mg BID in AURORA 1) or placebo, in both cases on a background of MMF (2 g/day) and rapidly tapered low-dose oral steroids (500–1000 mg intravenous pulse followed by 20–25 mg/day, depending on body weight, tapering to 2.5 mg/day by Week 16). Efficacy was defined in terms of CRR, defined as: UPCR ≤0.5 mg/mg; eGFR ≥60 mL/min/1.73 $m^2$ or no confirmed eGFR decrease >20% from baseline; no administration of rescue medication; and no more than 10 mg prednisone equivalent/day for ≥3 consecutive days or for ≥7 days in total during Weeks 16–26 in AURA-LV or Weeks 44–52 in AURORA 1.

In AURA-LV, the lower dose of voclosporin was associated with a statistically significantly greater CRR rate at 24 weeks (the primary endpoint) than placebo, with the benefit maintained at 48 weeks, when CRR with the higher dose voclosporin group was also significantly greater than placebo (Table 2) [39]. Complete renal response was achieved more rapidly with both voclosporin doses than with placebo. Voclosporin 23.7 mg BID was also associated with a significantly earlier time to partial remission (50% reduction from baseline in UPCR) compared to the control arm at Weeks 24 and 48.

In AURORA 1, the primary endpoint was CRR rate at 52 weeks, a later timepoint than in previous trials of CNIs in LN (Table 2) [18]. The addition of voclosporin to MMF and low-dose steroids resulted in an absolute increase in CRR rate of 18%, and an overall odds ratio (OR) of 2.65. Significant benefits of voclosporin were also seen for multiple prespecified key secondary endpoints including CRR at 24 weeks, partial renal response at 24 and 52 weeks, time to UPCR ≤0.5 mg/mg, and time to 50% reduction in UPCR (Table 2, Figure 2). A 50% reduction in UPCR from baseline at any time during the study was achieved by 97% of patients treated with voclosporin in comparison with 76% of patients receiving placebo. The steroid dose was tapered according to the trial protocol to 2.5 mg/day at Week 16, with adjustment thereafter at the investigator's discretion. At Week 52, 75% of the voclosporin group and 73% of the control group were on a dose of ≤2.5 mg/day. The improved efficacy associated with voclosporin was achieved with a steroid regimen resulting in significantly lower cumulative steroid dose than in any previous study (the control group achieved a CRR rate consistent with historical studies involving higher steroid doses) [12,16,18,66].

Pooled analysis of data from AURA-LV and AURORA 1 has shown that voclosporin was associated with improved renal response rates at 1 year across all biopsy classes, with highest OR in pure Class III (50.0% versus 19.1% with placebo, OR 4.26, $P$ = 0.0054); response rate in pure Class V was 37.5% with voclosporin versus 28.9% with placebo (OR 1.5, $P$ = 0.4090) [67].

Although AURA-LV and AURORA 1 were not powered to detect statistically significant differences between subgroups, they covered large and racially diverse populations, including Black, Hispanic, Latino, and Asian patients, with OR values in favor of voclosporin in all subgroups (Figure 3) [18,39].

One limitation of the AURA-LV and AURORA 1 trials was that activity and chronicity indices were not recorded in all enrollment biopsies. In addition, there are no published data on extra-renal SLE activity.

Patients treated in AURORA 1 were followed up in AURORA 2 (NCT03597464), an ongoing, 2-year, blinded, placebo-controlled continuation study to AURORA 1 in which enrolled patients continued with the same treatment as in AURORA 1 for a total of 3 years of treatment (Table 1) [68]. An interim analysis of 116 patients in the voclosporin arm and 100 patients in the control arm, of whom 90 and 78, respectively, had received 30 months total treatment (12 months in AURORA 1 and a further 18 months in AURORA 2), showed that the meaningful reductions in proteinuria seen in AURORA 1 were maintained over 30 months of treatment [69]. At 30 months, the least squares mean change in UPCR from pretreatment baseline was −3.32 mg/mg in the voclosporin arm versus −2.55 mg/mg in the control arm. These results are encouraging; however, it will be important to evaluate the longer-term efficacy of voclosporin in this chronic disease.

## 5. Clinical safety

Safety data for voclosporin are available from a total of 267 patients from AURA-LV and AURORA 1 treated with 23.7 mg BID and a further 88 patients treated with 39.5 mg BID (Table 3) [18,20,39]. In AURA-LV, most categories of AEs were more common in patients treated with voclosporin than placebo [39]. The mortality rate (4.9%), although similar to that in previous LN trials, was higher in the low-dose voclosporin group; the authors noted that most of the deaths

Table 2. Efficacy of voclosporin in clinical trials in lupus nephritis [18,39].

| | Voclosporin | | Placebo | OR (95% CI) | | OR (95% CI) | |
|---|---|---|---|---|---|---|---|
| Phase II AURA-LV | 23.7 mg BID ($n$ = 89) | 39.5 mg BID ($n$ = 88) | ($n$ = 88) | 23.7 mg BID | $P$ | 39.7 mg BID | $P$ |
| CRR at 24 weeks (primary endpoint), % | 32.6 | 27.3 | 19.3 | 2.03 (1.01–4.05) | 0.046 | 1.59 (0.78–3.27) | 0.204 |
| CRR at 48 weeks, % | 49.4 | 39.8 | 23.9 | 3.21 (1.68–6.13) | <0.001 | 2.10 (1.09–4.02) | 0.026 |
| Median time to CRR, weeks | 19.7 | 23.4 | NC[a] | NC | | NC | |
| Phase III AURORA 1 | Voclosporin23.7 mg BID ($n$ = 179)[b] | | Placebo ($n$ = 178) | OR (95% CI) | | $P$ | |
| CRR at 52 weeks (primary endpoint), % | 40.8 | | 22.5 | 2.65 (1.64–4.27) | | <0.0001 | |
| CRR at 24 weeks, % | 32.4 | | 19.7 | 2.23 (1.34–3.72) | | 0.002 | |
| PRR at 24 weeks, % | 70.4 | | 50.0 | 2.43 (1.56–3.79) | | <0.001 | |
| PRR at 52 weeks, % | 69.8 | | 51.7 | 2.26 (1.45–3.51) | | <0.001 | |
| | | | | HR (95% CI) | | | |
| Median time to UPCR ≤0.5 mg/mg, days (95% CI) | 169 (141–214) | | 372 (295–NC) | 2.02 (1.51–2.70) | | <0.001 | |
| Median time to 50% UPCR reduction, days (95% CI) | 29 (29–32) | | 63 (57–87) | 2.05 (1.62–2.60) | | <0.001 | |
| CRR components | | | | OR (95% CI) | | | |
| UPCR ≤0.5 mg/mg at 52 weeks, % | 45.2 | | 23.0 | 3.11 (1.93–5.00) | | <0.001 | |
| eGFR component of CRR[c], % | 82.1 | | 75.8 | 1.50 (0.89–2.52) | | 0.129 | |
| No rescue medication, % | 91.1 | | 86.5 | 1.62 (0.82–3.20) | | 0.164 | |
| Steroid component of CRR[d], % | 87.2 | | 85.4 | 1.26 (0.68–2.34) | | 0.465 | |

BID, twice daily; CI, confidence interval; CRR, complete renal response; eGFR, estimated glomerular filtration rate; HR, hazard ratio; NC, non-calculable; OR, odds ratio; $P$, probability value; PRR, partial renal response; UPCR, urine protein-to-creatinine ratio

[a]Could not be calculated as the control group did not reach 50% probability of UPCR ≤0.5 mg/mg in Kaplan–Meier analysis.

[b]Intent-to-treat population.

[c]eGFR ≥60 mL/min/1.73 $m^2$, eGFR <60 mL/min/1.73 $m^2$ with no confirmed decrease >20%, or eGFR <60 mL/min/1.73 $m^2$ with confirmed decrease of >20% but with no disease-related or treatment-related eGFR-associated adverse event at time of assessment.

[d]Did not receive >10 mg/day prednisone for ≥3 consecutive days or for ≥7 days in total during Week 44–52.

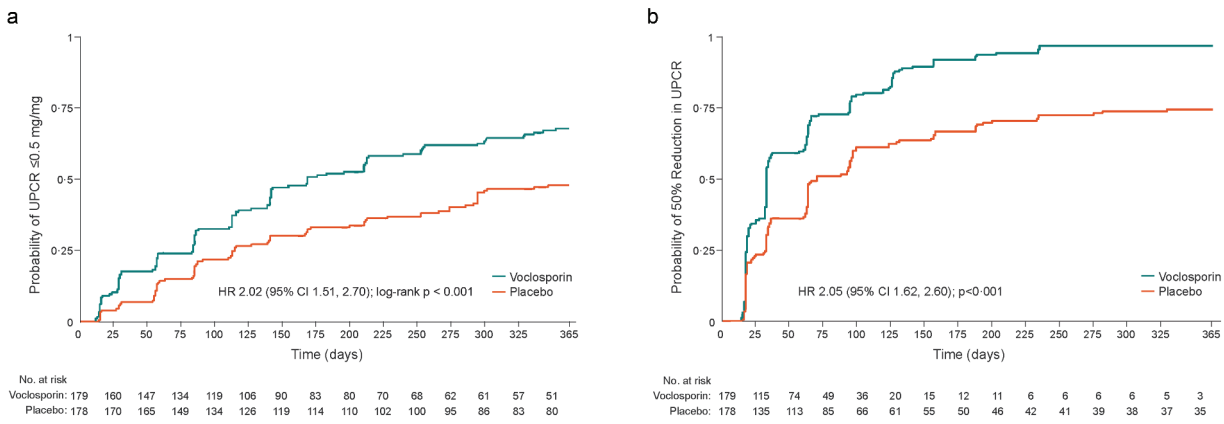


**Figure 2.** Probability of UPCR of ≤0.5 mg/mg and ≥50% reduction from baseline in UPCR in the AURORA 1 trial of voclosporin in combination with MMF and low-dose steroids (intention-to-treat population) in lupus nephritis [18]. Reproduced from *The Lancet*, with permission (doi: 10.1016/S0140-6736(21)00578-X).

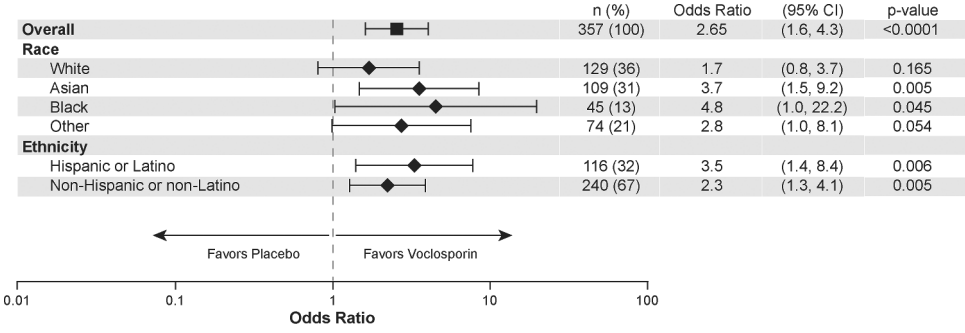


**Figure 3.** Subgroup analysis for complete renal response at 52 weeks in the AURORA 1 trial of voclosporin in combination with MMF and low-dose steroids (intention-to-treat) population in lupus nephritis [18]. Reproduced from *The Lancet*, with permission (doi: 10.1016/S0140-6736(21)00578-X).

occurred at a few sites, with seven out of the total of 13 deaths occurring at two sites in Bangladesh, and that more patients were randomized to low-dose voclosporin at these sites (these sites were excluded from the subsequent AURORA 1 study) [39,70,71]. Serious AEs were more frequent in patients treated with voclosporin; the excess of serious AEs in the low-dose group could be accounted for by multiple events in subjects from the Indian subcontinent who ultimately died (survivors showed similar event rates between study arms). In addition, a disproportionate number of patients from low-GDP Asian countries, with more severe baseline disease characteristics, were randomized to the low-dose voclosporin group [43]. In contrast to AURA-LV, more deaths were seen in the control group (5/178, 2.8%) than in the voclosporin group (1/178, 0.6%) in AURORA 1; no deaths were considered by the investigators to be related to study treatment [18]. Lupus nephritis is a serious, debilitating, and potentially life-threatening condition and, as such, it is not unexpected to observe mortality in LN clinical trials. Across the three reported clinical trials of voclosporin in a total of 631 patients with LN (AURION [an open-label study in 10 patients], AURA-LV and AURORA 1), all of which had a treatment duration of around a year, a total of 19 patients (3.0%) died, including any death following randomization until study completion [43]. Overall, the incidence of death was similar between patients who received placebo (6 of 266 patients, 2.3%) and patients who received any dose of voclosporin, including 23.7 mg BID and 39.5 mg BID (13 of 365 patients, 3.6%).

In AURORA 1, the AE profile was balanced between the voclosporin and control groups [18]. Infections and infestations were the most common AE; the most frequent serious AE involving infection was pneumonia (3.9% of the voclosporin group, 4.5% of the control group).

All patients in the voclosporin trials were on immunosuppressive therapy (MMF and low dose GC) and were therefore at increased risk of opportunistic infections. Opportunistic infections were reported in two patients treated with placebo, three patients treated with voclosporin 23.7 mg BID and one patient treated with voclosporin 39.5 mg BID (Table 3) [20]. A total of six opportunistic infections were seen in four patients treated with voclosporin, including herpes zoster, cytomegalovirus, and tuberculosis; the incidence of opportunistic infections was consistent with what would be expected in such an immunosuppressed population [20,43]. Calcineurin inhibitors have been associated with hair loss and tremor; hair loss was seen in 6% of patients treated with voclosporin 23.7 mg BID in comparison with 3% of placebo-treated patients, while tremor was reported by 3% (versus 1% with placebo) [20,27]. No dose-related increase in the incidence of CNI-related AEs was evident [43].

Table 3. Safety of voclosporin in clinical trials in lupus nephritis [18,20,39].

| Phase II AURA-LV | Voclosporin | | Placebo |
|---|---|---|---|
| | 23.7 mg BID ($n$ = 89) n (%) | 39.5 mg BID ($n$ = 88) $n$ (%) | (n = 88) n (%) |
| AE | 82 (92.1) | 85 (96.6) | 75 (85.2) |
| Serious AE | 25 (28.1) | 22 (25.0) | 14 (15.9) |
| Treatment-related AE | 45 (50.6) | 55 (62.5) | 15 (17.0) |
| Serious treatment-related AE | 4 (4.5) | 7 (8.0) | 1 (1.1) |
| AE leading to study drug discontinuation | 16 (18.0) | 14 (15.9) | 9 (10.2) |
| AE with outcome of death | 10 (11.2) | 2 (2.3) | 1 (1.1) |
| | Voclosporin23.7 mg BID ($n$ = 178)[a] $n$ (%) | | Placebo ($n$ = 178) $n$ (%) |
| Phase III AURORA 1 | | | |
| AE | 162 (91.0) | | 158 (88.8) |
| Serious AE | 37 (20.8) | | 38 (21.3) |
| Serious AE of infections and infestations | 18 (10.1) | | 20 (11.2) |
| Treatment-related serious AE | 8 (4.5) | | 8 (4.5) |
| AE leading to study drug discontinuation | 20 (11.2) | | 26 (14.6) |
| Death | 1 (0.6%) | | 5 (2.8) |
| Treatment-related AE leading to death | 0 | | 0 |

| Integrated safety analysis | Voclosporin | | Placebo |
|---|---|---|---|
| | 23.7 mg BID ($n$ = 267) $n$ (per 100 pt-yrs) | 39.5 mg BID ($n$ = 88) $n$ (per 100 pt-yrs) | ($n$ = 266) $n$ (per 100 pt-yrs) |
| Infections | 166 (135.2) | 58 (167.5) | 146 (107.4) |
| Serious infections | 27 (11.9) | 10 (14.4) | 27 (12.0) |
| Opportunistic infections | 3 (1.3) | 1 (1.4) | 2 (0.9) |
| Decreased GFR | 70 (37.1) | 27 (48.7) | 25 (11.3) |
| Renal AE[b] | 26 (11.3) | 11 (16.5) | 22 (9.5) |
| Serious renal AE | 13 (5.6) | 0 (0) | 9 (3.7) |
| Hypertension | 51 (25.2) | 16 (26.0) | 23 (10.3) |
| Serious hypertension | 5 (2.1) | 2 (2.8) | 1 (0.4) |
| Neurotoxicity | 74 (38.9) | 24 (42.5) | 44 (21.6) |
| Serious neurotoxicity | 9 (3.9) | 3 (4.3) | 2 (0.9) |
| Adverse reactions in ≥10% of patients treated with voclosporin | Voclosporin 23.7 mg BID ($n$ = 267) % | | Placebo ($n$ = 266) % |
| GFR decreased | 26 | | 9 |
| Hypertension | 19 | | 9 |
| Diarrhea | 19 | | 13 |
| Headache | 15 | | 8 |
| Anemia | 12 | | 6 |
| Cough | 11 | | 2 |
| Urinary tract infection | 10 | | 6 |

AE, adverse event; BID, twice daily; GFR, glomerular filtration rate; pt-yrs, patient-years.
[a]Safety population.
[b]Renal impairment, acute kidney injury, blood creatinine increased, azotemia, renal failure, oliguria, and/or proteinuria.

In an interim analysis of AURORA 2, after 30 months of total treatment, there were no unexpected new AEs with voclosporin compared to the control arm; six patients in the voclosporin arm and 10 patients in the control arm reported events of coronavirus (COVID-19) infection, which were serious in two and six patients, respectively [69].

The most frequently reported AE in AURA-LV and AURORA 1 was 'GFR decreased' (Table 3). Decreases in eGFR occurred early in the studies, were generally mild, reversible, and were managed by dose modifications according to the study protocols [18,39]. The effect of voclosporin on eGFR is consistent with the known hemodynamic effects of CNIs [61]. Mean eGFR showed a small decrease (1.5 mL/min/1.73 $m^2$) at Week 2 in patients treated with voclosporin in AURORA 1, thereafter remaining stable for the duration of the study [18]. In the interim analysis of 116 patients in AURORA 2, after the initial small, expected early decline in AURORA 1, mean eGFR remained stable over 30 months [69]. The rates of discontinuation of study drug due to eGFR decrease in AURA-LV and AURORA 1 were low (2–3%), and similar in voclosporin and control arms, indicating eGFR decreases were generally reversible and managed with the dosing guidance provided in the study protocol [18]. In AURA-LV, although there was a small decrease in mean eGFR during the study in the voclosporin treatment groups, mean eGFR returned to baseline within 2 weeks of discontinuation at the end of the study (equivalent data are not yet available for AURORA 1 as patients continued into AURORA 2 without discontinuing treatment). Hypertension, a known AE of CNIs, was seen in 19% of voclosporin patients and 9% of patients treated with placebo [19]. Monitoring of eGFR and blood pressure are required in clinical usage of voclosporin in patients with LN (Table 4) [20].

Table 4. Voclosporin usage and precautions in patients with lupus nephritis [20].

| Property | Recommendation |
|---|---|
| Indication | In combination with a background immunosuppressive therapy regimen in adults with active LN |
| Before initiating voclosporin | Establish accurate baseline eGFR and check BP. Not recommended in patients with baseline eGFR ≤45 mL/min/1.73 $m^2$ unless benefit outweighs risk. Do not initiate in patients with BP >165/105 mmHg. Contraindicated in patients concomitantly using strong CYP3A4 inhibitors. Avoid coadministration with strong and moderate CYP3A4 inducers. Avoid in patients with severe hepatic impairment |
| Recommended dose | 23.7 mg BID orally. 15.8 mg BID in patients with severe renal impairment. or mild/moderate hepatic impairment. 5.8 mg in the morning and 7.9 mg in the evening in patients using moderate CYP3A4 inhibitors |
| Modify dose based on eGFR | Assess eGFR every 2 weeks for the first month and every 4 weeks thereafter. If eGFR <60 mL/min/1.73 $m^2$ and >20% and <30% reduction from baseline, reduce dose by 7.9 mg BID. Reassess eGFR within 2 weeks, if still reduced from baseline by >20%, reduce dose again by 7.9 mg BID. If eGFR <60 mL/min/1.73 $m^2$ and ≥30% reduction from baseline, discontinue. Reassess within 2 weeks and consider re-initiating at lower dose (7.9 mg BID) when eGFR is ≥80% of baseline. For patients with dose decrease due to eGFR, consider increasing dose by 7.9 mg BID for each eGFR measurement that is ≥80% of baseline, but do not exceed starting dose |
| BP | Monitor every 2 weeks for the first month, and as clinically indicated thereafter. Discontinue if BP >165/105 mmHg |
| Serum potassium | Risk of hyperkalemia may be increased with other agents associated with hyperkalemia; periodically monitor serum potassium |
| QT prolongation | Risk of QT prolongation in combination with other drugs that cause QT prolongation (e.g. potassium-sparing diuretics, ACE inhibitors, angiotensin receptor blockers); consider obtaining ECG and monitoring electrolytes in patients at high risk |
| Neurotoxicity | Monitor for neurologic symptoms and discontinue if neurotoxicity occurs |

ACE, angiotensin-converting enzyme; BID, twice daily; BP, blood pressure; ECG, electrocardiogram; eGFR, estimated glomerular filtration rate; MMF, mycophenolate mofetil.

Although multiple factors contribute to electrolyte and acid–base abnormalities in renal transplant recipients, including level of allograft function, immunosuppressive medications and metabolic changes in the post-transplant period, CNIs such as tacrolimus and cyclosporine are considered major players [72]. Cyclosporine and tacrolimus have been associated with metabolic acidosis and abnormalities in all major electrolytes; up to 40% of renal transplant patients treated with these CNIs develop hyperkalemia, and the majority develop hypomagnesemia within the first few months after transplantation [26,73,74]. Importantly, in clinical studies in patients with LN, voclosporin treatment was not associated with clinically significant changes from baseline in magnesium or potassium; mean serum levels of these electrolytes remained within normal limits [18,43,75].

Tacrolimus and cyclosporine damage cells critical for the maintenance of glucose homeostasis, particularly pancreatic β-cells, and are associated with new onset diabetes after transplant (NODAT) [25,76]. In studies *in vitro*, clinically relevant doses of tacrolimus but not voclosporin inhibit insulin secretion by cultured human pancreatic islets, suggesting voclosporin may have an improved glucose profile in comparison with tacrolimus [76]. Consistent with this, voclosporin is potentially associated with a reduced incidence of NODAT compared with tacrolimus; in a Phase II study of renal transplant patients treated with tacrolimus or low-, mid- or high-dose voclosporin (starting doses 0.4, 0.6, or 0.8 mg/kg BID), incidence of NODAT with low-dose voclosporin was significantly lower than with tacrolimus, 1.6% with voclosporin 0.4 mg/kg BID versus 16.4% with tacrolimus, although the rates of NODAT with mid- (5.7%) and high-dose (17.7%) voclosporin were not statistically significantly different from that with tacrolimus [77]. In the 52-week AURORA 1 study, voclosporin had no significant impact on glucose; mean hemoglobin A1c and serum glucose concentrations remained stable, with one patient – in the control group – developing diabetes [18]. In AURA-LV, diabetes was reported in two patients, one who received placebo and one who received low-dose voclosporin [39].

Both tacrolimus and cyclosporine lead to hyperlipidemia in renal transplant patients, though cyclosporine has a more

pronounced effect [25]. Voclosporin is associated with favorable effects on lipids [18]. In AURORA 1, mean lipid concentrations (cholesterol, low-density lipoprotein cholesterol and triglycerides) were higher than normal at baseline and decreased in both voclosporin and control groups, with significantly greater decreases in cholesterol and low-density lipoprotein cholesterol in the voclosporin group after 1 year of treatment [18].

In addition to their acute nephrotoxic effects, cyclosporine and tacrolimus have been associated with chronic nephrotoxicity, irreversible deterioration of renal function as a result of progressive tubule-interstitial injury and glomerulosclerosis thought to result from a combination of hemodynamic changes and direct toxic effects including glomerular injury and electrolyte disturbances [26]. Chronic CNI-related nephrotoxicity is considered to be related to the degree of calcineurin inhibition; it is usually dose-dependent but can also be caused by drug–drug interactions influencing CNI bioavailability and intracellular concentrations [26,65]. Tacrolimus and cyclosporine have similar potential for chronic nephrotoxicity [65]. The majority of renal AEs associated with voclosporin in the AURA-LV and AURORA 1 trials were due to the decrease in eGFR or underlying LN activity [43]. Longer-term studies will be needed to determine the chronic nephrotoxic potential of voclosporin [43,65].

## 6. Regulatory affairs

Voclosporin is currently approved only in the USA, where it is indicated for adults with active LN in combination with a background immunosuppressive regimen [19]. A marketing authorization (MAA) in LN is under review by the European Medicines Agency [78].

## 7. Conclusion

Voclosporin is the first oral therapy to be approved for LN in the USA. Voclosporin has several features that distinguish it from the legacy CNIs (Table 5). In two multi-ethnic global clinical trials, voclosporin was associated with a rapid reduction in proteinuria, with a clinically meaningful and significantly higher renal response rate at 1 year than MMF and low-dose steroids alone. Reduction in proteinuria is known to be associated with preservation of kidney function and improved long-term outcomes in these patients. Given the chronic nature of LN, and the published one-year follow-up to date, it will be important to evaluate the three-year efficacy and safety of voclosporin.

## 8. Expert opinion

Lupus nephritis has long been a condition with significant unmet medical needs that is associated with substantial disease- and treatment-related comorbidities, and places patients, typically young women, at risk of chronic kidney disease and ESKD. Renal response rates with standard, off-label therapies are disappointing, such that there is a clear need for a therapeutic approach that achieves rapid remission and prevents progression of disease, while minimizing drug toxicity.

The AURA-LV and AURORA 1 studies have convincingly shown the added value of voclosporin treatment in patients with active LN, on top of MMF and low-dose GC therapy. Addition of voclosporin to standard therapy brought about a rapid reduction in proteinuria, with 18–26% more patients reaching UPCR <0.5 g/g. Although proteinuria at 12 months is the best-known predictor of long-term renal outcome in patients with LN, longer-term data will be needed to

Table 5. Comparison of calcineurin inhibitors in lupus nephritis.

| | Voclosporin (VCS) | Tacrolimus (TAC) | Cyclosporine (CsA) |
|---|---|---|---|
| US FDA approval in LN | January 2021 | Not approved[a] | Not approved |
| Initial dose | 23.7 mg twice daily | ~0.1mg/kg/day[b] | ~4mg/kg/day[b] |
| Drug–drug interaction with MMF | No | No | Reduces MPA exposure |
| Therapeutic drug monitoring | Not required | Recommended | Recommended |
| Warnings/precautions or AE noted in Prescribing Information[c] | | | |
| Diabetes mellitus | No | Warnings/precautions: NODAT (> CsA)[d] | Adverse event, seen in 1–3% of RA patients. NODAT (<TAC)[d] |
| Dyslipidemia | No | Adverse reaction: hyperlipidemia (<CsA)[e] | Adverse reaction: hyperlipidemia (>CsA)[e] |
| Hypertension | Warnings/precautions | Warnings/precautions | Warnings/precautions |
| Metabolic abnormalities | Hyperkalemia | Hyperkalemia, hypomagnesemia, hypophosphatemia, hypokalemia, hyperuricemia | Hyperkalemia, hypomagnesemia, hypophosphatemia, hyperuricemia |

AE, adverse event; FDA, US Food and Drug Administration; LN, lupus nephritis; MMF, mycophenolate mofetil; MPA, mycophenolic acid; NODAT, new onset diabetes after transplant.

[a]Approved in Japan in 2007 and in some Asian countries thereafter [79].

[b]Maintained for one month, with slow tapering to the lowest effective dose; patients should be carefully monitored during the first months of treatment to find the optimal individual dose [40].

[c]As immunosuppressants, voclosporin, tacrolimus, and cyclosporine carry a warning of increased risk for development serious infections and malignancies

[d]No head-to-head comparisons in LN are available. Caused NODAT in clinical trials of kidney, liver, and heart transplantation. In a Phase 3 study of TAC/MMF versus CsA/MMF in renal transplant, incidence of NODAT at 1 year was 75% with TAC and 61% with CsA [29].

[e]No head-to-head comparisons in LN are available. In a Phase 3 study in renal transplant patients, hyperlipidemia was seen in 18% of TAC/MMF patients versus 25% of CsA/MMF patients [29].

determine whether the short-term benefits of voclosporin in terms of proteinuria will translate into improvements of outcomes such as preservation of renal function and a reduced incidence of ESKD associated with LN.

Remarkably, these results were achieved with a CNI, a drug class with a poor reputation with respect to nephrotoxicity. Voclosporin, in comparison with legacy CNIs such as cyclosporine and tacrolimus, has a more consistent pharmacokinetic–pharmacodynamic relationship as a result of enhanced binding of the voclosporin–cyclophilin complex to calcineurin and reduced drug and metabolite load. The high potency of voclosporin, together with its favorable metabolic profile, allows achievement of efficacy in LN at a dose that is associated with a relatively low level of calcineurin inhibition. Potentially, this explains the lower incidence of off-target effects and an improved safety profile. At the doses studied in LN, voclosporin is associated with less hypomagnesemia and hypophosphatemia (tubular dysfunction) and less dyslipidemia. Furthermore, the voclosporin regimen used in the AURA-LV and AURORA 1 trials resulted in lower GC exposure than previous trials; this low GC exposure may reduce the GC-related AEs often seen during LN treatment, and longer-term GC-related side effects such as lymphoproliferative disorders and skin cancers. Monitoring of tacrolimus and cyclosporine blood levels is required to balance toxicity against therapeutic efficacy; the lack of requirement for therapeutic drug monitoring with voclosporin simplifies patient management, with no need for shipping blood samples to specialist laboratories.

In the pivotal AURA-LV and AURORA 1 studies, the comparator consisted of background immunosuppression plus placebo. A head-to-head comparison with belimumab has not been made, and, given the differences in study design, treatment regimens, patient populations and UPCR endpoints between the voclosporin trials and the BLISS-LN trial of belimumab as add-on to standard-of-care therapy, we can only speculate about potential differences in outcome. Both voclosporin and belimumab improve renal response rates when added to standard-of-care therapy, with a statistically significant effect demonstrated at 24 weeks with voclosporin and 104 weeks with belimumab. An advantage of voclosporin over belimumab is that it not only has an effect on the immunological pathways involved in LN but that it also has a stabilizing effect on podocyte function that would be anticipated to reduce proteinuria and potentially preserve the histology of the kidney. This activity, together with the rapidity of the reduction in proteinuria, means that voclosporin would be the add-on therapy of choice in Class III–V proteinuric patients. Patients in the voclosporin clinical trials were stratified according to MMF use at screening (yes/no), but the studies were not powered to detect any statistical difference between these two subgroups. Because reducing proteinuria in the first year of treatment of LN is known to be associated with improved long-term outcomes, and the available clinical data support the use of voclosporin as first-line therapy in combination with MMF and low-dose GC, our recommendation would be to use combination therapy with voclosporin initially to bring about a rapid reduction in proteinuria, rather than as an add-on therapy if there is suboptimal response to MMF and GC.

Although trials were not powered to detect differences in response between different subgroups such as race, efficacy in LN was demonstrated with voclosporin in large and racially diverse populations; this is a potentially important benefit, given the more aggressive disease course and poorer outcomes in several race and ethnicity subgroups.

The possibility of oral treatment can be considered an advantage, in comparison with the subcutaneous administration of belimumab. Whether or not there is a potential added benefit in combining voclosporin and belimumab therapy will need to be addressed in future studies, though it is tempting to speculate that such combination therapy, using agents with different mechanistic targets, might minimize or even replace use of the older agents.

### 8.1. Information resources

For further information, the reader is directed to articles on the two pivotal trials of voclosporin, AURA-LV and AURORA 1 [18,39], voclosporin prescribing information [20], and an article describing the results of a study specifically designed to investigate drug–drug interactions between mycophenolate and voclosporin [63]. An efficacy and value review of voclosporin has been published by the US Institute for Clinical and Economic Review [80].

## Acknowledgments

The authors would like to acknowledge Kate Ackrill (MediComm Partners, London, UK) for writing support.

## Disclosure statement

T van Gelder participated in studies supported by Chiesi, Aurinia Pharmaceuticals Inc. and Vitaeris/CSL Behring. TvG has participated in the Clinical Endpoints Committee of the AURA-LV and AURORA studies of Aurinia. He has also been on the speakers bureau of Astellas and Chiesi and has consulted for Roche Diagnostics and Thermo Fisher Scientific. E Lerma reports employment with Associates in Nephrology; consultancy agreements with Bayer and Vifor; ownership interest in Fresenius Joint Venture; receiving honoraria from Elsevier Publishing, MGraw-Hill Publishing, National Kidney Foundation, UpToDate and Wolters Kluwer Publishing; serving as a scientific advisor or member of Journal of Clinical Lipidology, International Urology and Nephrology, Journal of Vascular Access, Prescribers Letter, Renal and Urology News, ASN Kidney News, Reviews in Endocrinology and Metabolic Disorders, and American Journal of Kidney Diseases Blog; serving as a Visual Abstract Editor for CJASN; and speakers bureau for AstraZeneca, Bayer, Otsuka and Vifor. KJ Engelke and RB Huizinga are employees and stockholders of Aurinia. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

## Reviewer disclosures

Peer reviewers on this manuscript have no relevant financial or other relationships to disclose.

## Funding

Aurinia Pharmaceuticals Inc. provided funding for the voclosporin clinical studies and support for medical writing to develop the publication.

## ORCID

Edgar Lerma http://orcid.org/0000-0002-0976-5478

## References

**Papers of special note have been highlighted as either of interest (•) or of considerable interest (••) to readers.**

1. Almaani S, Meara A, Rovin BH. Update on lupus nephritis. Clin J Am Soc Nephrol. 2017;12(5):825–835.
2. Hanly JG, O'Keeffe AG, Su L, et al. The frequency and outcome of lupus nephritis: results from an international inception cohort study. Rheumatology (Oxford). 2016;55(2):252–262.
3. Hahn BH, McMahon MA, Wilkinson A, et al. American College of Rheumatology guidelines for screening, treatment, and management of lupus nephritis. Arthritis Care Res (Hoboken). 2012;64(6):797–808.
4. Tektonidou MG, Dasgupta A, Ward MM. Risk of end-stage renal disease in patients with lupus nephritis, 1971–2015: a systematic review and bayesian meta-analysis. Arthritis Rheumatol. 2016;68 (6):1432–1441.
5. Gasparotto M, Gatto M, and Binda V, et al. Lupus nephritis: clinical presentations and outcomes in the 21st century. Rheumatology (Oxford). 2020;59(Suppl 5):v39–v51.
6. Levey AS, Eckardt KU, Dorman NM, et al. Nomenclature for kidney function and disease: executive summary and glossary from a kidney disease: improving global outcomes (KDIGO) consensus conference. Perit Dial Int. 2021;41(1):5–14.
7. McCloskey O, Maxwell AP. Diagnosis and management of nephrotic syndrome. Practitioner. 2017;261(1801):11–15.
8. Bajema IM, Wilhelmus S, Alpers CE, et al. Revision of the international society of nephrology/renal pathology society classification for lupus nephritis: clarification of definitions, and modified national institutes of health activity and chronicity indices. Kidney Int. 2018;93(4):789–796.
9. Fanouriakis A, Kostopoulou M, and Cheema K, et al. Update of the joint European league against rheumatism and European renal association-European dialysis and transplant association (EULAR/ERA-EDTA) recommendations for the management of lupus nephritis. Ann Rheum Dis. 2019;79(6):713–723. 2020.
   • **European recommendations for management of patients with lupus nephritis.**
10. Dall'Era M, Cisternas MG, Smilek DE, et al. Predictors of long-term renal outcome in lupus nephritis trials: lessons learned from the euro-lupus nephritis cohort. Arthritis Rheumatol. 2015;67(5):1305–1313.
11. Rovin BH, Adler SG, Barratt J, et al. Executive summary of the KDIGO 2021 guideline for the management of glomerular diseases. Kidney Int. 2021;100(4):753–779.
12. KDIGO. Clinical practice guideline for the management of glomerular diseases. Kidney Int. 2021;100(4s):S1–S276.
   • **Guidelines for clinicians treating glomerular diseases including lupus nephritis.**
13. Anders HJ, Loutan J, Bruchfeld A, et al. The management of lupus nephritis as proposed by EULAR/ERA 2019 versus KDIGO 2021. Nephrol Dial Transplant. 2021 Dec 9. DOI:10.1093/ndt/gfab351.
   • **Useful article outlining similarities and differences between the EULAR/ERA-EDTA and KDIGO recommendations for patient management.**
14. Mok CC, Hamijoyo L, Kasitanon L, et al. The Asia-Pacific league of associations for rheumatology consensus statements on the management of systemic lupus erythematosus. Lancet Rheumatol. 2021;3:e517–31.
15. Rovin BH, Furie R, Latinis K, et al. Efficacy and safety of rituximab in patients with active proliferative lupus nephritis: the lupus nephritis assessment with rituximab study. Arthritis Rheum. 2012;64(4):1215–1226.
16. Furie R, Rovin BH, Houssiau F, et al. Two-year, randomized, controlled trial of belimumab in lupus nephritis. N Engl J Med. 2020;383(12):1117–1128.
17. Wofsy D, Hillson JL, Diamond B. Comparison of alternative primary outcome measures for use in lupus nephritis clinical trials. Arthritis Rheum. 2013;65(6):1586–1591.
18. Rovin BH, Teng YKO, Ginzler EM, et al., Efficacy and safety of voclosporin versus placebo for lupus nephritis (Aurora 1): a double-blind, randomised, multicentre, placebo-controlled, phase 3 trial. Lancet. 397(10289): 2070–2080. 2021.
   •• **Important phase 3 trial demonstrating efficacy and safety of voclosporin in lupus nephritis.**
19. Mejía-Vilet JM, Ayoub I. The use of glucocorticoids in lupus nephritis: new pathways for an old drug. Front Med (Lausanne). 2021;8:622225.
20. Lupkynis, voclosporin [prescribing information] 2021 cited 2022 Mar 15]. Available from 2022 Mar 15: https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/213716s000lbl.pdf.
   •**Important prescribing information for the use of voclosporin in adults with lupus nephritis.**
21. Benlysta B [prescribing information] 2017 cited 2022 Mar 15]. Available from 2022 Mar 15: https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/125370s062lbl.pdf.
22. Benlysta, belimumab [summary of product characteristics] 2016 cited 2022 Mar 15]. Available from 2022 Mar 15: https://www.ema.europa.eu/en/documents/product-information/benlysta-epar-product-information_en.pdf.
23. US Food and Drug Administration. Voclosporin Approval Letter, 2021 cited 2022 Mar 15]. Available from 2022 Mar 15: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2021/213716Orig1s000Approv.pdf.
24. Furie R, Aroca G, and Alvarez A, et al. Two-year results from a randomized, controlled study of obinutuzumab for proliferative lupus nephritis. Arthritis Rheumatol. 2020;72(suppl 10). [cited 2022 Jun, 27]. Available from: https://acrabstracts.org/abstract/two-year-results-from-a-randomized-controlled-study-of-obinutuzumab-for-proliferative-lupus-nephritis/. abstract 0988.
25. Jardine AG. Assessing the relative risk of cardiovascular disease among renal transplant patients receiving tacrolimus or cyclosporine. Transplant Int. 2005;18(4):379–384.
26. Naesens M, Kuypers DR, Sarwal M. Calcineurin inhibitor nephrotoxicity. Clin J Am Soc Nephrol. 2009;4(2):481–508.
27. Farouk SS, Rein JL. The many faces of calcineurin inhibitor toxicity – what the FK? Adv Chronic Kidney Dis. 2020;27(1):56–66.
28. Roy J, Cyert MS. Identifying new substrates and functions for an old enzyme: calcineurin. Cold Spring Harb Perspect Biol. 2020;12(3): a035436.
29. Prograf, tacrolimus [prescribing information] 2012 cited 2022 Mar 15]. Available from 2022 Mar 15: https://www.accessdata.fda.gov/drugsatfda_docs/label/2012/050709s031lbl.pdf.
30. Gengraf, cyclosporin. [prescribing information] 2021 cited 2022 Mar 15]. Available from 2022 Mar 15: https://www.gengraf.com/prescribinginformation.
31. Li Y, Palmisano M, Sun D, et al. Pharmacokinetic disposition difference between cyclosporine and voclosporin drives their distinct efficacy and safety profiles in clinical studies. Clin Pharmacol. 2020;12:83–96.
32. Bao H, Liu ZH, Xie HL, et al. Successful treatment of class V+IV lupus nephritis with multitarget therapy. J Am Soc Nephrol. 2008;19 (10):2001–2010.
33. Chen W, Tang X, Liu Q, et al. Short-term outcomes of induction therapy with tacrolimus versus cyclophosphamide for active lupus nephritis: a multicenter randomized clinical trial. Am J Kidney Dis. 2011;57(2):235–244.
34. Li X, Ren H, Zhang Q, et al. Mycophenolate mofetil or tacrolimus compared with intravenous cyclophosphamide in the induction treatment for active lupus nephritis. Nephrol Dial Transplant. 2012;27(4):1467–1472.

35. Wang S, Li X, Qu L, et al. Tacrolimus versus cyclophosphamide as treatment for diffuse proliferative or membranous lupus nephritis: a non-randomized prospective cohort study. Lupus. 2012;21 (9):1025–1035.
36. Liu Z, Zhang H, Liu Z, et al. Multitarget therapy for induction treatment of lupus nephritis: a randomized trial. Ann Intern Med. 2015;162(1):18–26.
37. Zhou T, Lin S, Yang S, et al. Efficacy and safety of tacrolimus in induction therapy of patients with lupus nephritis. Drug Des Devel Ther. 2019;13:857–869.
38. Brunet M, van Gelder T, Åsberg A, et al. Therapeutic drug monitoring of tacrolimus-personalized therapy: second consensus report. Ther Drug Monit. 2019;41(3):261–307.
39. Rovin BH, Solomons N, Pendergraft WF,3, et al. A randomized, controlled double-blind study comparing the efficacy and safety of dose-ranging voclosporin with placebo in achieving remission in patients with active lupus nephritis. Kidney Int. 2019;95(1):219–231.
40. Ponticelli C, Podestà MA. Calcineurin inhibitors in lupus nephritis. J Nephrol. 2021;34:399–402.
41. Kuglstatter A, Mueller F, Kusznir E, et al. Structural basis for the cyclophilin A binding affinity and immunosuppressive potency of E-ISA247 (voclosporin). Acta Crystallogr D Biol Crystallogr. 2011;67 (Pt 2):119–123.
42. Ling SY, Huizinga RB, Mayo PR, et al. Pharmacokinetics of voclosporin in renal impairment and hepatic impairment. J Clin Pharmacol. 2013;53(12):1303–1312.
43. US Food and Drug Administration. Multi-disciplinary review and evaluation, NDA 213716 2021 cited 2022 Mar 15]. Available from 2022 Mar 15: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2021/213716Orig1s000MultidisciplineR.pdf.
44. Ling SY, Huizinga RB, Mayo PR, et al. Cytochrome P450 3A and P-glycoprotein drug–drug interactions with voclosporin. Br J Clin Pharmacol. 2014;77(6):1039–1050.
45. Wang CP, Burckart GJ, Venkataramanan R, et al. Cyclosporine metabolite profiles in the blood of liver transplant patients. Transplant Proc. 1988;20(1 Suppl 1):173–175.
46. US National Library of Medicine PubChem 2021 cited 2022 Mar 15]. Available from 2022 Mar 15: https://pubchem.ncbi.nlm.nih.gov/compound/cyclosporin.
47. Wang CP, Burckart GJ, Ptachcinski RJ, et al. Cyclosporine metabolite concentrations in the blood of liver, heart, kidney, and bone marrow transplant patients. Transplant Proc. 1988;20(2 Suppl 2):591–596.
48. Kempkes-Koch M, Fobker M, Erren M, et al. Cyclosporine A metabolite AM19 as a potential biomarker in urine for CSA nephropathy. Transplant Proc. 2001;33(3):2167216–2167219.
49. Roby KA, Shaw LM. Effects of cyclosporine and its metabolites in the isolated perfused rat kidney. J Am Soc Nephrol. 1993;4 (2):168–177.
50. Faul C, Donnelly M, Merscher-Gomez S, et al., The actin cytoskeleton of kidney podocytes is a direct target of the antiproteinuric effect of cyclosporine A. Nat Med. 2008;14(9): 931–938.
51. Liao R, Liu Q, Zheng Z, et al. Tacrolimus protects podocytes from injury in lupus nephritis partly by stabilizing the cytoskeleton and inhibiting podocyte apoptosis. PLoS One. 2015;10(7): e0132724.
52. Mejía-Vilet JM, Romero-Díaz J. Voclosporin: a novel calcineurin inhibitor for the management of lupus nephritis. Expert Rev Clin Immunol. 2021;17(9):937–945.

•• **Manuscript showing that efficacy of CNIs in LN is not only immunologically based and T-cell mediated.**

53. Keisuke S, Kohei M, Takuji E, et al. Role of cathepsin L in idiopathic nephrotic syndrome in children. Med Hypotheses. 2020;141:109718.
54. Mayo PR, Huizinga RB, Ling SY, et al. Voclosporin food effect and single oral ascending dose pharmacokinetic and pharmacodynamic studies in healthy human subjects. J Clin Pharmacol. 2013;53 (8):819–826.
55. Bîrsan T, Dambrin C, Freitag DG, et al. The novel calcineurin inhibitor ISA247: a more potent immunosuppressant than cyclosporine in vitro. Transplant Int. 2005;17(12):767–771.
56. Stalder M, Bîrsan T, Hubble RW, et al. In vivo evaluation of the novel calcineurin inhibitor ISATX247 in non-human primates. J Heart Lung Transplant. 2003;22(12):1343–1352.
57. van Gelder T, Huizinga RB, Noukens J, et al. Use of TDM does not add clinical value for voclosporin in patients with lupus nephritis [abstract PO 1918]. J Am Soc Nephrol. 2020;31(Kidney Week 2020):594.
58. Quien RM, Kaiser BA, Dunn SP, et al. Calcineurin activity in children with renal transplants receiving cyclosporine. Transplantation. 1997;64(10):1486–1489.
59. Shaw LM, Holt DW, Keown P, et al. Current opinions on therapeutic drug monitoring of immunosuppressive drugs. Clin Ther. 1999;21 (10):1632–1652.
60. Mok CC. Therapeutic monitoring of the immuno-modulating drugs in systemic lupus erythematosus. Expert Rev Clin Immunol. 2017;13 (1):35–41.
61. Hošková L, Málek I, Kopkan L, et al. Pathophysiological mechanisms of calcineurin inhibitor-induced nephrotoxicity and arterial hypertension. Physiol Res. 2017;66(2):167–180.
62. Gregoor PJ, de S??vaux RG, Hen?? RJ, et al. Effect of cyclosporine on mycophenolic acid trough levels in kidney transplant recipients. Transplantation. 1999;68(10):1603–1606.
63. van Gelder T. How cyclosporin reduces mycophenolic acid exposure by 40% while other calcineurin inhibitors do not. Kidney Int. 2021;100(6):1185–1189.
64. van Gelder T, Huizinga RB, Lisk L, et al. Voclosporin: a novel calcineurin inhibitor without impact on mycophenolic acid in patients with SLE. Nephrol Dial Transplant. 2022 Apr 25;37(5):917-922. DOI: 10.1093/ndt/gfab022.

• **Study specifically designed to investigate drug–drug interactions between mycophenolate and voclosporin.**

65. Ponticelli C, Reggiani F, and Moroni G. Old and new calcineurin inhibitors in lupus nephritis. J Clin Med. 2021;10:4832.
66. Zeher M, Doria A, Lan J, et al. Efficacy and safety of enteric-coated mycophenolate sodium in combination with two glucocorticoid regimens for the treatment of active lupus nephritis. Lupus. 2011;20(14):1484–1493.
67. Askanase A, Randhawa S, Lisk L, et al. Efficacy of voclosporin across lupus nephritis biopsy classes: pooled data from the Aurora and AURA-LV trials. Presented at the virtual Nation Kidney Foundation 2021 Spring Clinical Meeting, 2021 Apr 6–10. Poster 283 [cited 2022 Mar 15]. https://casehippo.com/spa/symposium/national-kidney-foundation-2021-spring-clinical-meetings/event/gallery/abstracts?abstractId=1878
68. US National Library of Medicine ClinicalTrials.gov [Internet] 2021 cited 2022 Mar 15]. Available from 2022 Mar 15: https://clinicaltrials.gov/ct2/show/NCT03597464.
69. Saxena A, Mela C, Coeshall A, editors. Voclosporin for lupus nephritis: interim analysis of the Aurora 2 extension study [abstract 1425]. American College of Rheumatology Convergence; 2021. cited 2022 Mar 15]. Available from 2022 Mar 15 https://acrabstracts.org/abstract/voclosporin-for-lupus-nephritis-interim-analysis-of-the-aurora-2-extension-study/
70. Appel GB, Contreras G, Dooley MA, et al. Mycophenolate mofetil versus cyclophosphamide for induction treatment of lupus nephritis. J Am Soc Nephrol. 2009;20(5):1103–1112.
71. Mysler EF, Spindler AJ, Guzman R, et al. Efficacy and safety of ocrelizumab in active proliferative lupus nephritis: results from a randomized, double-blind, phase III study. Arthritis Rheum. 2013;65(9):2368–2379.
72. Pochineni V, Rondon-Berrios H. Electrolyte and acid–base disorders in the renal transplant recipient. Front Med (Lausanne). 2018 Oct 2; 5:261
73. Lee CH, Kim GH. Electrolyte and acid-base disturbances induced by calcineurin inhibitors. Electrolyte Blood Press. 2007;5(2):126–130.
74. De Waele L, Van Gaal PJ, Abramowicz D. Electrolytes disturbances after kidney transplantation. Acta Clin Belg. 2019;74(1):48–52.
75. Tumlin JA, Rovin BH, and Rahman M, et al. Voclosporin therapy in active lupus nephritis: reduced hypertension and electrolyte complications with CNI treatment [abstract]. 2017th ed. Vol.32, European renal association-European dialysis and transplant association Madrid Spain: Nephrology Dialysis Transplantation; 2017.

76. Kolic J, Beet L, Overby P, et al. Differential effects of voclosporin and tacrolimus on insulin secretion from human islets. Endocrinology. 2020;161(11):bqaa162.
77. Busque S, Cantarovich M, Mulgaonkar S, et al., The PROMISE study: a phase 2b multicenter study of voclosporin (ISA247) versus tacrolimus in de novo kidney transplantation. Am J Transplant. 11(12): 2675–2684. 2011.
• **Randomized, open-label study showing non-inferiority of voclosporin compared to tacrolimus in renal transplant patients.**
78. Otsuka press release 2021. [cited 2022 Mar 15]. Available from: https://www.otsuka.co.jp/en/company/newsreleases/2021/20210625_1.html.
79. Takeuchi T, Wakasugi N, Uno S, et al. Long-term safety and effectiveness of tacrolimus in patients with lupus nephritis: 5-year interim postmarketing surveillance study in Japan (TRUST). J Rheumatol. 2021;48:74–81.
80. Tice JA, Mandrik O, Thokala P, et al. The effectiveness and value of belimumab and voclosporin for lupus nephritis. J Manag Care Spec Pharm. 2021;27(10):1495–1499.