21 July 2022
EMA/681286/2022
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Lupkynis

International non-proprietary name: voclosporin

Procedure No. EMEA/H/C/005256/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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Table of contents

1. Background information on the procedure 6
1.1 Submission of the dossier 6
1.2 Legal basis, dossier content 6
1.3 Information on Paediatric requirements 6
1.4 Information relating to orphan market exclusivity 6
1.4.1 Similarity 6
1.4.2 New active substance status 6
1.5 Scientific advice 6
1.6 Steps taken for the assessment of the product 7

2. Scientific discussion 9
2.1 Problem statement 9
2.1.1 Disease or condition 9
2.1.2 Epidemiology 9
2.1.3 Clinical presentation, diagnosis and stage/prognosis 9
2.1.4 Management 10
2.2 About the product 11
2.3 Quality aspects 11
2.3.1 Introduction 11
2.3.2 Active substance 12
2.3.3. Finished medicinal product 16
2.3.4. Discussion on chemical, and pharmaceutical aspects 20
2.3.5. Conclusions on the chemical, pharmaceutical and biological aspects 20
2.3.6. Recommendation(s) for future quality development 20
2.4 Non-clinical aspects 20
2.4.1 2.4.Introduction 20
2.4.2. Pharmacology 21
2.4.3 Pharmacokinetics 23
2.4.4. Toxicology 25
2.4.5. Ecotoxicity/environmental risk assessment 34
2.4.6. Discussion on non-clinical aspects 34
2.4.7. Conclusion on the non-clinical aspects 40
2.5 Clinical aspects 41
2.5.1. Introduction 41
2.5.2. Clinical pharmacology 42
2.5.3. Discussion on clinical pharmacology 60
2.5.4. Conclusions on clinical pharmacology 68
2.5.5. Clinical efficacy 68
2.5.6. Discussion on clinical efficacy 127
2.5.7. Conclusions on the clinical efficacy 140
2.5.8. Clinical safety 140
2.5.9. Discussion on clinical safety 171
2.5.10. Conclusions on the clinical safety 178
2.6. Risk Management Plan 178

2.6.1. Safety concerns 178
2.6.2. Pharmacovigilance plan 179
2.6.3. Risk minimisation measures 179
2.6.4. Conclusion 180
2.7. Pharmacovigilance 180
2.7.1. Pharmacovigilance system 180
2.7.2. Periodic Safety Update Reports submission requirements 180
2.8. Product information 181
2.8.1. User consultation 181
2.8.2. Additional monitoring 181

3. Benefit-Risk Balance 181
3.1. Therapeutic Context 181
3.1.1. Disease or condition 181
3.1.2. Available therapies and unmet medical need 182
3.1.3. Main clinical studies 182
3.2. Favourable effects 183
3.3. Uncertainties and limitations about favourable effects 184
3.4. Unfavourable effects 185
3.5. Uncertainties and limitations about unfavourable effects 186
3.6. Effects Table 188
3.7. Benefit-risk assessment and discussion 189
3.7.1. Importance of favourable and unfavourable effects 189
3.7.2. Balance of benefits and risks 191
3.8. Conclusions 191

4. Recommendations 191

List of abbreviations

ACE	Angiotensin converting enzyme
ACR	American College of Rheumatology
ADR	Adverse drug reaction
AE	Adverse event
ALMS	Aspreva Lupus Management Study
ARB	Angiotensin receptor blocker
AUC	Area under the concentration-time curve
BCRP	Breast cancer resistance protein
BID	Twice daily (*bis in die*)
BP	Blood pressure
CEC	Clinical Endpoints Committee
CI	Confidence interval
CKD	Chronic kidney disease
CLCr	Creatinine clearance
CL/F	Apparent systemic clearance
C_{max}	Maximum concentration
C_{trough}	Trough concentration
CNI	Calcineurin inhibitor
CsA	Cyclosporine A
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
CYP	Cytochrome P450
EAIR	Exposure-adjusted incidence rate
ECG	Electrocardiogram
EMA	European Medicines Agency
E_{max}	Time to maximum effect
ESRD	End-stage renal disease
EULAR/ERA-EDTA	European League Against Rheumatism/European Renal Association-European Dialysis and Transplant Association
eGFR	Estimated glomerular filtration rate
GDP	Gross domestic product
GFR	Glomerular filtration rate
GI	Gastrointestinal
HDL	High-density lipoproteins
ICH	International Council for Harmonisation
ISN/RPS	International Society of Nephrology and the Renal Pathology Society
ITT	Intent-to-treat
IV	Intravenous
LDL	Low-density lipoproteins
LN	Lupus nephritis
MedDRA	Medical Dictionary for Drug Regulatory Activities
MMF	Mycophenolate mofetil
MMRM	Mixed Effects Model for Repeated Measures
OATP	Organic anion-transporting polypeptide
OR	Odds ratio
PBPK	Physiologically-based pharmacokinetic(s)
PD	Pharmacodynamics
P-gp	P-glycoprotein
PK	Pharmacokinetic(s)
PsU	Psoriasis and uveitis population
QTcF	QT interval duration corrected for heart rate using method of Fridericia
RBC	Red blood cell
SAE	Serious adverse event
SLE	Systemic lupus erythematosus
SLICC	Systemic Lupus International Collaborating Clinics

SMQ	Structured MedDRA query
SOC	System Organ Class
$t_{1/2}$	Elimination half-life
TEAE	Treatment-emergent adverse event
T_{max}	Time to reach the maximum concentration
UPCR	Urine protein-creatinine ratio

1. Background information on the procedure

1.1 Submission of the dossier

The applicant Otsuka Pharmaceutical Netherlands B.V. submitted on 22 June 2021 an application for marketing authorisation to the European Medicines Agency (EMA) for Lupkynis, through the centralised procedure falling within the Article 3(1) and point 3 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 13 December 2018.

The applicant applied for the following indication:

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

1.2 Legal basis, dossier content

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

1.3 Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) EMA/215117/2019 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0152/2019 was not yet completed as some measures were deferred.

1.4 Information relating to orphan market exclusivity

1.4.1 Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

1.4.2 New active substance status

The applicant requested the active substance voclosporin contained in the above medicinal product to be considered as a new active substance, as the applicant claims that it is not a constituent of a medicinal product previously authorised within the European Union.

1.5 Scientific advice

The applicant received the following scientific advice on the development relevant for the indication

subject to the present application:

Date	Reference	SAWP co-ordinators
23/03/2017	EMEA/H/SA/3483/1/2017/SME/III	Karin Janssen van Doorn, Kolbeinn Gudmundsson

The Scientific advice pertained to the following quality, non-clinical, and clinical aspects:

- Acceptance of the drug substance and drug product specifications for MAA.
- Sufficiency of the proposed nonclinical package to support a MAA.
- Acceptability to proceed to Phase 3 development based on available data. Design of the proposed pivotal Phase 3 study (AURORA), including dose selection, inclusion/exclusion criteria, background dosing with MMF and corticosteroid dosing and tapering, primary endpoint (a composite of UPCR and eGFR at 24 weeks (and without the need for rescue steroids)), secondary endpoints, PROs, sample size calculation and handling of withdrawing subjects. Acceptability to base a MAA on data from the AURA-LV study and the AURORA study.

1.6 Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Kristina Dunder Co-Rapporteur: Selma Arapovic Dzakula

The application was received by the EMA on	22 June 2021
The procedure started on	15 July 2021
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	4 October 2021
The CHMP Co-Rapporteur's critique was circulated to all CHMP and PRAC members on	15 October 2022
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	8 October 2021
The PRAC Rapporteur's updated Assessment Report was circulated to all PRAC and CHMP members on	26 October 2022
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	11 November 2021
The applicant submitted the responses to the CHMP consolidated List of Questions on	16 March 2022
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on	25 April 2022
The PRAC Rapporteur's updated Assessment Report was circulated to all PRAC and CHMP members on	05 May 2022
The PRAC agreed on the PRAC Assessment Overview and Advice to	05 May 2022

CHMP during the meeting on	
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint updated Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on	12 May 2022
The CHMP agreed on a list of outstanding issues <in writing and/or in an oral explanation> to be sent to the applicant on	19 May 2022
The applicant submitted the responses to the CHMP List of Outstanding Issues on	21 June 2022
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	14 July 2022
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Lupkynis on	21 July 2022
Furthermore, the CHMP adopted a report on New Active Substance (NAS) status of the active substance contained in the medicinal product (see Appendix on NAS)	21 July 2022

2. Scientific discussion

2.1 Problem statement

2.1.1 Disease or condition

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease which primarily affects women between the ages of 20 and 40 years. Lupus Nephritis (LN) is the most common serious manifestation of SLE and is a debilitating and potentially life-threatening condition.

2.1.2 Epidemiology

The prevalence of LN in Europe has been estimated to be between 0.44 and 1.4 per 10,000 based on studies of patients with LN in the UK, Norway and Denmark [Patel et al 2006, Eilertsen et al 2011, Hermansen et al 2016]. The prevalence of SLE and the chances of developing LN vary considerably across different regions of the world and across different races and ethnicities. Hanly and colleagues studied a large (N=1,827) multi-ethnic cohort of patients with SLE across the EU, US, Canada, Mexico and Asia [Hanly et al 2016]. SLE was diagnosed according to American College of Rheumatology (ACR) criteria and LN was defined by the ISN/RPS Classification [Hochberg 1997, Tan et al 1982, Weening et al 2004]. The proportion of patients with SLE who developed LN by race/ethnicity was: 20.3% Caucasian, 36.8% Asian, 39.9% African; 49.3% Hispanic and 33.8% other [Hanly et al 2016]. Similar findings have been reported by a study in the UK in which 10% of White patients with SLE developed LN compared with 27% of patients of Indo-Asian descent and 58% of patients of Afro-Caribbean descent [Patel et al 2006].

There is evidence that Black and Hispanic patients with SLE develop LN earlier and have worse outcomes than White patients with SLE, including death and end-stage renal disease (ESRD) [Almaani et al 2017, Contreras et al 2006].

2.1.3 Clinical presentation, diagnosis and stage/prognosis

In patients with LN, renal damage results in proteinuria and/or hematuria and a decrease in renal function as evidenced by reduced creatinine clearance and estimated glomerular filtration rate (eGFR).

It is estimated that 10%-30% of patients with LN will develop ESRD, the presence of which has been associated with a 26-fold increase in mortality risk compared with a demographically matched general population [Almaani et al 2017, Costenbader et al 2011, Tektonidou et al 2016, Yap et al 2012].

Proteinuria is the defining aspect of LN and indicates damage to the kidney; if not resolved this damage becomes permanent. A rapid reduction in proteinuria is, therefore, an important goal of treatment in LN [Fanouriakis et al 2020].

LN is divided into different classes (I-VI) according to the International Society of Nephrology and the Renal Pathology Society (ISN/RPS) 2003 Classification of LN [Weening et al 2004]. Treatment of LN is based in large part on the classification according to these criteria. The proliferative classes (III and IV) require aggressive treatment with corticosteroids and immunosuppressive agents. Class V (membranous LN) is treated similarly to Classes III/IV if it is associated with nephrotic range proteinuria or is combined with Classes III/IV. In contrast, Classes I and II generally do not require immunosuppressive therapy and patients with Class VI LN are considered to be candidates for renal transplant [Fanouriakis et al 2020, Hahn et al 2012].

In conclusion, LN is a serious condition which is associated with an increased risk of ESRD and mortality.

2.1.4 Management

The current treatment approach for LN has remained broadly unchanged over the past 10 years and consists of high dose corticosteroids plus off-label use of an immunosuppressant such as mycophenolate mofetil (MMF), cyclophosphamide, or azathioprine. In May 2021, belimumab was approved in the EU for use in combination with background immunosuppressive therapies for the treatment of adult patients with active LN.

The 2019 update of the European League Against Rheumatism/European Renal Association-European Dialysis and Transplant Association (EULAR/ERA-EDTA) recommendations for the management of LN provides guidance to physicians treating LN [Fanouriakis et al 2020]. Initial treatment with immunosuppressive agents (MMF [2 3 g/day] or intravenous (IV) low-dose cyclophosphamide [500 mg every 2 weeks for a total of 6 doses]) in combination with corticosteroids are recommended for Class III (±Class V) and Class IV (±Class V) LN, with similar recommendations for pure Class V LN where it is associated with nephrotic range proteinuria. If improvement after initial treatment is achieved, subsequent immunosuppression is recommended with either MMF (1 2 g/day) or azathioprine (2 mg/kg/day). Although the EULAR guidelines were published prior to the approval of belimumab, they state that belimumab may be considered as an off label add on treatment.

For patients with adverse clinical (GFR between 25 and 80 mL/min), histological (crescents or necrosis in >25% of glomeruli) or non-specific urinary sediment prognostic factors, the guidelines state that high dose cyclophosphamide (0.5-0.75 g/m2 monthly for 6 months) can be considered. In pure Class V LN, MMF is recommended at the same doses as in Class III/IV disease but the guidelines acknowledge that there is no high-quality evidence to guide treatment. A combination of MMF with a CNI such as tacrolimus is recommended as an alternative in patients with nephrotic range proteinuria [Fanouriakis et al 2020]. However, treatment with both tacrolimus and cyclosporine A is associated with a range of side effects which are associated with a need for therapeutic drug monitoring. Increased blood pressure and acute renal vasomotor effects are well-known potential toxicities of CNIs that are dose-related, reversible, and responsive to dose reduction or temporary interruption of treatment [Wiseman 2016]. Hydroxychloroquine is recommended for all patients with LN, in the absence of any contraindications, to reduce risk of kidney flares and improve survival [Fanouriakis et al 2020].

Cyclophosphamide is given as an IV infusion in one of two treatment regimens: low dose cyclophosphamide, which is commonly used in Europe, or the National Institutes of Health (NIH) regimen, which is most commonly used in the US. A large, double blind, international, randomised trial in 370 patients with LN - the Aspreva Lupus Management Study (ALMS) - investigated the efficacy of MMF and cyclophosphamide (modified NIH regimen) and found no difference in the efficacy of MMF plus corticosteroids versus cyclophosphamide plus corticosteroids [Appel et al 2009]. The efficacy of low-dose cyclophosphamide has been shown to be comparable to that of high-dose cyclophosphamide in the Euro-lupus trial which enrolled 90 patients with proliferative LN [Houssiau et al 2002]. Due to the toxicity concerns surrounding cyclophosphamide, MMF is widely used as the treatment of choice [Almaani et al 2017]. However, given the teratogenicity of MMF, azathioprine is used in women of child-bearing potential who may wish to become pregnant.

Historically, treatment for LN was divided into two distinct phases: an induction/initial treatment phase during which patients received cyclophosphamide or MMF and high doses of corticosteroids and a maintenance phase in which the doses of all drugs were reduced in order to improve tolerability [Hahn et al 2012]. This treatment paradigm has its origins in the early trials for LN where monthly infusions

of cyclophosphamide were established as the standard of care [Austin et al 1986]. Since IV cyclophosphamide is associated with considerable toxicity, including irreversible infertility and embryo fetal toxicity, there were concerns around long term use and several studies demonstrated that short-term therapy (3 6 months) with cyclophosphamide and corticosteroids could be used to induce remission, with MMF or azathioprine added as maintenance therapy [Contreras et al 2004, Chan et al 1995].

Although the recently published EULAR/ERA-EDTA guidelines still refer to initial treatment and maintenance treatment, the difference between the two phases has become less obvious. One key difference between the initial and maintenance phases is that cyclophosphamide is recommended only for the initial treatment phase with patients being switched to MMF or azathioprine for maintenance treatment. As discussed above, this is due to the toxicity of cyclophosphamide. However, if the initial treatment phase included MMF then the only difference is to consider reducing the dose from 2 3 g/day in the initial phase to 1 2 g/day in the maintenance phase, although no specific timeframe is recommended for this reduction.

A pulse of IV corticosteroid is used at the start of the initial treatment phase with patients being switched to oral corticosteroids after a few days. The realisation of the adverse effects of long term corticosteroid treatment together with the emerging evidence that following initial pulse corticosteroid treatment, lower doses of corticosteroids may be as efficacious as high doses led to the EULAR/ERA-EDTA recommendation to reduce the cumulative corticosteroid dose. The 2019 guidance recommends total IV methylprednisolone doses of 500 to 2,500 mg and a starting dose of oral methylprednisone of 0.3-0.5 mg/day for up to 4 weeks, reducing to ≤7.5 mg/day by 3 6 months [Fanouriakis et al 2020].

Damage due to both the disease and to treatment accumulates over time and contributes to the high morbidity and mortality [Lateef & Petri 2012]. Early treatment to prevent loss of nephrons and ultimately improve outcomes is critical. There is an unmet medical need arising from lower than desired levels of efficacy combined with organ damage resulting from corticosteroid treatment.

2.2 About the product

Voclosporin is a novel CNI which is structurally similar to cyclosporine A except for the modification of a functional group on amino acid-1 of the molecule [Kuglstatter et al 2011]. The immunosuppressant activity results in inhibition of lymphocyte proliferation, T-cell cytokine production, and expression of T-cell activation surface antigens. Some studies have indicated that CNIs may have a protective effect on kidney podocytes by stabilizing the cytoskeleton and inhibiting podocyte apoptosis [Liao et al 2015]. It is claimed by the applicant that voclosporin has several advantages over cyclosporine A and tacrolimus: a predictable PK/pharmacodynamic (PD) relationship allowing for flat dosing with no need for the monitoring of drug levels required by cyclosporine A and tacrolimus, a four-fold increase in potency over cyclosporine A and an enhanced metabolic profile potentially resulting in fewer CNI-associated side effects [Abel et al 2004, Mayo et al 2013].

2.3 Quality aspects

2.3.1 Introduction

The finished product is presented as a soft capsule containing 7.9 mg of voclosporin as active substance. Other ingredients of the capsule content are ethanol, vitamin E (E307) polyethylene glycol succinate (tocofersolan), polysorbate 40 and medium-chain triglycerides. The ingredients of the capsule shell are gelatin, sorbitol/glycerin blend, purified water, titanium dioxide (E171), iron oxide red

(E172) and iron oxide yellow (E172). Processing aids used during manufacture are medium-chain triglycerides, soya lecithin and ethanol.

The product is available in cold-formed aluminium blisters, laminated backing and lidding materials that are thermo-sealed together, as described in section 6.5 of the SmPC. Each blister contains 18 soft capsules. One carton contains 180 soft capsules.

2.3.2 Active substance

2.3.2.1 General information

The chemical name of voclosporin is cyclo{[(6E)-(2S,3R,4R)-3-hydroxy-4-methyl-2-(methylamino)-6,8-nonadienoyl]-L-2-aminobutyryl-N-methyl-glycyl-N-methyl-L-leucyl-L-valyl-N-methyl-L-leucyl-L-alanyl-D-alanyl-N-methyl-L-leucyl-N-methyl-L-leucyl-N-methyl-L-valyl} corresponding to the molecular formula C_{63} $H_{111}N_{11}O_{12}$. It has a relative molecular mass of 1214.6 g/mol and the following structure:

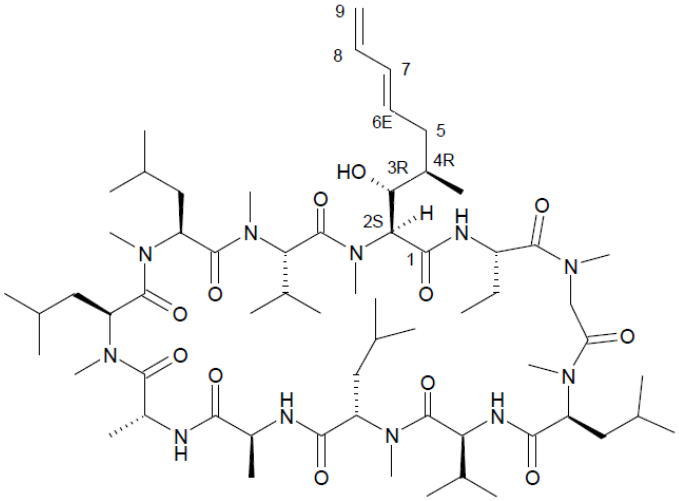


Figure 1: Active substance structure

The chemical structure of voclosporin was elucidated by a combination of IR, MS, ^{13}C-NMR and ^{1}H-NMR. The solid -tate properties of the active substance were measured by polymorph screening (including cooling crystallisation, evaporative crystallisation, precipitation by adding anti-solvent and slurry experiments with various solvents and temperatures), differential scanning calorimetry (DSC) and thermogravimetric analysis (TGA) studies.

The active substance is a white to off-white solid, crystalline hydrate, slight hygroscopic form. Besides amorphous material obtained in most of crystallisation experiments, polymorphic forms were produced under certain conditions. The form manufactured by the active substance manufacturer is the stable form which contains about one molecule of water in the crystal lattice (not tightly bound) and for which it has been confirmed that is slightly hygroscopic. DSC and TGA thermograms of the polymorphic forms are compared, showing that the forms can be differentiated by thermal analysis. The stable form was chosen for development based on crystallinity, physico-chemical and chemical stability, low hygroscopicity and synthetic accessibility. As the voclosporin is completely solubilised in the finished product formulation, polymorphism is not considered as a critical quality attribute (CQA) for voclosporin. Therefore, this attribute is not included as part of the release and stability specification.

Voclosporin is practically insoluble in water. The active substance does not bear readily ionisable groups, therefore the pH dependence of the solubility in water is limited. The solubility of voclosporin in organic solvents at ambient temperature is stated in Table 1.

Table 1. Solubility of voclosporin in organic solvents at ambient temperature

Solvent	**Solubility (USP, Ph. Eur. 5.11)**
Acetone	Freely soluble
Acetonitrile	Freely soluble
Ethanol	Freely soluble
Methanol	Freely soluble
Heptane	Practically insoluble

Voclosporin exhibits stereoisomerism due to the presence of 12 chiral centres and one C=C double bond. Voclosporin consists of a mixture of E (*trans*) and Z (*cis*) isomers, although the commercial synthetic method was developed to produce voclosporin predominantly as the *trans* isomer (*trans* content between 90% and 95%). Chiral centers are fixed based on the stereochemistry of the incoming active substance intermediate, ciclosporin A (CsA). The specific optical rotation of voclosporin is controlled in the active substance specification (determined at 20°C in chloroform solution according to Ph. Eur. 2.2.7).

Voclosporin is to be qualified as a new active substance in itself, based on the modification of a functional group on the amino acid-1 residue of the ciclosporin A molecule that has led to voclosporin. Specifically, voclosporin is a new chemical entity that is not a prodrug of ciclosporin A, is not an enantiomer or diastereoisomer of ciclosporin A, is not considered a complex, does not contain an ester or ether functional group, is not a salt, and is not a different solid state of ciclosporin A (or any other active substance).

2.3.2.2. Manufacture, characterisation and process controls

Detailed information on the manufacturing of the active substance has been provided in the restricted part of the ASMF and it was considered satisfactory.

Voclosporin is synthesised in five main steps using cyclosporine A as active substance intermediate and a starting material, with acceptable specifications. Ciclosporin A contributes as the main structural element of voclosporin. As there is a monograph of ciclosporin A in the European Pharmacopoeia, the manufacturer of ciclosporin A has been granted a Certificate of Suitability of the European Pharmacopoeia (CEP) which has been provided within the current Marketing Authorisation Application. The starting material contributes to the terminal olefinic moiety to the modified amino acid-1 sidechain of voclosporin.

The five synthesis steps consist of four chemical steps, resulting in four isolated intermediates and a final purification step. The chemical steps include protection, deprotection and two chemical transformation steps. The proposed route of synthesis is considered appropriate and in general the manufacturing process description is provided in sufficient detail (including quantities of all raw materials, process parameters incl. proven acceptable ranges for non-critical parameters and qualified ranges for critical parameters, in-process controls employed and expected yields).

The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of new active substances. Potential and actual impurities were well discussed with regards to their origin, fate, purge and characterisation. Nine specified impurities, arising from the

cyclosporine A active substance intermediate, voclosporin synthesis, purification and storage, have been included in the active substance release specification.

The proposed control strategy for each of them takes into consideration their origin and the material attributes and/process parameters that impact their presence. An evaluation of the potential genotoxic impurities has been provided, in line with ICH M7(R1) provisions, and demonstrates that all specified impurities are Class 4 or Class 5 compounds and designated as non-mutagenic, with the exception of some impurities classified as Class 2 (known mutagens with unknown carcinogenic potential) for which the applicant adequately justified that neither routine testing as part of active substance release, nor additional controls of the voclosporin manufacturing stages are necessary.

Residual solvents are controlled in the release specifications with limits according to ICH Q3C guideline. All the solvents used in the synthesis of the starting materials are controlled in the specifications of the respective starting material.

An elemental impurities risk assessment was conducted as per ICH Q3D(R1) using a risk-based approach to determine the risk for carryover of Class 1 and Class 2A elemental impurities into the active substance. The outcome of the risk assessment supports that there is minimal risk for metal contamination that could originate from the active substance manufacturing process. Based upon the outcome of the risk assessment, it is concluded that neither routine testing as part of active substance release, nor additional controls of the voclosporin manufacturing stages are necessary to control any elemental impurity.

A nitrosamines impurities risk assessment was conducted as per EMA/369136/2020 guideline and Q&A EMA/409815/2020, using a risk-based approach to determine the risk for carryover of nitrosamines impurities into the active substance. The outcome of the full risk assessment indicated that there was a moderate risk for nitrosamines contamination that could originate from the active substance manufacturing process, namely N-NitrosoDimethylAmine (NDMA) and N-NitrosoDiethylAmine (NDEA), and that confirmatory testing on several voclosporin batches was required. NDMA and NDEA were tested in 8 voclosporin production batches and were found below LOQ of 0.03 ppm (less than 10% of the acceptable limit of 0.6 ppm, based on a MDD of 47.4 mg voclosporin and an acceptable intake of 26.5 ng/day of more potent NDEA, since more than one nitrosamine impurity is identified). The data provided support the conclusion that neither routine testing as part of active substance release, nor additional controls of the voclosporin manufacturing stages are necessary to control any nitrosamines impurity.

The active substance is packaged in double low-density polyethylene (LDPE) bags which comply with the EC directive 2002/72/EC and EC 10/2011 as amended. The LDPE bags are placed in a thermally sealed Polyethylene Terephtalate (PET)/aluminium/polyethylene triplex bag containing one desiccant sachet. The aluminium triplex bag is then placed in a suitable polyethylene drum with a lid that is sealed with a tamper evident seal for shipment.

2.3.2.3 Specification

The active substance specification includes tests for appearance and colour (visual examination), identity (IR, HPLC), assay (HPLC), impurities (HPLC), residual solvents (GC), water content (KF, Ph. Eur.), specific rotation (Ph. Eur.), residue on ignition/sulfated ash (Ph. Eur.) and microbial count (Ph. Eur.).

The proposed active substance specification includes relevant testing parameters. The specification was established taking into account applicable ICH and EU guidelines and compendial considerations, as well as manufacturing capability, batch analysis data and stability results. Impurities present at higher

than the qualification threshold according to ICH Q3A were qualified by toxicological and clinical studies and appropriate specifications have been set. During the assessment, the tightening of acceptance criteria for unspecified impurities and for individual impurities was requested and has been implemented by the applicant. The control strategy for residual solvents has been detailed in the characterisation of the active substance section and the applied limits are in line with ICH Q3C. Justification for not controlling elemental impurities and tetramethylammonium ion in the voclosporin batches has been provided by the applicant and it is acceptable. Criteria for trans-isomer are in line with the batch analysis. Because the active substance is completely solubilised in the medicinal product formulation, polymorphism and particle size distribution are not considered critical quality attributes for the active substance and, therefore, not included as part of the commercial release specification for voclosporin.

The analytical methods used have been adequately described and (non-compendial methods) appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis data are provided for 27 batches of voclosporin active substance and 4 historical batches (purification step performed by chromatography instead of crystallisation). All results are within the proposed specification limits.

2.3.2.4. Stability

Results of stability studies on 6 primary registration stability batches, manufactured at proposed scale and packed in the proposed primary packaging, were presented for up to 60 months at -20°C ± 5°C, 5°C ± 3°C and 25°C/60% relative humidity (RH), and up to 6 months at 40°C/75% RH, according to the ICH guidelines. Batches packed in the less protective packaging are tested up to 60 months at -20°C ± 5°C and 25°C/60% RH, and up to 9 months at 40°C/75% RH, and are considered as supportive stability batches. Parameters tested during stability study are appearance, identity by HPLC and XRD, assay, impurities, water content and microbial purity. The analytical methods used were the same as for release and were stability indicating.

At 25°C/60% RH and 40°C/75% RH, significant assay decrease with out-of-specification (OOS) results at later testing points is observed. At -20°C ± 5°C and 5°C ± 3°C, the results are within proposed limits. This is considered acceptable.

There was no trend observed for specified impurities at any of the storage conditions. At -20°C ± 5°C and 5°C ± 3°C, total impurities are below 1.0%, while significant increase is seen at 25°C/60% RH (up to 2.5%), without an observed increase of specified and unspecified related impurities. This was due to the increase of impurities, which were not detected by the related substances method. Therefore, a new method has been developed, suitable for determination of impurities. The stability results indicate that no unspecified and no individual impurities are above identification threshold of 0.10% during the proposed retest period at proposed long-term storage condition. All other testing parameters were within the specification limits at all storage conditions.

Based on this, the active substance manufactured by the proposed supplier is deemed sufficiently stable. The stability results justify the proposed retest period of 24 months in the proposed container.

Adequate post-approval stability protocol information is presented and acceptable handling of any confirmed OOS is proposed.

2.3.3. Finished medicinal product

2.3.3.1. Description of the product and Pharmaceutical development

The finished product consists of a non-aqueous solution of voclosporin active substance, containing 7.9 mg of voclosporin per unit, filled into a size 5 (13 mm × 6 mm) opaque pink-orange to orange soft gelatin capsule. The composition of voclosporin soft capsule is adequately presented in the dossier.

Due to the low aqueous solubility of voclosporin, the objective during formulation development was to produce a non-aqueous formulation for oral administration which would form a relatively stable oil/water emulsion upon introduction into physiologically relevant aqueous media. Since drug permeation is associated with particle surface area, it was considered desirable to develop a formulation which would form a microemulsion when dissolved in aqueous media. Therefore, soft gelatin capsules were chosen as pharmaceutical form. Since the active substance is dissolved in the capsule fill, the physico-chemical characteristics of voclosporin (e.g., polymorphism and particle size) are not relevant for the quality of the finished product.

The selected excipients used for the finished product are sufficiently justified by the applicant. All excipients are commonly used for oral pharmaceutical dosage forms and their quality is compliant with the Ph. Eur., with the exception of Opacode® White WB NSP-78-18022 (used as the ink for printing on the outside of the capsule shell) and the excipients used as processing aids for the capsule shell (lecithin, denatured ethanol and Phosal® 53 MCT), which are non-compendial excipients and controlled against internal specifications. This is considered acceptable.

All excipients used in the production of the finished product are of non-human and non-animal origin, except for the gelatin used in production of the gelatin capsule shell of the finished product, derived from a bovine source and for which an appropriate TSE CEP has been provided. No novel excipients are used.

Definition of a Quality Target Product Profile (QTTP), the associated CQAs and identification of CPPs in each step of the finished product manufacturing process are considered sufficiently described. The suggested control strategy covering the active substance specification tests, finished product CPPs and IPCs, as well as the finished product specification tests are considered acceptable. No design spaces are claimed for the manufacturing process of the finished product.

The compatibility of the active substance and formulation components is demonstrated by the finished product stability data. The formulation development, including optimisation of the product formulation, is described and studies confirming the robustness of the finished product are presented. No overage of voclosporin is added for the manufacture of the finished product.

It is to be noted that initial development includes 5 mg and 10 mg voclosporin softgel capsule strengths that were used in clinical studies investigating other autoimmune indications (renal transplantation, plaque psoriasis, and non-infectious uveitis) before lupus nephritis (LN) clinical development. For the LN indication, a 7.9 mg voclosporin softgel capsule was developed based upon the historical efficacy and safety data of voclosporin obtained from clinical studies in other autoimmune indications. The qualitative composition of the fill formulation is identical for the 5 mg, 7.9 mg and 10 mg strengths, with minor differences in the quantitative composition to hold total fill volume fixed, as well as in qualitative composition of the capsule shell. The pivotal clinical efficacy studies for the LN indication were performed using the final intended commercial formulation.

The main physicochemical properties relevant for the finished product performance as identified and evaluated, are robust with regard to minor formulation changes. Further, a preliminary evaluation of the dissolution of the unencapsulated development formulations screened suggests that the dissolution

is rapid (<15 minutes), by visual evaluation. These data suggest that dissolution rate is mainly controlled by rupture time of the capsule shell.

The development of the dissolution method used for QC control is described and the discriminatory power of the method is sufficiently demonstrated. The choice of surfactant and the rotation speed have been adequately justified by the applicant. Dissolution profiles for pivotal batches and commercial finished product are presented and it is concluded the profiles can be considered similar. The dissolution method development studies were performed with the proposed commercial finished product formulation, as well as the previous 5 mg and 10 mg strengths of voclosporin softgel capsules, and are considered representative for the purposes of dissolution method development.

Studies confirming the comparability of pilot scale pivotal clinical and registration batches versus commercial scale are presented.

The primary packaging of the finished product is cold-formed aluminium blisters, laminated backing and lidding materials that are thermo-sealed together. The primary packaging material complies with Ph. Eur. and EC requirements. Each blister contains 18 soft capsules and ten such blister cards are packaged into a carton (non-functional secondary packaging) to achieve a sufficient quantity of capsules to meet a month's supply of the finished product. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

2.3.3.2. Manufacture of the product and process controls

The voclosporin finished product is manufactured, filled, packaged, inspected and tested in accordance with GMP.

The manufacturing process consists of 7 main steps:

Stage 1: Preparation of formulation fill material

Stage 2: Gel mass preparation/conversion

Stage 3: Encapsulation, capsule printing, and drying

Stage 4: Drying

Stage 5: Washing, sorting, and metal check

Stage 6: Inspection and bulk packaging

Stage 7: Packaging

The flow diagram for the manufacture of the finished product is provided in the dossier. There are no intermediates for the manufacture of voclosporin softgel capsules. The commercial batch size and corresponding formula for voclosporin softgel capsules is adequately described in the dossier.

A risk assessment was performed that has identified the CPPs for the manufacture of the voclosporin softgel capsules. In addition, an integrated control strategy for the manufacture of the finished product was developed that takes into account the manufacturing process history to date and the risk assessment performed for the finished product manufacturing process. The integrated control strategy ensures that each finished product CQA is appropriately controlled.

The process is considered to be a standard manufacturing process. The finished product manufacturing process has also been validated by three consecutive batches. Based on extensive knowledge, experience of manufacturing of this kind of pharmaceutical form (soft gelatin capsules), presented batch analysis data and adequacy of in-process controls and extensive pharmaceutical development

studies, it is considered that the manufacture is sufficiently robust to provide assurance that the process produces the finished product of consistent quality, complying with the designated specification.

2.3.3.3. Product specification

The finished product release specifications include appropriate tests for this kind of dosage form: appearance (visual inspection), identification (HPLC-UV), assay (HPLC-UV), degradation products (HPLC-UV, UPLC), uniformity of dosage units (HPLC-UV/Ph. Eur.), dissolution (HPLC-UV/Ph. Eur.), ethanol content (GC-FID), water content (Karl Fischer/Ph. Eur) and microbial limits (Ph. Eur.).

The proposed specification tests are in line with ICHQ6A and Ph. Eur. requirements. The parameters included in the finished product specification are found adequate to control the quality of the finished product at release and shelf-life. The acceptance criteria were selected on the basis of the available manufacturing and testing experience, manufacturing process capabilities, regulatory guidance, scientific knowledge, and the stability characteristics. During the assessment, inclusion of limits for some impurities (individual and total) and tightening of acceptance criteria for other impurities, ethanol content and assay (for shelf-life specification only) were requested and have been implemented by the applicant. Moreover, the applicant commits to further adjust the shelf-life assay specification when more data is available.

Appropriate rationale for not including in the finished product specification acceptance criteria for other tests has been provided by the applicant and is considered acceptable.

In accordance with ICH Q3B(R2), only degradation products are controlled in voclosporin softgel capsules. Impurities that are synthetic process-related impurities are controlled in the active substance and are not further controlled in the finished product. This approach is endorsed.

Residual solvents used as part of the voclosporin active substance manufacturing process are controlled as per the active substance specification. For the finished product, an evaluation of residual solvents in the finished product was performed, confirm that the finished product complies with the requirements of ICH Q3C(R7) and that there is no need to control residual solvents also in the finished product. This is considered acceptable. Of note, for the finished product ethanol is employed as an excipient that is used as a solubilizing agent for the active substance. Therefore, ethanol is treated as an excipient and testing for ethanol is performed as part of the finished product specification.

The potential presence of elemental impurities in the finished product has been assessed on a risk-based approach in line with the ICH Q3D Guideline for Elemental Impurities. Based on the risk assessment, it can be concluded that it is not necessary to include any elemental impurity controls. The information on the control of elemental impurities is satisfactory.

A risk evaluation concerning the presence of nitrosamine impurities in the finished product has been performed (as requested) considering all suspected and actual root causes in line with the "Questions and answers for marketing authorisation holders/applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products" (EMA/409815/2020) and the "Assessment report- Procedure under Article 5(3) of Regulation EC (No) 726/2004- Nitrosamine impurities in human medicinal products" (EMA/369136/2020). Based on the information provided it is accepted that no risk was identified on the possible presence of nitrosamine impurities in the active substance or the related finished product. Therefore, no additional control measures are deemed necessary.

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. The voclosporin primary reference standard used for finished

product testing is the same as the primary standard used to test the active substance and is considered acceptable.

Batch analysis results are provided for one qualification batch, five clinical batches and three commercial full-scale batches, confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification. he finished product is released on the market based on the above release specifications, through traditional final product release testing.

2.3.3.4. Stability of the product

Stability studies have been performed on several batches of the finished product, using a range of stability conditions (25°C/60%RH and 40°C/75%RH). The analytical methods and acceptance criteria applied during stability studies are identical to the finished product release specifications, except for assay testing, for which slightly broader limits are set.

Stability data are available for all three primary registration batches through 36 months and 6 months of storage at 25°C/60%RH and 40°C/75%RH, respectively. For both storage conditions, no significant changes were observed in any of the monitored parameters throughout the entire testing period, compared to the initial values.

Supportive stability data are also available for two clinical batches of finished product through 48 months and 60 months of storage at 25°C/60%RH, respectively. No changes were observed in any of the monitored parameters compared to the initial values.

All stability indicating parameters remain within the proposed commercial specifications when stored at the long-term storage condition (25°C/60%RH) through 24 to 60 months or at the accelerated storage condition (40°C/75%RH) through 6 months for each primary and supportive registration stability batch of voclosporin softgel capsules.

Photostability study results demonstrated that voclosporin softgel capsule is stable following exposure to the conditions defined in ICH Q1B, Option 2. All finished product quality attributes remained within the specifications after light exposure and all degradation products were found at or near the limit of quantification for both the light exposed samples in an open dish, light exposed in the blister and dark control samples. Based on these results, no special storage statement is required to be added to the labelling for voclosporin softgel capsules.

For the temperature cycling study, no significant change was observed in any of the following test attributes evaluated: appearance, assay, uniformity of dosage units, dissolution, moisture content, ethanol content (whole capsule), degradation products and microbial limits. The results demonstrate that voclosporin softgel capsules are chemically and physically stable when exposed to extremes in temperature for several days through three cycles. Therefore, no precautionary statement to avoid freezing is required to be added to the labelling for voclosporin softgel capsules.

Force degradation stability studies have been performed to demonstrate stability indicating of the analytical methods. The results presented demonstrated that the methods are stability indicating methods.

The applicant commits to continue the ongoing primary registration stability study through at least the end of the proposed finished product shelf-life according to the stability protocols. Adequate post-approval stability protocol information is presented and acceptable handling of any confirmed out-of-specification (OOS) is proposed. Furthermore, as part of the post-approval stability commitment, one finished product batch per year will be subjected to stability testing and evaluation for continuous stability monitoring.

Based on available stability data, the proposed shelf-life of 36 months for the finished product stored under the following storage conditions: "Store in the original package, in order to protect from moisture.", as stated in the SmPC (section 6.3), are acceptable.

2.3.3.5 Adventitious agents

Gelatine obtained from bovine sources is used in the product. Valid TSE CEP from the suppliers of the gelatine used in the manufacture is provided.

2.3.4. Discussion on chemical, and pharmaceutical aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

The applicant has applied QbD principles in the development of the finished product and its manufacturing process. However, no design spaces were claimed for the manufacturing process of the finished product.

2.3.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

2.3.6. Recommendation(s) for future quality development

N/A

2.4 Non-clinical aspects

2.4.1 2.4.Introduction

Voclosporin consists of 2 geometric isomers; a trans-isomer and a cis-isomer, depending on the orientation of the modified functional group at amino acid-1. The drug substance/formulation used in early nonclinical and clinical studies was an approximately equal mixture of both isomers (45-50% trans-, 50-55% cis-). This formulation is referred to throughout the dossier as mix-ISA247 and ISATX247 in the study reports. From 1999 to 2002, the pharmacodynamics of mix-ISA247 was studied *in vitro* and *in vivo*. A decision was made in 2003 to develop a new formulation, enriched with the trans-isomer (90 to 95% trans-isomer) which is current formulation referred to as voclosporin.

Voclosporin is structurally similar to cyclosporine A except for a modification of a functional group on amino acid-1 of the molecule and is claimed to reversibly inhibit immunocompetent lymphocytes, particularly T lymphocytes, in the G0 or G1 phase of the cell cycle and reversibly inhibit the production and release of lymphokines and to mediate its immunosuppressive effects by binding to the intracellular protein, cyclophilin.

The recommended dose of Lupkynis is 23.7 mg (three 7.9 mg soft capsules), twice daily. Each soft capsule contains 21.6 mg ethanol and 28.7 mg sorbitol. Formulation excipients also include vitamin E polyethylene glycol succinate (also known as Tocofersolan), polysorbate 40, and medium chain triglycerides. The vehicle used in most of the nonclinical studies performed is stated to be the same as that utilised for human administration. The oral route of administration was used, as this is the proposed route for administration in humans.

2.4.2. Pharmacology

2.4.2.1. Primary pharmacodynamic studies

The pharmacological activity of voclosporin has been demonstrated both *in vitro* and *in vivo* using calcineurin inhibition and lymphocyte proliferation as markers of pharmacological effect and using different animal models for autoimmune uveitis, arthritis and organ transplants.

In *in vitro* studies in human whole blood voclosporin, in the form of trans-ISA247 (containing 18% cis- and 82% trans-isomer), was shown to inhibit calcineurin activity with an IC50 of 0.46 µM and to be 1.5 times more potent than cyclosporine A (CsA). In another study Mix-ISA247 (containing 45-50% trans- and 50-55% cis isomers) was shown to be 1.8 and 1.2 more potent than CsA, in two different laboratories, using a simple E-max model. Using a human lymphocyte proliferation assay it was shown that the IC50 for voclosporin was 15.8±10.2 ng/ml and that all major metabolites investigated (IM9, IM4, IM4n, IM1c and IM1-Diol-1) had IC50 values that were at least 9-fold higher than voclosporin.

In vivo, voclosporin gave a dose-related increase in calcineurin inhibition in whole blood in monkeys with an indicated direct relationship between PD effect and drug concentration. A length of time with >50% inhibition of calcineurin of 6 to 9 hours was said to indicate significant immunosuppression in high dosed animals (75 and 150 mg/kg/day). When T Cell Function was studied in monkeys, mix-ISA247 demonstrated a greater overall PD effect compared to CsA, both *in vitro* and *in vivo*, even though drug concentrations for mix-ISA247 were lower *in vivo* at the doses used (mix-ISA247 25 and 50 mg/kg, and CsA 25 mg/kg).

In an animal model for Uveitis the therapeutic efficacy of voclosporin appeared to be similar to cyclosporine. In this study the *in vitro* voclosporin induced inhibition of proliferation of lymphocytes from rodents and humans, and Th1, Th2, and Th17 cytokine levels in human lymphocytes were also studied and indicate that voclosporin efficacy may be mediated through the inhibition of T-cell effector responses.

Mix-ISA247 were also shown to have greater potency than CsA in the treatment of established collagen-induced arthritis in mice and in treatment of established antigen-induced arthritis in rabbits based on dose comparisons (exposure levels were not analysed).

After allotransplantation of pancreatic isle cells ISATX247 (containing 45-50% trans- and 50-55% cis isomers) enhanced graft survival and seemed to be more potent at delaying the onset of diabetes as compared with the same dose (20 mg/kg) of cyclosporine A. Mix-ISA247 also showed enhanced potency with respect to overall survival in comparison with CsA at a dose of 1.75 mg/kg/day (ip 0.875 mg/kg BID) in a rat heterotopic heart transplant model. In a similar study in this model survival times for ISA247-(mix), trans-ISA247, and CsA at the same dose (1.75 mg/kg/day) were all significantly greater than the survival time for control animals, with mix-ISA247 and voclosporin prolonging graft survival in all animals during the treatment period as compared to 83% survival in CsA and 33% survival in cis-ISA247 treated animals.

Survival of cynomolgus monkeys with heterotopic renal allografts were also shown to be higher in monkeys treated with ISATX247 as compared to CsA at equal exposure levels suggesting a more potent immunosuppressive effect of ISATX247.

2.4.2.2. Secondary pharmacodynamic studies

In monkeys with kidney transplants mix-ISA247 (50 mg/kg) seemed to have lesser effects on kidney mitochondrial dysfunction than CsA (25 mg/kg) when activation of cytosolic glycolysis and glucose utilisation were analysed using MRS (magnetic resonance spectrometry). Less cellular oedema and papillar necrosis was also present after treatment with mix-ISA247 as compared to CsA treatment and less renal lipid peroxidation was also indicated after treatment with mix-ISA247.

No adverse renal effects were observed in rabbits following 7 days of intravenous administration followed by 23 days of subcutaneous administration of mix-ISA247 at doses up to 25 mg/kg/day. The 2 animals treated with 25 mg/kg/day died at 5 and 7 days, respectively, with metabolic effects preceding the death, but without adverse renal effects.

In dogs with islet cell autografts, mix-ISA247 (20 mg/kg/day for 4 weeks) was not toxic to islet cells, while CsA (20 mg/kg/day for 4 weeks) showed an adverse effect on islet cell function. However, the average through concentration was ~3 times higher for CsA.

In conclusion, except for the "metabonomics" data obtained in monkeys using MRS, indicating a lower potency for mix-ISA247 to cause mitochondrial dysfunction in the kidney than CsA, no clear difference between mix-ISA247 and CsA regarding effects on kidneys and islet cells were obtained. No effects were seen on kidneys at the CsA dose level used in rabbits, and the CsA exposures levels obtained in dogs where 3 times higher as compared to that obtained for mix-ISA247. No other potential secondary pharmacological effects have been analysed or discussed by the applicant. This is considered acceptable, considering the similarity of the toxicological profile of voclosporin and CsA and the only 1.5-fold increase in potency towards calcineurin, as well as the presence of clinical data.

In rabbits, a reduction in spermatogenesis was detected, which was concluded to be drug related in one study (ISA99-02) and possibly drug related in another study (ISA00-21). The applicant was asked to discuss this point during the evaluation and agrees that voclosporin, like CsA, can reduce the prostate and testicular weights in the rat.

2.4.2.3. Safety pharmacology programme

In vitro studies on CHO cells expressing recombinant hERG channels and in rabbit Purkinje fibres indicate that mix-ISA247, cis-ISA247 and voclosporin block repolarizing currents through hERG channels *in vitro* at twenty percent inhibitory concentration (IC20) values of approximately 6 to 18 µM (7300 -21900 ng/mL). These concentrations are well in excess of estimated therapeutic whole blood concentrations of Cmax bound 120 ng/mL with a free fraction of 3.6 ng/mL. In the rabbit Purkinje fiber assay, mix-ISA247 was not associated with the induction of arrhythmias at the concentration range tested (nominally 0.01-10 µM), while slowing of cardiac action potential depolarisation indicated that ISA-247 may produce ventricular conduction abnormalities *in vivo* (QRS-prolongation) at free myocardial concentrations above ~3 µM (3660 ng/mL).

In two *in vivo* studies in conscious monkeys, mix-ISA247, cis-ISA247 and voclosporin lengthened QT intervals and corrected QT intervals (QTc) at a dose level of 200 mg/kg and were considered to have an effect on ventricular repolarisation. In these studies, no effects on heart rate were observed and the electrocardiogram (ECG) waveforms showed no effect on RR, PR or QRS complex duration. A Cmax of ~600 ng/mL was seen after a dose of 200 mg/kg (as compared to a clinical Cmax of 120 ng/mL).

Safety pharmacology studies were also conducted in rats to assess the potential respiratory, CNS, and renal effects of voclosporin. At a dose of 25 mg/kg, the highest dose tested, voclosporin was associated with a slight decrease in respiration rate, without an increase in tidal volume, at 120 minutes after dose administration. Voclosporin did not cause any neuropharmacological or toxicological signs at doses up to 25 mg/kg except for a 0.5ºC decrease in body temperature (a decrease of body temperature ≤0.5 °C was also seen in one of the studies in monkeys at 200 mg/kg). In the renal safety study, the only effect of voclosporin was a marginal decrease in urine volume at a dose of 25 mg/kg, the highest dose tested. Based on AUC from a 13-week rat toxicology study (ISA03-03) the estimated exposure margin relative to clinical exposure is approximately 24 times at a dose of 25 mg/kg.

2.4.2.4. Pharmacodynamic drug interactions

2.4.3 Pharmacokinetics

Absorption

Oral bioavailability of voclosporin ranged from 7.6% to 7.8% for male and female Sprague-Dawley rats with a higher exposure seen in male rats as compared with female. There was no evidence of accumulation. Upon repeat dosing the rate and extent of absorption of mix-ISA247 decreased over time. Time to maximum concentration (Tmax) values were typically between 1 and 4 hours and were consistent among the species evaluated. In general, voclosporin was eliminated at a moderate to rapid rate ($t_{1/2}$ 3-8 hours) in mice, rats, rabbits, and monkeys. Data suggest that the trans-isomer is more bioavailable than the cis-isomer. Systemic exposure seemed to be higher for CsA than for mix-ISA247.

The trans-isomer of voclosporin has been shown not to convert to the cis-isomer in whole blood *in vivo* and the conversion of cis-ISA247 to trans-ISA247 (or vice versa) do not occur *in vitro* either in human whole blood or denatured human whole blood.

Distribution

Plasma protein binding ranged between 96.97% (human) to 98.34% (rat) in all species investigated (mouse, rat, rabbit, dog, monkey and human). High distribution to red blood cells showed that whole blood is the most appropriate biological matrix for quantifying voclosporin.

Following a single oral administration of voclosporin to Sprague-Dawley rats (4.1-4.3 mg/kg 14C-Voclosporin (42.6 µCi/mg)) drug related material was rapidly distributed into essentially all major organs/tissues analysed. Tissue concentrations of radioactivity were generally higher in males than in females and radioactivity in the tissues also appeared to decline more rapidly in females than in males. The highest concentrations of radioactivity were generally associated with the gastrointestinal tract, liver and kidney. However, concentrations were also relatively high in the pancreas, thyroid, spleen, adrenals and mesenteric lymph node in both males and females. Tissue concentrations in the brain and spinal cord were low in both sexes. The concentrations of radioactivity were notably higher in the female sexual organs than in male sexual organs. Similar results were obtained after administration of a single oral dose of [3H]-mix-ISA247 (25 mg/kg, 45-63 µCi/animal). Tissue radioactivity concentrations in male rats generally declined after reaching peak levels, such that at 72 hours post-dose (the final sampling time) more than half of the tissues/organs in male rats and almost all of the tissues/organs in female rats, were below the limit of quantification and only the exorbital and intra-orbital lacrimal glands in male rats contained greater than 0.1 µg equivalents/g.

There were no significant differences in the [14C]-voclosporin distribution profile of Lister Hooded (pigmented) rats versus the Sprague-Dawley (non-pigmented) rats (for the selected organs

evaluated), or between pigmented and non-pigmented skin in Lister Hooded rats, suggesting negligible binding of voclosporin to melanin.

Tissue distribution of radioactivity, following oral administration of [14C]-voclosporin (40 mg/kg, 260 µCi/kg) to cynomolgus monkeys, was similar to the pattern observed in rats. Once absorbed, drug-derived radioactivity was rapidly and widely distributed to all tissues and organs analysed. The highest concentrations of drug-derived radioactivity were associated with the walls of the GI tract, bile (gall bladder contents), liver, aorta (female only), lymph nodes (mesenteric) and kidney. Radioactivity concentrations were low in the tissues of the central nervous system. Exposure to both parent drug and radioactivity appeared to be comparable between the two sexes with time of maximum concentration (Tmax) at around 2-3 h post-dose. At 168 h post-dose (one female only), tissue : whole-blood ratios generally declined or remained at a similar level to those at 2 h post-dose. Exceptions to this were pigmented skin, non-pigmented skin and mammary glands, where notable increases (20 – 47-fold) in the ratio were observed. This was concluded to likely reflect the lipophilic nature of voclosporin and/or its metabolites.

Distribution in pregnant animals was similar to that in non-pregnant animals. Radiolabelled material was observed in foetal tissues after administration of [14C]-Voclosporin to pregnant rats, suggesting that dose-related material had crossed the placental barrier, although distribution was slow and limited and the levels in foetal carcasses were low (0.019% of the dose administered to the dam was observed in foetal tissues at 8 hours (Tmax) post-dose).

Metabolism

Voclosporin is extensively metabolised by hydroxylation and oxidative N-demethylation reactions in all species, including humans. CYP3A4/5 is the primary CYP450 enzyme involved in the Phase 1 metabolism of voclosporin. The proposed metabolic scheme consists of a CYP450-catalyzed oxidation of amino acids, other than amino acid-1, to yield the metabolites IM9, IM4 and IM4n, or a CYP450-catalyzed oxidation of amino acid-1 to generate the metabolites IM1-Diol-1, IM1c (R), and IM1w. Other metabolites are observed *in vivo* but at levels too low to quantitate. In addition, IM1-Diol-2 and IM1-Diol-3 are only formed from cis-ISA247 (of which voclosporin contains ≤10%), while the trans-isomer preferentially forms IM1-Diol-1. The major metabolite in all species is IM9 with a relative % distribution of 16.7%, based on total radioactivity in 0-24h human pooled blood samples.

Metabolism of voclosporin is similar across species with no unique human metabolite.

IM1-Diol-1 is close to be classified as a major human metabolite that would need to be characterised in nonclinical studies in accordance with the ICH M3 guideline. The relative distribution for IM1-Diol-1 is reported to be 9.47±1.66% of total radioactivity, as compared to the classification limit stated in the M3 Guideline; "greater than 10% of the measured total exposure to drug and metabolites". It is of interest that a proposed possible pathway for the formation of IM1-diol-1 as well as IM1w and IM1A includes an initial oxidation of the terminal double bound in amino acid 1 and the formation of an epoxide intermediate. This suggests a possible formation of reactive intermediates during the formation of M1-diol-1. However, the absence of detectable levels of GSH adducts in incubations with human liver microsomes in combination with the absence of time dependent inhibition of cytochrome P450 enzymes suggest that no, or very low levels of reactive intermediates are formed during voclosporin metabolism, including the formation of IM1-diol-1.

No additional nonclinical characterisation of IM1-diol-1 is considered needed based on the absence of detectable levels of reactive intermediates and the average relative distribution being below 10%.

Excretion

The major route of excretion in rats, monkeys and humans following oral administration is faecal (~96%, ~79% and ~93%, respectively) with only minimal urinary secretion.

A rapid and substantial distribution to milk is seen in lactating rats after oral administration of voclosporin.

PK interactions

PK interactions were investigated *in vivo* in rats in a steroid interaction study with voclosporin and prednisone and a interaction study with voclosporin, CsA, or tacrolimus (Tac) co-administered with mycophenolate mofetil (MMF). Voclosporin exposure was generally higher when administered alone compared to administration with prednisone. There was no evidence of accumulation of voclosporin when administered alone or with prednisone. In male rats, following dosing of voclosporin (25 mg/kg/day) and prednisone (0.5 mg/kg/day) a sign of a possible accumulation of prednisone/prednisolone was detected. In other groups, administration of voclosporin up to 10 mg/kg/day did not seem to affect exposure to prednisone/prednisolone. Daily oral administration of voclosporin for 7 days and co-administration of a single dose of mycophenolate mofetil on Day 7 had no effect on MPA plasma concentrations, but MPAG plasma concentrations were increased relative to control. This was in contrast to CsA which reduced MPA plasma concentrations and increased MPAG plasma concentrations.

2.4.4. Toxicology

The applicant has developed voclosporin, a calcineurin inhibitor indicated for the treatment of patients with lupus nephritis (LN). The structure is similar to cyclosporine A (CsA), except for a modification to the amino acid-1 region which was introduced to give an alteration of the metabolic profile and improved potency compared to CsA. The recommended oral dose is 23.7 mg twice daily (BID). Voclosporin consists of 2 geometric isomers, a trans-isomer and a cis-isomer, and most studies in the programme have evaluated a mixture of the two isomers (mix-ISA247; 45-50% trans-, 50-55% cis-), whereas a few newer studies have evaluated the clinical product. A bridging programme with the two formulations has been performed which consisted of a 13-week oral voclosporin study in rats, an EFD study in rabbits and an Ames' test. In several studies, CsA has been included as a "positive control" to enable comparison regarding toxicological profile and potency.

A full programme of studies has characterised the toxicity of voclosporin, and the pivotal studies were performed in accordance with GLP regulations. Repeated-dose toxicity studies were performed in rat (up to 26weeks), mice (up to 13 weeks), dog (up to 13 weeks) and monkey (up to 39-weeks). Further, genotoxicity studies, carcinogenicity studies (rat and mouse), EFD-studies (including a 10-week juvenile toxicity study) and local tolerance studies were included in the study programme. The primary species used for multiple-dose toxicity studies were Sprague-Dawley rats and Cynomolgus monkeys, why focus was put on the pivotal studies in these species in this assessment report. A limited number of studies have also been performed in CD-1 mice and Beagle dogs of which limited studies were included. The dog studies were limited by frequent emesis findings resulting in variable TK data, why the use of dog was discontinued in the development programme. Except for emesis in dogs, no changes occurred in mice or dogs that were not also seen in rats or monkeys. While the applicant has not provided with a clear justification for the species used in the toxicology programme, rat, rabbit and monkey are considered appropriate main species for the studies based on pharmacodynamics and metabolic profile.

The vehicle used in all oral toxicology studies was Vitamin E TPGS (D-alpha-tocopheryl-polyethylene glycol 1000 succinate)/medium chain triglyceride (MCT) oil/Tween 40/95% ethanol (4:2:2:1, w/w/w/w). From a toxicological perspective this vehicle was suboptimal as it generated toxicities which

may have masked voclosporin-induced effects. These toxicitites include GI-effects in all species tested and effects on haematology parameters, coagulation and organ weights (also in 13-week study) in the 39-week study in monkey. In addition, in the carcinogenicity study in mouse, increased mortalities were noted in the vehicle group, whereas an increased incidence of cervical granular tumours were noted in the vehicle group compared to controls in the rat carcinogenicity study. Voclosporin and mix-ISA247 are extensively metabolised by hydroxylation and oxidative N-demethylation reactions. The major metabolite in all species including human is IM9. Metabolism of voclosporin is similar across species, with no unique human metabolites, and no separate toxicity studies have been performed for the metabolites.

The toxicity profile of voclosporin is mostly reflective of the calcineurin inhibitory action of the substance, and the profile is very similar to CsA.

2.4.4.1. Single dose toxicity

Two non-GLP single-dose TK studies have been performed, one in SD rat and one MTD study in Beagle dog which used repeated single doses. No deaths or apparent toxicities were noted in the rat. In the dog, vomiting and/or regurgitation was the only toxicity reported.

2.4.4.2.Repeat dose toxicity

Repeat-dose toxicity studies have been performed in rat and cynomolgus monkey using oral (gavage) administration. As most studies were performed using mix-ISA247, a bridging programme was performed with voclosporin which included a 13-week study in the rat. The overall impression is that mix-ISA247 and voclosporin have overlapping toxicological profiles. Further, 13-week studies in the rat were performed to evaluate whether vitamin E in the formulation may mask voclosporin-induced liver toxicity. Based on the study results presented, it was concluded that the toxicological profile of voclosporin was similar regardless of if the formulation contained vitamin E or not. A 13-week combination toxicity study with voclosporin and prednisone to determine the toxicological interaction and toxicokinetic profile of the test articles did not identify new toxicities in the combination groups compared to the separate voclosporin and prednisone groups. In the combination toxicity study, the lowest effective dose of prednisone was used for rats (0.5 mg/kg) without titration of the corticosteroid dose throughout the study, while the voclosporin dose was changed from 0 to 25 mg/kg. It is unclear if there would be any toxicities from the combination if prednisone was used in higher effective doses, but since one of the clinical goals is to lower corticosteroid usage in patients, this is considered to be of minor concern and was not further pursued by the CHMP.

Treatment related mortalities were identified in the repeated-dose toxicity studies. In the 13-week study in rats, two recovery animals' demise (10 and 25mg/kg/day) are considered related to treatment. This is based on clinical signs which correlated with neuropathological findings of multifocal vascular/perivascular infiltrate (associated with gliosis and vacuolation) in the brain and spinal cord.

In the rat 26-week study, the 7 deaths in the cyclosporin group (compared to 2 in the control) were according to the study report treatment related. However, the 4 deaths in the Mix-ISA247 group (4/66 animals) were not considered biologically different from that of the control group. The basis for this position is unclear as no cause of death was identified for most of the animals, and the overall findings in the study suggest that the substances are very similar from a toxicological perspective. However, this issue was note further pursued by the CHMP.

In the 39-week study in Cynomolgus monkey, three deaths occurred during the study, of which one was in the control group. A vehicle-treated male died of pneumonia, which is of unclear treatment

relation. One female administered 150 mg/kg/day died on SD 132 from lymphosarcoma. This death is considered treatment-related as 5 animals (4 females, 1male) in the high-dose group were diagnosed with the disease at necropsy (see subsection on lymphosarcoma below).

Clinical signs and body weights

GI effects (soft/loose feces, diarrhea and dark feces) were evident in all species tested (including the rabbit EFD-study) and increased with dose in several studies. In the dog, diarrhea and emesis was noted in 14-day and 13-week studies (despite attempts to use enterically coated capsules). This limited the usefulness of the species for longer studies as the emesis resulted in highly variable pharmacokinetics. In studies with recovery groups, the GI effects recovered. Bodyweights correlated with the GI effects from 10mg/kg/day in the rat but recovered or showed signs of recovery. In monkey, no effects on body weight were noted.

Gingival hyperplasia

In the 13-week study in cynomolgus monkey, macroscopic findings of gingival epithelial hyperplasia (3 vehicle monkeys+3 at 75 mg/kg/day) were seen which correlated with inflammation. In the 39-week study clinical signs of increased swelling of the gums were evident from 75mg/kg/day with a clear dose-relationship. This correlated macroscopically with gingival thickening and microscopically with lymphocytic infiltration into tissues and increased rete peg development. Gingival hyperplasias were also seen in the dog but not in the rat.

Cataracts

Cataracts noted at ophthalmoscopy which correlated with lenticular degeneration microscopically was evident in rat studies from 28-days duration at dose levels at and above 2.5mg/kg/day mostly in males (perhaps related to higher exposures in males). The findings generally increased at recovery. No cataracts were noted in mouse dog, rabbit or monkey suggesting a species-specificity. Cataracts are known effects of CsA in the rat, and studies have suggested increased rates of steroid-induced cataracts with the use of cyclosporin. However, in a 13-week combination toxicity study with voclosporin and prednisone, no increased cataracts were noted in the combination groups compared to voclosporin alone.

Renal toxicity

In rat, the kidney was a sensitive target of toxicity with effects noted already from 28 days of exposure and included increased BUN and increased urinary glucose and specific gravity which correlated with macro and microscopic findings. In the 28-day study, increased kidney weights from 24.2 mg/kg/day correlated with microscopic findings of renal corticomedullary mineralisation and trace to minimal bilateral renal tubular basophilia in mid- and high-dose males. In the 13-week study, renal corticomedullary mineralisation was evident in the kidney from 10mg/kg/day including increased incidence of bilateral renal tubular basophilia. In the 26-week study, minimal to mild microscopic findings of degeneration/regeneration of cortical tubules were evident which showed dose-relation. These findings persisted through recovery. In cynomolgus monkey, increased kidney weights from 25mg/kg/day did not correlate with macro- or microscopic findings.

Neurological findings

Major neurohistological effects of CsA, cis-ISA247, voclosporin and mix-ISA247 were noted in the rat in studies from 13-weeks duration. In the 26-week study, histopathological findings were observed in the central and peripheral nervous systems after CsA and mix-ISA 247 exposure. In the spinal cord, the cervical, thoracic and lumbar segments showed subacute inflammation and/or nerve fiber degeneration and gliosis with various incidences from 1.25mg/kg/day. Further, in the brain of males at 10mg/kg/day from both substance groups, multifocal subacute perivascular inflammation characterised

by accumulation of mononuclear cells, gliosis, nerve fiber degeneration was noted. Findings in the cranial and sciatic nerves were observed in high-dose males (mix-ISA247 or CsA) which included nerve fiber degeneration and/or lymphocytic infiltration and/or gliosis. The findings in the CNS and PNS remained through recovery. Interestingly, despite these clear toxicities to the nervous system, no treatment-related effects were evident in the performed FOB evaluation. The underlying reason for this is unclear but may reflect that areas of the brain important for the execution of these tests (e.g. striatum, hippocampus) were not affected. No recovery was seen, and similar neurotoxic effects were noted also in the 13-week study

Lymphoid tissues

In the 13-week study in mouse, reduced absolute lymphocyte counts in the mid- and high-dose groups correlated with depletion of lymphoid cells and hypocellularity in the thymus and lymph nodes. This is likely related to the immunosuppressant effects of the substance. Lymphopenia and reduction of lymphoid cells were identified in the thymus and lymph nodes.

In the rat 13- and 26-week studies treatment with mix-ISA247 and CsA was associated with medullary atrophy in the thymus and cortical lymphocytolysis. The effects remained after recovery. Absence of germinal centres in the spleen was noted more frequently in animals at 10 and 25 mg/kg/day and in the mandibular lymph node at 25mg/kg/day. Collectively, these findings are considered exaggerated pharmacology effects and related to the immunosuppressant effect of the substances.

Liver

The liver was not a major target organ of toxicity, but increased expression of liver enzymes (AST, ALT, ALP) were noted in rats treated with mix-ISA247 and CsA in the rat 26-week study, suggestive of liver engagement.

Haematology and clinical chemistry

Across all species, treatment with mix-ISA247 and CsA resulted in reduced lymphocyte counts. A reduction of Mg is noted for both sexes from 10mg/kg/day in the 13-week and 26-week studies in rat. According to the applicant, this reflects a class effect of calcineurin inhibitor drugs noted in animals and humans, thought to be drug-induced intracellular redistribution of Mg within renal tubular epithelium. However, the exact mechanism is uncertain, but serum Mg levels rapidly return to normal after the cessation of drug treatment.

Reproductive organs

In the 13- and 26-week repeated-dose toxicity studies in rat and in the 13-week study in monkey, prostate and testes (only rat) weights were reduced without microscopic correlation.

Lymphosarcomas

Macro- and microscopic examination of monkeys in the 39-week study revealed lymphosarcomas in 5 high-dose (150/300 mg/kg/day) animals (one of which died on SD132) which were very extensive and invasive in 2 animals. Lymphosarcomas were also identified in the rat carcinogenicity studies (see below). According to the applicant, other compounds of this class have been associated with lymphosarcomas, and they can be related to excessive immunosuppression. Indeed, at the high dose, calcineurin inhibition was substantial, and studies referenced by the applicant have shown increased development of lymphosarcomas in non-human primates treated with immunosuppressive drugs.

2.4.4.3. Genotoxicity

A full programme of genotoxicity studies has been performed. Voclosporin was not mutagenic in a bacterial reverse mutation assay (Ames) or in a vitro chromosomal aberration assay using CHO cells. An isomer mix (Mix-ISA247), used in early development, showed no genotoxic potential in an *in vivo* micronucleus assay with bone marrow smears. Voclosporin was not tested in an *in vivo* assay. This is acceptable since the dosing with Mix-ISA247 most likely resulted in sufficient exposure of the trans-isomer. In summary, the genotoxicity studies presented do not indicate a genotoxic risk for voclosporin.

2.4.4.4. Carcinogenicity

Two long term studies with voclosporin were performed in mice and rats. Planned to be 2-year studies, both had to be early terminated due to decreased survival. In both studies, two separate control groups (vehicle and saline) were used and there was vehicle-related toxicity and vehicle-related effects on the survival of mice and rats.

Main findings were malignant lymphomas in mice. Moreover, there were increases in benign granular cell cervix and vaginal granular cell tumours in female rats given vehicle or voclosporin.

Mouse 89-week carcinogenicity study

The applicant conducted an 89-week carcinogenicity study in mice. The study was planned to last 104-weeks (2 years) but was terminated early due to decreased survival and poor condition of the mice in the low- and high-dose. The exposure levels in the mid-dose group, which can be considered the NOAEL for neoplastic findings, were comparable to clinical exposure.

The vehicle was not well-tolerated over time and vehicle-related effects on overall survival and histopathology as described below were observed. All groups had 50% or higher survival through study week 48. Survival at termination of each group was in the saline control, vehicle control, 3, 10 and 30 mg/kg/day groups 51%, 31%, 23%, 31% and 23%, respectively, for males and 63%, 40%, 37%, 34% and 31%, respectively for females.

There were increases in malignant lymphomas in high-dose males (at 9 times human exposure) and females (at 7,5 times human exposure) compared to vehicle or saline groups. Voclosporin has immunosuppressive effects and an increased risk for neoplastic lesions would therefore be expected.

There was also a statistically significant increase in mid-dose females when comparing combined bronchiolar-alveolar adenoma and carcinoma with the vehicle group. This finding is considered incidental with limited clinical relevance.

Rat 96-week carcinogenicity study

The 2-year rat study had to be terminated early (at week 96) due to decreased survival of vehicle control group animals. At termination, survival in the saline control, vehicle control, 0,05, 0,25 and 1,25 mg/kg/day group males was 40%, 31%, 29%, 33% and 25%, respectively, and in the saline control, vehicle control, 0,1, 0,5 and 2,5 mg/kg/day group females was 35%, 32%, 46%, 32% and 46%, respectively. All groups had 50% or higher survival through study week 79 which is considered low. A NOEL was not determined due to mortality. At all dose-levels, the exposure levels in the rats were below human exposure.

Pancreatic islet tumours (adenoma and carcinoma combined) were increased in the high-dose males compared to vehicle control group, but not compared to the saline control group.

There was an increase in granular cell tumours in the female reproductive tract (benign granular cell cervix and vaginal granular cell tumours) compared to saline control group but not when compared to vehicle control group.

The benign granular cell tumours of the cervix were statistically significantly increased in the mid-dosed females when compared to the saline control group, but not the vehicle control group. When benign granular cell tumours of the cervix were combined with benign granular cell tumour of the vagina, statistical significance was also reached for the high-dose females when compared to the saline control group, but not the vehicle control group.

2.4.4.5. Reproductive and developmental toxicity

A full programme of reproductive and developmental studies has been performed with voclosporin, which included FEED, EFD PPND and juvenile toxicity studies in SD rat as well as EFD studies in NZW rabbit. In all studies, mix-ISA247 administration was used. Further, an EFD bridging study was performed in NZW rabbit using voclosporin administration.

FEED

In males the incidence of swollen snout, localised alopecia of the limbs, swollen forepaw digits and urine-stained abdominal fur showed a clearly increased incidence in the 25mg/kg/day dose-group. Further, body weight and food consumption were reduced in males at 25mg/kg/day. This difference in clinical signs between the sexes can be explained by the roughly double exposure (AUC) noted in males compared to females. Interestingly, body weights were increased in males at 2.5 and 10mg/kg/day which correlated with increased food consumption at 10mg/kg/day. The underlying reason for this effect is unclear, and since no data have been made available on water consumption, a relation is not possible to clarify. This issue was not further pursued.

Reproductive organ weights (left cauda epididymis, left and right epididymis, seminal vesicles with and without fluid prostate) and testes (abs.) weights were reduced or significantly reduced at 25mg/kg/day. However, no microscopic correlation was noted, and sperm motility, count and density were unaffected. Nor did the changes in reproductive organ weights translate into reduced fertility in the males of this study. However, it is noted that in the 13- and 26-week repeated-dose toxicity studies in rat and in the 13-week study in monkey, prostate and testes (only rat) weights were reduced, also without microscopic correlation. Further, according to the pharmacology study report ISA 99-02 decreased spermatogenesis in all male rabbits treated with mix-ISA247 at 15 mg/kg/day was treatment related (similar findings were also noted in study ISA00-21 but reported to need additional analysis). Caesarean section parameters and litter data were unaffected by treatment. Collectively, considering the effects in reproductive organs in males, a paternal NOAEL is considered to be 10 mg/kg/day, whereas the maternal and reproductive NOAELS were 25mg/kg/day, the highest doses tested.

EFD studies

Based on the dose-range finding studies in rat and rabbit, it was concluded that mix-ISA247 has a reproductive toxicity potential. A dose of 20mg/kg/day was identified as high dose for the pivotal studies in both rat and rabbit. The voclosporin DRF-study in NZW rats showed similar toxicities as previously noted in rabbits administered mix-ISA247. Based on effects on fetal and maternal body weights from 40mgkg/day and effects on implantation also from 40mg/kg/day, 20mg/kg/day was considered a reasonable maximum dose for the pivotal study.

Rat

In the pivotal rat EFD study, dam mortalities were evident in the study and the clinical signs included increased incidences of scant feces, excess salivation, urine-stained abdominal fur and alopecia from 2,5mg/kg/day. Further, at 25mg/kg/day (the highest dose tested) a red perioral substance of unclear composition was noted. At 25mg/kg/day, maternal body weights and body weight gains were reduced which correlated with a significantly reduced food consumption from GD15. Also at this dose, the total number of resorptions, the percent dead or resorbed conceptuses per litter and early and late resorptions were significantly increased, which led to a reduced gravid uterus weight and mean litter size and also a reduced number of live fetuses.

With the exception of a reduced number of ossified metatarsals, which are likely reversible manifestations of the reduced body weight, no treatment-related malformations or variations were reported. Given the major developmental effects evident at 25mg/kg/day, this is surprising. Collectively, the maternal and fetal toxicities were considered adverse were seen in the 25mg/kg/day dose-group why maternal and fetal NOAELs are considered to be 10mg/kg/day, corresponding to a margin to clinical exposure of 7.2.

Rabbit

In the rabbit EFD-study with mix-ISA247, 4 does were found dead or were sacrificed. Of these, one doe at 10mg/kg/day was terminated on GD21 after abortion and two does at 20mg/kg/day were terminated on GD21 and 24 respectively after abortions. These abortions are considered related to mix-ISA247-treatment.

Clinical signs included ungroomed coat and liquid feces from 2mg/kg/day. Bodyweight and bodyweight gain was increased at 20mg/kg/day, but after correction for gravid uterine weight (reduced at 10 and 20mg/kg/day), dam body weights were significantly increased from 10mg/kg/day. At 20 mg/kg/day, increased resorptions were evident (early and late resorptions) and the litter size and the number of live fetuses was decreased suggestive of developmental toxicity. Further, fetal weights were significantly reduced from 10mg/kg/day. However, no increase in external, visceral or skeletal malformations were noted. From 10mg/kg/day, reduced metacarpal ossification was reported, which is considered a developmental delay of minor toxicological importance. Since treatment-related deaths were noted from 10mg/kg/day along with effects on body weight development, a maternal NOAEL of 2mg/kg/day is set. The developmental NOAEL is set at 2mg/kg/day based on the reduced fetal weights. At this dose, all TK values were BLQ why there are no margins to clinical exposure. Of note, the MoE to the dose associated with increased early and late resorptions is only 1.9.

In the EFD-study with voclosporin, 3 dams were found dead or euthanised in the study, none of which was considered treatment-related. Clinical signs included increased incidences of soft stool and brown material on various body surfaces noted in all treated groups including vehicle group. Similar findings but at lesser incidence was noted in control group. According to the applicant, the vehicle (a lipophilic carrier) is causing the toxicity which was increased at voclosporin exposure at 20mg/kg/day. It is in this respect noted that GI problems with the vehicle have been evident throughout the study programme. Body weight was significantly increased at 20mg/kg/day (up to 10%) whereas food consumption was decreased. As the gravid uterus weight was also reduced in this dose-group, dam body-weight increase was likely even larger.

Fetal weights were decreased from 5mg/kg/day, which also correlated with skeletal variations (increased incidences of unossified sternebrae no 5 and 6 from 5mg/kg/day and unossified hyoid body and/or arches only at 20mg/kg/day). No other malformations or variations considered treatment-related were noted. According to the applicant, the maternal and fetal NOAELs should be 1mg/kg/day based on swollen mammary glands and effects on fetal body weight at 5mg/kg/day. This was agreed by the CHMP.

PPND

A pre and postnatal development study has been performed in SD rats administered mix-ISA247 at doses up to 25mg/kg/day. No mortalities in F0 dams were considered treatment-related, and clinical signs included findings of red and/or brown substance in the vaginal and/or perivaginal areas, pale mucous membranes, soft or liquid feces, dehydration and emaciation. Gestational body weight losses were evident from 10mg/kg/day, whereas lactational body weights did not differ among groups. Further, feed consumption values were significantly reduced during gestation in the 25 mg/kg/day dosage group whereas no effects were evident during lactation. 12 dams at 25mg/kg/day were euthanised between GD27-31 due to failures to complete parturition (dystocia). Among these dams, clinical signs of ataxia, impaired righting reflex and decreased motor activity were noted. As a result of the dystocia, the mean number of total pups delivered, surviving pups per litter and the number of liveborn pups was significantly reduced in the 25 mg/kg/day dosage group. At ≥10 mg/kg/day the number of fetuses with umbilical hernias was increased, suggestive of reproductive toxicity.

No effects on body weights or sexual maturation were seen in the F1-generation. However, no data on pup physical and functional development (e.g. eye opening, incisor eruption, pinna unfolding) were identified. While these data should be available, the lack of effect on other developmental parameters (e.g. body weight development, sexual maturation) suggest that treatment related effects are not considered likely. Further, no differences were found in the values for learning, short-term retention, or response inhibition. Finally, no effects on mating or fertility parameters, including gross alterations of the F2 generation were evident. Therefore, the maternal and fetal NOAELs are considered to be 2.5 mg/kg/day, as the 25 mg/kg/day administration caused dystocia in dams and reduced fetal weights in the F1 offspring. Further, at 10mg/kg/day, umbilical hernias were noted, as well as adverse reduced maternal body weight gain.

Based on a placental transfer and milk transfer study in SD rat, drug-derived radioactivity was observed in milk by 1 hour post-dose and increased with a Tmax (blood and milk) at 4 hours post-dose. At Tmax, the milk/blood concentration ratio was nearly 1. Radioactivity in the stomach contents of the pups indicated lactational transfer (0.7% of the dose 23h post-dose) of voclosporin from the mother to the pup. Low levels of radioactivity were observed in pup carcasses indicating that drug material had been absorbed.

Juvenile toxicity

A juvenile toxicity study was performed in SD rat with voclosporin exposure from PND28-PND101. In a previous satellite study (not made available by the applicant), mortalities were evident around PND 7-14 which according to the applicant were presumably related to adverse interactions with the milk and the vehicle/voclosporin. Therefore, this study was initiated post weaning. As previous rat studies in the programme have shown increased exposures in males compared to females, a maximal dose of 5 mg/kg/day was given to males, whereas 10 mg/kg/day was the high dose in females.

Two unscheduled deaths were apparent in the study, but they were not considered to be related to voclosporin treatment.

No clinical signs or body weight effects with relation to treatment were identified. However, males in the vehicle group showed significantly increased body weights (up to 8%) across the study duration, which correlated with a decreased mean number of rears, and an increased mean score for urination in the open field compared to the control group. Further vehicle-related findings included presence of blood in the urine and increased urine specific gravity. Presence of blood in urine was also seen in this group during recovery along with increased levels of ketone bodies. Given the mortalities noted in the satellite study and the clear vehicle induced effects noted here (and elsewhere in the study programme) it is clear that the vehicle used is suboptimal.

Voclosporin-induced changes were identified in kidneys of female rats where voclosporin administration at 10 mg/kg/day resulted in an increased incidence of mineral deposition at the corticomedullary junction. This finding remained after recovery. In males from 2.5mg/kg/day and females from 5mg/kg/day, thymus changes were recognised as cortical vacuolation associated with tangible body macrophage accumulation. This finding remained in one female after recovery. Nervous system findings of mild vacuolation of the neuropil in the brain (1 female), and mild, multifocal lymphocytic infiltration of the sciatic nerve (1 female) noted after the dosage period were not evident after recovery. Finally, findings in male recovery animals associated with chronic progressive nephropathy were identified in 1, 2, 1, 1 and 3 males at control, vehicle, 1.25, 2.5 and 5mg/kg/day respectively. To conclude, no toxicities considered new for the juvenile patient population were identified in this study. However, findings considered adverse were identified in the kidney and the thymus from 2.5mg/kg/day.

2.4.4.6. Local Tolerance

A dermal irritation study in NZW rabbit does not support that voclosporin has corrosive or irritating potential. An eye irritation study in rats was performed where 3 NZW rabbits were instilled with voclosporin (100mg neat powder/eye) in the right eye (left eye was control). Following observation of the eyes at several time-points up to 72 hours post-dose, it was concluded that voclosporin is considered a slight ocular irritant. Given that the clinical route of administration is oral, the significance of the finding for the clinical situation is considered minor and this issue was not further pursued.

2.4.4.7. Other toxicity studies

Antigenicity

A delayed dermal contact hypersensitivity study in Guinea pig demonstrated that, under the conditions of the study, voclosporin did not elicit a delayed contact hypersensitivity response in induced guinea pigs when challenged with topically applied voclosporin. Accordingly, voclosporin is not considered a sensitiser.

Impurities and reagents

No dedicated studies on impurities were performed. A number of voclosporin-related impurities were evaluated for genotoxic structural alerts using the Leadscope Model Applier, a quantitative structure-activity relationship (QSAR) software program which includes both expert rule- and statistical-based models. No structural alerts were identified, why the impurities can be classified as ICH M7 class 5 compounds and thus treated as non-mutagens.

The applicant has also provided with genotoxicity evaluations for eight voclosporin reagents using the Leadscope Model Applier. Further, a literature review was also conducted for each compound to identify available genotoxicity data to support the determination of genotoxicity classification. Two compounds were classified as ICH M7 Class 2 (known mutagens with unknown carcinogenic potential). The remaining six compounds were classified as Class 5 (i.e. non-mutagenic impurities) and should thus be reported and qualified according to the principles laid out in ICH Q3A/B.

Specified impurities were present in toxicology batches in concentrations that allowed for qualification of impurities in nonclinical studies. Proposed acceptance criteria for specified impurities can be accepted.

Phototoxicity

According to the applicant, voclosporin does not absorb light in the wavelength of 290-700nm, suggesting that the substance has no phototoxic potential.

2.4.5. Ecotoxicity/environmental risk assessment

An ERA has been produced by the applicant. Log Pow was determined to 5.5 in a OECD 107 study, why a definitive PBT assessment was triggered. No study report for the OECD 107 study was provided. When asked to substantiate the log Kow of 5.5 with the study report the applicant stated that the slow stirring method (OECD 123) was considered more appropriate and referred to the study submitted in the application. CHMP agreed that for compounds with log Kow > 4, the slow-stirring method should be used. Based on the OECD 123 study, the log Kow is considered to be 6.26.

Regarding PBT assessment, the applicant submitted an OECD301F study with voclosporin which was performed in accordance with relevant guidelines. Based on the study, it can be concluded that voclosporin is readily biodegradable. According to the draft EMA "Guideline on the environmental risk assessment of medicinal products for human use" (EMEA/CHMP/SWP/4447/00 Rev. 1), when a non-natural peptide/protein is demonstrated to be excreted in amounts < 10% of the dose, or shown to be readily biodegradable in an OECD 301 test, the ERA stops. Therefore, no further ERA data are considered needed for voclosporin and it can be concluded that voclosporin in the proposed use is not expected to pose a risk to the environment.

Substance (INN/Invented Name):voclosporin			
CAS-number (if available): 515814-01-4			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD123 or …	6.26	Potential PBT (Y)
PBT-assessment			
Parameter	**Result relevant for conclusion**		**Conclusion**
Bioaccumulation	log K_{ow}	6.26	B
	BCF	N/A	N/A
Persistence	OECD 301	Voclosporin is readily metabolised. Metabolic pathways of voclosporin include and oxidative N-demethylation and hydroxylation at numerous sites.	not P
Toxicity	NOEC or CMR	Not provided	Potentially T
PBT-statement :	No further studies needed to conclude on the PBT properties.		
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
PEC $_{surfacewater}$, default or refined (e.g. prevalence, literature)	N/A	μg/L	> 0.01 threshold (N)
Other concerns (e.g. chemical class)			(N)

2.4.6. Discussion on non-clinical aspects

Pharmacology

The pharmacological activity of voclosporin has been demonstrated both *in vitro* and *in vivo* using calcineurin inhibition and lymphocyte proliferation as markers of pharmacological effect and using different animal models for autoimmune uveitis, arthritis and organ transplants.

Voclosporin is a calcineurin-inhibitor immunosuppressant that inhibits calcineurin in a dose-dependent manner up to a maximum dose of 1.0 mg/kg. Activation of lymphocytes involves an increase in intracellular calcium concentrations. Calcineurin is a calcium/calmodulin-dependent phosphatase whose activity is required for the induction of T-cell lymphokine production and proliferation. The immunosuppressant activity results in inhibition of lymphocyte proliferation, T-cell cytokine production, and expression of T-cell activation surface antigens.

In vitro studies showed that voclosporin was 1.5 times more potent than cyclosporine A (CsA) and to inhibit calcineurin activity with an IC50 of 0.46 µM. In general, voclosporin was also more potent *in vivo* as compared to CsA. Results from studies using a human lymphocyte proliferation assay indicated that the metabolites of voclosporin studied (including the major circulating metabolites IM9 and IM1-Diol-1) were at least 9-fold less potent than voclosporin. Only three studies were performed on secondary pharmacodynamics. This is considered acceptable, considering the similarity of the toxicological profile of voclosporin and CsA, the only 1.5-fold increase in potency towards calcineurin, as well as the presence of clinical data.

Safety pharmacology studies suggested only minor respiratory, CNS, and renal effects at an estimated maximum single dose exposure approximately 24-fold higher than that observed in clinical studies and are thus not considered of relevance for the clinical situation. Prolongation of QT interval and corrected QT interval were seen in monkeys at exposures ~5 times the estimated clinical exposure level without any significant *in vitro* effects on hERG detected. No additional studies are required considering that two clinical thorough QT-studies have been performed (see clinical part).

Pharmacokinetics

Pharmacokinetic studies have been performed in mouse, rat, rabbit, dog and monkey, with a focus on rat and monkey. Oral bioavailability of voclosporin was ~8% in rat with a higher exposure seen in male rats as compared with female. There was no evidence of accumulation. Data suggest that the trans-isomer is more bioavailable than the cis isomer. No conversion between the isomers were detected either *in vitro* or *in vivo*. Protein binding was high (97-98%) in all species investigated. 14C-voclosporin drug related material was rapidly distributed into essentially all major organs/tissues analysed with tissue concentrations in the brain and spinal cord being low. No significant differences in the distribution profile between pigmented and non-pigmented rats were seen, suggesting negligible binding of voclosporin to melanin. Distribution across the placental barrier was detected.

Metabolism of voclosporin is similar across species with no unique human metabolite. One major metabolite, IM9, with a relative distribution of 16.4% of total exposure was identified in human blood. A second metabolite, IM1-Diol-1, proposed to possibly be formed via an epoxide intermediate, was close to be classified as a major human metabolite having a relative distribution of 9.47±1.66% of total radioactivity. No additional nonclinical characterisation of IM1-diol-1 is considered needed, based on the absence of detectable levels of reactive intermediates and the average relative distribution being below 10% of total exposure in humans. The major route of excretion was faecal in all species investigated with only minimal urinary secretion. A rapid and substantial distribution to milk was seen in lactating rats after oral administration of voclosporin (see below). The pharmacokinetic characterisation of voclosporin is considered sufficient and no additional studies are required. The pharmacokinetic data obtained support the use of rodents and monkey as the primary toxicological species.

Toxicology

A full programme of toxicology studies has characterised the toxicity of voclosporin, and the pivotal studies were performed in accordance with GLP regulations. The toxicology profile of voclosporin is mostly reflective of the calcineurin inhibitory action of the substance, and the profile is very similar to

CsA. Therefore, several findings can be considered related to the class of calcineurin inhibitors. The vehicle used in all oral toxicology studies was Vitamin E TPGS (D-alpha-tocopheryl-polyethylene glycol 1000 succinate)/medium chain triglyceride (MCT) oil/Tween 40/95% ethanol (4:2:2:1, w/w/w/w). From a toxicological perspective this vehicle was suboptimal as it generated toxicities which may have masked voclosporin-induced effects. These toxicities include gastro-intestinal (GI)-effects in all species tested and effects on haematology parameters, coagulation and organ weights in the 39-week study in monkey. In addition, in the carcinogenicity study in mouse, increased mortalities were noted in the vehicle group, whereas an increased incidence of cervical granular tumours were noted in the vehicle group compared to controls in the rat carcinogenicity study. Therefore, the applicant was asked to discuss the toxicities found with the vehicle throughout the non-clinical development and correlate the findings with possible clinical implications. In the response, the applicant acknowledged that the vehicle is partly responsible for GI toxicities found in nonclinical and clinical studies. It is agreed that the GI effects are most probably caused by partly vehicle and partly active substance, even though the pharmacological effect of active substance is not completely understood. From a clinical perspective, gastrointestinal disorders were the second-most frequent adverse events by System Organ Class and are included in SmPC. The applicant argues that other nonclinical vehicle toxicity findings are not consistent or clear enough to point out the vehicle used as responsible for effects seen. This is agreed and taking into consideration the multiples to clinical exposure presented (26 – 258) and lack of clinical implications of vehicle toxicity. This issue was not further pursued by the CHMP.

No metabolite studies have been performed by the applicant. During the assessment, the applicant was asked to discuss whether IM1-Diol-1 should be considered a major metabolite. The low exposure levels obtained with this metabolite in the toxicological species used in studies on genotoxicity, carcinogenesis and embryo-foetal development should especially be considered. It should be noted that in accordance with guidelines it would be sufficient to show that animal exposure is at least 50% of the exposure seen in humans in one species used. In the response, the applicant presented clinical PK data and considerations regarding borderline results from the mass balance study. Additionally, in the response to clinical PK question on major metabolite, the applicant presented metabolite-to-parent ratios based on AUC0-12 at steady-state across different doses used in 4 studies. The CHMP concluded that it can be agreed that steady-state M-P data do not suggest that IM1-Diol-1 should be considered a major metabolite and no further evaluation of protein binding or DDI potential is requested from a clinical PK point of view. Therefore, the CHMP concluded that no discussion of the toxicological characterisation of this metabolite was required.

Gingival hyperplasias were seen in the dog but not in the rat. This is a well-known clinical problem associated with exposure to immunosuppressant drugs and is a common ADR noted in the Lupkynis clinical trials. It has been included in SmPC section 4.8.

Major neurohistological effects of CsA, cis-ISA247, voclosporin and mix-ISA247 were noted in PNS and CNS in rat studies from 13-weeks duration. The findings included multifocal subacute perivascular inflammation characterised by accumulation of mononuclear cells, gliosis and nerve fiber degeneration and remained through recovery. Despite these clear toxicities to the nervous system, no treatment-related effects were evident in the performed FOB evaluation. The underlying reason for this is unclear but may reflect that areas of the brain important for the execution of these tests (e.g. striatum, hippocampus) were not affected. Neurotoxicity is a clinically recognised AE of voclosporin (and CsA) and are included in sections 4.4. and 4.8 of the SmPC. Still, given that no recovery was seen, and similar neurotoxic effects were noted also in the 13-week study, the applicant was asked to reflect on the clinical relevance of these findings and include them in section 5.3 of the SmPC. Of note, the lack of similar effects in the repeat-dose toxicity studies in dogs and monkeys suggest that there could be species differences.

No mechanistic explanation was proposed by the applicant to explain the increased neurotoxicity noted in the rat compared to dog or monkey, but it was noted that the effects are dose-dependent and occur in the rat at voclosporin concentrations (based on AUC) which were also reached in the monkey. This suggests an increased susceptibility to the neurotoxicity in the rat compared to monkey. However, the lack of dramatic neurotoxicities in the clinical studies performed with voclosporin thus far indicates that the findings noted in the rat may not reflect clinically relevant effects.

Lymphosarcomas were identified in the repeated-dose toxicity studies in monkey and in the carcinogenicity study in rat. In the 39-week study in cynomolgus monkey, lymphosarcomas were identified in five animals in the high-dose group (150/300 mg/kg/day). One of these animals died on SD132 and the findings were regarded as very extensive and invasive in two animals. According to the applicant, other compounds of this class have been associated with lymphosarcomas, and they can be related to excessive immunosuppression. Indeed, calcineurin inhibition was substantial in high-dose group animals, and studies referenced by the applicant have shown increased development of lymphosarcomas in non-human primates treated with immunosuppressive drugs. It was therefore considered likely that the lymphosarcomas were related to the extensive immunosuppression. Lymphosarcomas are described in the key safety findings from non-clinical studies in the RMP, and in section 5.3 of the SmPC.

A full programme of genotoxicity studies has been performed, which did not indicate a genotoxic risk for voclosporin. This is adequately described in the Section 5.3 of the SmPC.

Malignant lymphomas were observed in the carcinogenicity study in mice. Lymphomas are not uncommon findings with immunosuppressive drugs and lymphosarcomas were also observed in the 39-week monkey study. Given the immunomodulatory effects of calcineurin inhibition, the lymphoma findings are most likely linked to voclosporin-induced immunosuppression. The non-clinical lymphoma findings are adequately listed in the SmPC and the increased risk for malignancies, including lymphomas, are listed as an important potential risk in the risk management plan.

The applicant considers that the high mortality rate observed in vehicle control and treatment groups, when compared to saline controls, in the mouse carcinogenicity study is due to procedure and gavage errors and not vehicle or treatment related (see also issue discussed above). Although findings in the oesophagus (perforation, inflammation) and swollen necks could indicate that more mice in the vehicle or treatment groups showed increased frequencies of gavage-related deaths, gavage and procedure-related deaths are not considered to be able to fully account for the increased mortality seen with the vehicle. At the CHMP's request, the applicant has presented an explanation of the terms "gavage error" and "local procedure related injury". Moreover, the applicant argues that if total local procedural and gavage error are subtracted, there is no consistent difference in mortality. While this seems to be the case, the applicant agrees that it is not clear why there was an increase in vehicle-related occurrence of gavage-related injuries, although several hypothetical arguments are made. Based on the applicant's response, the CHMP considered that it is not meaningful to further pursue this issue.

In the rat carcinogenicity study, pancreatic islet tumours (adenoma and carcinoma combined) were increased in the high-dose males compared to vehicle control group, but not compared to the saline control group. The applicant considers these findings to be incidental due to the lack of a dose-related trend and the sex differences which is acknowledged. Although lack of dose-response is not a sufficient argument by itself, the incidence of pancreatic islets cell tumours were within the range of the historical controls and there was not a clear difference to both control groups. The clinical relevance of the pancreatic tumours is therefore considered uncertain and not likely toxicologically significant.

There was an increase in granular cell tumours in the female reproductive tract (benign cervix and vaginal granular cell tumours). The applicant considers the lack of dose-response at mid- and high-dose animals supportive of that the findings are incidental. The absence of dose-response is not

considered a sufficient argument on its own to conclude that they are not related to treatment. Granular cell tumours are very uncommon and the historical control database of the CRO shows very low mean incidences of 0,09% (2/2341) and 0,13% (3/2344) in the cervix and vagina, respectively, while the present study showed incidences of saline control: 1,5% (1/65), vehicle control: 6,2% (4/65), low-dose voclosporin: 3,1% (2/65), mid-dose voclosporin 9,2% (6/65) and high-dose voclosporin 7,7% (5/65) for cervical granular tumours. A publication *(Markovits JE and Sahota P.S. Granular Cell Lesions in the Distal Female Reproductive Tract of Aged Sprague-Dawley Rats. Vet Pathol 37:439–448, 2000)* indicates that granular cell lesions in aging female SD rats are in general more common and seen at similar rates as in the present study. The publication further adds uncertainty when it comes to clinical relevance of the findings. A sufficient programme of reproductive and developmental studies has been performed with voclosporin. In the FEED study in SD rat, reproductive organ weights (left cauda epididymis, left and right epididymis, seminal vesicles with and without fluid prostate) and testes (abs.) weights were reduced or significantly reduced at 25mg/kg/day. However, no microscopic correlation was noted, and sperm motility, count and density were unaffected. Nor did the changes in reproductive organ weights translate into reduced fertility in the males of this study. However, it is noted that in the 13- and 26-week repeated-dose toxicity studies in rat and in the 13-week study in monkey, prostate and testes (only rat) weights were reduced, also without microscopic correlation. Further, according to the pharmacology study report ISA 99-02, decreased spermatogenesis in all male rabbits treated with mix-ISA247 at 15 mg/kg/day was treatment related (similar findings were also noted in study ISA00-21 but was reported to need additional analysis). At the CHMP's request, the applicant agrees that repeated administration of voclosporin can result in a reduction in testicular and prostate weights from 10 mg/kg/day and decreases in cauda epididymal, epididymal, and seminal vesicle weights at 25 mg/kg/day. However, no histological findings or effects on sperm analysis parameters or fertility were noted. While the fertility parameter is considered an insensitive measure in the rat, it is curious that no sperm or histological effects were identified, not even in the 26-week study. No clear mechanisms for the reduced weights have been presented, and none were expected. Possible hypotheses by the applicant includes indirect disturbances of the HPG axis given that the prostate and seminal vesicles androgen dependent organs. Another possibility would that the reduced weights may be early indicators of atrophy reflecting a direct cytotoxic effect on prostatic glandular cells.

Based on published data, CsA has been shown to target male reproductive organs in the rat and induce reduced reproductive organ weights, degeneration and atrophy of seminiferous tubules, and impaired spermatogenesis. CsA was active comparator in several non-clinical studies in the present application. In the 26-week study in rats, CsA and voclosporin at 10mg/kg/day significantly reduced mean absolute prostate weights and prostate/brain ratio without histopathological correlation. In the animals administered voclosporin, but not CsA, significantly reduced testis weights and testis/brain ratios were also evident but without histopathological correlation. According to the applicant, the lack of comparable microscopic findings in the animals administered voclosporin in the 26-week study to the published CsA effects makes it unclear if the effects are exerted through similar pathways. This line of reasoning is hard to follow. In the 26-week study, no correlation to histopathology was seen for CsA either, why we have currently no obvious reason to assume that the substances differ with regard to their effects on male reproductive organs in the rat.

Regarding the effects in the non-GLP studies in rabbit, important aspects of the studies are missing (testes weight, gross pathology, histopathology, PK). Still, the study supports that voclosporin, like CsA, can induce reduced spermatogenesis and degenerative changes in the testis. That said, given the lack of GLP and other limitations with the studies the CHMP agreed that they need not be included in the SmPC. Regarding the reduced prostate and testis weights in the monkey 13-week study, the CHMP agreed that the mean weights in the vehicle group animals were also reduced further supporting that

the vehicle is suboptimal (see also discussion above) and that these data do not need to be included in the SmPC.

To conclude, the applicant agreed that voclosporin, like CsA, can reduce the prostate and testicular weights in the rat. The data has been included in section 5.3 of the SmPC.

In the EFD study in SD rat with mix-ISA247, maternal body weights and body weight gains were reduced at 25mg/kg/day which correlated with a significantly reduced food consumption from GD15. Also at this dose, the total number of resorptions, the percent dead or resorbed conceptuses per litter and early and late resorptions were significantly increased, which led to a reduced gravid uterus weight and mean litter size and also a reduced number of live fetuses. In the rabbit EFD study with mix-ISA 247, increased resorptions were evident at 20mg/kg/day (early and late resorptions) and the litter size and the number of live fetuses was decreased suggestive of developmental toxicity. Further, fetal weights were significantly reduced from 10mg/kg/day. In the rabbit EFD study with voclosporin, fetal weights were decreased from 5mg/kg/day, which also correlated with skeletal variations (increased incidences of unossified sternebrae no 5 and 6 from 5mg/kg/day and unossified hyoid body and/or arches only at 20mg/kg/day). No other malformations or variations considered treatment-related were noted. It has to be emphasised that exposures in the EFD studies in rabbits were significantly below expected human exposure.

A PPND study was performed in SD rat. Gestational body weight losses were identified from 10mg/kg/day, whereas lactational body weights did not differ among groups. Further, feed consumption values were significantly reduced during gestation in the 25 mg/kg/day dosage group whereas no effects were evident during lactation. 12 dams at 25mg/kg/day were euthanised between GD27-31 due to failures to complete parturition (suggestive of dystocia). Among these dams, clinical signs of ataxia, impaired righting reflex and decreased motor activity were noted. As a result of the dystocia, the mean number of total pups delivered, surviving pups per litter and the number of liveborn pups was significantly reduced in the 25 mg/kg/day dosage group. At the CHMP's request, the applicant included the findings including margins to clinical exposure in section 5.3 of the SmPC.

Based on a placental transfer and milk transfer study in SD rat, drug-derived radioactivity was observed in milk by 1 hour post-dose and increased with a Tmax (blood and milk) at 4 hours post-dose. At Tmax, the milk/blood concentration ratio was nearly 1. Radioactivity in the stomach contents of the pups indicated lactational transfer (0.7% of the dose 23h post-dose) of voclosporin from the mother to the pup. Low levels of radioactivity were observed in pup carcasses indicating that drug material had been absorbed. As the drug is present in animal milk, it is assumed that the drug will be present in human milk unless we have data indicating otherwise. Given the risk for adverse reactions related to the lupkynis pharmacology (e.g., increased risk for infection), breastfeeding is not recommended during treatment with Lupkynis. This is adequately reflected in Sections 4.6 and 5.3 of the SmPC.

In the juvenile toxicity study, no toxicities considered new for the juvenile patient population were identified. However, findings considered adverse were identified in the kidney and the thymus from 2.5mg/kg/day.

According to the applicant, voclosporin does not absorb light in the wavelength of 290-700nm, but no study could be identified in the dossier (non-clinical or quality) as evidence for this statement. At the CHMP's request, the applicant presented an absorbance spectrum substantiating that voclosporin does not absorb light in the wavelength of 290- 700nm.

An ERA has been produced by the applicant. Log Pow was determined to 5.5 in a OECD 107 study, why a definitive PBT assessment was triggered. No study report for the OECD 107 study has been provided why the applicant was asked to submit the study. When asked to substantiate the log Kow of 5.5 with

the study report the applicant stated that the slow stirring method (OECD 123) was considered more appropriate and that the report can be found in Module 3.2.S.4.3. It is agreed that for compounds with log Kow > 4, the slow-stirring method should be used. The applicant re-submitted the OECD 123 study and based on the data the log Kow is considered to be 6.26.

Regarding PBT assessment, the applicant submitted an OECD301F study with voclosporin which was performed in accordance with relevant guidelines. Based on the study, it can be concluded that voclosporin is readily biodegradable. According to the draft EMA "Guideline on the environmental risk assessment of medicinal products for human use" (EMEA/CHMP/SWP/4447/00 Rev. 1), when a non-natural peptide/protein is demonstrated to be excreted in amounts < 10% of the dose, or shown to be readily biodegradable in an OECD 301 test, the ERA stops. Therefore, no further ERA data are considered needed for voclosporin and it can be concluded that voclosporin in the proposed use is not expected to pose a risk to the environment.

2.4.7. Conclusion on the non-clinical aspects

Voclosporin is a calcineurin-inhibitor immunosuppressant that inhibits calcineurin in a dose-dependent manner up to a maximum dose of 1.0 mg/kg. Activation of lymphocytes involves an increase in intracellular calcium concentrations. Calcineurin is a calcium/calmodulin-dependent phosphatase whose activity is required for the induction of T-cell lymphokine production and proliferation. The immunosuppressant activity results in inhibition of lymphocyte proliferation, T-cell cytokine production, and expression of T-cell activation surface antigens. Pharmacology studies showed that voclosporin inhibited calcineurin with a 1.5-fold higher potency compared to cyclosporine *in vitro* and also that voclosporin had a higher potency *in vivo* in animal models. Secondary pharmacodynamics has not been well characterised, but this is considered acceptable due to the similarity of the toxicological profile of voclosporin and CsA, the only 1.5-fold increase in potency towards calcineurin, as well as the presence of clinical data. Safety pharmacology studies showed prolongation of QT interval and corrected QT interval in monkeys at exposures ~5 times the estimated clinical exposure level (Cmax) without any significant effects *in vitro* on hERG detected. Only minor respiratory, CNS, and renal effects where seen, without relevance for the clinical situation. No additional pharmacological studies have therefore been requested by the CHMP.

The pharmacokinetic characterisation of voclosporin is considered sufficient and no additional studies are required. No unique human metabolite has been identified. The pharmacokinetic data obtained support the use of rat and monkey as the primary toxicological species.

The review of the non-clinical toxicology data for Lupkynis indicates no major issues for concern. The toxicity profile of voclosporin is mostly reflective of the calcineurin inhibitory action of the substance (neurotoxicity, lymphomas, reduction of the prostate and testicular weights in the rat). This information is adequately reflected in the SmPC and the RMP. Of note, the non-clinical toxicology profile is very similar to CsA in the comparative studies.

As the drug is present in animal milk, it is assumed that the drug will be present in human milk unless we have data indicating otherwise. Given the risk for adverse reactions related to the lupkynis pharmacology (e.g., increased risk for infection), breastfeeding is not recommended during treatment with Lupkynis. This is adequately reflected in Sections 4.6 and 5.3 of the SmPC.

Based on the provided ERA studies it can be concluded that voclosporin in the proposed use is not expected to pose a risk to the environment.

2.5 Clinical aspects

2.5.1. Introduction

GCP aspects

The Clinical trials were performed in accordance with GCP as claimed by the applicant

The applicant has provided a statement to the effect that clinical trials conducted outside the Community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- **Tabular overview of clinical studies**

Study ID/Name (Phase)	Study Design	Patient Population	Dose, Route, and Regimen	No. of Subjects
AUR-VCS-2016-01 / AURORA 1 (Phase 3)	Prospective, randomised, placebo-controlled, double-blind, parallel-group, 52-week, international, multicentre, 2-arm comparison study of voclosporin versus matching placebo	SLE patients aged 18-75 with LN class III, IV-G, IV-S (confirmed UPCR ≥1.5 mg/mg) or Class V (UPCR ≥2.0 mg/mg)	Voclosporin 23.7 mg BID or placebo BID for 52 weeks All subjects also received background therapy with MMF and an initial treatment with IV methylprednisolone, followed by a reducing taper of oral corticosteroids	357 23.7 mg BID: 179 Placebo: 178
AUR-VCS-2012-01 / AURA-LV (Phase 2)	Prospective, randomised, placebo-controlled, double-blind, parallel-group, international, multicentre, 3-arm comparison study of voclosporin versus matching placebo	SLE patients aged 18-75 with LN class III, IV-G, IV-S (confirmed proteinuria ≥1,500 mg/24 hours / UPCR ≥1.5 mg/mg) or Class V (confirmed proteinuria ≥2,000 mg/24 hours / UPCR ≥2.0 mg/mg)	Voclosporin 23.7 mg BID or 39.5 mg BID or placebo BID for 48 weeks All subjects also received background therapy with MMF and an initial treatment with IV methylprednisolone, followed by a reducing taper of oral corticosteroids	265 23.7 mg BID: 89 39.5 mg BID: 88 Placebo: 88
AUR-VCS-2014-01 / AURION (Phase 2)	Prospective, single-arm, open-label, pilot study of voclosporin combined with standard of care	SLE patients aged 18-75 with LN class III, IV-G, IV-S (confirmed proteinuria ≥1,000 mg/24 hours / UPCR ≥1.0 mg/mg) or Class V (confirmed proteinuria ≥1,500 mg/24 hours / UPCR ≥1.5 mg/mg)	Voclosporin 23.7 mg BID for 48 weeks All subjects also received background therapy with MMF and an initial treatment with IV methylprednisolone, followed by a reducing taper of oral corticosteroids	10
AUR-VCS-2016-02 / AURORA 2 (Phase 3) (Study ongoing)	Prospective, placebo-controlled, double-blind, parallel-group, 24-month continuation study to AURORA 1	SLE patients with LN who completed 52 weeks of treatment in Study AURORA 1	As assigned in AURORA 1 (voclosporin 23.7 mg BID or placebo BID) for up to a further 24 months On entry, all subjects continued to receive background therapy with MMF and oral corticosteroids at the same dose as at the end of AURORA 1.	216 23.7 mg BID: 116 Placebo: 100

2.5.2. Clinical pharmacology

2.5.2.1. Pharmacokinetics

Voclosporin (LX211, ISA247) is a next generation calcineurin inhibitor (CNI) structurally similar to cyclosporine A (CsA) except for a modification to the amino acid-1 region. It is a new chemical entity and the pharmacokinetic studies should thus aim at describing the disposition and also to identify subgroups where an increased or decreased exposure can be expected based on the pharmacokinetic properties. Potential interactions based on the pharmacokinetic properties should also be evaluated in the clinical pharmacology development.

Table 2 provides an overview of the Phase 1 studies in the voclosporin clinical pharmacology programme, which included 13 studies in healthy subjects (including a bridging study in healthy Japanese subjects, 5 DDI studies and 2 thorough QT studies), two special population studies, in hepatically impaired and renally impaired subjects (and their matched controls) and a DDI study in subjects with systemic lupus erythematosus (SLE) with or without LN. In addition, two Phase 2 studies (AURA-LV and AURION) and a Phase 3 study (AURORA 1) provided PK data for voclosporin.

Table 2 Overview of Voclosporin Phase 1 Clinical Studies

Study ID (name)	Description	Dosing Regimen	Study Population (Treated/Completed)
Voclosporin biopharmaceutic studies			
ISA04-01	Bioequivalence	Voclosporin: 4 x single doses, separated by 10-day washout. 100 mg fixed dose, as an oral solution (50 mg/mL) or 2 x 50 mg softgel capsules with water or apple juice	Healthy subjects 19/13
ISA04-02	Food Effect	Voclosporin: 3 x single doses, separated by 12-day washout of 1.5 mg/kg, as an oral solution (50 mg/mL) fasted, after a high-fat or low-fat breakfast	Healthy subjects 18/15
Voclosporin healthy subject PK and initial tolerability studies			
ISA03-10	Single ascending dose	A single dose of voclosporin 0.25, 0.5, 1.5, 3.0 or 4.5 mg/kg, as an oral solution under fasted conditions, 1 mg/kg mix-ISA247, as an oral solution under fasted conditions Placebo: Matched to voclosporin	Healthy subjects (42/40) (6-13 subjects/dose cohort)
ISA03-12	Single and multiple ascending dose	A single dose of voclosporin 0.25, 0.5, 1.0 or 1.5 mg/kg on Day 1, voclosporin 0.25, 0.5, 1.0 or 1.5 mg/kg BID from Days 3 to 12 with a morning dose on Day 13 administered as oral solution under fasted conditions Placebo: Matched to voclosporin	Healthy subjects (35/30) (8-9 subjects/cohort)
AUR-VCS-2015-J01	Single and multiple ascending dose/ Japanese PK	Single dose of voclosporin 0.25, 0.5, 1.0 or 1.5 mg/kg on Day 1, voclosporin 0.25, 0.5, 1.0 or 1.5 mg/kg BID from Days 3 to 12 with a morning dose on Day 13 administered as 7.9 mg capsules under fasted conditions Placebo: Matched to voclosporin	Healthy subjects 32/32 (8 subjects/dose cohort)
LX211-05	ADME/Mass Balance	A single dose as oral solution containing approximately 70 mg (approximately 200 µCi radioactivity) of [^{14}C]-voclosporin	Healthy subjects 6/6

Voclosporin studies in special populations (intrinsic factors)			
ISA07-08	Renal Impairment	A single dose of voclosporin 0.4 mg/kg (as 10 mg capsules) on Day 1 and Day 10, voclosporin 0.4 mg/kg BID on Days 3 to 9. (a single 0.4 mg/kg voclosporin on Day 1 for subjects with severe renal impairment only)	Healthy subjects 8/8 Mild renal imp. 8/8 Moderate renal imp. 8/7 Severe renal imp. 9/9
ISA07-09	Hepatic Impairment	A single dose of voclosporin 0.4 mg/kg (as 10 mg capsules) on Day 1 and Day 10, voclosporin 0.4 mg/kg BID on Days 3 to 9. (a single 0.4 mg/kg voclosporin on Day 1 for subjects with moderate hepatic impairment only)	Healthy subjects 6/6 Mild hepatic imp. 6/6 Moderate hepatic imp. 6/6
Voclosporin studies of drug-drug interactions (extrinsic factors)			
LX211-06	DDI with ketoconazole	Voclosporin 0.4 mg/kg BID (as 10 mg capsules) from Day 1 to 20. Ketoconazole 400 mg QD from Days 11 to 20.	Healthy subjects 24/11
LX211-07	DDI with verapamil	Voclosporin 0.4 mg/kg BID (as 10 mg capsules) from Day 1 to 20. Verapamil 80 mg TID from Days 11 to 20.	Healthy subjects 24/20
LX211-09	DDI with rifampin	A single dose of voclosporin 0.4 mg/kg on Day 1 and Day 16. Rifampin 600 mg QD from Day 6 to 15.	Healthy subjects 24/23
ISA07-07	DDI with midazolam	Voclosporin 0.4 mg/kg BID (as 10 mg capsules) from Day 2 to 12. A single oral dose of midazolam 7.5 mg on Day 1 and Day 12.	Healthy subjects 24/22
LX211-08	DDI with digoxin	Voclosporin 0.4 mg/kg BID (as 10 mg capsules) from Day 8 to 18. A single dose of digoxin 0.5 mg on Day 1, digoxin 0.25 mg QD from Day 2 to 18.	Healthy subjects 24/23
AUR-VCS-2018-01	DDI with MMF	Voclosporin 23.7 mg BID (as 7.9 mg capsules) from Day 1 to Day 7 (beginning with evening dose of Day 1). MMF 1 g BID for at least 28 days prior to screening and continued throughout the study.	SLE Patients (with or without LN) 25/23
Voclosporin pharmacodynamic studies			
ISA03-11	Thorough QT (parallel)	A single dose of voclosporin 0.5, 1.5, 3.0, 4.5 mg/kg, as an oral solution (50 mg/mL) under fasted conditions A single dose of moxifloxacin 400 mg Placebo: Matched to voclosporin	Healthy subjects 240/240
ISA05-03	Thorough QT (crossover)	Voclosporin 0.3, 0.5, 1.5 mg/kg BID for 7 days, as 10 mg capsules under fasted conditions A single dose of moxifloxacin 400 mg Placebo: Matched to voclosporin A 10-day washout between treatments in randomized sequences; followed by single-dose of moxifloxacin	Healthy subjects 60/31 (Note: 20 subjects withdrawn due to risk to entire group from tuberculosis reported in 1 subject)

Notes: Voclosporin 0.4 mg/kg (given as 10 mg softgel capsules, rounded to the nearest multiple of 10 mg).
AE = Adverse event; AUC = Area under the concentration-time curve; BID = Twice daily; C_{max} = Maximum concentration; DDI = Drug-drug interaction; imp. = impairment; LN = Lupus nephritis; MMF = Mycophenolate mofetil; MPA = Mycophenolic acid; MPAG = Mycophenolic acid glucuronide; PD = pharmacodynamics; PK = Pharmacokinetics; QD = Once a day; QTcF = QT interval corrected for heart rate according to Fredericia's method; QTcI = QT interval corrected for heart rate using individual-specific correction factor; SLE = Systemic lupus erythematosus; TID = three times a day.

The oral solution formulation (50 mg/mL) was used in the initial Phase 1 studies. It shares the same composition as the fill used in capsules used in later clinical studies and intended for market. In the drug product intended for commercialisation, the oral solution is filled in a size 5 oval softgel capsule containing 7.9 mg voclosporin.

An *in vitro* package characterising *in vitro* metabolism, transporters, protein binding, blood to plasma partitioning as well as potential to inhibit or induce enzymes or transporters is also provided.

The voclosporin structure contains 12 centres of chirality as well as one C=C double bond and exists predominantly (90 to 95%) as the E (trans) configuration. However, one early clinical study included a mixture of 45%-50% trans-isomer/50%-55% cis-isomer of voclosporin (mix-ISA27) as a bridge to earlier non-clinical data.

The initial tolerability studies evaluated the PK of voclosporin after single doses of 0.25 to 4.5 mg/kg and after multiple doses of 0.25 to 1.5 mg/kg BID. The majority of clinical pharmacology studies (e.g., drug-drug interactions (DDI), effect of renal and hepatic impairment) were conducted using a voclosporin 0.4 mg/kg dose. The proposed dose for treatment of LN is 23.7 mg (three 7.9 mg capsules) BID, which corresponds to a dose of 0.37 mg/kg BID based on a body weight of 64 kg (the median body weight of subjects receiving active treatment in AURORA 1). Dose reduction is proposed in case of concomitant treatment with moderate CYP3A4 inhibitors and in patients with mild or moderate hepatic impairment or severe renal impairment. Dose adjustment is also required based on reduction of eGFR during treatment with voclosporin.

In all clinical studies, voclosporin is measured in whole blood instead of in plasma, which is also the common practice for cyclosporin A.

Voclosporin has one major metabolite and several minor metabolites. The metabolites provide little or no contribution to the pharmacological effect of voclosporin.

Methods

Bioanalysis

Voclosporin and several of its metabolites have been measured in whole blood and urine using validated HPLC/MS methods. In whole blood, isomer-specific as well as non-isomer-specific methods have been used.

Non-compartment data analysis

Standard non-compartmental analysis was performed in all studies where rich sampling was applied.

Population PK analysis

A population PK analysis was used to describe voclosporin PK collected in AURA-LV and AURORA 1 studies. A two-compartmental population PK model with first order oral absorption and linear elimination was developed for voclosporin in LN patients. A covariate analysis was performed to evaluate the impact of intrinsic and extrinsic factors on exposure.

Physiologically-based pharmacokinetic model-based analysis

A PBPK model based on prior *in vitro* and *in vivo* information on the metabolism and PK of voclosporin was constructed with the aim of predicting whole blood concentration-time profiles of voclosporin following single and multiple dosing in healthy subjects, evaluating the relative contribution of CYP3A4 and P-gp in the metabolism and transport of voclosporin, evaluating the likely impact of co-administration of CYP3A4 inhibitors and inducers on the PK of voclosporin, and evaluating the impact of co-administration of voclosporin on the PK of OATP1B1 substrate drugs.

Absorption

Oral absorption of voclosporin is relatively rapid, achieving median peak whole blood concentrations at approximately 1.5 hours (range: 0.75 to 2 hours) under fasted conditions in subjects following voclosporin 23.7 mg BID (study AUR-VCS-2018-01).

At steady state, the whole blood mean C_{max} and pre-dose trough values for voclosporin were 120 ng/mL (32% CV) and 15.0 ng/mL (49% CV), respectively. (study AUR-VCS-2018-01).

Voclosporin is a low solubility drug substance. The solubility is not pH dependent.

Voclosporin is a possible P-gp substrate.

Absolute bioavailability studies have not been performed. In the mass balance study (Study LX211-05) in which healthy subjects ingested an oral dose of [^{14}C]-voclosporin 71.6±0.4 mg, 5% of the dose was excreted unchanged in feces recovered over 168 hours, suggesting a high fraction absorbed.

Bioequivalence

During the clinical development of voclosporin, an oral solution as well as different softgel capsule dose strengths have been used.

Study ISA04-01 was a Phase I, single centre, randomised, single-dose open-label, 4-way crossover study comparing liquid versus capsule formulations of orally administered voclosporin 100 mg in water or apple juice in 19 healthy volunteers under fasting conditions. Bioequivalence was demonstrated between a 100 mg dose administered as an oral solution (50 mg/mL) dissolved in apple juice or water and as 50 mg softgel capsules fille with the same 50 mg/mL oral solution. The drug product used in the pivotal LN clinical trials and to-be-marketed 7.9 mg softgel capsule as well as the 10 mg softgel capsule used in the clinical pharmacology studies have the same relative ratio of formulation fill components as the 50 mg softgel capsule, consisting of the 50 mg/mL solution filled into a smaller softgel capsule. Consequently, the 7.9 mg and 10 mg softgel capsules can also be considered to be bioequivalent to the oral solution when administered at the same dose. T_{max} was comparable between oral solution and capsule when administered with water, with median (range) values of 1.26 (1.00-2.00) hours and 1.50 (1.50-2.00) hours, after administration as oral solution and capsule, respectively. When administered with apple juice, T_{max} was slightly delayed for the capsule 2.50 (1.50-4.00) hours compared to the oral solution 1.50 (1.00-2.50) hours.

Influence of food

Study ISA04-02 was a Phase I, single centre, randomised, single-dose, open-label, 3-way crossover food interaction study to assess the effects of fasting, consumption of a high-fat breakfast, and consumption of a low-fat breakfast on the PK of voclosporin in 18 normal, healthy volunteers. The administration of a single 1.5 mg/kg voclosporin dose with either low- or high-fat meals decreased both the rate and extent of absorption, which appeared to be related to the fat content of the meal. With a high fat meal, C_{max} and AUC were reduced by 53% and 25%, respectively. The effect of a low-fat breakfast appeared to be less; C_{max} and AUC were decreased by approximately 29% and 15% respectively after a low-fat breakfast. Median T_{max} (range) was observed at 2.00 (1.00-2.50), 1.52 (1.00-3.00) and 2.07 (1.00-4.15) hours after administration under fasting conditions, after a low-fat breakfast and after a high-fat breakfast, respectively.

Distribution

A population pharmacokinetic analysis (Population PK Report 19 041) using a two compartment model resulted in a total apparent volume of distribution (Vss/F) of 2,154 L.

Plasma protein binding in human plasma was investigated *in vitro* using equilibrium dialysis. Voclosporin was found to be highly bound to plasma proteins (97%), ie with a fraction unbound of 3%. There was no indication of concentration dependency in the studied concentration range. For the major metabolite M4 (IM9) the protein binding was lower than for parent drug and appeared to be dependent on concentration (at a nominal concentration of 0.1 µM (the concentration most clinically relevant) the protein binding was 72.4%).

Concentration measurement for voclosporin has been made in whole blood in the clinical studies, similar to the case of cyclosporin. Blood/plasma ratio was measured *in vitro* and depended on temperature and concentration but a mean value of 1.6 has been reported. In the mass balance study (Study LX211-05), mean C_{max} and AUC for [^{14}C]-voclosporin in blood were approximately 3-fold higher than in plasma, indicating that voclosporin and/or its metabolites may be associated with red blood cells.

Elimination

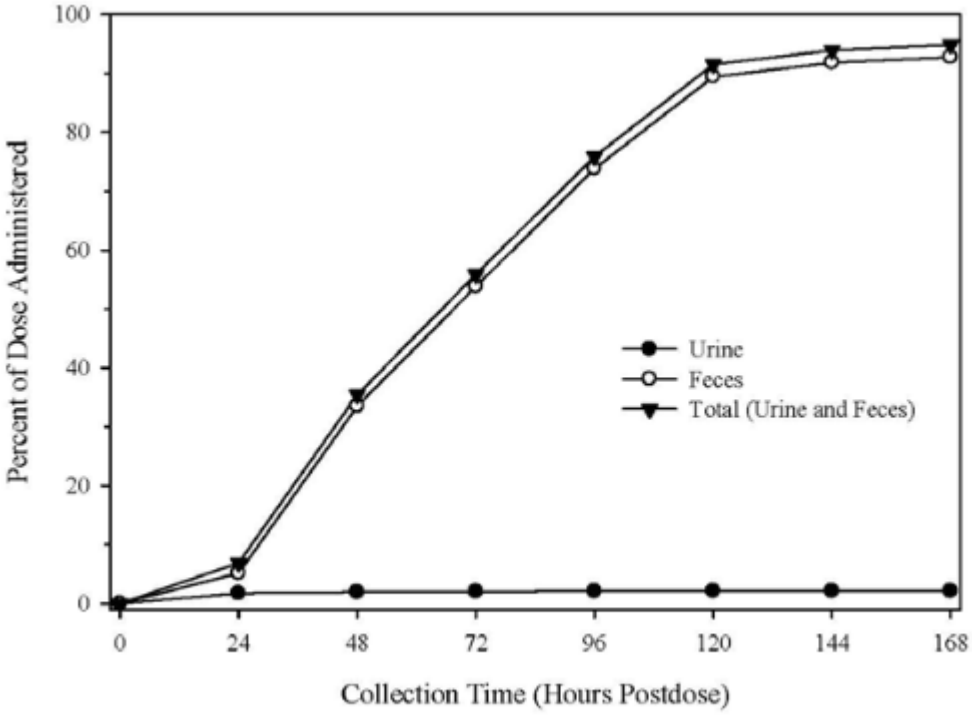
Voclosporin whole blood concentrations demonstrated biphasic elimination after oral dosing. With sufficiently large doses and extended sampling time, a third compartment could be determined. Mean $t_{1/2}$ estimates after multiple dosing ranged from 24.9 to 36.5 hours, independent of dose, with a mean half-life at steady state of approximately 30 hours. After a single dose, the reported $t_{1/2}$ values appeared to be variable and ranged from 6.9 to 58.2 hours. The estimate of terminal $t_{1/2}$ is dependent on the sampling duration and assay limit of quantification used in the study. The clinical mass balance Study LX211-05 (lower LLOQ than other studies) showed that the $t_{1/2}$ of voclosporin was 58.2 hours based on whole blood concentration data.

The mean apparent clearance at steady state (CL_{ss}/F) after voclosporin 23.7 mg twice daily is 63.6 L/h (37.5% CV) (study AUR-VCS-2018-01).

Mass balance

Study LX211-05 was a single dose mass balance study of [^{14}C]-voclosporin administered as an oral solution (voclosporin 50 mg/ml solution with the same composition as the formulation fill used in the capsules intended for commercialisation, diluted in apple juice) containing approximately 70 mg (approximately 200 µCi radioactivity) of [^{14}C]-voclosporin (equivalent to a 1.0 mg/kg dose in a 70 kg subject) to 6 healthy male subjects following a 10-hour fast. Overall mean recovery of [^{14}C]voclosporin in urine and faeces through 168 hours post-dose was 94.8%. Mean recovery in feces and urine was 92.7% and 2.11%, respectively.

The mean total amount of unchanged voclosporin accounted for about 5% of the administered dose recovered in pooled fecal samples. Unchanged [^{14}C]-voclosporin accounted for a mean of 0.25% of the administered dose recovered in the 0 to 48 hours pooled urine sample.



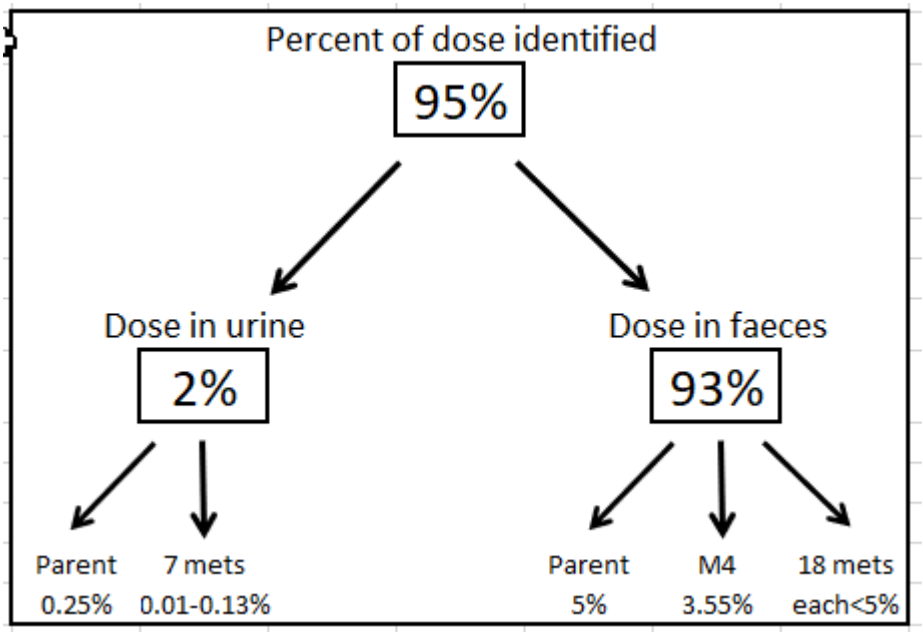


Figure 2: Mean cumulative percent of dose recovered in urine and faeces at specified intervals after a single target 70-mg (200-µCi) oral dose of [^{14}C]voclosporin to healthy male subjects (from Covance Study No. 8105-100)

Metabolism

Based on *in vitro* data, CYP3A4 was the main enzyme involved in CYP3A4 metabolism. In the *in vivo* study with the strong CYP3A4 inhibitor ketoconazole there was a 19-fold increase in AUC of voclosporin (see Drug Drug Interaction part).

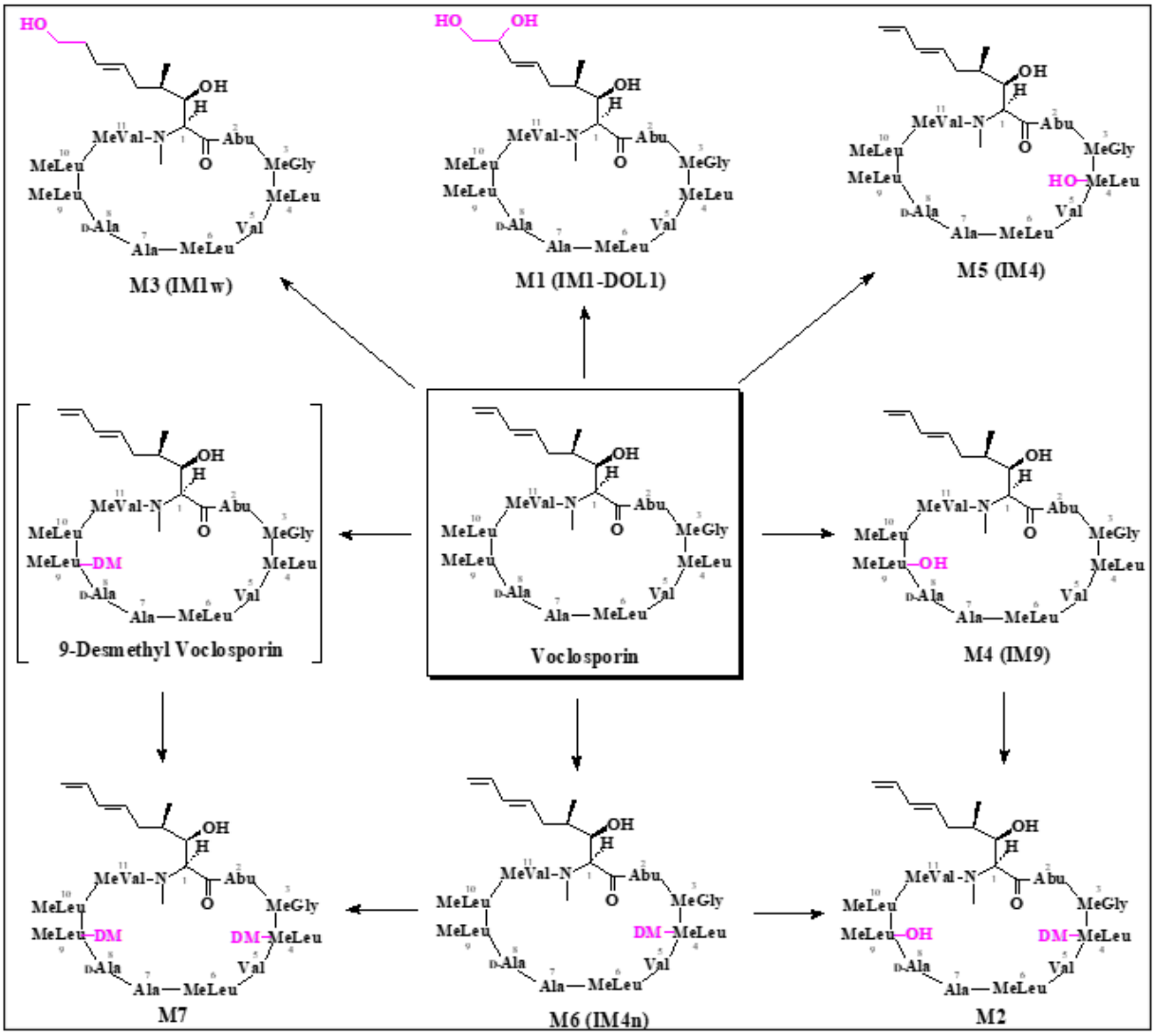
In the metabolite profiling of the mass balance study, seven circulating metabolites (M1 through M7) were identified in human blood. M1 to M7 were also present in urine and/or faeces. Twelve additional metabolites, M8 to M18, were also characterised in human faeces.

Unchanged voclosporin was the major radioactive component in plasma, accounting for approximately 37% of the total radioactivity in pooled 0 to 24-hour human blood samples. The five most abundant circulating metabolites, M1 (IM1-Diol-1), M2 (IM4n9), M3 (IM1w), M4 (IM9) and M6 (IM4n), exhibited AUC_{0-24} that were approximately 25%, 10%, 9%, 44% and 10% of voclosporin AUC_{0-24}, respectively (9.5, 4, 3, 17 and 4% of total radioactivity respectively). M4 (IM9) is a major metabolite according to the definition given in the Guideline on the investigation of drug interactions. Two minor circulating metabolites, M5 (IM4) and M7 (IM4n9n) were observed at approximately 1% and 4% of the voclosporin AUC_{0-24}. In addition, an impurity, voclosporin vinyl, which was observed in the dosing solution, was also detected in human blood and represented 4% of the total radioactivity in blood. Each of the remaining radio-labeled components represented less than 5% of the parent AUC_{0-24} in blood.

After oral administration of [^{14}C]-voclosporin, renal excretion was limited as 2.11% of the dose was recovered in the urine (1.9% recovered during the first 48 hours). Unchanged [^{14}C]-voclosporin accounted for a mean of 0.25% of the administered dose recovered in the 0 to 48 hours pooled urine sample. Seven (7) metabolites, M1 (IM1-Diol-1), M2 (IM4n9), M3 (IM1w), M4 (IM9), M5 (IM4), M6 (IM4n) and M19 (unidentified) were detected, each accounting for 0.01% to 0.13% of the dose in the 0 to 48 hours urine samples.

In feces, unchanged [^{14}C]-voclosporin was a minor radioactive component, accounting for about 5% of the administered dose recovered in the pooled fecal samples. Nineteen (19) minor metabolites were tentatively identified, each accounting for less than 5% of the dose in the pooled fecal samples. This study also demonstrated that voclosporin does not undergo metabolic degradation when incubated (aerobic incubation) for 24 hours at ~37°C in human feces, suggesting that the metabolites in feces come from hepatic metabolism followed by biliary excretion.

Voclosporin is mainly eliminated by metabolism, primarily by CYP3A4 to form oxidative metabolites, followed by excretion in faeces. The metabolism scheme suggested by the applicant is presented in Figure 2.



Notes: 9-Desmethyl voclosporin (structure in [ ]) was not detected in human blood.
The structures of voclosporin and its metabolites are depicted in abbreviated form (the abbreviated names of amir
acids 2 to 11 are shown) where Abu = L-2-aminobutanoic acid, MeGly = N-methyl-glycine, MeLeu = N-methyl-
leucine, Val = L-valine, Ala = L-alanine, D-Ala = D-alanine and MeVal = N-methyl-L-valine.
DM = desmethyl

Figure 3: Proposed Metabolic Pathway for Voclosporin in Humans

Pharmacokinetics of metabolites

Voclosporin is metabolised to a number of oxidative metabolites. Several of the metabolites have been evaluated in one or more clinical studies after single and/or multiple administration of voclosporin. Overall exposure of major metabolite M4 (IM9) and total metabolites was uniformly less than parent drug. Apparent elimination half-lives for all metabolites were similar to or less than the $t_{1/2}$ of voclosporin and IM9 demonstrated an accumulation ratio similar to parent drug while substantial accumulation was observed for IM1-Diol-1.

Interconversion

Voclosporin comprises two geometric isomers, a *trans*-isomer and a *cis*-isomer, depending on the orientation of the modified functional group. Voclosporin is enriched with the *trans*-isomer (90% to 95% *trans*-isomer). *In vitro* and *in vivo* evaluations showed that there was no evidence for *trans*- to *cis*-isomer interconversion.

Dose proportionality and time dependencies

Dose proportionality of voclosporin was assessed in healthy subjects over a dose range of 0.25 to 4.5 mg/kg as a single dose and 0.25 to 1.5 mg/kg as multiple BID dose administration. A non-linearity between dose and exposure was observed at the lower end of the dose range studied, but the dose proportion factor was less than 1.5.

The population PK analysis in patients with LN did not detect non-linearity of the dose range studied.

Assessment of voclosporin pre-dose trough concentrations indicated that steady-state conditions were achieved after 6 days of twice daily dosing (Studies ISA03-12 and AUR-VCS-2015-J01). The accumulation ratio (measured as the ratio of AUC_{0-12} at steady-state to AUC_{0-12} after a single dose) after BID dosing for 7 to 10 days was independent of dose (0.25 to 1.5 mg/kg) and was around 2.

Intra- and inter-individual variability

After oral administration of voclosporin to healthy volunteers at single doses of 0.5 to 4.5 mg/kg inter-subject variability (%CV) for C_{max} and AUC_{0-inf} ranged from approximately 25% to 27% and 26% to 40%, respectively. After oral administration of voclosporin at multiple doses of 0.25 to 1.5 mg/kg BID, %CV for C_{max} and AUC_{0-12} ranged from approximately 21% to 53% and 34% to 48%, respectively. Similar variability in PK parameters was observed in Study AUR-VCS-2018-01, where subjects with LN received multiple doses of 23.7 mg BID*:* 32% for C_{max} and 43% for AUC_{0-12}.

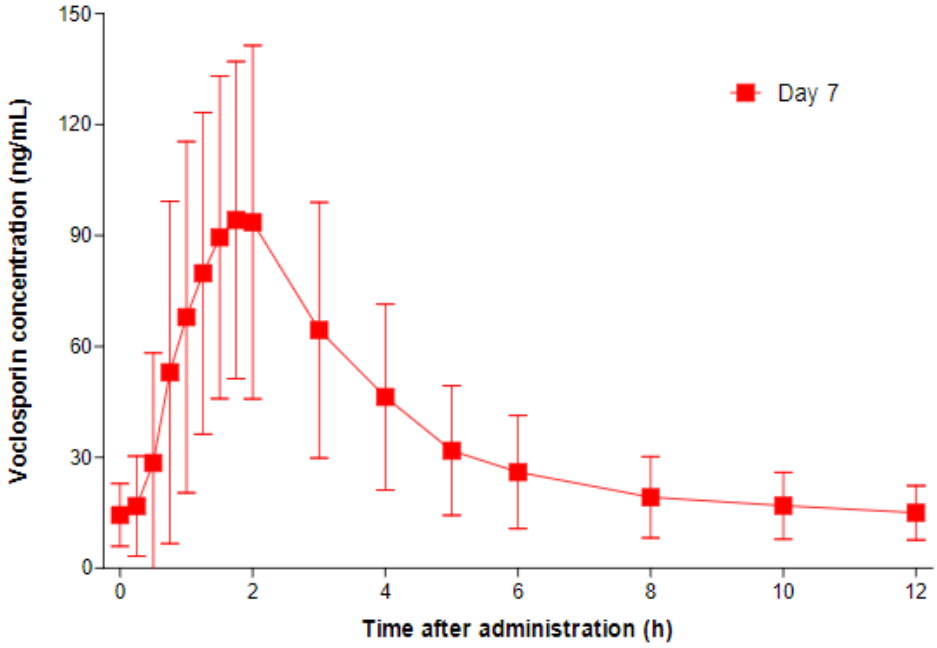
Intra-subject variability was estimated to be 16.1% and 14.2% for C_{max} and AUC_{0-inf}, respectively, indicating that the inter-subject variability was greater than the intra-subject variability (Study ISA04-01).

Based on the population PK analysis on data from sparse sampling in Phase 2 and 3 studies, the inter-subject variability on CL/F and the volume of the central compartment was 45% and 158%, respectively. The degree of inter-subject variability is supported by the 1.7-fold range in mean observed CL/F of voclosporin after a multiple dose of 0.4 mg/kg BID.

Pharmacokinetics in target population

Sparse sampling strategies were included in two Phase 2 studies (AURA-LV, AURION) and a Phase 3 study (AURORA 1) that evaluated the efficacy and safety of voclosporin in LN.

Intensive PK sampling for voclosporin was not performed in the LN patient population, precluding a direct comparison of PK parameters in subjects with LN and healthy subjects. However, a single DDI study was performed in subjects with SLE (with and without LN), receiving voclosporin 23.7 mg BID in the presence of MMF 1 g BID (Study AUR-VCS-2018-01). MMF is not considered to affect the exposures of voclosporin. The PK profile of voclosporin after 10 days of BID dosing is presented in Figure 3 and derived PK parameters over a dosing interval at steady-state are presented in *Table 3*.



Notes: BID = twice daily; MMF = mycophenolate mofetil; SD = standard deviation.

Figure 4: Mean (±SD) Whole Blood Concentration versus Time Profiles of Voclosporin After Administration of 23.7 mg Voclosporin BID in the Presence of 1 g MMF BID (Day 7)

Table 3 Pharmacokinetic Results of Voclosporin After Administration of Voclosporin 23.7 mg BID in the Presence of MMF 1 g BID in Subjects with SLE

Voclosporin Parameter	C_{trough} (ng/mL)	C_{max} (ng/mL)	T_{max} (h)	AUC_{0-12} (ng.h/mL)	C_{avg} (µg/mL)	CL_{ss}/F (L/h)
Day 7 (1 g MMF BID + 23.7 mg Voclosporin BID)						
n	24	24	24	24	24	24
Mean (SD)	15.0 (7.35)	120 (38.8)	-	433 (186)	36.1 (15.5)	63.6 (23.9)
CV%	49.1	32.3	-	43.0	43.0	37.5
Median	12.6	108	1.50	392	32.7	60.5
Min – Max	5.10 – 31.8	68.7 – 216	0.75 – 2.00	204 – 927	17.0 – 77.3	25.6 – 116

Notes: CV = coefficient of variation; MMF = mycophenolate mofetil; SD = standard deviation.

There does not appear to be a consistent difference in exposure between healthy subjects and subjects with LN.

Special populations

Impaired renal function

As LN is an immune-complex mediated renal disease, renal impairment is an inherent characteristic of subjects affected with LN. A dedicated study has been performed in otherwise healthy subjects with renal impairment (study ISA07-08).

Study ISA07-08 was an open-label, multi-arm, PK and PD study of voclosporin administered orally in male (14) and female (19) subjects with defined renal impairment (as measured by the Cockcroft-Gault formula) and matched normal healthy subjects under fasting conditions. In the original study report, subjects were not classified according to the current guideline on the evaluation of the pharmacokinetics in subjects with impaired renal function, but a reclassification was performed based

on the recommendations in the current guideline: normal renal function (CLCr ≥90 mL/min), mild renal impairment (CLCr 60-89 mL/min), moderate renal impairment (CLCr 30-59 mL/min) and severe renal impairment (CLCr <30 mL/min). In line with the conclusion in the original CSR, after single and multiple doses, C_{max} and AUC were similar in subjects with mild and moderate renal impairment compared to subjects with normal renal function. After a single dose, severe renal impairment resulted in a 1.46- and 1.74-fold higher C_{max} and AUC_{0-48}, respectively.

The cumulative amount of voclosporin excreted in urine over 24 hours decreased with increasing impairment of renal function, with amounts excreted ranging from 0.06 to 0.02 mg, representing less than 0.1% of the administered dose.

Markers of renal damage, baseline 24-hour UPCR and eGFR (based on CKD-EPI formula) obtained in subjects with LN were also evaluated as potential covariates in the population PK analysis. UPCR and eGFR were not not found to influence any of the model parameters in the final population PK model (Population PK Report 19 041).

The LN studies (AURA-LV, AURORA 1) excluded subjects with eGFR ≤45 mL/min/1.73 m^2 and eGFR was monitored at every visit. In the event of a decrease in eGFR while on treatment, subjects were re-evaluated at an unscheduled visit and dose adjustment or dose interruption was considered.

Impaired hepatic function

Since voclosporin is primarily eliminated through hepatic metabolism and biliary excretion, hepatic impairment is likely to decrease its clearance. A dedicated HI study was conducted to characterize the effect of impaired hepatic function on the single- and multiple-dose PK of voclosporin and its metabolites.

Study ISA07-09 was a Phase 1, multi-centre, sequential, open-label study to evaluate the PK and PD of voclosporin 0.4 mg/kg and metabolites in male and female subjects with defined mild and moderate hepatic impairment (assessed by Child-Pugh scale) compared to healthy subjects.

Administration of voclosporin to subjects with mild (Class A) to moderate (Class B) hepatic impairment significantly increased exposure to voclosporin. In subjects with mild hepatic impairment, pre-dose concentrations increased 2-fold, while C_{max} and AUC increased approximately 1.5- and 1.7-fold, respectively, after a single dose, and 1.5- and 1.8-fold, respectively, after multiple doses. In subjects with moderate hepatic impairment, C_{max} and AUC increased 1.5- and 2-fold, respectively, after a single dose.

The cumulative amount of voclosporin excreted in urine over 24 hours increased with a decrease in hepatic function, with amounts excreted ranging between 0.08 and 0.17 mg, representing less than 0.1% of the administered dose.

Markers of liver impairment (serum albumin, total bilirubin, alanine phosphatase, alanine aminotransferase [ALT] and aspartate aminotransferase [AST]) were also evaluated as potential covariates in the population PK analysis in subjects with LN. These markers were not found to influence any of the model parameters in the final population PK model. (Population PK Report 19 041).

Subjects with severe hepatic impairment were not included in the study and there is limited clinical experience with administration of voclosporin in subjects with hepatic impairment, as subjects with liver dysfunction (AST, ALT, or bilirubin ≥2.5 times the upper limit of normal) were excluded from the Phase 2 and 3 trials.

Sex, race/ethnicity, weight, age

The effect of body weight on voclosporin PK was assessed in the population PK analysis of Phase 2 and 3 data (Population PK Report 19 041). Baseline body weight ranged from 37 to 133 kg. Body weight

was not found to influence the PK of voclosporin. Body weight did not appear to have a relevant impact on exposure.

Table 4 PK trials in elderly population

	Age 65-74 (Older subjects number /total number)	Age 75-84 (Older subjects number /total number)	Age 85+ (Older subjects number /total number)
PK Trials	14	5	-

The effect of age on voclosporin PK was assessed in the population PK analysis of Phase 2 and 3 data. Baseline age ranged from 18 to 66 years; hence, limited data in elderly subjects (≥65 years) is available. Age was not not found to influence any of the model parameters in the final population PK model. Age did not appear to have an impact on exposure.

The effect of sex on voclosporin PK was assessed in the population PK analysis of Phase 2 and 3 data. Few subjects were male (11%), lowering the power to predict a potential effect, if present. Sex was not retained as covariate in the population PK model. However, based on individual predicted AUC_{0-12}, male subjects showed on average a 17% lower exposure compared to female subjects. No dose adjustment for male subjects is required as the clinical relevance of this change in AUC_{0-12} is limited.

The effect of race was assessed in a population PK analysis of sparse sampling data obtained in subjects with LN. The proportion of black subjects was relatively low (9.3%) diminishing the power to predict potential effect, if present. In addition, Study AUR-VCS-2015-J01 examined the PK of single and multiple doses of voclosporin in healthy Japanese subjects; PK parameters were compared to those obtained in non-Japanese subjects in a comparable study. Asian versus non-Asian on bioavailability was found to be a significant covariate and was included in the final model. Asian subjects appeared to have a 22% higher exposure (median AUC_{0-12} (90% CI) ratio of 1.22 [1.14-1.30]) compared to non-Asian subjects. Based on individual predicted AUC_{0-12}, black subjects showed on average 18% lower exposure compared to non-black subjects. Taken together, the results indicate that at a therapeutic dose in subjects with LN, race has no clinically relevant impact on PK of voclosporin and no dose adjustment is required as the clinical relevance of the changes in AUC_{0-12} are limited.

The pharmacokinetics of voclosporin has not been studied in subjects less than 18 years of age.

Pharmacokinetic interaction studies

Voclosporin as victim of drug interactions

Voclosporin is a possible substrate of P-gp based on *in vitro* data, but does not appear to be a substrate of OATP1B1 or OATP1B3.

In vitro data indicate that CYP3A4 is the main CYP enzyme involved in voclosporin metabolism. An *in vivo* study has been performed, investigating the effect of multiple doses of the strong CYP3A4 (and P-gp) inhibitor ketoconazole (400 mg QD for 9 days) on voclosporin exposure following multiple dose treatment, that resulted in 19-fold increase of voclosporin AUC and 6-fold increase in C_{max} (study LX211-06). There is also an *in vivo* study with multiple doses of the moderate CYP3A4 inhibitor (and P-gp inhibitor) verapamil (80 mg three times per day (TID) for 10 consecutive days), that resulted in

2.7-fold increase in voclosporin AUC and 2.0-fold increase in C_{max} (study LX211-07). The applicant concludes that the results of the *in vivo* studies with ketoconazole and verapamil are predominately due to CYP3A4 inhibition and not P-gp inhibition. Multiple doses of the strong CYP inducer rifampicin (600 mg QD for 10 consecutive days) resulted in 87% lower voclosporin AUC and 68% lower C_{max} (study LX211-09). A PBPK model was constructed with the aim of evaluating the relative contribution of CYP3A4 and P-gp in the metabolism and transport of voclosporin and the likely impact of co-administration of CYP3A4 inhibitors and inducers on the PK of voclosporin.

Voclosporin as perpetrator of drug interactions
The following cut-offs have been used for voclosporin for assessment of interaction potential *in vivo*:

Table 5 Cut-offs for voclosporin for assessment of interaction potential in vivo

$50 \times C_{max(u)}$[a] (µM)	$25 \times$Inlet $C_{max(u)}$[b] (µM)	0.1×Dose/250 ml[c] (µM)
0.1	0.6	7.8

a) Input parameters were C_{max} 120 ng/ml in whole blood (study AUR-VCS-2018-01), fu = 0.03, Mw = 1214.63 g/mol.
Note that plasma C_{max} is normally used for calculation of systemic cut-off, but since voclosporin concentrations are only measured in whole blood, this input parameter has been used instead. Plasma concentrations are lower than whole blood concentrations; thus using whole blood concentrations is a conservative approach (as cut-offs based on plasma concentrations would be lower).

b) Input parameters F=1, ka= 0.1 min^{-1}, blood-plasma ratio 1.6
Note that hepatic inlet is calculated based on blood concentrations and thus there is no need to recalculate from plasma to blood concentration in this case (blood-plasma ratio is however used to calculate fu in blood).

c) Dose = 23.7 mg

For the major metabolite IM9 the cut-off was 0.6 µM based on a Cmax value of 0.043 µM (from a study where a voclosporin dose of 0.5 mg/kg BID) and using a protein binding of 72.4% (obtained at a nominal concentration of 0.1 µM).

The *in vitro* CYP direct inhibition data by voclosporin is summarised in the table below:

Table 6 In vitro CYP direct inhibition data by voclosporin

	Voclosporin
	Ki (µM)
CYP1A2	> 5
CYP2B6	> 5
CYP2C8	> 5
CYP2C9	> 5
CYP2C19	> 5
CYP2D6	> 5
CYP3A	1.1*

Assuming Ki = IC50/2 (except for CYP3A4 where Ki was determined)

*Value below relevant cut-off

In vitro transporter inhibition data by voclosporin is summarised in the table below:

Table 7 In vitro transporter inhibition data by voclosporin

	Voclosporin	
	IC_{50} (µM)	**Ki (µM)**
Transporters (demanded)		
P-gp	Signal of inhibition but not possible to determine IC50 value	-
BCRP	>10 µM	>5 µM*
OATP1B1	0.49 µM*	0.25*
OATP1B3	0.24 µM*	0.12*
OAT1	>2 µM	>1 µM
OAT3	>2 µM	>1 µM
OCT2	>2 µM	>1 µM
Transporters (optional)		
MATE1	>2 µM	>1 µM
MATE2-K	>2 µM	>1 µM

Assuming Ki = IC50/2

*Value below relevant cut-off

In vitro CYP direct inhibition data by the major metabolite IM9 is summarised in the table below:

Table 8 In vitro CYP direct inhibition data by the major metabolite IM9

	IM9
	Ki (µM)
CYP1A2	> 1.5
CYP2B6	> 1.5
CYP2C8	> 1.5
CYP2C9	> 1.5
CYP2C19	> 1.5
CYP2D6	> 1.5
CYP3A	> 1.5

Assuming Ki = IC50/2

Based on *in vitro* studies, voclosporin does not inhibit CYP1A2, 2B6, 2C8, 2C9, 2C19 or 2D6. There is a risk for clinically relevant inhibition of intestinal CYP3A4 based on *in vitro* data. There was no indication of time-dependent inhibition.

There was no signal of induction of CYP1A2, CYP2B6 or CYP3A4 (or of CYP2C8, CYP2C9 or CYP2C19) at concentrations relevant for systemic interaction.

The major metabolite IM9 does not inhibit CYP1A2, 2B6, 2C8, 2C9, 2C19, CYP3A4 or 2D6.

An *in vivo* study has been performed investigating the effect of multiple doses of voclosporin on the sensitive CYP3A4 substrate midazolam, where no relevant effect was seen on midazolam exposure (AUC within BE criteria and Cmax almost within BE criteria).

Based on *in vitro* studies, voclosporin is an inhibitor of P-gp, OATP1B1 and OATP1B3 but is not a clinically relevant inhibitor of OAT1, OAT3, OCT2, MATE1 and MATE2-K. Voclosporin may also be a clinically relevant inhibitor of intestinal BCRP. An *in vivo* study has been performed investigating the effects of multiple doses of voclosporin on the P-gp substrate digoxin, resulting in 1.5-fold increase in digoxin C_{max} and 1.25-fold increase in digoxin AUC. The applicant has not performed an *in vivo* study with an OATP1B1/ OATP1B3 substrate. Attempts were made to claim that no clinically relevant effects were expected based on PBPK, but the applicant has proposed an SmPC warning regarding concomitant use with statins, and thus did not rely on the PBPK model. This was considered acceptable to the CHMP.

Voclosporin has been co-administered with MMF in the pivotal clinical study, and therefore the effect of multiple doses of voclosporin on blood levels of MMF's active metabolite MPA or the main inactive metabolite MPAG was investigated in an *in vivo* study. AUC and C_{max} of the active metabolite MPA was similar following treatment with voclosporin compared to without voclosporin.

Exposure relevant for safety evaluation

In study AUR-VCS-2018-01, a DDI study performed in subjects with SLE (with and without LN), receiving voclosporin 23.7 mg BID in the presence of MMF 1 g BID (not considered to affect the exposures of voclosporin), the following exposure parameters were reported at steady state (after 10 days of BID dosing):

$AUC_{0\text{-}12h}$: 433 ng*h/ml, corresponding to $AUC_{0\text{-}24h}$ of 866 ng*h/ml

C_{max}: 120 ng/ml

2.5.2.2. Pharmacodynamics

Mechanism of action

Primary and Secondary pharmacology

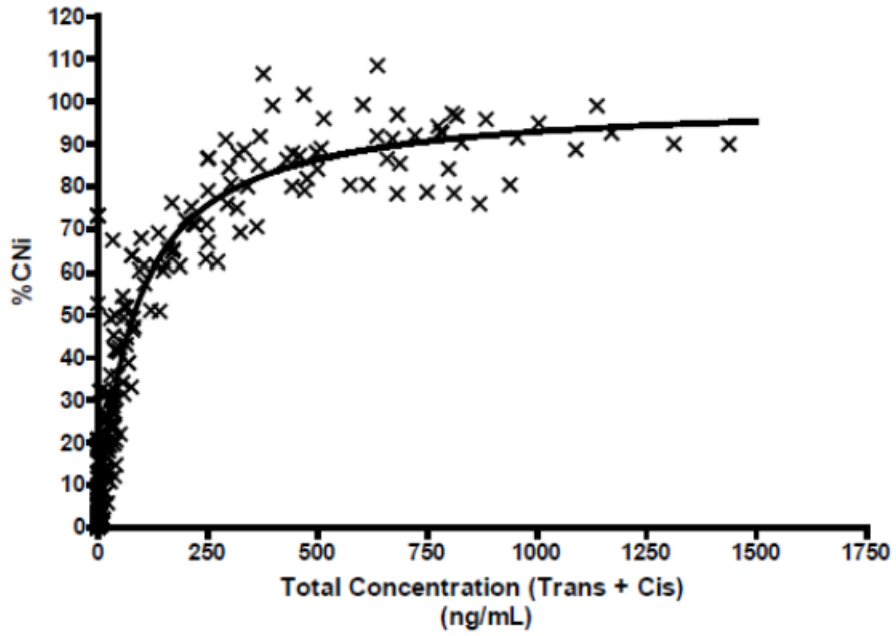
Voclosporin is a calcineurin-inhibitor immunosuppressant. Activation of lymphocytes involves an increase in intracellular calcium concentrations. Calcineurin is a calcium/calmodulin-dependent phosphatase whose activity is required for the induction of T-cell lymphokine production and proliferation. The immunosuppressant activity results in inhibition of lymphocyte proliferation, T-cell cytokine production, and expression of T-cell activation surface antigens.

According to the applicant, studies in animal models also support a non-immunological role for calcineurin inhibition in kidney function to stabilise actin cytoskeleton and stress fibres in podocytes leading to increased podocyte integrity in glomeruli.

Clinical studies

Single Ascending Dose (Study ISA03-10) in healthy subjects

This was a single-centre, double-blind, randomised, placebo-controlled, single ascending dose study. The results are summarised below.



Notes: %CNi = % calcineurin inhibition; Cis = *Cis*-isomer of voclosporin; Trans = *Trans*-isomer of voclosporin.

Figure 5 Voclosporin Concentrations vs. Calcineurin Inhibition

According to the applicant, calcineurin inhibition appeared to increase with dose. PK-PD correlation demonstrated a strong relationship between drug concentration and calcineurin inhibition. At the maximum dose tested the maximal effect (E_{max}) also appeared to decrease from a maximum 91% calcineurin inhibition observed at 1.5 and 3.0 mg/kg to 89% at 4.5 mg/kg suggesting saturation of the immunophilin. Based on a simple E_{max} model, a half maximal effect concentration (EC_{50}) of 82.7±5.8 ng/mL was observed for voclosporin.

Single and Multiple Ascending Dose (Study ISA03-12)

This was a single-centre, double-blind, placebo-controlled, single-dose followed by multiple-dose study to assess the safety, tolerability and PK of voclosporin in healthy subjects.

The relationship between calcineurin inhibition and exposure to voclosporin is presented in Table 9.

Table 9 Calcineurin Inhibition and Pharmacokinetics of Voclosporin After Single and Multiple (BID) Doses of Voclosporin

Dose (mg/kg)	Day	N	T_{max} (h)	C_{max} (ng/mL)	TE_{max} (h)	E_{max} (% CNi)
0.25	1	9	1 (1-2)	49.3±10.7	1 (1-2)	44.4±14.4
	13	8	1 (0-1.5)	44.2±18.4	1 (1-2)	47.6±19.2
0.5	1	9	1 (1-2.5)	120.6±48.5	1 (1-4)	58.8±12.2
	13	9	1 (1-1.5)	196.1±50.7	2 (1-4)	70.2±14.4
1.0	1	8	1.5 (1-2.5)	507.0±181.4	1 (1-12)	74.5±28.1
	13	8	1.5 (1.5-1.5)	620.6±193.0	1 (1-2)	88.7±6.3
1.5	1	9	1.5 (1-1.5)	719.4±81.2	2 (1-4)	82.6±5.2
	13	7	1.5 (1-2)	867.6±334.0	1.5 (1-4)	77.4±24.3

Notes: Mean±SD. Median (range) for T_{max} and TE_{max}.
% CNi = % calcineurin inhibition, BID = Twice daily; C_{max} = Maximum concentration; E_{max} = Maximum effect; SD = standard deviation; TE_{max} = Time to each the maximum effect; T_{max} = Time to reach the maximum concentration.

According to the applicant, a strong correlation between drug concentration and calcineurin inhibition was observed. Calcineurin inhibition appeared to increase with dose. At the highest dose levels tested, on Day 13 the E_{max} appeared to decrease from a maximum 88.7% calcineurin inhibition at 1.0 mg/kg BID to 77.4% at 1.5 mg/kg BID. This may be due to saturation of the immunophilin binding site. Thus, the ability of voclosporin to inhibit calcineurin appears to be dose related up to a maximum dose of 1.0 mg/kg BID. Based on a simple E_{max} model, an EC_{50} of 83.9±9.9 ng/mL and 63.5±8.3 ng/mL was observed for voclosporin on Day 1 and Day 13, respectively (Study ISA03-12).

In Study AUR-VCS-2018-01 (DDI with MMF), multiple PK samples were taken during a 12-hour dosing interval at steady-state in subjects with SLE (with or without LN) receiving voclosporin 23.7 mg BID. Mean (SD) C_{trough}, C_{max} and C_{avg} were 15.0±7.35 ng/mL, 120±38.8 ng/mL and 36.1±15.5 ng/mL, respectively. Based on the mean values obtained at a dose of voclosporin 23.7 mg BID, calcineurin inhibition was determined to be 15.7% at C_{trough} and 58.1% at C_{max}, which results in an average inhibition of 30.6% during a dosing interval (Table 10).

Table 10 Voclosporin Concentrations versus Calcineurin Inhibition

Study	Dose (mg/kg)	Day	E_{max} (%)	EC_{50} (ng/mL)	Calcineurin Inhibition (%)		
					C_{trough}	C_{avg}	C_{max}
ISA03-10	0.25-4.5	Day 1	100.6	82.7	15.4	30.6	59.6
ISA03-12	0.25-1.5	Day 1	93.2	83.9	14.1	28.0	54.9
ISA03-12	0.25-1.5	Day 13	91.6	63.5	17.5	33.2	59.9
Mean					**15.7**	**30.6**	**58.1**

Notes: C_{trough} = 15 ng/mL, C_{max} = 120 ng/mL, C_{avg} = 36.1 ng/mL (obtained from Study AUR-VCS-2018-01)
C_{avg} = Average concentration over a dosing interval at steady-state; C_{max} = Maximum concentration; C_{trough} = Trough concentration (measured concentration at the end of a dosing interval at steady-state); EC_{50} = Half maximal effect concentrations; E_{max} = Maximum effect.

Similar results were observed based on the calcineurin inhibition obtained in the subjects with plaque psoriasis including receiving 0.2, 0.3 and 0.4 mg/kg voclosporin BID (Study ISA04-03 PK/PD Report: E_{max}=104%; EC_{50}=152 ng/mL) and in renal transplant subjects receiving 0.4, 0.6 and 0.8 mg/kg voclosporin BID (Study ISA05-01 PK/PD Report: E_{max}=100%; EC_{50}=159.5 ng/mL).

The tolerability of voclosporin up to 1.5 mg/kg BID was evaluated in healthy subjects (Studies ISA03-12, ISA05-03 and AUR-VCS-2015-J01). Safety evaluations demonstrated that voclosporin was

generally well tolerated, particularly in subjects receiving the lower doses (0.25, 0.50, and 1.0 mg/kg) BID. Subjects receiving 1.5 mg/kg BID had the highest incidence of adverse events (AEs). No relevant differences between doses were observed with respect to clinical laboratory parameters, vital signs, and ECG results. However, AEs of decreased heart rate, increased blood pressure (BP), increased blood potassium, decreased blood magnesium and proteinuria were more frequent following voclosporin treatment (primarily the 1.5 mg/kg dose) than with placebo. Serum magnesium generally decreased more from baseline with voclosporin than with placebo, most notably at the highest dose (1.5 mg/kg BID). However, these changes were not clinically significant. In summary, the 1.5 mg/kg BID dose may represent the upper limit of tolerability.

The therapeutic dose for subjects with LN is 23.7 mg BID (or 0.37 mg/kg BID based on the median weight of subjects receiving active treatment in AURORA 1). This dose is approximately 4-fold lower than the 1.5 mg/kg BID dose which is considered to be the upper limit of tolerability.

Exposure Response Evaluation

To assess whether eGFR decreases were related to higher voclosporin exposures, the exposure before an eGFR-related dose modification was assessed in LN patients using the population PK model. Simulated PK parameters were summarised by eGFR category per the study dose modification guidance for both the 23.7 mg BID and 39.5 mg BID (AURA-LV only) dosing regimens. Based on this evaluation, there was no distinction between the simulated exposure parameters C_{max}, C_{trough} and AUC_{0-12} in subjects meeting the eGFR-related dose modification criteria and subjects with an eGFR ≥60 mL/min/1.73 m^2 for both dosing regimens. Voclosporin exposures in subjects who experienced decreases in eGFR meeting the criteria for dose modification were within the ranges seen in subjects who did not. This suggests that eGFR decreases are not due to higher exposure to the drug, a conclusion that is supported by the observation that treatment with the higher dose of 39.5 mg BID did not result in a higher rate of eGFR decreases.

In addition, an exposure (AUC_{0-12}) quartile analysis was performed based on the efficacy response in AURA-LV and AURORA 1. The odds ratio (OR) of 1-year adjudicated complete and partial renal response was evaluated by exposure quartiles (23.7 mg BID dosing regimen only). The average exposure over a dosing interval was obtained based on the final population PK model. Within the 23.7 mg BID dosing regimen, no relationship between AUC and response was observed.

A summary of the QT studies is presented in 2.5.8. (clinical safety).

2.5.3. Discussion on clinical pharmacology

Therapeutic window

The applicant claimed that based on data from the AURA-LV study, it is safe to use voclosporin up to doses (and related exposure) of at least 1.67-fold the therapeutic dose of 23.7 mg BID. However, an eGFR monitoring schedule, with recommended dose adjustments based on a decrease in eGFR, should be applied. The applicant was asked to discuss this further as there seemed to be a dose-dependent risk for adverse events with a higher risk of for example infections and renal failure with the 39.5 mg dose. Based on the submitted response, it is agreed with the applicant that the overall data does not support a potential dose-dependent risk for infections. Based on the overall data, there seems to be a small but consistent dose-dependent risk for kidney injury/decreased GFR, however the difference between the arms is very small and the clinical relevance is unclear. The potentially higher risk for renal adverse events and hypertension in patients with increased exposure is considered possible to handle through monitoring of GFR and blood pressure, followed by dose reduction if clinically needed. When combining the predicted AUC0-12h from both 23.7 mg and 39.5 mg BID dose groups the 5th and

95th percentile values were 297 and 1223 ng.h/mL, respectively. The median value for the 23.7 mg BID dose group was 573 ng.h/mL, and the exposure range studied in phase 3 was approximately 2-fold the median value for the 23.7 mg dose. Given adequate monitoring, a 1.7- to 2-fold increase from 573 ng.h/mL can be acceptable.

The applicant was also asked to discuss the lower limit of the therapeutic window. Given a 23.7 mg dose, the simulated AUC0-12 ranged from 137 to 1418 ng.h/mL, with a median value of 573 ng.h/mL. The 5th and 95th percentile with 287 and 988 ng.h/mL, respectively. Compared to the median value, the 5th percentile value was approximately 2-fold lower. It is agreed that this is the therapeutic exposure range that has been studied. However, patients that are already in the lower part of the AUC range could decrease even further due to e.g. DDI. The lower limit of exposure for loss of efficacy remains uncertain. A caution for potential loss of efficacy for scenarios where a decrease in exposure could be expected might be advisable.

Based on this, dose adjustments in case of concomitant treatment with interacting substances as well as in case of organ impairment have been proposed as discussed below.

Methods

Bioanalytical methods

Based on the submitted full and partial validation reports, the methods are considered adequately validated. Overall, the within study validation reports show that the methods performed satisfactorily.

Population PK analysis

The population PK analysis is overall considered adequate. In the analysis of AURA-LV and AURORA 1 PK data, 35 patients were found to have aberrant PK profiles and to describe PK in these patients a mixture model for central volume of distribution (Vc/F) was applied. Thus, two different Vc/F values were reported from the analysis which somewhat decrease the interpretability of the model. However, the Vc/F value (34.4 L) reported for the main proportion of patients was largely in line with the Vc/F value reported in the analysis of AURA-LV alone (41.0 L, Population PK Report AURA-LV). Given that the population PK model describes data well, the parameterisation of the PK model is accepted. However, eta shrinkage was moderate to high (18% for CL/F and 61% for Vc/F), subsequently exposure predictions from individual Bayes estimates should be interpreted with caution.

Physiologically-based pharmacokinetic model-based analysis

The PBPK model for voclosporin was based on prior *in vitro* and *in vivo* information across single and multiple dosing over a range of dose levels. It is noted that the Km-value for CYP3A4 from *in vitro* did not describe data well and was optimised during model development with the result of a 20-fold reduction. It is questionable whether this procedure is reliable. Nevertheless, the main concern with the developed PBPK model is the poor prediction of the voclosporin PK profile. To develop a reliable PBPK model it is of essence that the model can predict voclosporin PK over a range of dose levels. The presented results display both over and under prediction of voclosporin concentration in various scenarios. The predicted PK profiles clearly indicate that the elimination phase is not well described but also that Cmax is not well predicted. The poor predictive ability of voclosporin PK propagate into a large uncertainty of the reliability of simulated voclosporin PK given a DDI. In the verification exercise the predicted magnitude of interaction displayed less deviation in the prediction ratio (with the exception of verapamil). However, the actual voclosporin exposure levels (Cmax and AUC) consistently display both under and over predictions. In conclusion, due to the poor prediction of voclosporin PK, the simulated Cmax and AUC-values under a DDI scenario are not considered reliable and cannot be used to support dosing recommendations. See further discussions below on the dosing recommendations.

Absorption

In the mass balance study, a total of 93% of the dose was recovered in faeces. When looking at samples used for metabolite characterisation, 88% of the dose was recovered in faeces and very little of this was as unchanged parent drug (5% of the dose). This would indicate a high degree of absorption, provided that metabolites have not been formed in lumen or faeces (ie by unabsorbed parent drug). Although a large part of the metabolites have not been identified in faeces, there is data that indicate stability of parent drug in faeces. Thus, it can be concluded that the degree of absorption is high, although an exact figure of fraction absorbed is difficult to determine.

The initial SmPC proposal recommended intake on an empty stomach. This was based on the fact that all patients in the phase 3 studies were instructed to take the investigational medicinal product (voclosporin or placebo) on an empty stomach. The protocols did however not specify the amount of time before or after a meal subjects should wait until taking investigational medicinal product and meal intake was not recorded in the studies. Administration of voclosporin with food decreased both the rate and extent of absorption. Cmax and AUC of voclosporin were reduced by 53% and 25%, respectively, when given with high-fat food and by 29% and 15%, respectively, when given with low-fat food. In their responses to CHMP's questions, the applicant considered that a reduction in AUC up to 25% would not affect the efficacy of voclosporin and concluded that voclosporin can be taken irrespective of food and that it is not possible to know the conditions of intake in the patient population of the studies and thus no instruction on how long to wait between capsule and food intake can be provided. As discussed above, there is not much data to support the lower range of the therapeutic window and to conclude that a 50% decrease in exposure would not be clinically relevant as claimed by the applicant (especially for patients already having an exposure in the lower range). However, the decrease in exposure observed with a high-fat meal is considerably lower than 50%. In addition, patients in the clinical study will likely not have been strictly fasted as in a fasted PK study, and thus the difference between the exposure in the clinical studies and the exposure with a high-fat meal will likely be less than 25%. Thus, the effect of food on the AUC of voclosporin is not considered to be clinically relevant. CHMP agreed that voclosporin can be taken with or without food and this is adequately reflected in the SmPC.

Distribution

Voclosporin has one metabolite that can be classified as major, M4 (IM9), and for which the potential to inhibit CYP enzymes should be investigated according to the DDI guideline. Data regarding plasma protein binding data for the major metabolite M4 (IM9) has been submitted as requested, in order to determine cut-offs for DDI potential.

It can be concluded based on *in vitro* and *in vivo* data that voclosporin is extensively partitioned into red blood cells, although an exact figure of blood/plasma ratio should be given with caution considering the dependence on experimental conditions.

Elimination

It can be concluded that metabolism followed by biliary secretion in faeces is the main elimination pathway for voclosporin. The very large effects on voclosporin exposure by the CYP3A4 inhibitor ketoconazole supports that CYP3A4 is the main enzyme involved in the metabolism of voclosporin.

Urinary excretion of parent drug is a minor elimination pathway.

The elimination pathways of voclosporin are considered sufficiently well characterised.

The Guideline on interactions recommends that more than 80% of the excreted dose should be identified, and this was not fulfilled as 44% of the dose is described as "unidentified miscellaneous components" in faeces. However, the unidentified components are likely numerous trace-level metabolites (possibly from further oxidation of primary voclosporin metabolites). Hence, no concern was raised from CHMP.

There is no investigation of absolute bioavailability of voclosporin. The fact that very little unchanged parent drug was recovered in faeces would indicate a high degree of absorption, provided that metabolites have not been formed in lumen or faeces (ie by unabsorbed parent drug). As stated above, a large part of the metabolites has not been identified in faeces. However, there is data that indicate stability of parent drug in faeces. Thus, it can be concluded that the degree of absorption is high.

Renal clearance following oral administration was 0.469 L/h and filtration (fu*GFR) is expected to be around 0.2 L/h; thus active renal secretion may be involved in the renal elimination. However, as renal clearance of unchanged parent drug is a very minor elimination pathway, any effect on renal transporters is not likely to affect the elimination of voclosporin.

Several metabolites are formed. The applicant claims that these metabolites do not contribute to the effect of voclosporin, and this is agreed, as they are less potent and have lower exposure in plasma.

According to the Guideline on the investigation of drug interactions, it is recommended to investigate the enzyme inhibitory potential of phase I metabolites with an AUC both larger than one fourth of the AUC of parent drug and larger than 10% of the drug-related exposure. This is fulfilled for one of the metabolites, M4 (IM9), that has an AUC that is 44% of voclosporin and 17% of total radioactivity. Thus, this metabolite should be considered as major and investigated for CYP inhibiting potential. Metabolite M1 (IM1-Diol-1) is borderline to be considered a major metabolite, as AUC is 9.5% of total radioactivity and 24.8% of parent drug, ie just below the recommended limits. The applicant was asked to discuss whether IM1-Diol-1 should be considered a major metabolite, considering the borderline results from the mass balance study and the significant accumulation of this metabolite observed in the MAD study. Overall, based on data presented, it can be agreed that steady-state M-P data do not suggest that IM1-Diol-1 should be considered a major metabolite. All other metabolites detected in plasma can be considered minor metabolites.

No major consequences of genetic polymorphism are expected as CYP3A4 is the most important enzyme involved in the metabolism of voclosporin.

Dose proportionality and time dependency

A non-linearity between dose and exposure was observed in the studies in healthy volunteers at the lower end of the dose range studied, but the dose proportion factor was less than 1.5. The population PK analysis in patients with LN did not detect non-linearity of the dose range studied.

When comparing AUC_{tau} on day 13 to AUC_{inf} on day 1 in study ISA03-12, the ratio is slightly more than unity (range 1-1.7). However, based on the midazolam study, autoinduction is not expected, and there is thus no clear mechanism for a time dependency. It can be concluded that there is little or no time dependency for voclosporin.

Special populations

Renal impairment

Lupus nephritis is a condition inherently associated with reduced renal function, however patients with eGFR ≤45 mL/min/1.73 m2 were excluded from the AURA-LV and AURORA 1 clinical studies. Voclosporin is excreted renally to a very small extent; thus large effects of renal impairment on voclosporin exposure are not expected. However, severe RI may affect the elimination also of non-renally eliminated drugs, and a dedicated RI study has been performed.

One weakness with the performed study is however that unbound concentrations were not measured and thus PK data based on unbound concentrations were not determined. This is recommended for substances that exhibits high extent of plasma protein binding (>90%) in addition to PK parameters based on total concentrations. As expected, AUC and C_{max} of voclosporin were largely similar when comparing subjects with mild or moderate RI to subjects with normal renal function. For subjects with severe RI, higher exposure was observed (1.46- and 1.74-fold higher C_{max} and AUC_{0-48}, respectively when using data from the revised classification according to the current guideline). The SmPC section 4.2 proposed by the applicant recommends dose reduction to 2/3 of the normal dose if voclosporin is used in patients with severe renal impairment. The proposed dose adjustment in severe RI is considered reasonable from a pharmacokinetic perspective, as this would be expected to result in largely similar exposure compared to the normal dose in patients with normal renal function. Also, from a PK perspective, a reduction of starting dose in patients with mild or moderate RI would not seem necessary. See 0Considering that eGFR is monitored during treatment and that other aspects than PK are relevant regarding the possibility to use voclosporin in subjects with renal impairment, no concern is raised regarding the fact that unbound concentrations were not measured in the RI study.

Hepatic impairment

Subjects in the moderate HI group were affected in aspects primarily related to elimination capacity of drugs, i.e. in markers that are likely to be relevant for the elimination capacity of drugs (such as albumin, bilirubin and prothrombin time).

Unbound concentrations were not measured in the hepatic impairment study, although this is recommended in the EMA guideline. If the drug or metabolites exhibit a high extent of plasma protein binding, the pharmacokinetics should be described and analysed with respect to the unbound concentrations of the drug and active metabolites in addition to total concentration. The applicant was asked to discuss the possibility that unbound concentrations would be more affected by HI than total concentrations, also considering the binding of voclosporin to erythrocytes. The applicant discussed whether patients with lower levels of albumin, which could potentially result in an increased unbound fraction of voclosporin, also had an increased safety risk. Low albumin levels are related to disease activity (proteinuria). CHMP agreed with the applicant that the frequency of adverse events is larger in

patients with lower albumin levels both in the voclosporin group and the placebo group, thus likely due to disease activity, but it is not known how low albumin levels due to hepatic impairment would affect safety. It would have been preferrable if unbound concentrations had been determined in the HI study as recommended in the EMA guideline. However, the HI study was performed in subjects with mild and moderate hepatic impairment only, and the largest effect on albumin levels would be expected in subjects with severe hepatic impairment. In addition, the protein binding is not extremely high (97%). For these reasons, it can be accepted that only total concentrations were measured in the HI study and that dose adjustment is based on total concentrations.

Administration of voclosporin to subjects with mild (Class A) to moderate (Class B) hepatic impairment significantly increased exposure to voclosporin. In subjects with mild hepatic impairment, pre-dose concentrations increased 2-fold, while C_{max} and AUC increased approximately 1.5- and 1.7-fold, respectively, after a single dose, and 1.5- and 1.8-fold, respectively, after multiple doses. In subjects with moderate hepatic impairment, C_{max} and AUC increased 1.5- and 2-fold, respectively, after a single dose.

The proposed dose adjustment in patients with mild and moderate hepatic impairment (dose-reduction to 2/3 of the normal dose expected to lead to slightly higher total exposure (1.3-fold) than in patients with normal hepatic function taking a normal dose, based on HI study showing up to 2-fold increase in total exposure) can be accepted.

Other special populations

It is agreed that no dose adjustments are necessary for other special populations. A population pharmacokinetic analysis assessing the effects of age, sex, race and body weight did not suggest any clinically significant impact of these covariates on voclosporin exposures.

Interactions

Voclosporin as victim of interactions

The ketoconazole study confirmed that voclosporin is a very sensitive CYP3A4 substrate and that CYP3A4 is the main enzyme involved in voclosporin metabolism. Possibly, an even higher effect would have been seen with a longer ketoconazole treatment, but it is clear that voclosporin is very sensitive to the effects of ketoconazole.

Based on *in vitro* data, voclosporin is a possible P-gp substrate but the study is inconclusive. It is however agreed that the results of the *in vivo* studies with ketoconazole and verapamil are predominately due to CYP3A4 inhibition and not P-gp inhibition, as the mass balance study shows high absorption (indicating that P-gp is not significantly involved in absorption) and as renal/biliary excretion of unchanged voclosporin are very minor routes of elimination (indicating that P-gp is not significantly involved in elimination). Thus, it is not considered necessary to mention P-gp inhibitors in the SmPC. The *in vitro* study investigating voclosporin as substrate of BCRP is considered inconclusive. However, even if voclosporin would be a BCRP substrate, similar as for P-gp, large effects of BCRP-inhibitors would not be expected.

Active secretion of unchanged drug is not a major route of drug elimination based on the mass balance study, and thus it is not mandatory to investigate if voclosporin is a substrate of transporters involved in renal/biliary excretion.

Concomitant use with strong CYP3A4 inhibitors is proposed to be contraindicated, which is agreed. The PBPK model cannot be used to support any claims regarding DDI potential (see above); thus, the effect of additional moderate CYP3A4 inhibitors or mild CYP3A4 inhibitors cannot be predicted using the PBPK model. Regarding use with moderate CYP3A4 inhibitors, there is *in vivo* data with verapamil that can be used to support dose adjustments. The proposed dose adjustment in case of concomitant

administration with moderate CYP3A4 inhibitors (dose-reduction to half the normal dose expected to lead to slightly larger exposure than with the normal dose without moderate CYP3A4 inhibitors (1.4-fold increase), based on verapamil *in vivo* data showing 2.7-fold increase in exposure) was accepted by CHMP.

In case of concomitant treatment with mild CYP3A4 inhibitors, the exposure of a sensitive CYP3A4 substrate could by definition increase up to 2-fold. This is borderline to what has been studied, and it should be noted that the upper limit of the therapeutic window discussed above is based on median exposure; thus, a patient who is in the higher exposure range could be outside the studied range if the exposure was increased 2-fold. However, a dose adjustment is not considered adequate as most mild inhibitors would result in less than 2-fold increase in exposure. CHMP considered that this was possible to handle through adequate monitoring and a statement regarding this has been added in the SmPC.

Concomitant use of voclosporin with moderate or severe CYP3A4 inducers is not recommended. This is adequately reflected in the SmPC. A mild CYP3A4 inducer may according to definition result in up to 50% decrease in AUC of a sensitive substrate. As previously concluded, there is not much data to support the lower range of the therapeutic window and to conclude that a 50% decrease in exposure would not be clinically relevant (especially for patients already having an exposure in the lower range). It is not necessary to have a recommendation that concomitant use is not recommended (as for moderate/strong inducers); however, this has been added to the SmPC and endorsed by the CHMP.

Voclosporin is to be used with background therapy consisting both of MMF and corticosteroids. Interaction potential of voclosporin to influence the MMF pharmacokinetics was evaluated in a dedicated clinical study showing no significant interaction. The published literature suggests that corticosteroids may have a CYP3A4 inducing effect, although the data are conflicting. Voclosporin, being a sensitive CYP3A4 substrate, could be affected by corticosteroids co-administration. The applicant was asked to discuss the interaction potential between corticosteroids and voclosporin. PK sampling in study AUR-VCS-2018-01 allowed estimation of Cmax and AUC0-12. Voclosporin exposure with prednisone co-administration (different doses combined as well as individual doses) was comparable to voclosporin exposure without prednisone co-administration. In AURORA 1 study, only sparse PK sampling was performed, but no difference was observed in voclosporin concentrations with and without corticosteroid background therapy. Overall, based on provided data no clinically relevant interaction is expected between voclosporin and corticosteroid background therapy.

Voclosporin as perpetrator of interactions

In some *in vitro* studies there were issues with non-specific binding and low recovery, while this was not investigated in other *in vitro* studies and thus it is not known if actual studied concentrations were lower than nominal concentrations. This gives some uncertainty to the observed IC50 values, but regarding inhibition of CYP enzymes (except CYP3A4) and inhibition of the transporters OAT1, OAT3, OCT2, MATE1 and MATE2-K , a clinically relevant interaction may still be excluded as Ki values were well above the relevant cut-offs.

There was no signal of induction of CYP1A2, CYP2B6 or CYP3A4 (or of CYP2C8, CYP2C9 or CYP2C19) by voclosporin at concentrations relevant for systemic interaction. For CYP3A4, the highest studied concentration of 7 µM was lower than the cut-off of 7.8 µM relevant for intestinal induction, and at the highest studied concentration of 7 µM there were also issues with cell toxicity so that results should be interpreted with caution. At the concentrations of 3 µM and 7 µM there was no sign of induction of CYP3A4, but rather of down-regulation. There is an *in vivo* midazolam study that did not demonstrate a clinically relevant effect of voclosporin on midazolam exposure; thus any inhibition/induction/down-regulation resulted in no net effect on the sensitive CYP3A4 substrate midazolam. The applicant has also presented *in vitro* induction data for other PXR regulated enzymes (CYP2C8, 2C9, or 2C19) that do

not indicate a risk for induction. It can be concluded that a clinically relevant induction by voclosporin can be excluded.

An *in vivo* study has been performed investigating the effects of multiple doses of voclosporin on the P-gp substrate digoxin, resulting in 1.25-fold increase in digoxin AUC. Digoxin is however not a sensitive substrate for intestinal inhibition (due to its rather high oral bioavailability), and the effect may be larger on P-gp substrates that are more sensitive to intestinal P-gp inhibition, such as dabigatran etexilate.

In vitro inhibition data indicate a risk for *in vivo* inhibition of OATP1B1 and OATP1B3 by voclosporin at clinically relevant concentrations and the PBPK model cannot be used to exclude a clinically relevant effect on OATP1B1/OATP1B3 substrates. The applicant has agreed to perform an *in vivo* study with a sensitive OATP1B1/OATP1B3 substrate and the CHMP recommends the applicant to submit the results of this study when available.

The observed IC50 value for BCRP is well above the cut-off for systemic inhibition (0.1 µM). The applicant was asked to discuss the risk of *in vivo* relevant inhibition of intestinal BCRP considering that the observed IC50 value (>10 µM (45% inhibition at 10 µM)) is close to the relevant cut-off (7.8 µM) and as stability and non-specific binding of voclosporin in the *in vitro* inhibition experiment has not been discussed (thus IC50 may possibly be overestimated in the study). Also, Ki should generally be used in the interpretation of *in vitro* results, and this has not been discussed by the applicant. The applicant concluded that an *in vivo*-relevant inhibition could not be excluded and included a warning regarding BCRP substrates in the SmPC section 4.5. This was agreed by the CHMP.

There is one major metabolite, M4 (IM9), that has been investigated for potential to inhibit CYP enzymes according to the guideline. It can be concluded that there is no signal for *in vivo*-relevant inhibition of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP3A4 or CYP2D6 by the major metabolite M4 (IM9).

Exposure response evaluation

To assess whether eGFR decreases were related to higher voclosporin exposures, the exposure over 12-hours prior to an eGFR-related dose modification was derived in LN patients using the population PK model. For patients without an eGFR decrease the exposure over the last dosing interval was used. This strategy assumes that it is the exposure just prior to the measured eGFR decrease that is driving the effect, which might not be the case. Furthermore, the reported results are categorised according to percent eGFR reduction from baseline for patients with eGFR values <60 mL/min/1.73 m2, whereas a reduction from baseline eGFR for patients above 60 mL/min/1.73 m2 is not reported. The categorisation of eGFR reduction decrease the information content compared to an analysis of change from baseline eGFR for all patients. Nonetheless, CHMP agreed that the presented results do not indicate an impact of exposure on reduction of eGFR and thus it is not foreseen that therapeutic drug monitoring would be meaningful in predicting eGFR reduction.

Exposure-safety trends were investigated by reporting the first occurrence of observed adverse events in the pivotal studies summarised by predicted exposure quartiles. However, it is not clear how the number of events (E) can be larger than the number of subjects (n) if it is the first event that is reported. Nevertheless, the only trend of increasing AEs with increasing exposure was for vascular disorders which will be monitored (elevated blood pressure) in LN patients with voclosporin treatment. Thus, the questions regarding the descriptive exposure-safety summary was not be further pursued by the CHMP.

In addition, a logistic regression analysis based on 1-year adjudicated complete and partial renal response by exposure quartiles (23.7 mg BID dosing regimen only) has been presented. However, due to dose adjustment based on eGFR the average exposure over a dosing interval from 0-24 weeks is

not considered meaningful as the exposure could change over time whereas the renal response is only measured at one point in time.

Individual predictions from the population PK analysis should be used with caution due to shrinkage the calculation of individual clearance and volume of distribution values, subsequently the exposure-response analyses should be interpreted with caution. In addition, the dose adjustment regimen used in the pivotal studies further introduces uncertainty of the interpretation of exposure-response relationships for voclosporin. Nevertheless, no alarming exposure-response trends have been detected thus there is no indication that therapeutic drug monitoring would be meaningful in predicting eGFR reduction.

The clinical pharmacology information is adequately reflected in the SmPC.

2.5.4. Conclusions on clinical pharmacology

Voclosporin is metabolised by CYP3A4 and is an inhibitor of P-glycoprotein (P-gp). It is an inhibitor of organic-anion-transporting polypeptide (OATP)1B1 and OATP1B3 *in vitro*. Co-administration of voclosporin with strong CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, clarithromycin) is contra indicated.

The CHMP recommends the applicant to submit the results of the planned *in vivo* DDI study, investigating the effects of voclosporin on simvastatin and its active metabolite simvastatin acid as substrates for OATP1B1/OATP1B3, when available.

Limited data are available on the use of Lupkynis in LN patients with baseline eGFR 30 to < 45 mL/min/1.73 m2. It is recommended to use Lupkynis in these patients, only if the benefit outweighs the risk, and at a starting dose of 23.7 mg twice daily. Lupkynis has not been studied in LN patients with severe renal impairment (eGFR < 30 mL/min/1.73 m2) and is not recommended in these patients unless the benefit outweighs the risk. If used, the recommended starting dose is 15.8 mg twice daily.

The CHMP concluded that the clinical pharmacology data supported the application for voclosporin.

2.5.5. Clinical efficacy

2.5.5.1. Dose response study(ies)

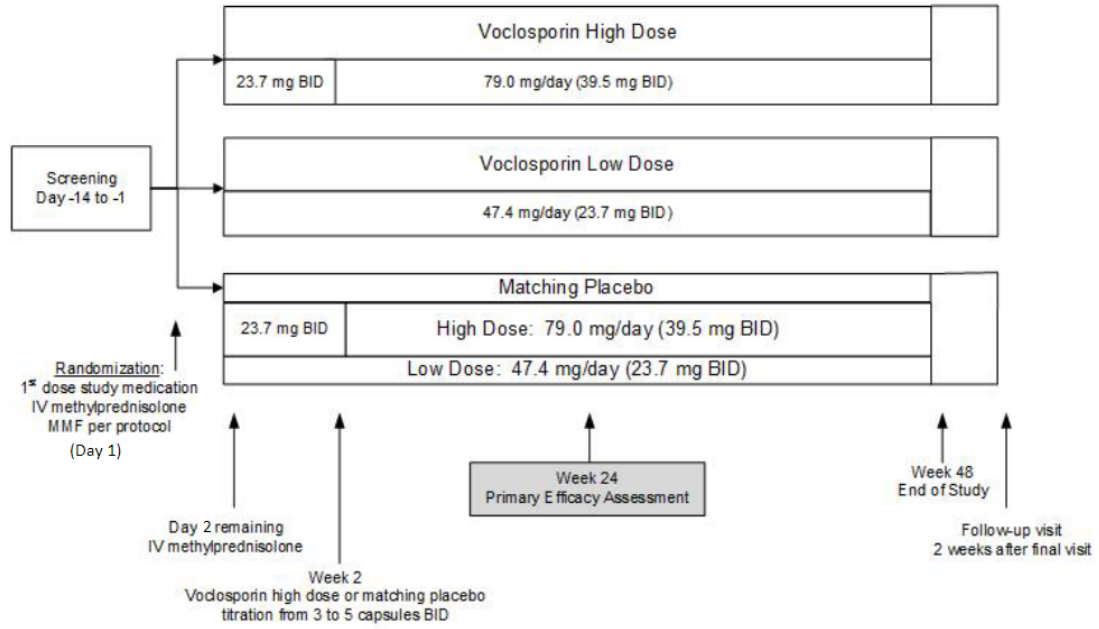
The selection of VCS doses was based on previous experience with VCS in healthy subjects and in other autoimmune indications (i.e., renal transplant, plaque psoriasis, and non-infectious uveitis). In these autoimmune indications, subjects were administered VCS at doses ranging from 0.2 mg/kg BID to 0.8 mg/kg BID. In an integrated analysis of safety comparing doses of 0.2 mg/kg BID, 0.3 mg/kg BID, 0.4 mg/kg BID, and 0.6 mg/kg BID, a difference was observed between the 0.6 mg/kg BID dose and the lower doses. Subjects in the higher dose group had more AEs, serious adverse events (SAEs), and AEs leading to discontinuation, and the frequency of AEs related to renal dysfunction and changes in serum creatinine were also higher in the high-dose group. In addition, population PK analyses of VCS concentrations from the clinical development programme (including healthy subjects and subjects from other autoimmune indications) demonstrated that weight did not have a significant effect on the PKs of VCS. Therefore, weight-based dosing is not considered necessary. In consideration of the efficacy and safety of VCS in the studies discussed above, doses equivalent to approximately 0.3 to 0.4 mg/kg BID (low-dose) and 0.5 to 0.6 mg/kg BID (high-dose)

were selected for the AURA-LV study, i.e., 23.7 mg BID (three capsules BID) and 39.5 mg BID (five capsules BID). Voclosporin was administered as fixed doses without the use of therapeutic drug monitoring. To ensure the safety of subjects randomised to the high-dose (39.5 mg BID) group, subjects were started on low-dose (23.7 mg BID) VCS for the first 2 weeks after randomisation and titrated up to high-dose VCS at Week 2. The protocol contained detailed provisions for management of dose based on safety concerns, in particular, blood pressure and renal function. The applicant states that the safety data from the use of VCS demonstrates that these risks are dose-related, reversible, and can be managed by dose reduction and temporary interruption. Therefore, close monitoring of eGFR and blood pressure and dose modification as needed was included in the protocol to prevent and manage potential CNI-associated nephron toxicity.

AURA-LV (AUR-VCS-2012-01): A Randomized, Controlled Double-Blind Study Comparing the Efficacy and Safety of Voclosporin (23.7 mg BID, or 39.5 mg BID) with Placebo in Achieving Remission in Patients with Active Lupus Nephritis.

Methods

This was a phase II randomised controlled Double-Blind Study Comparing the Efficacy and Safety of Voclosporin (23.7 mg BID, or 39.5 mg BID) with Placebo in Achieving Remission in Patients with Active Lupus Nephritis.



Notes: It should be noted that in the study protocol, the day of randomization (which was also the first day of study drug) was referred to as Day 0; however, Day 1 is used throughout the clinical study report and all data presentations, including the tables, figures, and listings in Sections 14 and 16, with the exception of clinical laboratory parameters and vital signs where data was collected at every visit and windowed according to the SAP.
BID=Twice daily; IV=Intravenous; MMF=Mycophenolate mofetil; SAP=Statistical analysis plan.

Figure 6 Study design Aura LV

Study participants should be male or female subjects aged 18 to 75 with a diagnosis of SLE and with a histologic diagnosis of LN (ISN/RPS 2003 classification of LN) Classes III, IV or Class V, alone or in combination with Class III or IV and laboratory evidence of active nephritis at screening in need of high dose corticosteroids and immunosuppressive therapy.

Inclusion and exclusion criteria were in line with the pivotal phase 3 AURORA 1 study, except for the following: In the AURA-LV study, all subjects had to have a kidney biopsy performed within 6 months of screening. In the AURORA 1 study, in addition to subjects with biopsies within 6 months before screening, subjects with older biopsies up to 2 years before screening could also be eligible.

In the AURA-LV study an additional exclusion criteria of serum potassium >5.5 mmol/L at screening, and a medical history of pancreatitis or gastrointestinal haemorrhage within 6 months of screening or active unhealed peptic ulcer within 3 months of screening. AURORA 1 had an additional exclusion criterion on the use of live vaccines during the study.

Treatments

Study treatments administered during the study were as follows:

Treatment Arm	Randomization to Week 2 Visit	After Week 2 Visit
Arm A: low-dose VCS	23.7 mg VCS (3 capsules) BID in combination with MMF and oral corticosteroids	23.7 mg VCS (3 capsules) BID in combination with MMF and oral corticosteroids
Arm B: high-dose VCS	23.7 mg VCS (3 capsules) BID in combination with MMF and oral corticosteroids	39.5 mg VCS (5 capsules) BID in combination with MMF and oral corticosteroids
Arm C: low-dose placebo	3 capsules placebo BID in combination with MMF and oral corticosteroids	3 capsules placebo BID in combination with MMF and oral corticosteroids
Arm D: high-dose placebo	3 capsules placebo BID in combination with MMF and oral corticosteroids	5 capsules placebo BID in combination with MMF and oral corticosteroids

Notes: BID=Twice daily; MMF=Mycophenolate mofetil; VCS=Voclosporin.

Dose modification of VCS/placebo was permitted for tolerability reasons. A specific schedule was implemented for dose reduction with regards to decrease in kidney function or increase in blood pressure. In addition to VCS/placebo, all subjects received background standard of care with MMF and corticosteroids.

Objectives

Primary Objective:

To assess the efficacy of two doses of voclosporin (VCS) compared to placebo in achieving complete remission after 24 weeks of therapy in subjects with active LN.

Secondary Objectives:

To assess the safety and tolerability of two doses of VCS over 48 weeks compared to placebo in subjects with active LN.

To assess the efficacy of two doses of VCS versus placebo over 48 weeks in subjects with active LN

Primary Efficacy Endpoint: The primary efficacy endpoint was the number of subjects showing complete remission at Week 24, defined as follows:

- a confirmed decrease in proteinuria as defined by a UPCR of ≤0.5 mg/mg;

  AND

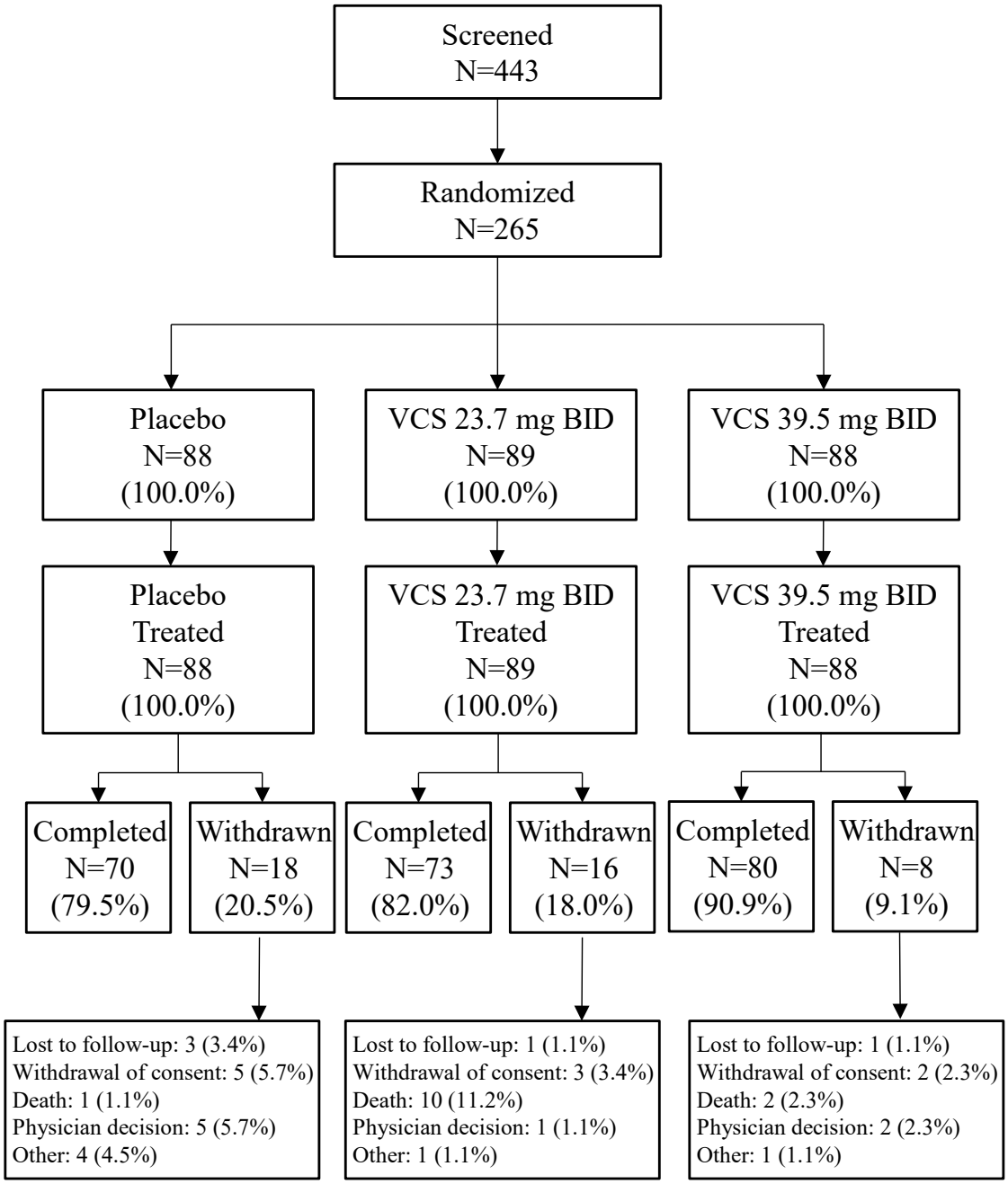
- no confirmed eGFR <60mL/min/1.73 m2 or no confirmed decrease from BL in eGFR of ≥20% (and without the use of rescue medications)

Secondary Efficacy Endpoints:

- Complete remission at Week 48 (confirmation of UPCR not required)
- Complete remission at Week 24 and Week 48 using 24-hour urine measurements (instead of FMV)
- Complete remission in the presence of low dose steroids at Week 24 (defined as complete remission and ≤5 mg prednisone for ≥8 weeks) and Week 48 (defined as complete remission (no UPCR confirmation required) and ≤5 mg prednisone for ≥12 weeks)
- Time to complete remission
- Time to sustained complete remission (defined as the first occurrence of complete remission that was sustained through Week 48)
- Time to (and proportion achieving) sustained early complete remission (defined as complete remission that occurred on or before Week 24 and was sustained through Week 48)
- Duration of complete remission (in months)
- Partial remission (defined as a 50% reduction in UPCR from BL) at Week24 and Week 48
- Time to partial remission
- Time to sustained partial remission (defined as the first occurrence of partial remission that was sustained through Week 48)
- Time to (and proportion achieving) sustained early partial remission(defined as partial remission that occurred on or before Week 24 and was sustained through Week 48) Change from BL in UPCR at Week 24 and Week 48
- Change from BL in eGFR, serum albumin, urine protein, and serum creatinine at each time point

Results

Participant flow



Notes: The number of deaths reported here does not include 3 additional deaths reported in the placebo group after study completion Notification of these deaths was received in a retrospective high-level safety follow-up post-study completion and incudes data received up to 11 April 2017.
The primary reasons for not completing the study recorded by the Investigator as "Other" were as follows: Placebo: subject refused follow-up visit, lack of efficacy, and protocol violation; Low-dose VCS: subject withdrew from study procedures; High-dose VCS: due to AE of glomerular filtration rate decreased.
AE=Adverse event; BID=Twice daily; VCS=Voclosporin.

Figure 7 Disposition of Study Subjects

Recruitment

The first subject was screened on 26 June 2014, the first subject was randomised on 03 September 2014, and the last subject visit for the study was on 06 January 2017.

Conduct of the study

The study was conducted in 79 centres in 20 countries in Europe, the Americas, and Asia.

The original version of the study protocol was issued, 12 July 2012. There were three (global) amendments, protocol version amendment 1.0, 15 October 2012, protocol version amendment 2.0, 05 March 2014 and protocol version amendment 3.0, 15 October 2014.

Table 11 Summary of Major Protocol Deviations (FAS, N=265)

Major Protocol Deviation	Placebo (N=88) n (%)	Voclosporin 23.7 mg BID (N=89) n (%)	Voclosporin 39.5 mg BID (N=88) n (%)
Any major protocol deviation	11 (12.5%)	11 (12.4%)	12 (13.6%)
Prohibited medication	1 (1.1%)	5 (5.6%)	5 (5.7%)
Oral steroid taper	4 (4.5%)	2 (2.2%)	2 (2.3%)
Oral steroid	2 (2.3%)	1 (1.1%)	1 (1.1%)
Baseline IV steroid	0 (0.0%)	0 (0.0%)	1 (1.1%)
Discontinued treatment	3 (3.4%)	1 (1.1%)	3 (3.4%)
Exclusion Criterion #3	0 (0.0%)	0 (0.0%)	1 (1.1%)
Inclusion Criterion #1	1 (1.1%)	1 (1.1%)	0 (0.0%)
Inclusion Criterion #4	0 (0.0%)	1 (1.1%)	0 (0.0%)
Inclusion Criterion #5	1 (1.1%)	0 (0.0%)	0 (0.0%)

Notes: Major protocol deviations were defined as deviations affecting subject eligibility to enter study and/or affecting efficacy endpoints. Steroid tapering deviations were considered major if the deviation did or reasonably could have affected inclusion criteria or key efficacy endpoints and/or safety. Prohibited medication deviations were considered major if the medication did or reasonably could have affected inclusion criteria or key efficacy endpoints and/or safety. It was considered a major deviation if in the 4 weeks prior to screening a subject changed ACE/ARB, or if in the 4 weeks prior to key efficacy endpoints a subject increased ACE/ARB. Use of ACE/ARB for <4 days was not considered a major protocol deviation.
Subjects can have more than 1 deviation
Exclusion Criterion #3: Currently taking a prohibited therapy.
Inclusion Criterion #1: Written informed consent.
Inclusion Criterion #4: Kidney biopsy within 6 months prior to screening.
Inclusion Criterion #5: Laboratory evidence of active nephritis.
ACE/ARB= Angiotensin converting enzyme inhibitor/angiotensin II receptor blocker; BID=Twice daily; FAS=Full analysis set; IV=Intravenous.

Baseline data

Table 12 Summary of Demography (FAS, N=265)

Demographic Variable	Placebo (N=88)	Voclosporin 23.7 mg BID (N=89)	Voclosporin 39.5 mg BID (N=88)	Total (N=265)
Age, years				
Mean (SD)	33.1 (10.03)	31.4 (11.78)	30.6 (9.59)	31.7 (10.53)
Median	32.0	28.0	28.0	30.0
Min/Max	18/65	18/66	18/62	18/66
Sex, n (%)				
Male	15 (17.0%)	13 (14.6%)	7 (8.0%)	35 (13.2%)
Female	73 (83.0%)	76 (85.4%)	81 (92.0%)	230 (86.8%)
Weight, kg				
Mean (SD)	65.0 (16.26)	62.5 (16.67)	66.3 (19.18)	64.6 (17.42)
Median	61.9	60.0	59.0	60.6
Min/Max	40/125	38/133	42/128	38/133
Race, n (%)				
White	42 (47.7%)	30 (33.7%)	36 (40.9%)	108 (40.8%)
Asian – Indian Subcontinent[1]	18 (20.5%)	22 (24.7%)	20 (22.7%)	60 (22.6%)
Asian – Other[1]	18 (20.5%)	30 (33.7%)	24 (27.3%)	72 (27.2%)
Black	5 (5.7%)	3 (3.4%)	6 (6.8%)	14 (5.3%)
American Indian or Alaska Native	3 (3.4%)	4 (4.5%)	2 (2.3%)	9 (3.4%)
Native Hawaiian or Other Pacific Islander	1 (1.1%)	0 (0.0%)	0 (0.0%)	1 (0.4%)
Missing	1 (1.1%)	0 (0.0%)	0 (0.0%)	1 (0.4%)
Ethnicity				
Hispanic or Latino	13 (14.8%)	9 (10.1%)	13 (14.8%)	35 (13.2%)
Not Hispanic or Latino	75 (85.2%)	80 (89.9%)	75 (85.2%)	230 (86.8%)

Table 13 Key Baseline Disease Characteristics (FAS, N=265)

	Placebo (N=88)	Voclosporin 23.7 mg BID (N=89)	Voclosporin 39.5 mg BID (N=88)	Total (N=265)
Time since initial LN diagnosis, years				
Mean (SD)	3.5 (4.03)	4.2 (5.14)	3.2 (4.36)	3.7 (4.54)
Median	1.2	1.7	1.4	1.4
Min/Max	0.1/16.7	0.1/31.7	0.1/27.8	0.1/31.7
Time since first significant proteinuria[1], years				
n	86	87	88	261
Mean (SD)	3.6 (4.06)	4.5 (5.53)	3.3 (4.22)	3.8 (4.66)
Median	1.4	1.8	1.5	1.6
Min/Max	0.1/17.7	0.1/31.7	0.1/25.8	0.1/31.7
Biopsy Class, n (%)				
Class V[2]	29 (33.0%)	33 (37.1%)	25 (28.4%)	87 (32.8%)
Pure Class V[3]	13 (14.8%)	12 (13.5%)	14 (15.9%)	39 (14.7%)
Class III/IV	59 (67.0%)	56 (62.9%)	63 (71.6%)	178 (67.2%)
All except Pure Class V[3]	75 (85.2%)	77 (86.5%)	74 (84.1%)	226 (85.3%)
Baseline eGFR (mL/min/1.73 m^2)				
n	82	83	82	247
Mean (SD)	100.2 (27.05)	95.3 (28.4)	104.0 (27.30)	99.8 (27.71)
Median	99.5	95.0	108.5	101.0
Min/Max	49.0/153.0	41.0/148.0	42.0/165.0	41.0/165.0
Baseline UPCR (mg/mg)				
n	87	89	88	264
Mean (SD)	4.43 (3.58)	5.16 (4.15)	4.48 (3.03)	4.69 (3.62)
Median	3.11	3.81	3.65	3.46
Min/Max	0.8/19.3	0.8/29.7	1.0/17.4	0.8/29.7
MMF at screening, n (%)				
Yes	32 (36.4%)	31 (34.8%)	29 (33.0%)	92 (34.7%)
No	56 (63.6%)	58 (65.2%)	59 (67.0%)	173 (65.3%)

1 Significant proteinuria defined as >0.5 g/24 hours or 0.5 mg/mg UPCR by first morning void.
2 Includes combination biopsy classes (i.e., III+V and IV+V) as well as pure Class V.
3 Determined post-hoc.
Notes: BID=Twice daily; eGFR=Estimated glomerular filtration rate; FAS=Full analysis set, LN=Lupus nephritis, Max=Maximum, Min=Minimum, MMF=Mycophenolate mofetil; UPCR=Urine protein creatinine ratio; SD=Standard deviation.
Baseline eGFR is defined in this table strictly as the mean of two values which were not available for 18 subjects.

Table 14 eGFR Category at Screening (FAS, N=265)

eGFR Category at Screening (mL/min/1.73 m^2)	Placebo N=88 n (%)	Voclosporin 23.7 mg BID N=89 n (%)	Voclosporin 39.5 mg BID N=88 n (%)
≥90	55 (62.5%)	49 (55.1%)	57 (64.8%)
≥60 to <90	28 (31.8%)	29 (32.6%)	25 (28.4%)
≥30 to <60	5 (5.7%)	11 (12.4%)	6 (6.8%)
<30	0 (0.0%)	0 (0.0%)	0 (0.0%)

Notes: BID=Twice daily; eGFR=Estimated glomerular filtration rate; FAS=Full analysis set.

Table 15 Summary of Prior and Current SLE Involvement (SS, N=265)

System Involvement	Placebo (N=88) n (%)	Voclosporin 23.7 mg BID (N=89) n (%)	Voclosporin 39.5 mg BID (N=88) n (%)
Mucocutaneous			
Ever involved	67 (76.1%)	74 (83.1%)	68 (77.3%)
Currently involved	32 (36.4%)	40 (44.9%)	28 (31.8%)
Musculoskeletal			
Ever involved	68 (77.3%)	74 (83.1%)	67 (76.1%)
Currently involved	38 (43.2%)	38 (42.7%)	34 (38.6%)
Hematology			
Ever involved	48 (54.5%)	62 (69.7%)	50 (56.8%)
Currently involved	28 (31.8%)	45 (50.6%)	28 (31.8%)
Cardiorespiratory			
Ever involved	30 (34.1%)	21 (23.6%)	19 (21.6%)
Currently involved	12 (13.6%)	8 (9.0%)	9 (10.2%)
Vasculitis			
Ever involved	8 (9.1%)	15 (16.9%)	15 (17.0%)
Currently involved	3 (3.4%)	8 (9.0%)	7 (8.0%)
Antiphospholipid Syndrome			
Ever involved	9 (10.2%)	10 (11.2%)	13 (14.8%)
Currently involved	8 (9.1%)	10 (11.2%)	6 (6.8%)
Neurological			
Ever involved	10 (11.4%)	9 (10.1%)	9 (10.2%)
Currently involved	1 (1.1%)	3 (3.4%)	5 (5.7%)

Notes: BID=Twice daily; SLE=Systemic lupus erythematosus; SS=Safety set.

Table 16 Summary of Prior LN Treatment (SS, N=265)

Medication Prior Use: Yes	Placebo (N=88) n (%)	Voclosporin 23.7 mg BID (N=89) n (%)	Voclosporin 39.5 mg BID (N=88) n (%)
Corticosteroids	79 (89.8%)	82 (92.1%)	76 (86.4%)
Antimalarial	58 (65.9%)	58 (65.2%)	49 (55.7%)
MMF	39 (44.3%)	43 (48.3%)	39 (44.3%)
IVC	40 (45.5%)	36 (40.4%)	31 (35.2%)
Azathioprine	34 (38.6%)	28 (31.5%)	39 (44.3%)
Methotrexate	5 (5.7%)	7 (7.9%)	3 (3.4%)
Biologic	4 (4.5%)	4 (4.5%)	9 (10.2%)
CNI	3 (3.4%)	3 (3.4%)	7 (8.0%)
Other	12 (13.6%)	15 (16.9%)	8 (9.1%)

Notes: Prior LN treatments were defined as any LN treatment taken prior to the first dose of study drug.
BID=Twice daily; CNI=Calcineurin inhibitor; IVC=Intravenous cyclophosphamide; LN=Lupus nephritis; MMF=Mycophenolate mofetil; SS=Safety set.

Table 17 Randomisation According to GDP Subgroup (FAS, N=265)

GDP Subgroup of Countries	Placebo (N=88) n (%)	Voclosporin 23.7 mg BID (N=89) n (%)	Voclosporin 39.5 mg BID (N=88) n (%)
Low-GDP[1]	28 (31.8%)	42 (47.2%)	33 (37.5%)
Non-Low-GDP[2]	60 (68.2%)	47 (52.8%)	55 (62.5%)
Chi^2 p-value vs. placebo for imbalance in low-GDP vs. non-low-GDP		p=0.0365	0.4284

1 Includes Bangladesh, Sri Lanka, and the Philippines.
2 Countries excluding the low-GDP subgroup (i.e., excluding Bangladesh, Sri Lanka, and the Philippines).
Note: BID=Twice daily; FAS=Full analysis set; GDP=Gross Domestic Product.

Numbers analysed

Table 18 Summary of Analysis Sets - All Subjects Randomised (N=265)

Analysis Set	Placebo (N=88) n (%)	Voclosporin 23.7 mg BID (N=89) n (%)	Voclosporin 39.5 mg BID (N=88) n (%)	Total (N=265) n (%)
Screened	–	–	–	443
Randomized	88 (100.0%)	89 (100.0%)	88 (100.0%)	265 (100.0%)
SS (All subjects treated)	88 (100.0%)	89 (100.0%)	88 (100.0%)	265 (100.0%)
FAS	88 (100.0%)	89 (100.0%)	88 (100.0%)	265 (100.0%)
mITT	88 (100.0%)	100 (112%)	77 (87.5%)	265 (100.0%)
PPS	77 (87.5%)	78 (87.6%)	76 (86.4%)	231 (87.2%)

Notes: The SS was defined as all randomized subjects who received at least 1 dose of study drug.
The FAS was defined as all randomized subjects who received at least 1 dose of study drug and had 1 post-baseline assessment.
The PPS was defined as all subjects in the FAS who had no major protocol deviations (although for assessment of the Week 24 primary endpoint analysis, subjects with protocol violations after the Week 24 assessment were not excluded).
The mITT was derived from the FAS; however, subjects who were randomized to high-dose voclosporin (39.5 mg BID) but were prescribed this dose level for less than 14 days were analyzed in the low-dose voclosporin (23.7 mg BID) group.
BID=Twice daily; FAS=Full analysis set; mITT=Modified intent-to-treat; PPS=Per-protocol set; SS=Safety set.

Outcomes and estimation

Primary Efficacy Endpoint: Complete Remission at Week 24 (FAS)

For the primary analysis, the logistic regression included adjustment for the randomisation stratification factors of biopsy classification (Class V only (pure and mixed) versus Others) and MMF use at screening.

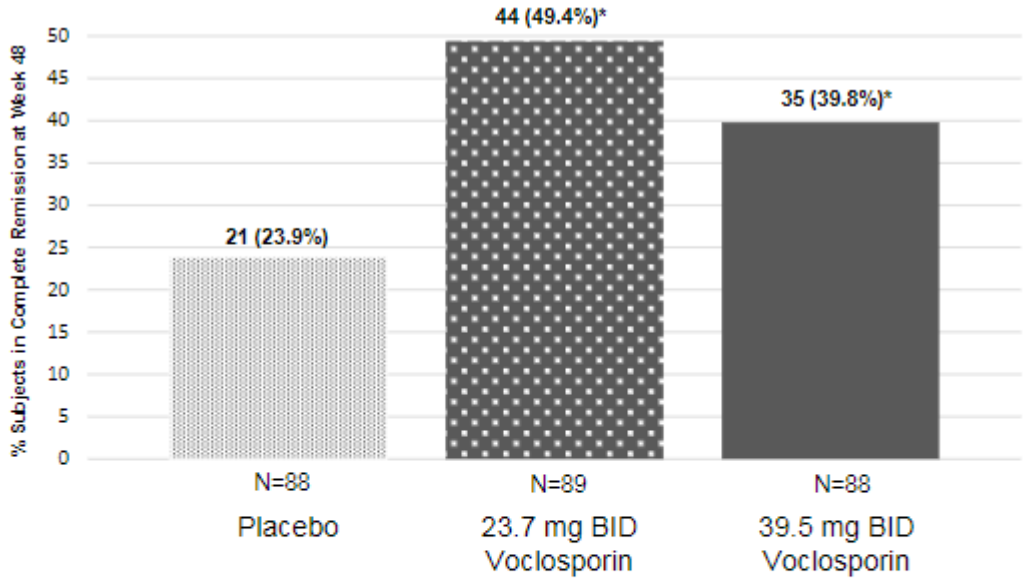
Table 19 Summary of Subjects with Complete Remission at Week 24 – Primary Endpoint Logistic Regression Analysis (FAS)

	Placebo (N=88)	Voclosporin 23.7 mg BID (N=89)	Voclosporin 39.5 mg BID (N=88)
Complete Remission at Week 24, n (%)			
Yes	17 (19.3%)	29 (32.6%)	24 (27.3%)
No	71 (80.7%)	60 (67.4%)	64 (72.7%)
Adjusted OR			
OR (95% CI) vs. placebo	–	2.03 (1.01, 4.05)	1.59 (0.78, 3.27)
p-value vs. placebo	–	0.045*	0.204
OR (95% CI) vs. voclosporin 23.7 mg BID	–	–	0.75 (0.39, 1.47)
p-value vs. voclosporin 23.7 mg BID	–	–	0.405
Unadjusted OR (sensitivity analysis)			
OR (95% CI) vs. placebo	–	2.02 (1.01, 4.03)	1.57 (0.77, 3.18)
p-value vs. placebo	–	0.046*	0.214
OR (95% CI) vs. voclosporin 23.7 mg BID	–	–	0.78 (0.41, 1.48)
p-value vs. voclosporin 23.7 mg BID	–	–	0.441

* Indicates a statistically significant difference ($p<0.05$).
Notes: ORs were generated from a logistic regression model. Adjusted models were adjusted for the randomization stratification factors of biopsy classification (Class V (pure or mixed) only vs. Others) and MMF use at screening. An OR >1 indicates that the odds of remission are greater for voclosporin than for placebo.
BID=Twice daily; CI=Confidence interval; FAS=Full analysis set; MMF=Mycophenolate mofetil; OR=Odds ratio.

Secondary Efficacy Endpoint Analyses of the Primary Efficacy Parameter of Complete Remission

Complete Remission at Week 48 (FAS)



	OR vs. Placebo	95% CI	p-value
23.7 mg BID Voclosporin	3.21	1.68, 6.13	<0.001*
39.5 mg BID Voclosporin	2.10	1.09, 4.02	0.026*

* Indicates a statistically significant difference in a logistic regression analysis comparing the OR for achievement of complete remission at Week 48 with voclosporin vs. placebo treatment ($p<0.05$).

Notes: ORs were generated from a logistic regression model adjusted for the randomization stratification factors of biopsy classification (Class V (pure and mixed) only vs. Others) and MMF use at screening. An OR >1 indicates that the odds of remission are greater for voclosporin than for placebo.

Complete remission was defined as a decrease in proteinuria (UPCR ≤0.5 mg/mg) and no eGFR <60 mL/min/1.73 m² or no decrease from baseline in eGFR of ≥20% at Week 48 (in the absence of rescue medication).

BID=Twice daily; CI=Confidence interval; eGFR=Estimated glomerular filtration ate; FAS=Full analysis set; MMF=Mycophenolate mofetil; OR=Odds ratio; UPCR=Urine protein creatinine ratio.

Figure 8 Complete Remission at Week 48 (FAS)

Complete remission occurred earlier in subjects treated with either low-dose or high-dose voclosporin compared to placebo (HR=2.26; 95% CI: 1.45, 3.51 for low-dose voclosporin and HR=2.25; 95% CI: 1.46, 3.47 for high-dose voclosporin). The median time to complete remission was 19.7 weeks in the low-dose voclosporin group and 23.4 weeks in the high-dose voclosporin group. The median time to complete remission in the placebo group was not calculable as the placebo curve did not reach probability of 0.5.

Difference between regions in demographic and baseline characteristics

Table 20 Differences between regions in demographic and baseline characteristics – low-GDP countries vs others (FAS)

Characteristic	Low-GDP Subgroup[1]	Non-Low-GDP Subgroup[2]		
	Bangladesh Sri Lanka Philippines N=103	Asia (Other)[3] N=27	Europe[4] N=84	Americas[5] N=51
Mean (SD) age, years	27.3 (8.40)	31.6 (10.47)	36.2 (11.30)	33.2 (9.76)
Female, %	89%	85%	82%	90%
Mean (SD) weight, kg	55.3 (11.56)	59.8 (12.46)	70.7 (16.43)	75.7 (20.60)
Mean (SD) duration since LN diagnosis (years)	2.4 (2.86)	5.1 (4.31)	3.6 (5.11)	5.7 (5.51)
Mean (SD) UPCR, mg/mg	5.4 (4.23)	4.1 (2.81)	4.4 (2.94)	4.0 (3.49)
Mean (SD) serum albumin, g/dL	2.7 (0.93)	2.9 (0.60)	3.3 (0.74)	3.2 (0.60)

1 Countries with GDP at the lower end of the GDP spectrum are referred to as "low-GDP" in this report.
2 Countries excluding the low-GDP subgroup.
3 Includes Hong Kong, Korea, Singapore, Taiwan, and Thailand.
4 Includes Belarus, Bulgaria, Georgia, Poland, Russia, Serbia, Spain, Ukraine.
5 Includes Ecuador, Guatemala, Mexico, USA.
Notes: FAS=Full analysis set; GDP=Gross domestic product; LN=Lupus nephritis; SD=Standard deviation; UPCR=Urine protein creatinine ratio.

Deaths

In total, 13 subjects (4.9% of the total study population) died during the study. The frequency of deaths was higher in the low-dose VCS treatment group (10 (11.2%) subjects) compared to either the high-dose VCS (2 (2.3%) subjects) or placebo (1 (1.1%) subject) treatment group. None of the deaths were considered related to study drug by the Investigators. A review of the deaths revealed that all but one death in the placebo group and one death in the low-dose VCS group occurred within the low-GDP subgroup; 54% (7/13) of all deaths occurred in two sites in Bangladesh. The causes of death were multi-factorial including sepsis and other lupus related complications. The majority of the deaths (69% (9/13)) occurred during the first few weeks of initiation of treatment with study drug. A dose relationship could not be established for the deaths.

After in-depth review of extensive post-hoc data analyses, the DSMB concluded that the higher incidence of deaths in the low-dose VCS group was attributable to factors predisposing subjects to fatal outcomes in the study and local imbalances in randomisation. The subjects who died had more severe renal disease, with clinical and laboratory features consistent with malnutrition and other comorbidities at BL. Key BL characteristics, independent of treatment group, that were shown to have a statistically significant association with an outcome of death were UPCR >5 mg/mg, low serum albumin (<2 mg/dL), high lymphocytes (>1.8 x 109/L), high diastolic blood pressure (>85 mmHg), elevated pulse (>90 bpm) and enrolment from low-GDP countries (Bangladesh, Sri Lanka and the Philippines).

2.5.5.2. Main studies

AURORA 1 (AUR-VCS-2016-01) 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

Methods

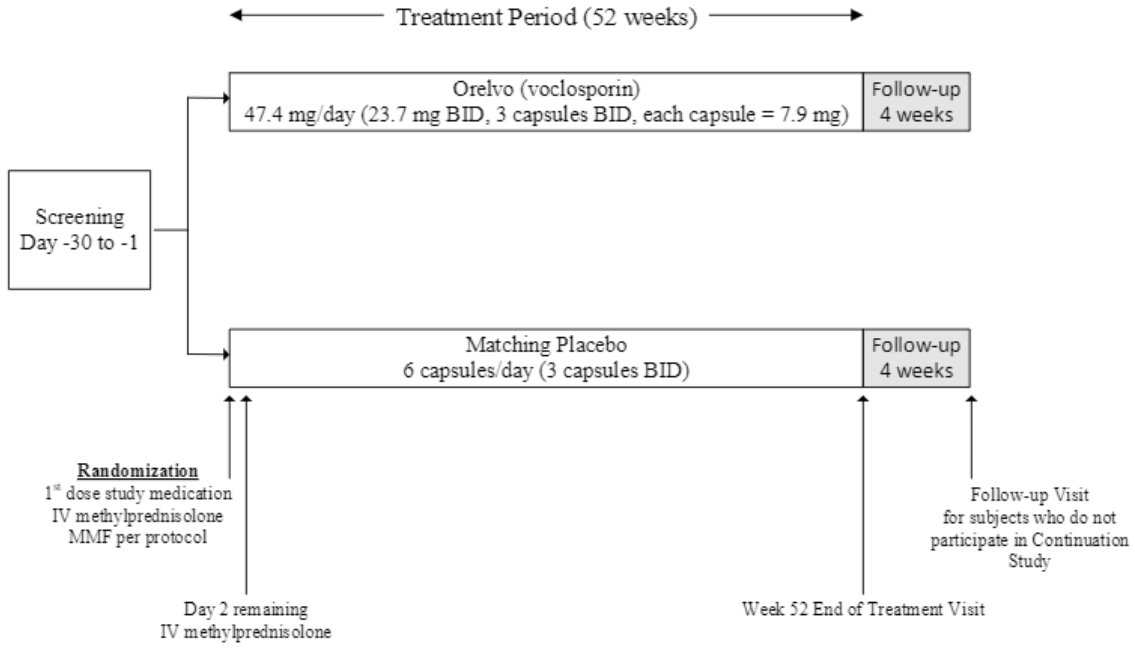


Figure 9 Study Design Aurora 1

AURORA 1 was a randomised, double-blind, parallel-group, placebo-controlled, multicentre, 2-arm study of voclosporin versus matching placebo. Voclosporin at a dose of 23.7 mg BID or matching placebo were administered for 52 weeks with a background therapy of MMF and corticosteroids with a tapering schedule.

Study Participants

Inclusion Criteria

Subjects were eligible for the study if they met all the following inclusion criteria:

Written informed consent before any study-specific procedures were performed.

Male or female subjects with a minimum age of 18 (or legal age of consent if >18 years) to 75 years of age, inclusive, at the time of screening (Visit 1).

Previous diagnosis of SLE according to the American College of Rheumatology criteria (1997).

Subjects with evidence of active nephritis, defined as follows:

Kidney biopsy result within 2 years prior to screening indicating Class III, IV-S, IV-G (alone or in combination with Class V), or Class V LN with a doubling or greater increase of UPCR within the previous 6 months to a minimum of ≥1.5mg/mg for Class III/IV or to a minimum of ≥2 mg/mg for Class V at screening. Biopsy results over 6 months prior to screening had to be reviewed with a medical monitor to confirm eligibility.

OR

Kidney biopsy result within 6 months prior to screening indicating Class III, Class IV-S, or Class IV-G (alone or in combination with Class V) LN with a UPCR of ≥1.5 mg/mg at screening.

OR

Kidney biopsy result within 6 months prior to screening indicating Class V LN and a UPCR of ≥2 mg/mg at screening.

5. In the opinion of the Investigator, subject required high-dose corticosteroids and immunosuppressive therapy.

6. Subject was willing to take oral MMF for the duration of the study, either by continuing current MMF therapy or by initiating it on or before the baseline visit.

7.Women of childbearing potential had to have a negative serum pregnancy test at screening and a negative urine pregnancy test at baseline. Two effective forms of contraception had to be used simultaneously unless abstinence was the chosen method. Subjects had to use effective contraception during the study

Exclusion Criteria

Subjects were excluded from participation if any of the following exclusion criteria were met:

Subjects unable or unwilling to give written informed consent and/or to comply with study procedures.

eGFR as calculated by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation of ≤45 mL/min/1.73 m2 at screening confirmed before randomisation.

Was currently taking or known need for any of the medications listed in Protocol Section 7.8 at screening or during the study. This included prohibited medications prior to screening.

Was currently requiring renal dialysis (haemodialysis or peritoneal dialysis) or was expected to require dialysis during the study period.

A previous kidney transplant or planned transplant within study treatment period.

Any known hypersensitivity or contraindication to MMF, mycophenolic acid, cyclosporine, corticosteroids, or any components of these drug products.

Had current or medical history of:

Congenital or acquired immunodeficiency.

In the opinion of the Investigator, clinically significant drug or alcohol abuse within 2 years prior to screening.

Malignancy within 5 years of screening, with the exception of basal and squamous cell carcinomas treated by complete excision. Subjects with cervical dysplasia that was cervical intraepithelial neoplasia 1 but had been treated with conisation or loop electrosurgical excision procedure and had a normal repeat Papanicolaou test were allowed.

Lymphoproliferative disease or previous total lymphoid irradiation.

Severe viral infection (e.g., cytomegalovirus, hepatitis B virus, hepatitis C virus) within 3 months of screening; or known human immunodeficiency virus infection. Severe viral infection was defined as active disease requiring antiviral therapy.

Active tuberculosis or known history of tuberculosis/evidence of old tuberculosis if not taking prophylaxis with isoniazid.

Other known clinically significant active medical conditions such as:

Severe cardiovascular disease including congestive heart failure, history of cardiac dysrhythmia or congenital long QT syndrome. QTcF exceeding 480 msec in the presence of a normal QRS interval (<110 msec) at time of screening resulted in exclusion.

Liver dysfunction (aspartate aminotransferase (AST), alanine aminotransferase (ALT), or bilirubin ≥2.5 times the upper limit of normal) at screening and, if abnormal at screening, then confirmed that the levels had returned to <2.5 times upper limit of normal before randomisation.

Chronic obstructive pulmonary disease or asthma requiring oral steroids.

Bone marrow insufficiency unrelated to active SLE (according to Investigator judgment) with white blood cell count <2,500/mm3; absolute neutrophil count (ANC) <1.3 × 103/μL; thrombocytopenia (platelet count <50,000/mm3).

Active bleeding disorders.

Had current infection requiring IV antibiotics.

Any overlapping autoimmune condition for which the condition or the treatment of the condition may have affected the study assessments or outcomes (e.g., scleroderma with significant pulmonary hypertension; any condition for which additional immunosuppression was indicated). Overlapping conditions for which the condition or treatment was not expected to affect assessments or outcomes (e.g., Sjögren's syndrome) were not excluded.

No vaccines using live organisms, virus or bacterial, were allowed during screening and while taking the study treatment.

Other major physical or psychiatric illness or major traumatic injury within 6 months prior to screening that may have affected study conduct or interfered with study assessments or outcome.

Any other medical condition which, in the Investigator's judgment, may have been associated with increased risk to the subject or may have interfered with study assessments or outcomes.

Subjects who were pregnant, breast feeding or, if of childbearing potential, not using adequate contraceptive precautions.

Participation in another clinical study within 4 weeks prior to screening and/or receipt of investigational drugs within 4 weeks or 5 half-lives of the drug (whichever was longer) prior to screening.

Subject was randomised and treated in a previous voclosporin clinical study.

Treatments

Voclosporin was orally administered at a dose of 23.7 mg BID given as three 7.9 mg soft gel capsules per dose for 52 weeks. Matching placebo soft gel capsules were orally administered at a dose of 3 capsules BID for 52 weeks.

Doses were taken with water on an empty stomach every 12 hours or as close to a 12-hour schedule as possible, with a minimum of 8 hours between doses. If the subject missed a dose of study treatment by less than 4 hours from the anticipated dosing time, the missed dose was to be taken immediately. The next dose was to be taken at the originally scheduled time. If a missed dose of study treatment was greater than 4 hours from the expected dosing time, the subject skipped the dose and took the next dose at the originally scheduled time.

All participants received concomitant MMF and corticosteroids.

Corticosteroid treatment

Table 21 Dosing Schedule for IV Methylprednisolone and Daily Oral Prednisone (mg)

	Subjects <45 kg	Subjects ≥45 kg	In Case of Prior IV Steroids During Screening (Pre-randomization)
Weeks 1-2[1]			
Days 1-2[2]	0.25 g (IV)	0.5 g (IV)	1 g minus prior IV steroids mg or (0.5 g minus prior IV steroids mg for subjects who weigh <45 kg)[3]
Days 3-13	20 mg (oral)	25 mg (oral)	
Week 2 (Day 14)	15 mg (oral)	20 mg (oral)	
Week 4 (Day 28)	10 mg (oral)	15 mg (oral)	
Week 6 (Day 42)[4]	10 mg (oral)	10 mg (oral)	
Week 8 (Day 56)	5 mg (oral)	5 mg (oral)	
Week 12 (Day 84)	5 mg (oral)	5 mg (oral)	
Week 16 (Day 112)	2.5 mg (oral)	2.5 mg (oral)	

1 Day 0-13: Oral steroids dosed according to subject weight and then tapered beginning at Day 14.
2 Oral corticosteroids may be commenced on Days 1 or 2 if corticosteroids are administered during screening.
3 It is recognized that dosing with IV methylprednisolone as described in Section 7.2.2.2, Corticosteroids may not be in the subject's best interest if they have already received therapy within the 3 months prior to screening. In this case, the Investigator may be permitted to omit the administration of further IV methylprednisolone but only after discussion with the Medical Monitor.
4 Week 6 is not a scheduled study visit, a phone call can be performed to decide further tapering for subjects.

Subjects with a lack of response were allowed one 4-week interval without dose reduction or one dose escalation to the previous dose for 2 weeks at any time during the study. Lack of response was defined as no or minimal change in UPCR per Investigator judgment over 3 visits or deterioration in UPCR not meeting the criteria for withdrawal. All deviations from the prescribed dosing schedule had to be discussed with the Medical Monitor and documented in the source notes and eCRF.

Mycophenolate Mofetil treatment

Subjects who were receiving MMF prior to randomisation continued without interruption. Subjects on azathioprine or mycophenolate sodium at screening were switched to MMF at baseline (Day 1). For subjects who were not already taking prescribed MMF prior to randomisation, the dosing of MMF started at 0.5 g BID for a total daily dose of 1 g/day for the first week, increasing to 1 g BID for a total daily dose of 2 g/day for the second and subsequent weeks (i.e., beginning on Day 8). A stable dose of MMF was to be maintained throughout the study. Dose changes or interruptions were permitted for clearly documented safety reasons only, including gastrointestinal disturbance and decreases in absolute neutrophil count.

Discontinuation from Study Treatment Due to Early Non-response to Therapy

Subjects could be discontinued from study treatment if their early disease response was suboptimal if the subject meets 1 of the 2 following criteria:

After 12 weeks of treatment, the subject shows a >30% decrease from baseline value in CKD-EPI eGFR in 2 successive measurements separated by at least 4 weeks

After 8 weeks of treatment, the subject shows a confirmed reduction in UPCR of ≤25% assessed by 2 consecutive measurements at least 2 weeks apart

Objectives

Primary Objective:

To assess the efficacy of voclosporin compared with placebo in achieving renal response after 52 weeks of therapy in subjects with active lupus nephritis (LN)

Secondary Objective:

To assess the safety and tolerability of voclosporin over 52 weeks compared with placebo in subjects with active

Outcomes/endpoints

Primary Endpoint:

The primary efficacy endpoint was the number of subjects showing renal response at Week 52. Renal response was adjudicated based on blinded data by the CEC based on meeting the following criteria:

UPCR of ≤0.5 mg/mg, and

eGFR ≥60 mL/min/1.73 m2 or no confirmed decrease from baseline in eGFR of >20%, and

Received no rescue medication for LN, and

Did not receive more than 10 mg prednisone for ≥3 consecutive days or for ≥7 days in total during Weeks 44-52, just prior to the renal response assessment.

Subjects who withdrew from the study prior to the Week 52 assessment were defined as non-responders.

Note: To be disqualified from renal response, the subject had to fail both eGFR measures (i.e., confirmed eGFR <60 mL/min/1.73 m2 AND confirmed >20% drop from baseline) and have an associated treatment-related or disease-related AE that impacted eGFR.

Key Secondary Endpoints:

- Time to UPCR of ≤0.5 mg/mg

- Renal response at Week 24 (based on definition of primary endpoint)
- Partial renal response, defined as 50% reduction from baseline in UPCR, at Weeks 24 and 52
- Time to 50% reduction in UPCR from baseline

Other Secondary Endpoints:

Duration of UPCR ≤0.5 mg/mg

Proportion of subjects experiencing a confirmed >30% decrease from baseline in eGFR at each time point

Change from baseline in UPCR at each time point

Change from baseline in urine protein, serum creatinine and eGFR

Change from baseline in immunology parameters (C3, C4 and anti-dsDNA) at Weeks 24 and 52

Renal response with low-dose steroids (defined as renal response in the presence of corticosteroids of ≤2.5 mg/day between Weeks 16 to 24 and Weeks 44 to 52)

Change from baseline in Safety of Estrogens in Lupus Erythematosus National Assessment - Systemic Lupus Erythematosus Disease Activity Index (SELENA-SLEDAI) score at Weeks 24 and 52

Change from baseline in health-related quality of life (HRQoL) at Weeks 12, 24, and 52

Health Resource Utilisation at Weeks 24 and 52

Sample size

The planned sample size was 324 subjects (162 subjects per treatment arm) based on a two-group continuity-corrected Chi squared test with a 0.05 two-sided significance level and 80% power. The assumptions made at the planning stage were a placebo response rate of 20.0% and a voclosporin response rate of 34.4%. Adjustment of sample size for withdrawals was not planned since subjects withdrawing for any reason were to be counted as non-responders in the primary analysis.

Randomisation and Blinding (masking)

All subjects meeting eligibility criteria were randomised at baseline/Day 1 (Visit 2) in a ratio of 1:1 to receive either voclosporin 23.7 mg BID or matching placebo using an interactive web response system (IWRS). Randomisation was stratified by biopsy class (Class V versus Others) and prior MMF use at screening (yes versus no). Region was used as a blocking factor to ensure balance within each region: North America, Latin America, Europe/South Africa, and Asia Pacific. According to the applicant, regional differences were not expected and blocking by region was more for drug distribution reasons. As a sensitivity analysis the primary endpoint analysis was repeated omitting region from the model; the impact on the point estimate for the difference was shown to be only minor.

Study AUR-VCS-2016-01 had a double-blind design and voclosporin and placebo were to be identical in taste, smell, and appearance. All study personnel and subjects were to be blinded to study treatment until the end of the study. In case of emergency, there was an unblinding process in place with procedures for unblinding provided in a separate manual. It has been reported that the blind was broken for only one patient (in the placebo arm).

A Clinical Endpoints Committee (CEC) adjudicated renal response by reviewing blinded data. The working procedures and responsibilities of the CEC was described in a separate charter document. The submitted AURORA 1 CEC Charter was version Draft V2 dated 03 July 2019. Changes made compared to any earlier version was not described. Upon request, the applicant clarified that renal response was to be reviewed once a subject had completed the study. This was expected to occur on an ongoing

basis between July 2019 and the database lock in November 2019, but as has been explained, the actual CEC review did not start before mid-October. With this clarification along with the confirmation that the CEC charter dated 03 July 2019 is the final version, a concern for that CEC adjudications could have been performed based on different instructions is alleviated.

Statistical methods

All statistical analyses were performed at study closure and incorporated all Week 24 and Week 52 endpoints. There were no interim analyses planned and none was performed.

Details of the statistical analysis were provided in a Statistical Analysis Plan (SAP). The AUR-VCS-2016-01 SAP version 5.0 (dated 21 Oct 2019) contained an amendment history describing revisions/additions made before database lock (01 November 2019) and their rational.

The primary analysis population was the intent-to-treat (ITT) population consisting of all randomised subjects. Analyses were based on the treatment to which the subject had been randomised.

Primary endpoint

The primary endpoint was the number of subjects with renal response week 52 based on pre-defined criteria (see above) and adjudicated by the CEC).

The CEC was also to consider the following:

• Subjects who withdraw from the study prior to the Week 52 assessment and provide insufficient week 52 data to determine response will be defined as non-responders. Subjects who discontinued study drug but continued to attend study visits (as was the expectation) were to have their data assessed for response.

• eGFR values eliminating a subject from complete remission should be accompanied by a treatment or disease-related treatment-emergent adverse event (TEAE) that impacts eGFR.

An estimand was defined with SAP version 3.0 (March 2019).

Intercurrent events included:

• Treatment discontinuation for any reason
o the subject remains on study allowing the primary endpoint to be assessed at 1 year.

• Study discontinuation
o resulting in insufficient information at 1 year to ascertain response status leading to assumed non-response.
• Rescue medication taken at any time prior to the primary assessment at 1 year
o results in non-response. Rescue medication is adjudicated by the Clinical Endpoints Committee.

• Death at any time prior to the 1-year primary assessment
o results in assumed non-response.

Primary endpoint analysis

Renal response week 52 was analysed using logistic regression. The logistic regression model included terms for treatment, baseline UPCR, biopsy class, MMF use at baseline and region. The proportion of subjects achieving renal response at Weeks 52 were summarised by treatment group and the comparison between treatments was displayed with the odds ratio, a 2-sided 95% CI and the p-value.

Subjects who withdraw from the study prior to the Week 52 assessment were defined as non-responders.

Sensitivity analyses of the primary endpoint

The primary endpoint was analysed based on the ITT population using two different logistic regression models; one including only a term for treatment and the other including terms for treatment, baseline UPCR, biopsy class and MMF use at baseline, i.e., omitting the regional covariate. The odds ratios, 95% confidence intervals and p-values for voclosporin compared to placebo were reported.

In addition, a number of subgroup analyses were defined to be based on age (≤30 versus >30), gender, race (White, Asian, Other), biopsy class, region (defined at the continental level and, where numbers allow, country level), MMF use at screening, and Maximum MMF Dose (≤2g versus >2g).

Supplementary analyses based on the primary endpoint

A number of supplementary analyses were planned and have been presented.

• Renal response at Week 52 was derived programmatically and analysed in an identical fashion to the primary analysis. All components of the primary response endpoint were independently programmed apart from the use of rescue medication for which the CEC adjudication was used and incorporated into the programmed endpoint.

• The primary endpoint analysis was repeated for the per protocol analysis set.

• The primary endpoint analysis was repeated for each biopsy class category (Class III, Class III/V, Class IV, Class IV/V, Class V and Class VI). A separate category defined as "All but Pure Class V" was also to be defined.

• For both the adjudicated week 52 renal response (primary endpoint) and the programmed week 52 renal response (supplementary endpoint), each individual component (and some component groups) of the endpoint was to be summarised by treatment group and analysed in the same manner using a logistic regression.

Tipping point analysis for primary endpoint

The impact of withdrawals on the primary endpoint was investigated in a tipping point analysis.

Key secondary endpoints

Key secondary binary endpoints were analysed in a similar manner to the primary endpoint and endpoints measured as a time-to-event were displayed using Kaplan-Meier methodology. Comparisons between voclosporin and placebo were performed using a log rank test and Cox proportional hazard regression.

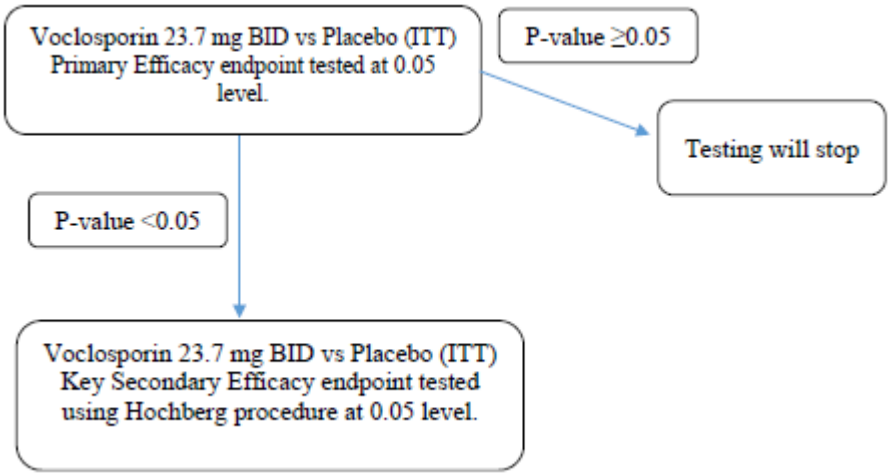
Other secondary endpoints

Continuous (/change from baseline) endpoints have been analysed using Mixed Effect Model Repeated Measures (MMRM) based on a model including terms for treatment, visit, treatment by visit interaction and baseline.

Multiplicity

An overall type 1 error rate of 5% for the primary and key secondary efficacy endpoints was to be maintained; the Hochberg step-up procedure was used to adjust for multiple comparisons amongst key secondary endpoints, see figure below.

Hochberg procedure



Post-hoc analyses in reply to CHMP advice

Regarding the eGFR assessment, the applicant was strongly recommended (CHMP advice, EMEA/H/SA/3483/1/2017/SME/III) to remove the ">60 ml/min/1.73m2" component from the definition of stable renal function and instead define it solely on an acceptable confirmed % reduction in eGFR, preferably < 10-15% and using different cut-offs for confirmed %reduction in eGFR as part of sensitivity analyses. The criterion for eGFR ⩾60 mL/min/1.73 m2 was retained and post-hoc analyses using no confirmed decrease from baseline >10%/>15%/>20% in corrected eGFR, respectively were conducted.

Results

Participant flow

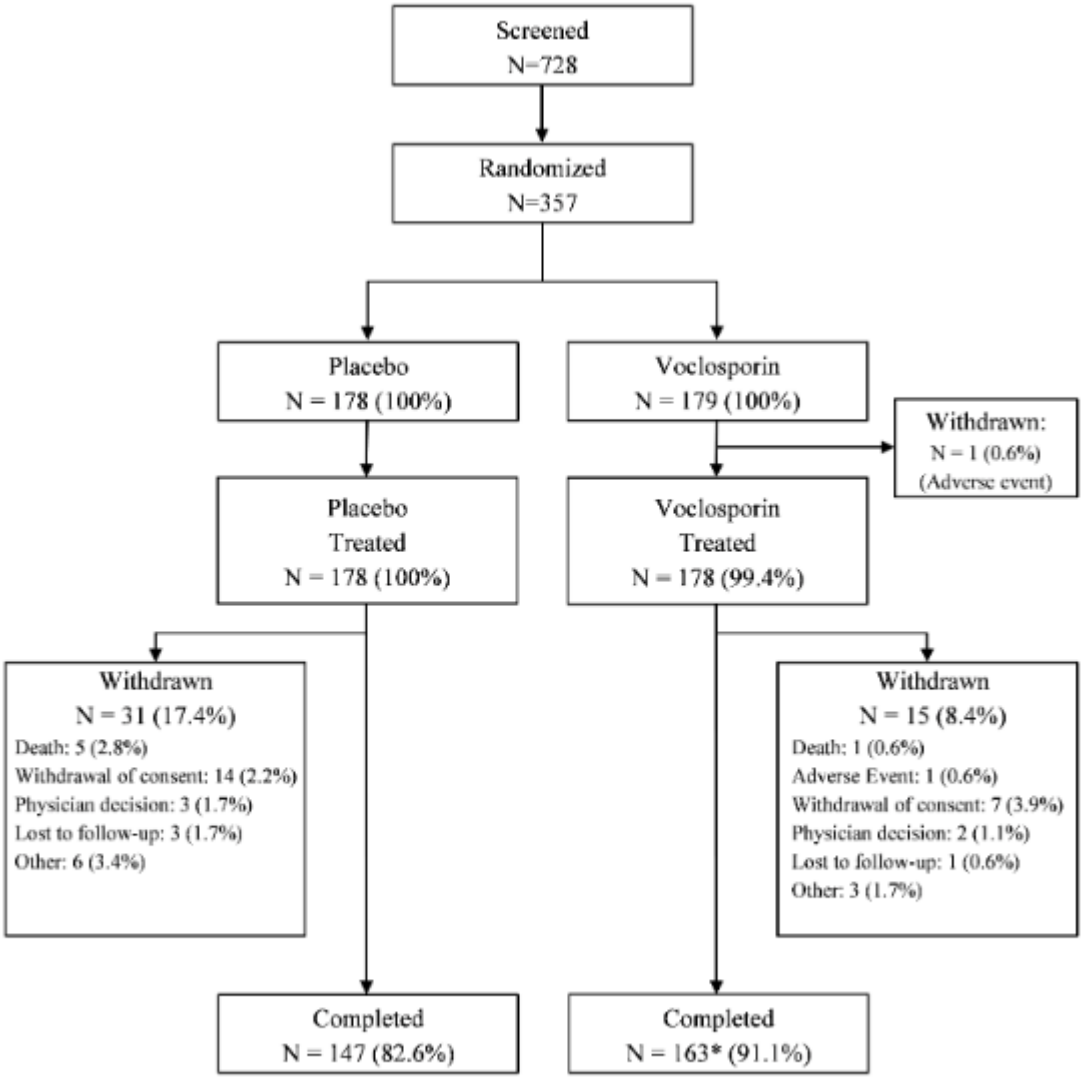


Figure 10 Study Participant flow AURORA 1

The most common reason for screen failure was a lack of evidence of active nephritis. A total of 357 eligible subjects were randomised into the study: 178 to the placebo arm and 179 to the voclosporin arm. A large number of subjects entered screening towards the end of the study. They were permitted to complete screening and enrol if eligible, hence the total number of subjects was greater than planned. Overall, 309 subjects (86.6%) completed the study, with more subjects in the voclosporin arm (162 subjects [90.5%]) than the placebo arm (147 subjects [82.6%]) reaching Week 52.

Study treatment was discontinued in 59 subjects (33.1%) in the placebo arm and 43 subjects (24.0%) in the voclosporin arm. The most common reason for study treatment discontinuation was intolerable AE, recorded for a similar number of subjects in each arm (24 subjects [13.5%] in the placebo arm and 23 subjects [12.8%] in the voclosporin arm). More subjects in the placebo arm discontinued study treatment due to lack of efficacy than in the voclosporin arm (11 [6.2%] and 4 [2.2%] subjects, respectively).

Recruitment

First subject enrolled: 17 May 2017

Last subject last visit: 10 October 2019

Conduct of the study

The study was conducted in 142 centres in 27 countries in North America, Latin America, Europe, South Africa and Asia.

The original protocol was finalised on 01 December 2016 and the protocol was amended once during the study (protocol Version 2, 04 May 2017).

The key changes were:

The time point for the primary efficacy endpoint of renal response was changed from Week 24 to Week 52, based on data from other clinical studies (see Section 9.2) and feedback from regulatory authorities. Renal response at Week 24 was included as a secondary endpoint.

The primary efficacy endpoint of UPCR of ≤0.7 mg/mg was amended to UPCR of ≤0.5 mg/mg, in line with current guidelines and EMA recommendations.

The time duration limits for prednisone use for renal response were modified from 'Received ≤10 mg/day prednisone from Weeks 16 through 24' to 'Did not receive more than 10 mg prednisone for ≥3 consecutive days or for ≥7 days in total during Weeks 44 through 52' for consistency with the Phase 2 AURA-LV study.

The secondary endpoint 'Proportion of subjects experiencing a confirmed >30% decrease from baseline in eGFR at each time point' was added following discussions with PMDA and EMA to ensure that the clinical profile of voclosporin was fully characterised.

The time window for the biopsy used for screening was extended from 'within 6 months of screening' to 'within 2 years of screening'. Any subject having a biopsy over 6 months old was reviewed by the Medical Monitor for recent disease activity and clinical features of a renal flare to ensure eligibility.

The final approval of Protocol Version 2 was received on 11 February 2019. As a result of regulatory agency feedback, changes were made to the planned analyses which were described in the SAP but not reflected in the protocol.

- In the randomisation, regional differences were not expected and blocking by region was done more for drug distribution reasons. While the analysis specified in the protocol stipulated that the regional blocking factor was not to be used in the analysis models, the final model included terms for each of the factors used in the randomisation process: −Biopsy class (Class V vs Others) MMF use at screening (Yes vs No)−Region (North America, Latin America, Europe + South Africa and Asia Pacific)
- 'Duration of UPCR ≤0.5 mg/mg' and 'Proportion of subjects experiencing a confirmed >30% decrease from baseline in eGFR at each time point' were changed from key secondary endpoints to 'other' secondary endpoints and removed from the hierarchical testing procedure.

Protocol deviations

Major protocol deviations were recorded for 61 subjects (34.3%) in the placebo arm and 67 subjects (37.4%) in the voclosporin arm. The most common deviations related to study procedures (38 subjects [10.6%]), study drug (33 subjects [9.2%]), restricted concomitant medication (31 subjects [8.7%]) and randomisation procedure (26 subjects [7.3%]). Protocol deviations resulting in the exclusion of a subject from the PP population were identified in 22 subjects (12.4%) in the placebo arm and 18 subjects (10.1%) in the voclosporin arm.

Table 22 Summary of Major Protocol Deviations Leading to Exclusion from the Per-Protocol Population (ITT Population)

Deviation Category	Placebo (N = 178) n (%)	Voclosporin (N = 179) n (%)	Overall (N = 357) n (%)
ANY EXCLUSION FROM PP POPULATION	22 (12.4)	18 (10.1)	40 (11.2)
Compliance	18 (10.1)	10 (5.6)	28 (7.8)
Steroid Taper	3 (1.7)	3 (1.7)	6 (1.7)
Prior Prohibited Medication	2 (1.1)	2 (1.1)	4 (1.1)
Dialysis	0	2 (1.1)	2 (0.6)
Entry Criteria	1 (0.6)	1 (0.6)	2 (0.6)
Incorrect Kit Dispensation	0	1 (0.6)	1 (0.3)
On-Study Medications	1 (0.6)	0	1 (0.3)

Baseline data

Table 23 Summary of Demographics (ITT Population)

Parameter	Placebo (N = 178)	Voclosporin (N = 179)	Overall (N = 357)
Age at time of consent (years)			
Mean (SD)	33.6 (11.00)	32.8 (10.93)	33.2 (10.96)
Median	31.5	31.0	31.0
Min, Max	18, 72	18, 62	18, 72
Sex, n (%)			
Female	152 (85.4)	161 (89.9)	313 (87.7)
Male	26 (14.6)	18 (10.1)	44 (12.3)
Ethnicity, n (%)			
Hispanic or Latino	59 (33.1)	57 (31.8)	116 (32.5)
Not Hispanic or Latino	118 (66.3)	122 (68.2)	240 (67.2)
Unknown	1 (0.6)	0	1 (0.3)
Race, n (%)			
White	61 (34.3)	68 (38.0)	129 (36.1)
Black or African American	13 (7.3)	21 (11.7)	34 (9.5)
American Indian or Alaska Native	4 (2.2)	0	4 (1.1)
Asian	56 (31.5)	53 (29.6)	109 (30.5)
Multiple Race	1 (0.6)	0	1 (0.3)
Other	43 (24.2)	37 (20.7)	80 (22.4)
Height (cm)			
Mean (SD)	162.04 (8.661)	161.13 (8.687)	161.58 (8.674)
Median	160.95	160.50	160.90
Min, Max	126.0, 188.0	141.0, 193.0	126.0, 193.0
Weight (kg)			
Mean (SD)	66.55 (16.113)	66.49 (17.074)	66.52 (16.578)
Median	63.50	64.60	64.10
Min, Max	36.0, 138.2	36.0, 142.0	36.0, 142.0
Weight Category, n (%)			
<45 kg	11 (6.2)	10 (5.6)	21 (5.9)
≥45 kg	167 (93.8)	169 (94.4)	336 (94.1)

Notes: Asian race includes Asian Indian, Chinese, Filipino, Japanese, Korean, Vietnamese and Other Asian.
Other race includes mixed races.

Table 24 Summary of SLE History (ITT Population)

Parameter		Placebo (N = 178)	Voclosporin (N = 179)	Overall (N = 357)
Number of Years since Diagnosis of SLE				
	n	177	179	356
	Mean (SD)	6.9 (6.07)	6.6 (6.41)	6.7 (6.23)
	Median	6.0	4.0	5.0
	Min*, Max	1, 30	1, 38	1, 38
Mucocutaneous				
Ever involved	n (%)	144 (80.9)	145 (81.0)	289 (81.0)
Currently involved	n (%)	80 (44.9)	88 (49.2)	168 (47.1)
Neurological				
Ever involved	n (%)	29 (16.3)	33 (18.4)	62 (17.4)
Currently involved	n (%)	11 (6.2)	16 (8.9)	27 (7.6)
Musculoskeletal				
Ever involved	n (%)	147 (82.6)	147 (82.1)	294 (82.4)
Currently involved	n (%)	73 (41.0)	83 (46.4)	156 (43.7)
Cardiorespiratory				
Ever involved	n (%)	52 (29.2)	52 (29.1)	104 (29.1)
Currently involved	n (%)	26 (14.6)	26 (14.5)	52 (14.6)
Vasculitis				
Ever involved	n (%)	21 (11.8)	23 (12.8)	44 (12.3)
Currently involved	n (%)	12 (6.7)	10 (5.6)	22 (6.2)
Hematology				
Ever involved	n (%)	117 (65.7)	112 (62.6)	229 (64.1)
Currently involved	n (%)	80 (44.9)	70 (39.1)	150 (42.0)
Antiphospholipid Syndrome				
Ever involved	n (%)	25 (14.0)	24 (13.4)	49 (13.7)
Currently involved	n (%)	17 (9.6)	20 (11.2)	37 (10.4)
Any Other Current SLE Involvement				
Ever involved	n (%)	N/A	N/A	N/A
Currently involved	n (%)	56 (31.5)	43 (24.0)	99 (27.7)

* Durations of <1 year were rounded to 1 year

Table 25 Summary of SLE Comorbidities (ITT Population)

Parameter	Placebo (N = 178) n (%)	Voclosporin (N = 179) n (%)	Overall (N = 357) n (%)
Diabetes Mellitus			
Diagnosed	6 (3.4)	4 (2.2)	10 (2.8)
SLE Related	2 (33.3)	1 (25.0)	3 (30.0)
Not SLE Related	4 (66.7)	3 (75.0)	7 (70.0)
Hypertension			
Diagnosed	123 (69.1)	125 (69.8)	248 (69.5)
SLE Related	97 (78.9)	109 (87.2)	206 (83.1)
Not SLE Related	25 (20.3)	16 (12.8)	41 (16.5)
Myocardial Infarction			
Diagnosed	0	2 (1.1)	2 (0.6)
SLE Related	0	1 (50.0)	1 (50.0)
Not SLE Related	0	1 (50.0)	1 (50.0)
Stroke			
Diagnosed	6 (3.4)	6 (3.4)	12 (3.4)
SLE Related	4 (66.7)	6 (100.0)	10 (83.3)
Not SLE Related	2 (33.3)	0	2 (16.7)
Deep Vein Thrombosis			
Diagnosed	8 (4.5)	5 (2.8)	13 (3.6)
SLE Related	5 (62.5)	4 (80.0)	9 (69.2)
Not SLE Related	3 (37.5)	1 (20.0)	4 (30.8)
Hyperlipidemia			
Diagnosed	92 (51.7)	82 (45.8)	174 (48.7)
SLE Related	65 (70.7)	70 (85.4)	135 (77.6)
Not SLE Related	27 (29.3)	12 (14.6)	39 (22.4)

Notes: Percentages for 'SLE Related'/'Not SLE Related' are based on the number of subjects diagnosed.

Table 26 Summary of Renal History (ITT Population)

Parameter	Placebo (N = 178)	Voclosporin (N = 179)	Overall (N = 357)
Number of years since the 1st instance of a significant proteinuria (>500 mg/day)			
n	158	161	319
Mean (SD)	4.6 (4.51)	4.8 (5.20)	4.7 (4.86)
Median	3.0	2.0	2.0
Min*, Max	1, 23	1, 26	1, 26
Number of years since the first diagnosis of LN			
n	178	179	357
Mean (SD)	4.7 (4.89)	4.6 (5.07)	4.6 (4.97)
Median	2.0	2.0	2.0
Min*, Max	1, 28	1, 26	1, 28
Any previous dialysis, n (%)			
Yes	3 (1.7)	3 (1.7)	6 (1.7)
No	175 (98.3)	176 (98.3)	351 (98.3)
Number of years since the last dialysis			
n	2	3	5
Mean (SD)	8.5 (9.19)	2.3 (1.53)	4.8 (5.81)
Median	8.5	2.0	2.0
Min, Max	2, 15	1, 4	1, 15

* Durations of <1 year were rounded to 1 year

Table 27 Summary of Kidney Biopsy, UPCR and eGFR at Baseline (ITT Population)

Parameter	Placebo (N = 178)	Voclosporin (N = 179)	Overall (N = 357)
KIDNEY BIOPSY CLASS*, n (%)			
Pure CLASS III	29 (16.3)	18 (10.1)	47 (13.2)
Pure CLASS IV	77 (43.3)	91 (50.8)	168 (47.1)
Pure CLASS V	25 (14.0)	25 (14.0)	50 (14.0)
CLASS II and CLASS V Only	1 (0.6)	0	1 (0.3)
CLASS III and CLASS V Only	20 (11.2)	24 (13.4)	44 (12.3)
CLASS IV and CLASS V Only	26 (14.6)	19 (10.6)	45 (12.6)
UPCR (mg/mg)			
n	178	178	356
Mean (SD)	3.87 (2.363)	4.14 (2.711)	4.00 (2.543)
Median	3.13	3.36	3.22
Min, Max	0.79, 14.47	0.22, 15.01	0.22, 15.01
eGFR (mL/min/1.73m²)			
n	178	178	356
Mean (SD)	90.4 (28.97)	92.1 (30.60)	91.2 (29.77)
Median	97.0	91.0	93.5
Min, Max	25, 140	39, 168	25, 168

* Kidney biopsy class summarized for 177/179 voclosporin patients. Of the remaining 2 subjects, one was Class III/Class IV mix, one was mixed Class III

Notes Baseline UPCR is defined as the average of the latest 2 pre-randomization values.
One subject in the voclosporin arm who withdrew prior to receiving treatment had only a single UPCR and eGFR value recorded and was not included in the baseline summary statistics.

The applicant states that a total of 39 subjects (11%) had a biopsy more than 6 months prior to screening; of these subjects, the majority had a biopsy between 6 and 12 months prior with 12 (3%) having a biopsy more than 12 months prior to screening. The applicant also states that the timing of biopsies taken more than 6 months prior to screening was balanced between treatment groups (>6 months to 12 months: 14 placebo and 13 voclosporin subjects; and >12 months: 7 placebo and 5 voclosporin subjects).

Table 28 Previous Treatments for Lupus Nephritis

LN Therapy	Placebo (N = 178) n (%)	Voclosporin (N = 178) n (%)	Overall (N = 357) n (%)
Corticosteroids	168 (94.4)	168 (94.4)	336 (94.4)
Antimalarial	121 (68.0)	118 (66.3)	239 (67.1)
MMF	110 (61.8)	114 (64.0)	224 (62.9)
IVC	58 (32.6)	65 (36.5)	123 (34.6)
Azathioprine	60 (33.7)	47 (26.4)	107 (30.1)
Other	22 (12.4)	33 (18.5)	55 (15.4)
Biologic	18 (10.1)	18 (10.1)	36 (10.1)
CNI	11 (6.2)	19 (10.7)	30 (8.4)
Methotrexate	11 (6.2)	15 (8.4)	26 (7.3)

Notes: CNI = calcineurin inhibitor; IVC = intravenous cyclophosphamide; MMF = mycophenolate mofetil.

Concomitant medication at baseline (within the screening period) are provided in the table below:

Table 29 Summary of selected therapies administered within the screening period (Day-30 to Day -1) (AURORA 1 safety population)

ATC Level 2 Decode Preferred Term	Placebo (N = 178)		Voclosporin 23.7 mg BID (N = 178)	
	n (%)	M	n (%)	M
Corticosteroids for systemic use	143 (80.3)	196	143 (80.3)	179
Any Screening Period Mycophenolate[a]	101 (56.7)	120	103 (57.9)	114
Any Screening Period Hydroxychloroquine[b]	106 (59.6)	111	95 (53.4)	98
Agents acting on the renin-angiotensin system	129 (72.5)	136	114 (64.0)	117
Any screening period antihypertensive	104 (58.4)	213	100 (56.2)	189
Diuretics	71 (39.9)	95	67 (37.6)	95
Calcium channel blockers	59 (33.1)	62	39 (21.9)	46
Beta blocking agents	37 (20.8)	40	33 (18.5)	34
Antihypertensives	16 (9.0)	16	13 (7.3)	14
Lipid modifying agents	55 (30.9)	60	42 (23.6)	47

ATC = Anatomic Therapeutic Chemical; M = medications.
Medications contributing to summary: Medications starting prior to the first dose of voclosporin/placebo that are either ongoing or end within 30 days of first dose of voclosporin/placebo.
a Mycophenolate includes mycophenolate mofetil, mycophenolate sodium, and mycophenolic acid.
b Hydroxychloroquine includes hydroxychloroquine and hydroxychloroquine sulphate.

Table 30 Summary of Concomitant Medications Starting After First Dose Reported by ⩾10% of Subjects in Either Arm (Safety Population)

ATC Level 2/ Preferred Name	Placebo (N = 178) n (%)	Voclosporin (N = 178) n (%)	Overall (N = 357) n (%)
Number of Subjects With One or More Concomitant Medications	146 (82.0)	157 (88.2)	303 (85.1)
ANTIBACTERIALS FOR SYSTEMIC USE	80 (44.9)	79 (44.4)	159 (44.7)
ANALGESICS	68 (38.2)	61 (34.3)	129 (36.2)
PARACETAMOL	46 (25.8)	50 (28.1)	96 (27.0)
DIURETICS	52 (29.2)	57 (32.0)	109 (30.6)
FUROSEMIDE	39 (21.9)	38 (21.3)	77 (21.6)
CALCIUM CHANNEL BLOCKERS	37 (20.8)	59 (33.1)	96 (27.0)
AMLODIPINE	20 (11.2)	30 (16.9)	50 (14.0)
DRUGS FOR ACID RELATED DISORDERS	41 (23.0)	51 (28.7)	92 (25.8)
OMEPRAZOLE	14 (7.9)	22 (12.4)	36 (10.1)
ANTIINFLAMMATORY AND ANTIRHEUMATIC PRODUCTS	37 (20.8)	42 (23.6)	79 (22.2)
HYDROXYCHLOROQUINE	15 (8.4)	20 (11.2)	35 (9.8)
ANTIANEMIC PREPARATIONS	33 (18.5)	40 (22.5)	73 (20.5)

ATC Level 2/ Preferred Name	Placebo (N = 178) n (%)	Voclosporin (N = 178) n (%)	Overall (N = 357) n (%)
COUGH AND COLD PREPARATIONS	28 (15.7)	41 (23.0)	69 (19.4)
ANTIHISTAMINES FOR SYSTEMIC USE	27 (15.2)	34 (19.1)	61 (17.1)
MINERAL SUPPLEMENTS	32 (18.0)	28 (15.7)	60 (16.9)
AGENTS ACTING ON THE RENIN-ANGIOTENSIN SYSTEM	31 (17.4)	25 (14.0)	56 (15.7)
CORTICOSTEROIDS FOR SYSTEMIC USE	33 (18.5)	23 (12.9)	56 (15.7)
LIPID MODIFYING AGENTS	31 (17.4)	25 (14.0)	56 (15.7)
BETA BLOCKING AGENTS	20 (11.2)	32 (18.0)	52 (14.6)
ANTIVIRALS FOR SYSTEMIC USE	18 (10.1)	30 (16.9)	48 (13.5)
DRUGS FOR FUNCTIONAL GASTROINTESTINAL DISORDERS	19 (10.7)	27 (15.2)	46 (12.9)
VITAMINS	17 (9.6)	26 (14.6)	43 (12.1)
ANTIDIARRHEALS, INTESTINAL ANTIINFLAMMATORY/ANTIINFECTIVE AGENTS	17 (9.6)	21 (11.8)	38 (10.7)
ANTIHYPERTENSIVES	17 (9.6)	19 (10.7)	36 (10.1)
ANTITHROMBOTIC AGENTS	16 (9.0)	19 (10.7)	35 (9.8)
BLOOD SUBSTITUTES AND PERFUSION SOLUTIONS	15 (8.4)	18 (10.1)	33 (9.3)

Numbers analysed

Table 31 Summary of Analysis Populations (All Randomised Subjects)

Parameter	Placebo (N = 178) n (%)	Voclosporin (N = 179) n (%)	Overall (N = 357) n (%)
Intent-to-Treat Analysis Set	178 (100.0)	179 (100.0)	357 (100.0)
Safety Analysis Set	178 (100.0)	178 (99.4)	356 (99.7)
Per-Protocol Analysis Set	156 (87.6)	161 (89.9)	317 (88.8)

The primary efficacy analysis population included all randomised patients.

Outcomes and estimation

A summary of the results in primary and key secondary endpoints is provided below:

Table 32 Summary of Primary and Key Secondary Efficacy Endpoints (AURORA 1 ITT Population)

Parameter Comparison to Placebo		Results with Unadjusted P-value	Significance Level
Primary Endpoint			
Renal Response at Week 52 (Adjudicated)	Odds Ratio (95% CI)	2.65 (1.64, 4.27)	
	p-value	<0.001	0.0500
Key Secondary Endpoints			
Renal Response at Week 24 (Adjudicated)	Odds Ratio (95% CI)	2.23 (1.34, 3.72)	
	p-value	0.002	0.0500
Partial Renal Response at Week 52 (Programmed)	Odds Ratio (95% CI)	2.26 (1.45, 3.51)	
	p-value	<0.001	0.0250
Partial Renal Response at Week 24 (Programmed)	Odds Ratio (95% CI)	2.43 (1.56, 3.79)	
	p-value	<0.001	0.0167
Time (days) to UPCR of ≤0.5 mg/mg (Programmed)	Hazard Ratio (95% CI)	2.02 (1.51, 2.70)	
	p-value	<0.001	0.0125
Time (days) to 50% Reduction in UPCR from Baseline (Programmed)	Hazard Ratio (95% CI)	2.05 (1.62, 2.60)	
	p-value	<0.001	0.0100

Primary Endpoint: CEC Adjudicated Renal Response at Week 52

The primary endpoint was the number of subjects showing renal response at Week 52 as adjudicated by the CEC, analysed using a logistic regression model with terms for treatment, baseline UPCR, biopsy class, MMF use at baseline and region.

Table 33 Adjudicated Renal Response at Week 52 (ITT Population)

	Placebo (N = 178) n (%)	Voclosporin (N = 179) n (%)
Number of Renal Responders	40 (22.5)	73 (40.8)
Number of Renal Non-Responders	138 (77.5)	106 (59.2)
Odds Ratio (vs Placebo)		2.65
95% CI of OR (vs Placebo)		1.64, 4.27
P - value		<.001

Note The model is based on a logistic regression with terms for treatment, baseline UPCR, biopsy class, MMF use at baseline and region.

Upon request the applicant clarified that for most non-responders, a subject's status could be calculated owing to that sufficient data was available at week 52; non-responder imputation was used for 14/179 (7.8%) and 25/178 (14.0%) subjects in the voclosporin and placebo arm, respectively.

Supplementary analysis

Similar results were seen for supplementary analyses, i.e., for the PP population (OR 2.55; 95% CI: 1.55, 4.18; p<0.001), and for the programmed renal response (OR 2.32; 95% CI: 1.43, 3.78; p<0.001); and for sensitivity analyses including only a term for treatment (OR2.38; 95% CI: 1.50, 3.77; p<0.001) and omitting the regional covariate (OR 2.58; 95% CI: 1.61, 4.14; p<0.001).

Logistic regression analyses for each individual component of response (UPCR ≤0.5 mg/mg, eGFR success, no rescue medication and not more than 10 mg prednisone for ≥3 consecutive days or for ≥7 days during Weeks 44-52) showed that UPCR ≤0.5 mg/mg was the only significant factor in the observed difference in adjudicated renal response between the two treatment arms (OR 3.11; 95% CI: 1.93, 5.00; p<0.001). UPCR≤0.5 mg/mg(OR 2.53; 95% CI: 1.57, 4.09; p<0.001) and, to a lesser extent, eGFR success (OR 2.04; 95% CI: 1.08, 3.84; p=0.027) were both significant components of the results based on programmed renal response.

Table 34 Logistic Regression of Components of Renal Response Related Endpoints (Adjudicated Response)Intent-to-Treat Population

Component	Statistic	Placebo (N = 178)	Voclosporin (N = 179)
UPCR ≤ 0.5 mg/mg			
Yes	n (%)	41 (23.0)	81 (45.3)
No	n (%)	137 (77.0)	98 (54.7)
Odds Ratio (vs Placebo)			3.11
95 CI of OR (vs Placebo)			1.93, 5.00
P - value			<.001
eGFR success			
Yes	n (%)	135 (75.8)	147 (82.1)
No	n (%)	43 (24.2)	32 (17.9)
Odds Ratio (vs Placebo)			1.50
95 CI of OR (vs Placebo)			0.89, 2.52
P - value			0.129

Component	Statistic	Placebo (N = 178)	Voclosporin (N = 179)
eGFR ≥ 60 mL/min/1.73m^2			
Yes	n (%)	130 (73.0)	139 (77.7)
No	n (%)	48 (27.0)	40 (22.3)
Odds Ratio (vs Placebo)			1.29
95 CI of OR (vs Placebo)			0.79, 2.11
P - value			0.300
eGFR < 60 mL/min/1.73m^2 with no confirmed decrease >20%			
Yes	n (%)	13 (7.3)	10 (5.6)
No	n (%)	165 (92.7)	169 (94.4)
Odds Ratio (vs Placebo)			0.73
95 CI of OR (vs Placebo)			0.30, 1.74
P - value			0.474

Component	Statistic	Placebo (N = 178)	Voclosporin (N = 179)
eGFR < 60 mL/min/1.73m^2 with confirmed decrease of >20% but with no disease-related or treatment-related eGFR associated AE present at time of assessment			
Yes	n (%)	6 (3.4)	7 (3.9)
No	n (%)	172 (96.6)	172 (96.1)
Odds Ratio (vs Placebo)			1.19
95 CI of OR (vs Placebo)			0.39, 3.63
P - value			0.763
UPCR ≤ 0.5 mg/mg and eGFR success			
Yes	n (%)	41 (23.0)	77 (43.0)
No	n (%)	137 (77.0)	102 (57.0)
Odds Ratio (vs Placebo)			2.81
95 CI of OR (vs Placebo)			1.75, 4.53
P - value			<.001

Component	Statistic	Placebo (N = 178)	Voclosporin (N = 179)
Received no rescue medication for LN			
Yes	n (%)	154 (86.5)	163 (91.1)
No	n (%)	24 (13.5)	16 (8.9)
Odds Ratio (vs Placebo)			1.62
95 CI of OR (vs Placebo)			0.82, 3.20
P - value			0.164
No withdrawal prior to remission assessment			
Yes	n (%)	153 (86.0)	165 (92.2)
No	n (%)	25 (14.0)	14 (7.8)
Odds Ratio (vs Placebo)			1.98
95 CI of OR (vs Placebo)			0.98, 3.97
P - value			0.056

Component	Statistic	Placebo (N = 178)	Voclosporin (N = 179)
Did not receive more than 10 mg prednisone for ≥3 consecutive days or for ≥7 days in total during Weeks 44 through 52			
Yes	n (%)	152 (85.4)	156 (87.2)
No	n (%)	26 (14.6)	23 (12.8)
Odds Ratio (vs Placebo)			1.26
95 CI of OR (vs Placebo)			0.68, 2.34
P - value			0.465

Additional analysis regarding the primary endpoint provided with alternative definition of stable renal function is displayed below.

Table 35 Renal Response in AURORA 1 at One Year: Alternative Definition of Stable Renal Function

Definition of Stable Renal Function	Parameter	Placebo (N=178)	Voclosporin 23.7 mg BID (N=179)
No confirmed decrease from baseline of >10% in corrected eGFR	Renal Responders n (%)	38 (21.3)	62 (34.6)
	Adjusted Odds Ratio (95% CI)		2.11 (1.30, 3.43)
	p-value		0.0026*
No confirmed decrease from baseline of >15% in corrected eGFR	Renal Responders n (%)	38 (21.3)	65 (36.3)
	Adjusted Odds Ratio (95% CI)		2.31 (1.42, 3.75)
	p-value		0.0008*
No confirmed decrease from baseline of >20% in corrected eGFR	Renal Responders n (%)	39 (21.9)	67 (37.4)
	Adjusted Odds Ratio (95% CI)		2.34 (1.44, 3.78)
	p-value		0.0006*

*Statistically Significant

Notes: The definition of Renal Response is as per the primary endpoint in AURORA 1 (adjudicated renal response) with the exception that the requirement for estimated glomerular filtration rate (eGFR) ≥60 mL/min/1.73 m^2 has been removed and stable renal function is solely defined based on no confirmed decrease in corrected eGFR of >10%, 15% or 20%. Note that urine protein-creatinine ratio (UPCR) ≤0.5, no rescue medication and corticosteroid use were all adjudicated as per the primary endpoint but eGFR was programmatically defined.
Adjusted analysis uses a logistic regression model with terms for study, treatment group, baseline UPCR, biopsy class, mycophenolate mofetil (MMF) use at screening and region. Odds ratios greater than unity indicate benefit of voclosporin.

Key Secondary Endpoints

Renal Response at Week 24

Table 36 Logistic Regression of Renal Response at Week 24 (ITT Population)

	Placebo (N = 178) n (%)	Voclosporin (N = 179) n (%)	Odds Ratio vs. Placebo (95% CI)	p-value
Adjudicated Renal Response				
Number of Responders	35 (19.7)	58 (32.4)	2.23 (1.34, 3.72)	0.002
Number of Non-Responders	143 (80.3)	121 (67.6)		
Programmed Renal Response				
Number of Responders	35 (19.7)	58 (32.4)	2.19 (1.32, 3.63)	0.002
Number of Non-Responders	143 (80.3)	121 (67.6)		

Upon request, the applicant explained that although the total number of responders and non-responders were the same in the adjudicated and programmed renal response analysis respectively, the individual responding subjects differed concerning a total of six subjects all in the voclosporin arm. The difference in subjects led to a different covariate pattern and the slightly different estimates.

Partial Renal Response at Weeks 24 and 52

Table 37 Logistic Regression of Partial Renal Response at Week 24 and Week 52 (ITT Population)

	Placebo (N = 178) n (%)	Voclosporin (N = 179) n (%)	Odds Ratio vs. Placebo (95% CI)	p-value
Baseline 1				
Week 24				
Number of Responders	89 (50.0)	126 (70.4)	2.43 (1.56, 3.79)	<.001
Number of Non-Responders	89 (50.0)	53 (29.6)		
Week 52				
Number of Responders	92 (51.7)	125 (69.8)	2.26 (1.45, 3.51)	<.001
Number of Non-Responders	86 (48.3)	54 (30.2)		
Baseline 2				
Week 24				
Number of Responders	72 (40.4)	108 (60.3)	2.29 (1.48, 3.53)	<.001
Number of Non-Responders	106 (59.6)	71 (39.7)		
Week 52				
Number of Responders	82 (46.1)	115 (64.2)	2.16 (1.40, 3.33)	<.001
Number of Non-Responders	96 (53.9)	64 (35.8)		

Notes: Baseline 1 UPCR is defined as the average of the latest 2 pre-randomization values.
Baseline 2 UPCR is defined as the lowest measurement available prior to dosing.

Time to UPCR ≤0.5 mg/mg

Table 38 Analysis of Time (Days) to UPCR ≤0.5 mg/mg (ITT Population)

		Placebo (N = 178)	Voclosporin (N = 179)
Number with UPCR ≤0.5 mg/mg	n (%)	78 (43.8)	116 (64.8)
Number without UPCR ≤0.5 mg/mg	n (%)	100 (56.2)	63 (35.2)
Time (days) to UPCR ≤0.5 mg/mg			
25th percentile (95% CI)		127 (85, 200)	84 (56, 86)
50th percentile (95% CI)		372 (295, NC)	169 (141, 214)
75th percentile (95% CI)		NC (NC, NC)	NC (371, NC)
Comparison to Placebo			
Log-Rank P-Value			<.001
Hazard Ratio (95% CI)			2.02 (1.51, 2.70)
P-value			<.001

Notes: Percentiles are estimated using Kaplan-Meier methodology.
The hazard ratios are from a Cox's proportional hazards model with terms for treatment arm, baseline UPCR, biopsy class, MMF use at baseline and region.
NC = Not Calculated.

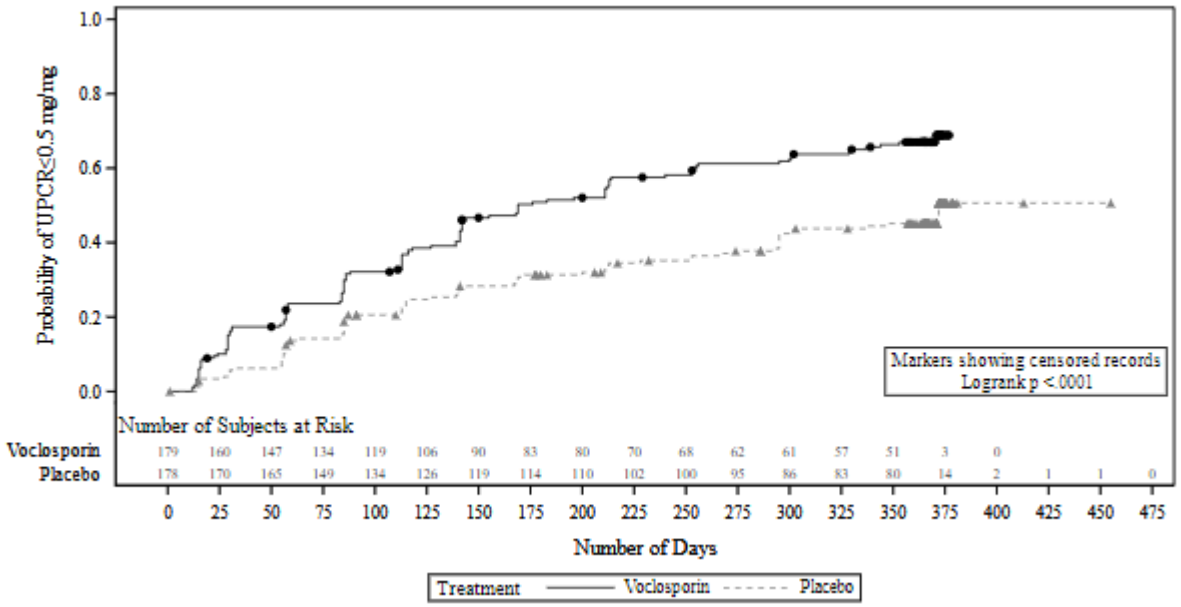


Figure 11 Kaplan-Meier Curve of Time (Days) to UPCR ⩽0.5 mg/mg (ITT Population)

Time to 50% Reduction in UPCR

A 50% reduction in UPCR from baseline at any time during the study was achieved by 96.6% of subjects treated with voclosporin compared with 75.8% of subjects receiving placebo The time taken to reach a 50% reduction in UPCR was significantly shorter for the voclosporin arm than the placebo arm (HR 2.05; 95% CI: 1.62, 2.60; p<0.001). Median time to 50% reduction in UPCR was 29 days for voclosporin versus 63 days for placebo. Similar results were seen when using the lowest available pre-dose UPCR measurement as baseline.

Table 39 Analysis of Time (Days) to 50% Reduction in UPCR from Baseline (ITT Population)

		Placebo (N = 178)	Voclosporin (N = 179)
Number with 50% reduction	n (%)	135 (75.8)	173 (96.6)
Number without 50% reduction	n (%)	43 (24.2)	6 (3.4)
Time (days) to 50% reduction			
25th percentile (95% CI)		29 (16, 30)	16 (15, 17)
50th percentile (95% CI)		63 (57, 87)	29 (29, 32)
75th percentile (95% CI)		337 (170, 379)	85 (58, 111)
Comparison to Placebo			
Log-Rank P-Value			<.001
Hazard Ratio (95% CI)			2.05 (1.62, 2.60)
P-value			<.001

Notes Baseline is defined as the average of the latest 2 pre-randomization values.

Consistent with the time to UPCR ≤0.5 mg/mg, the difference between the two treatment arms in the time to 50% reduction in UPCR was apparent within the first month of treatment and was sustained throughout the study (see figure below). The Kaplan-Meier curve shows that a small number of subjects in the placebo arm achieved a 50% reduction in UPCR late on the study (beyond Day 350).

However, most subjects in the voclosporin arm achieved this response earlier, with only 6 subjects still "at risk" beyond Day 300 compared to 38 subjects in the placebo arm.

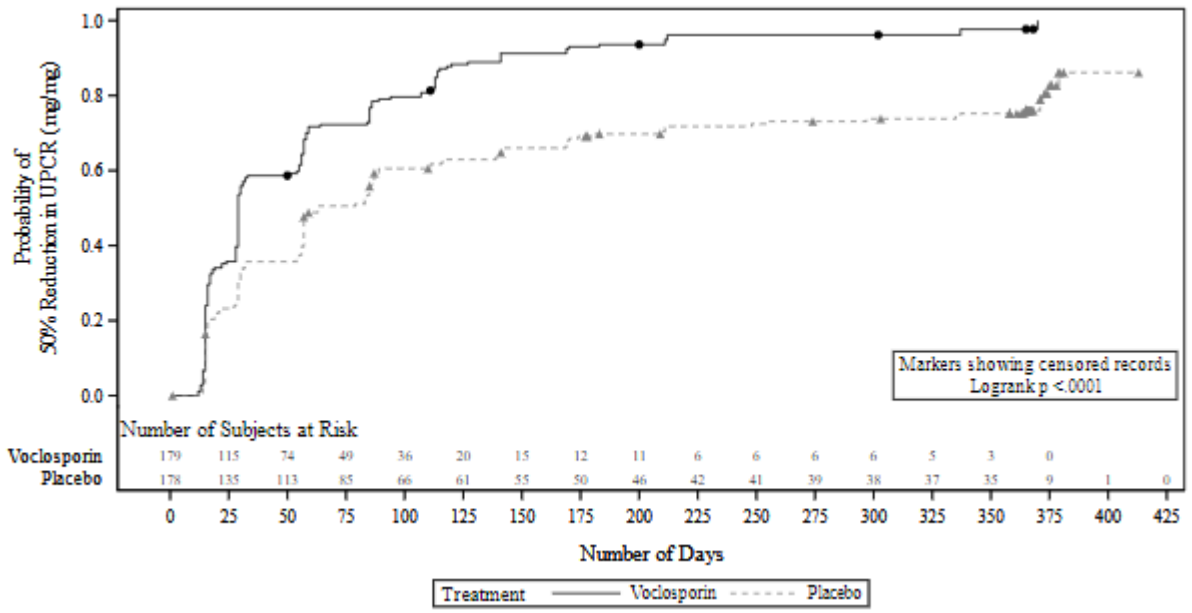


Figure 12 Kaplan-Meier Curve of Time (Days) to 50% Reduction in UPCR from Baseline (ITT Population)

Other Secondary Endpoints

Duration of UPCR ≤0.5mg/mg

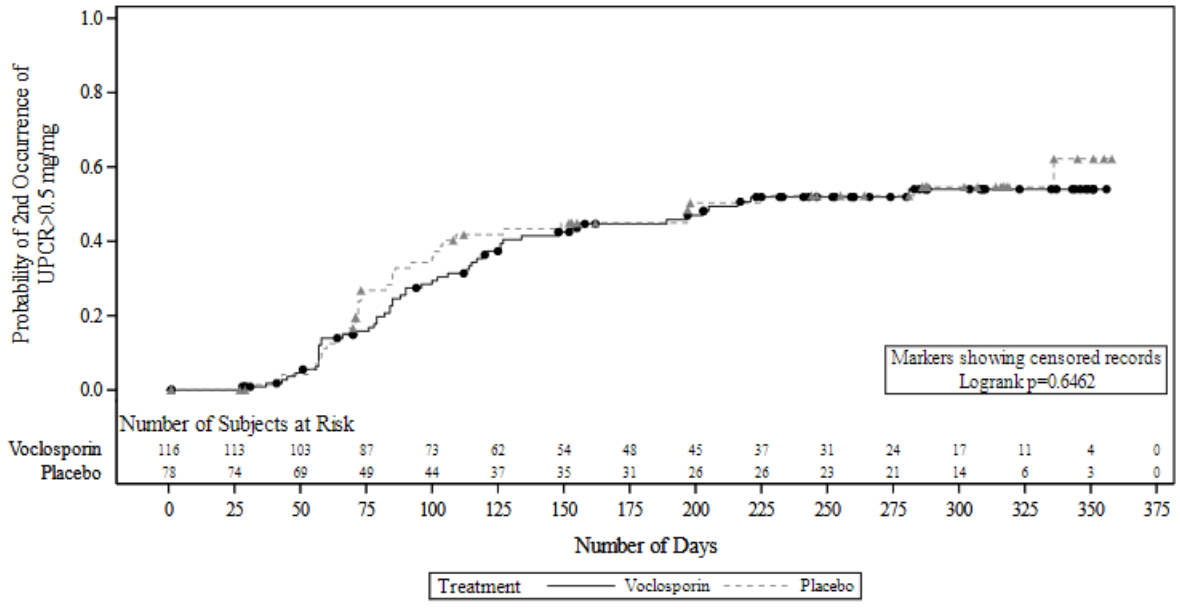


Figure 13 Kaplan-Meier Curve of Duration (Days) of UPCR ≤0.5 mg/mg (ITT Population)

Proportion of Subjects With >30% Decrease in eGFR by Time Point

A total of 18 subjects (10%) in each arm recorded a confirmed decrease of >30% from baseline in corrected eGFR during the study. More occurrences were reported during the second half of the treatment period (i.e., Week 24 onwards). The applicant states there were no notable differences

between two treatment arms at any time point. However, it is noted that from week 16 onwards at each time point numerically more >30% decreases in eGFR were recorded in voclosporin compared to placebo. The total number of occurrences of >30% decrease in eGFR was 61 for voclosporin compared to 43 in placebo arm.

Change from Baseline in UPCR by Time Point

Mean UPCR at baseline (defined as the average of the last 2 pre-randomisation values) was similar for the two treatment arms: 4.14 mg/mg in the voclosporin arm and 3.87 mg/mg in the placebo arm. Decreases in mean UPCR were observed for both treatments Week 2. In the voclosporin arm, mean UPCR levels of less than 1.5 mg/mg were observed from Week 16 onwards, while in the placebo arm, levels reduced to around 2.5 mg/mg by Week 8 and continued to slowly decrease to approximately 2.0 mg/mg by Week 42. The MMRM analysis confirmed that statistically significantly greater reductions from baseline in UPCR were achieved in the voclosporin arm compared with the placebo arm at every time point. The significant difference between treatments was also seen when using the more stringent baseline definition for UPCR of lowest available measurement prior to dosing.

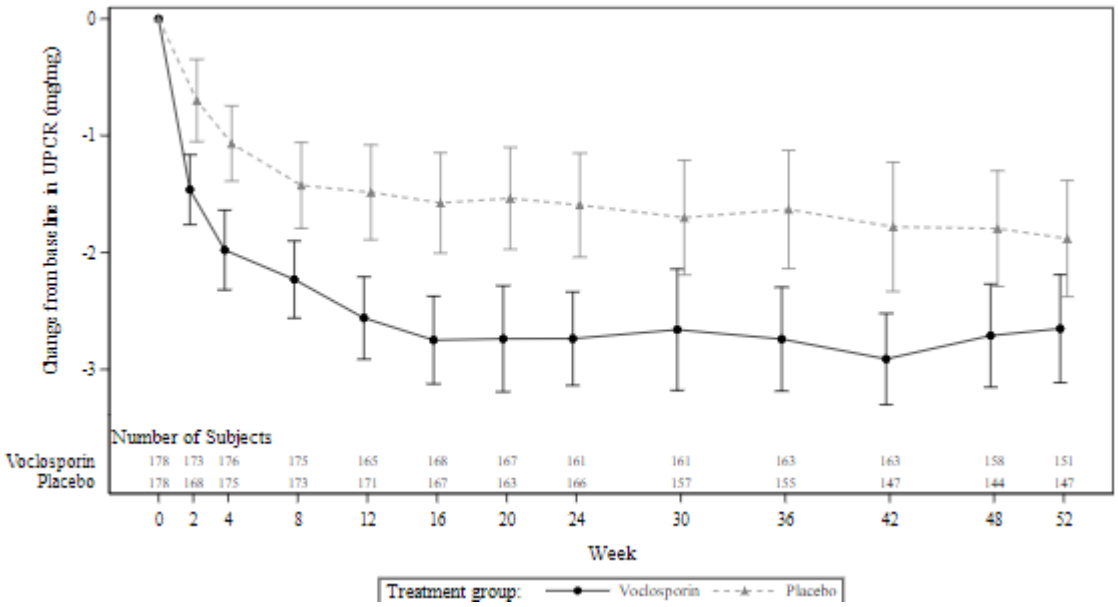


Figure 14 Mean (±95% CI) Change in UPCR (mg/mg) from Baseline by Visit (ITT Population)

Change from Baseline in Urine Protein, Serum Creatinine and eGFR by Time Point

Mean urine protein levels in the study were similar in both treatment arms at baseline (384 mg/dL and 379 mg/dL in the voclosporin and placebo arms, respectively). Changes in urine protein during the study reflected changes in UPCR; decreases in mean urine protein were observed in both arms with a difference between treatment arms observed around Week 2.

Mean corrected eGFR values at baseline were similar in both arms (78.3 mL/min/1.73m2 in the voclosporin arm and 77.4 mL/min/1.73m2 in the placebo arm). At Week 2, the mean corrected eGFR had decreased slightly in the voclosporin arm while the mean value in the placebo arm showed a small increase. For the remainder of the study, mean levels followed a similar pattern in both arms, remaining relatively stable with a slight decrease across the second half of the study

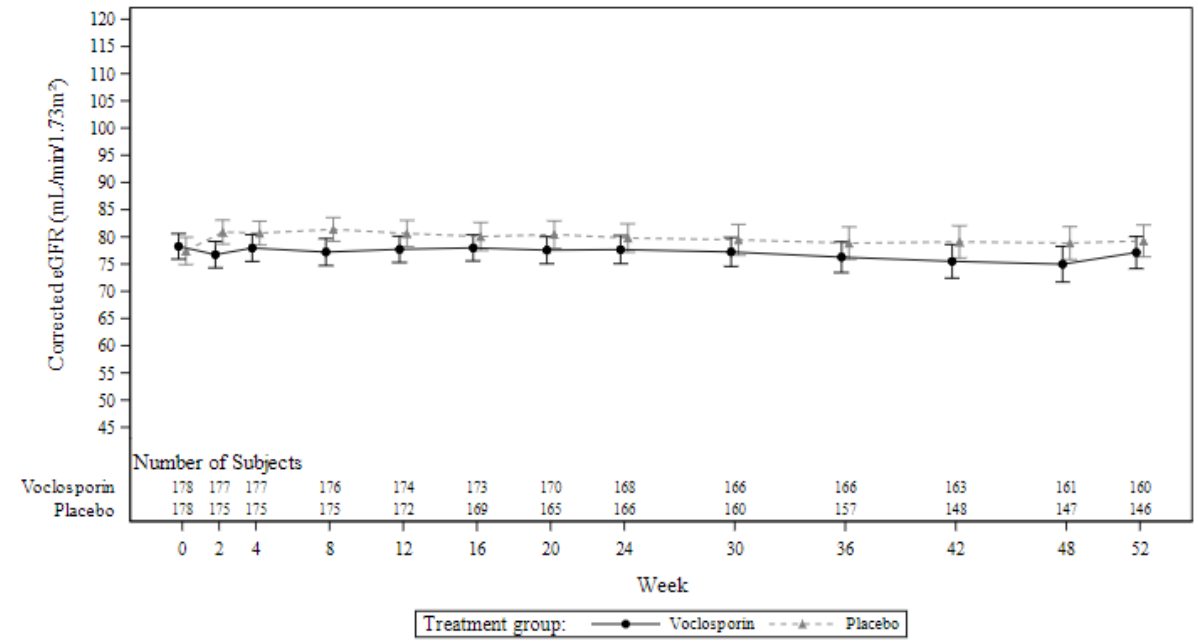


Figure 15 Mean (±95% CI) Observed Corrected eGFR (mL/ min/1.73m2) by Visit (ITT Population)

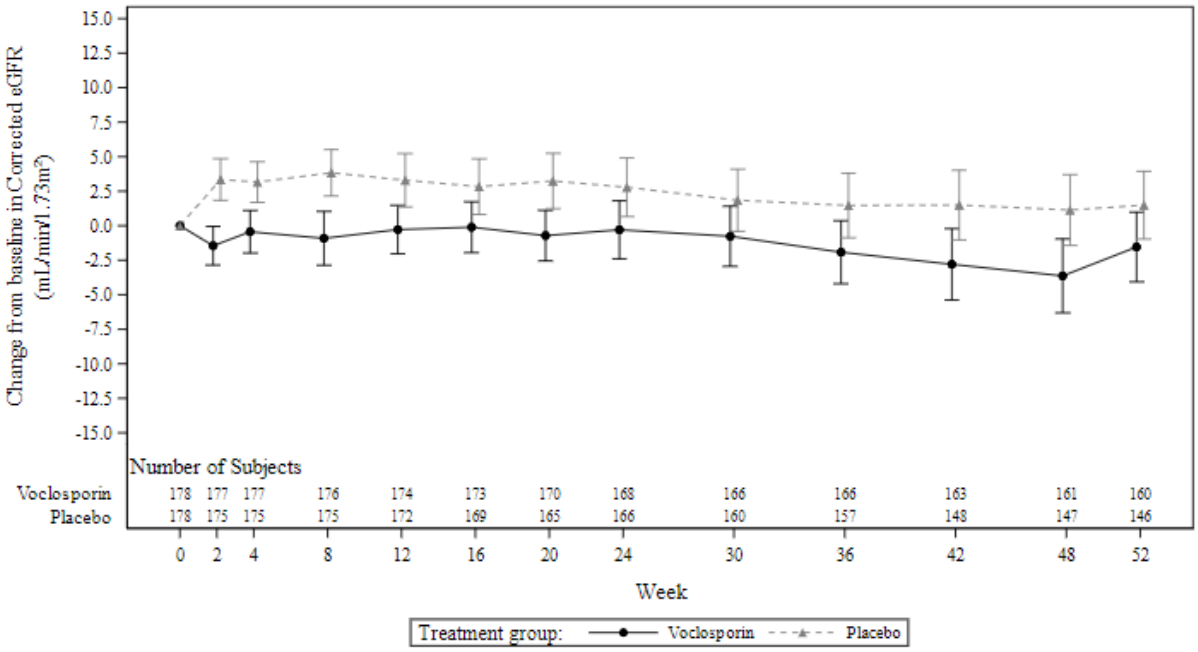


Figure 16 Mean (±95% CI) Change from Baseline in Corrected eGFR(mL/min/1.73m2) by Visit (ITT Population)

Renal Response with Low-dose Steroids at Weeks 24 and 52

Table 40 Subjects with Oral Corticosteroid dose ≤2.5 mg Prednisone Equivalent(ITT Population)

Dose	Placebo (N=178)	Voclosporin (N=179)	Overall (N=357)
Study Day 118 (last possible day for Week 16)			
Subjects ongoing	171/178 (96.1)	174/179 (97.2)	345/357 (96.6)
>2.5 mg	33 (19.3)	32 (18.4)	65 (18.8)
<=2.5 mg	138 (80.7)	142 (81.6)	280 (81.2)
Study Day 168 (Week 24)			
Subjects ongoing	169/178 (94.9)	172/179 (96.1)	341/357 (95.5)
>2.5 mg	29 (17.2)	33 (19.2)	62 (18.2)
<=2.5 mg	140 (82.8)	139 (80.8)	279 (81.8)
Study Visit 15 (Week 52)			
Subjects completed visit	147/178 (82.6)	162/179 (90.5)	309/357 (86.6)
>2.5 mg	39 (26.5)	41 (25.3)	80 (25.9)
<=2.5 mg	108 (73.5)	121 (74.7)	229 (74.1)

Notes: Dose is the maximum dose taken on the Study Day.
Percentages are based on the number of subjects in the study at each study day. For 'Subjects ongoing at study day'/'Subjects completed visit' row, percentages are based on subjects in the Safety Population.

Table 41 Logistic Regression of Renal Response with Low-Dose Steroids (ITT Population)

	Placebo (N = 178) n (%)	Voclosporin (N = 179) n (%)	Odds Ratio vs. Placebo (95% CI)	p-value
Week 24				
Number of Responders	16 (9.0)	32 (17.9)	2.44 (1.26, 4.71)	0.008
Number of Non-Responders	162 (91.0)	147 (82.1)		
Week 52				
Number of Responders	36 (20.2)	64 (35.8)	2.44 (1.48, 4.00)	<.001
Number of Non-Responders	142 (79.8)	115 (64.2)		

Notes: The model is based on a logistic regression with terms for treatment, baseline UPCR, MMF use at baseline and region.

Change from Baseline in SELENA-SLEDAI Index Score

Table 42 MMRM Model of Change from Baseline in SELENA-SLEDAI Index Score (ITT Population)

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

Notes: Results are based on a Mixed Effect Model Repeated Measures analysis with Change from baseline at each visit as the response variable, while treatment arm, visit, treatment by visit interaction, biopsy class, MMF use at baseline, region and baseline SELENA-SLEDAI Index score are included effects in the model.
Model is using unstructured covariance structure.

Change from Baseline in Patient Reported Outcomes

Improvements (increases) in mean scores from baseline were seen in both treatment arms for the health-related quality of life assessments SF-36 and for the health-related domains of the LupusPRO assessment (HRQoL). Smaller changes were seen in both arms for the non-health-related domains of the LupusPRO assessment (N-HRQoL). There was no significant difference in the degree of improvement between the two treatments.

Health Resource Utilisation

Health resource utilisation was assessed based on the frequency of visits to health care providers and diagnostic tests (excluding study visits and assessments). There were no apparent differences between the two treatment arms in health resource utilisation at baseline or during the study.

Dose changing during the study

A summary of dose changing during the study is provided below. Dose modification of VCS/placebo was permitted for tolerability reasons. A specific schedule was implemented for dose reduction with regards to decrease in kidney function or increase in blood pressure (see 2.5.8.).

Table 43 Summary of Voclosporin/Placebo Dose Changes (Safety Population)

	Placebo (N = 178) n (%) / C	Voclosporin (N = 178) n (%) / C	Overall (N = 356) n (%) / C
Overall			
No Change	128 (71.9)	86 (48.3)	214 (60.1)
Decrease	7 (3.9)	31 (17.4)	38 (10.7)
Increase	47 (26.4)	81 (45.5)	128 (36.0)
Temporary Interruption	45 (25.3)	78 (43.8)	123 (34.6)
Reason for Change			
Due to eGFR	11 (6.2) / 14	42 (23.6) / 59	53 (14.9) / 73
Due to eGFR Recovered	14 (7.9) / 23	43 (24.2) / 82	57 (16.0) /105
Due to BP Increase	1 (0.6) / 1	1 (0.6) / 3	2 (0.6) / 4
Due to BP Recovered	0	4 (2.2) / 7	4 (1.1) / 7
Due to AE Other than eGFR or BP	12 (6.7) / 15	26 (14.6) / 36	38 (10.7) / 51
AE Resolved	29 (16.3) / 36	37 (20.8) / 57	66 (18.5) / 93
Other	13 (7.3) / 15	21 (11.8) / 30	34 (9.6) / 45

Note: AE = adverse event; BP = blood pressure; C = number of changes; eGFR = estimated glomerular filtration rate.

In most subjects, study treatment was resumed once the event resulting in a dose decrease/interruption had resolved. More subjects in the voclosporin arm than the placebo arm were restarted on 1 capsule (7.9 mg) or 2 capsules (15.8 mg) BID instead of the full dose of 3 capsules (23.7 mg) BID and stayed on this lower dose for the remainder of the study. At the end of the study, 42.9% of voclosporin subjects who had a dose decrease/interruption were back on 23.7 mg BID compared with 65.3% of placebo subjects.

Table 44 Summary of Voclosporin/Placebo Dose Decreases and Final Dose (BID) (Safety Population)

	Placebo (N = 178)	Voclosporin (N = 178)	Overall (N = 356)
Subjects with any dose decrease (a)	49 (27.5)	91 (51.1)	140 (39.3)
Final Dose in subjects with decrease (b)			
0 mg	2 (4.1)	0	2 (1.4)
7.9 mg	7 (14.3)	26 (28.6)	33 (23.6)
15.8 mg	8 (16.3)	26 (28.6)	34 (24.3)
23.7 mg	32 (65.3)	39 (42.9)	71 (50.7)

(a) Percentages are based on the number of subjects in the Safety Population.
(b) Percentages are based on the number of subjects with decreases

Table 45 Summary of Exposure to MMF (Safety Population)

	Placebo (N = 178)	Voclosporin (N = 178)
Overall Duration of Exposure (days)		
Mean (SD)	316.1 (97.83)	330.9 (87.16)
Median	365.0	365.0
Min, Max	1, 408	26, 420
Overall g/day Exposure		
Mean (SD)	1.960 (0.3779)	1.875 (0.4005)
Median	1.981	1.981
Min, Max	0.58, 3.00	0.22, 3.00

Duration of exposure is calculated as the number of days from the first to the last dose date. For subjects lost to follow up the date of the last available visit will be used as the last dose date.

Ancillary analyses

Results of the covariate analyses by age, sex, race, region, biopsy class, MMF at screening and maximum dose of MMF are provided below.

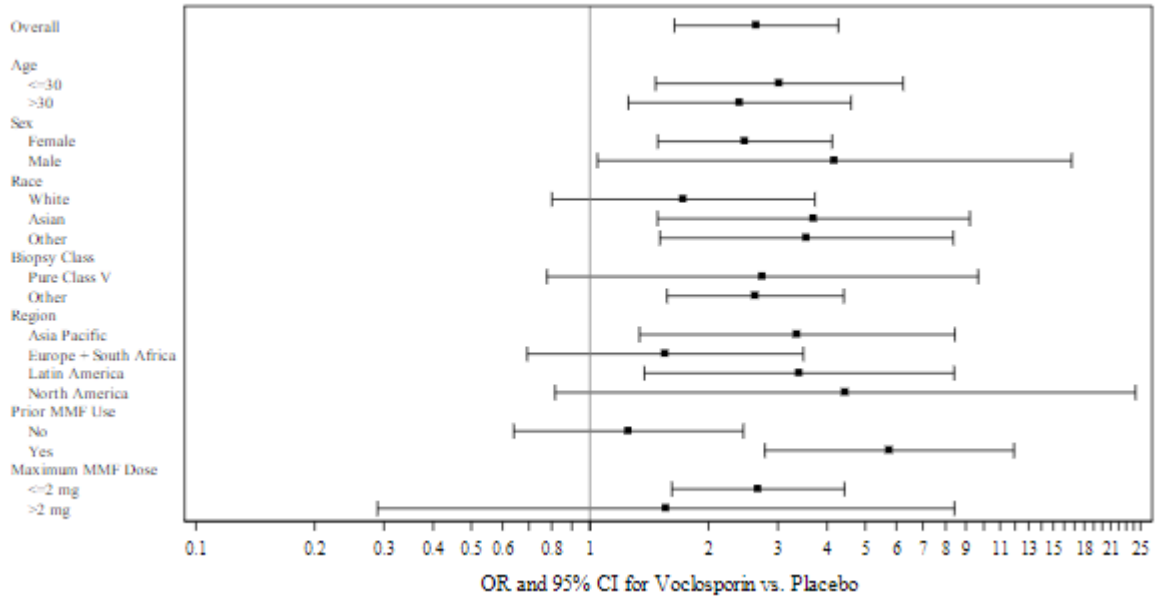


Figure 17 Forest Plot of Adjudicated Renal Response at Week 52 by Subgroup (ITT Population)

Table 46 Logistic Regression of Adjudicated Renal Response at Week 52 by Subgroup (ITT Population)

	Placebo (N = 178) n (%)	Voclosporin (N = 179) n (%)	Odds Ratio vs. Placebo (95% CI)	p-value
Age				
≤ 30 Years	15 (18.1)	36 (40.4)	3.03 (1.47, 6.24)	0.003
> 30 Years	25 (26.3)	37 (41.1)	2.40 (1.25, 4.60)	0.008
Sex				
Female	35 (23.0)	65 (40.4)	2.48 (1.49, 4.12)	<.001
Male	5 (19.2)	8 (44.4)	4.18 (1.04, 16.71)	0.043
Race				
White	18 (29.5)	26 (38.2)	1.73 (0.80, 3.72)	0.164
Asian	10 (17.9)	22 (41.5)	3.70 (1.48, 9.22)	0.005
Other	12 (19.7)	25 (43.1)	3.55 (1.51, 8.36)	0.004
Biopsy Class				
Pure Class V	6 (24.0)	11 (44.0)	2.74 (0.78, 9.68)	0.117
Other	34 (22.2)	62 (40.3)	2.63 (1.57, 4.41)	<.001
Region				
Asia Pacific	9 (17.3)	21 (40.4)	3.36 (1.34, 8.44)	0.010
Europe + South Africa	18 (34.6)	23 (44.2)	1.55 (0.69, 3.48)	0.285
Latin America	11 (22.9)	22 (44.9)	3.40 (1.38, 8.41)	0.008
North America	2 (7.7)	7 (26.9)	4.45 (0.82, 24.27)	0.085
MMF Use at Screening				
MMF at Screening	13 (13.5)	44 (44.0)	5.76 (2.78, 11.93)	<.001
No MMF at Screening	27 (32.9)	29 (36.7)	1.25 (0.64, 2.45)	0.509
Maximum MMF Dose				
≤2g	36 (24.0)	70 (42.9)	2.67 (1.61, 4.43)	<.001
>2g	4 (14.3)	3 (18.8)	1.56 (0.29, 8.42)	0.605

Notes: Asian includes Asian Indian, Chinese, Filipino, Japanese, Korean, Other Asian and Vietnamese.
Other race includes Black or African American, American Indian or Alaska Native, Multiple Race and Other.
Each model is based on a logistic regression with terms for treatment, baseline UPCR, biopsy class, MMF use at baseline, region, a subgroup term and subgroup by treatment interaction.

Summary of main efficacy results

The following table summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 47 Summary of efficacy for trial AUR-VCS-2016-01 (AURORA 1)

Title: 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 identifier	AUR-VCS-2016-01 AURORA 1 (Aurinia Renal Response in Active Lupus with Voclosporin) EudraCT Number: 2016-004045-81		
Design	Multicentre, randomised, double-blind, parallel-group, placebo-controlled, 2-arm study of voclosporin versus matching placebo. All subjects received background standard of care comprising mycophenolate mofetil (MMF) at 2 g/day, plus an initial treatment with 0.5 – 1.0 g intravenous (IV) methylprednisolone followed by a reducing taper of oral corticosteroid to a target of 2.5 mg/day by Week 16. Subjects who discontinued study treatment remained in the study and completed all visits and study assessments per schedule.		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		52 weeks Not applicable Not applicable
Hypothesis	Superiority		
Treatments groups	Placebo		Placebo 3 capsules twice daily (BID) for 52 weeks, N=178.
	Voclosporin 23.7 mg BID		Voclosporin 23.7 mg (3 capsules) BID for 52 weeks, N=179.
Endpoints and definitions	Primary	Adjudicated RR at Week 52	Adjudicated renal response (RR) at Week 52: Number of subjects showing RR at Week 52 as adjudicated by the Clinical Endpoints Committee (CEC) based on the following definition: urine protein creatinine ratio (UPCR) of ≤0.5 mg/mg; AND estimated glomerular filtration rate (eGFR) ≥60 mL/min/1.73 m^2 or no confirmed decrease from baseline in eGFR of ≥20% AND received no rescue medication for lupus nephritis (LN) AND did not receive more than 10 mg prednisone for ≥3 consecutive days or for ≥7 days in total during Weeks 44-52, just prior to the renal response assessment
	Secondary 1	Adjudicated RR at Week 24	Adjudicated RR at Week 24: Number of subjects showing RR at Week 24 as adjudicated by the CEC based on the definition above considering prednisone dose between Weeks 16-24
	Secondary 2	Partial RR at Week 52	Partial renal response (PRR) at Week 52: Number of subjects achieving PRR (defined as a 50% reduction in UPCR from baseline) at Week 52
	Secondary 3	PRR at Week 24	PRR at Week 24: Number of subjects achieving PRR (defined as above) at Week 24
	Secondary 4	Time to UPCR ≤ 0.5	Time to first instance of UPCR of ≤0.5 mg/mg (days)

	Secondary 5	Time to 50% reduction in UPCR from baseline	Time to first instance of 50% reduction in UPCR from baseline (days)
Database lock	01 November 2019		
Results and Analysis			
Analysis description	**Primary Analysis: Adjudicated Renal Response at Week 52**		
Analysis population	Intent to treat (ITT) (All randomised subjects, analysed based on randomised treatment)		
Descriptive statistics and estimate variability	Treatment group	Placebo	Voclosporin 23.7 mg BID
	Number of subjects	178	179
	Number (%) of Subjects achieving Adjudicated RR at Week 52	40 (22.5%)	73 (40.8%)
	Standard deviation	Not calculated	Not calculated
Effect estimate per comparison	Adjudicated RR at Week 52	Comparison groups	Voclosporin 23.7 mg BID vs Placebo
		Adjusted Odds Ratio	2.65
		95% CI	1.64, 4.27
		P-value (logistic regression)	<0.001
Notes	All subjects contributed to the analysis. Patients who withdrew from the study are treated as non-responders.		
Analysis population	Per protocol (PP) (All ITT subjects with no major protocol violations)		
Descriptive statistics and estimate variability	Treatment group	Placebo	Voclosporin 23.7 mg BID
	Number of subjects	156	161
	Number (%) of Subjects achieving Adjudicated RR at Week 52	38 (24.4%)	69 (42.9%)
	Standard deviation	Not calculated	Not calculated
Effect estimate per comparison	Adjudicated RR at Week 52	Comparison groups	Voclosporin 23.7 mg BID vs Placebo
		Adjusted Odds Ratio	2.55
		95% CI	1.55, 4.18
		P-value (logistic regression)	<0.001

Notes	A total of 40 subjects (11.2%) were excluded from the PP population, primarily due to non-compliance (18 subjects in the placebo arm and 10 subjects in the voclosporin arm). All subjects in the PP population contributed to the analysis. Subjects who withdrew from the study were treated as non-responders.		
Analysis description	**Secondary analysis 1: Adjudicated Renal Response at Week 24**		
Analysis population	Intent to treat		
Descriptive statistics and estimate variability	Treatment group	Placebo	Voclosporin 23.7 mg BID
	Number of subjects	178	179
	Number (%) of Subjects achieving Adjudicated RR at Week 24	35 (19.7%)	58 (32.4%)
	Standard deviation	Not calculated	Not calculated
Effect estimate per comparison	Adjudicated RR at Week 24	Comparison groups	Voclosporin 23.7 mg BID vs Placebo
		Adjusted Odds Ratio	2.23
		95% CI	1.34, 3.72
		P-value (logistic regression)	0.002
Notes	All subjects contributed to the analysis. Subjects who withdrew from the study were treated as non-responders.		
Analysis description	**Secondary analysis 2: Partial Renal Response at Week 52**		
Analysis population	Intent to treat		
Descriptive statistics and estimate variability	Treatment group	Placebo	Voclosporin 23.7 mg BID
	Number of subjects	178	179
	Number (%) of Subjects achieving PRR at Week 52	92 (51.7%)	125 (69.8%)
	Standard deviation	Not calculated	Not calculated
Effect estimate per comparison	Adjudicated RR at Week 52	Comparison groups	Voclosporin 23.7 mg BID vs Placebo
		Adjusted Odds Ratio	2.26
		95% CI	1.45, 3.51
		P-value (logistic regression)	<0.001
Notes	All subjects contributed to the analysis. Subjects who withdrew from the study were treated as non-responders.		
Analysis description	**Secondary analysis 3: Partial Renal Response at Week 24**		
Analysis population	Intent to treat		

Descriptive statistics and estimate variability	Treatment group	Placebo	Voclosporin 23.7 mg BID
	Number of subjects	178	179
	Number (%) of Subjects achieving PRR at Week 24	89 (50.0%)	126 (70.4%)
	Standard deviation	Not calculated	Not calculated
Effect estimate per comparison	Adjudicated RR at Week 24	Comparison groups	Voclosporin 23.7 mg BID vs Placebo
		Adjusted Odds Ratio	2.43
		95% CI	1.56, 3.79
		P-value (logistic regression)	<0.001
Notes	All subjects contributed to the analysis. Subjects who withdrew from the study were treated as non-responders.		
Analysis description	**Secondary analysis 4: Time to UPCR ≤0.5 mg/mg**		
Analysis population	Intent to treat		
Descriptive statistics and estimate variability	Treatment group	Placebo	Voclosporin 23.7 mg BID
	Number of subjects	178	179
	Median time to UPCR ≤0.5 mg/mg (days)	372	169
	95% CI	295, NC	141, 214
Effect estimate per comparison	Time to UPCR≤0.5	Comparison groups	Voclosporin 23.7 mg BID vs Placebo
		Hazard Ratio	2.02
		95% CI	1.51, 2.70
		P-value (log rank test)	<0.001
Notes	All subjects contributed to the analysis. Subjects who withdrew from study without achieving UPCR ≤0.5 were censored at their last UPCR assessment. NC = not calculated		
Analysis description	**Secondary analysis 5: Time to 50% reduction in UPCR**		
Analysis population	Intent to treat		
Descriptive statistics and estimate variability	Treatment group	Placebo	Voclosporin 23.7 mg BID
	Number of subjects	178	179
	Median time to 50% reduction in UPCR (days)	63	29

	95% CI	57, 87	29, 32
Effect estimate per comparison	Time to 50% reduction in UPCR	Comparison groups	Voclosporin 23.7 mg BID vs Placebo
		Hazard Ratio	2.05
		95% CI	1.62, 2.60
		P-value (log rank test)	<0.001
Notes	All subjects contributed to the analysis. Subjects who withdrew from study without achieving a 50% reduction in UPCR were censored at their last UPCR assessment.		

2.5.5.3. Analysis performed across trials (pooled analyses and meta-analysis)

Comparison and Analyses of Results Across Studies

The LN ITT population of the integrated analysis comprises 268 subjects in the voclosporin 23.7 mg BID group and 266 subjects in the placebo group from studies AURORA-1 and AURA-LV. With the exception of one subject in the voclosporin arm, all randomised subjects were treated with at least one dose of study treatment (and thus included in the safety population).

Table 48 Comparison of Primary Efficacy Endpoints in the AURORA 1 and AURA-LV Studies and in the Integrated Analysis

	AURORA 1	AURA-LV	Integrated Analysis
Terminology	Renal response	Complete remission	Renal response
Time point	Primary endpoint at 52 weeks, key secondary endpoint at 24 weeks	Primary endpoint at 24 weeks, secondary endpoint at 48 weeks	1-year (48-week data from AURA-LV and 52-week from AURORA 1) and 6-month time points used
Derivation	Adjudicated by CEC prior to unblinding; programmed response was secondary endpoint	Programmatically	Both approaches used. Post-hoc, blinded adjudication of response in AURA-LV was done using AURORA 1 definitions

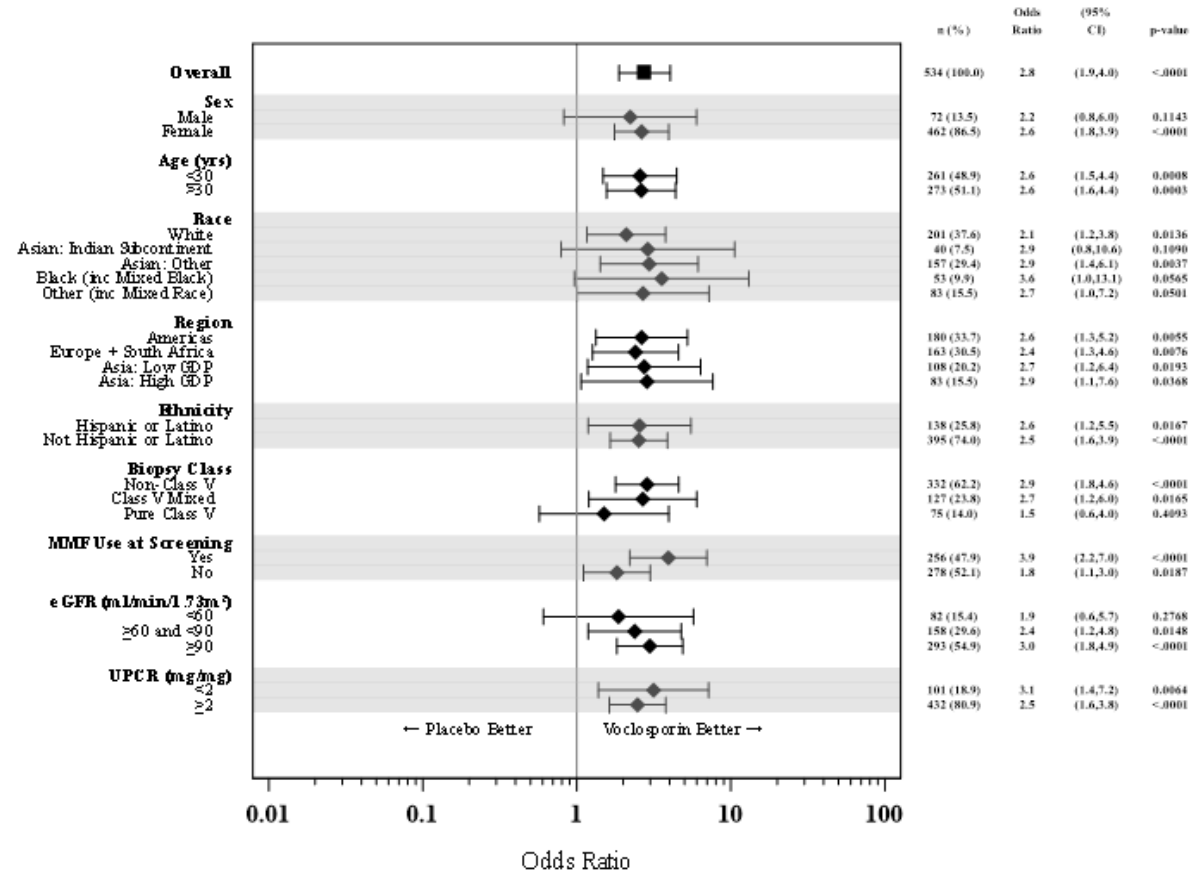
Notes: CEC = Clinical Endpoints Committee.

Table 49 Summary of Integrated Renal Response Analyses (Pooled LN ITT Population)

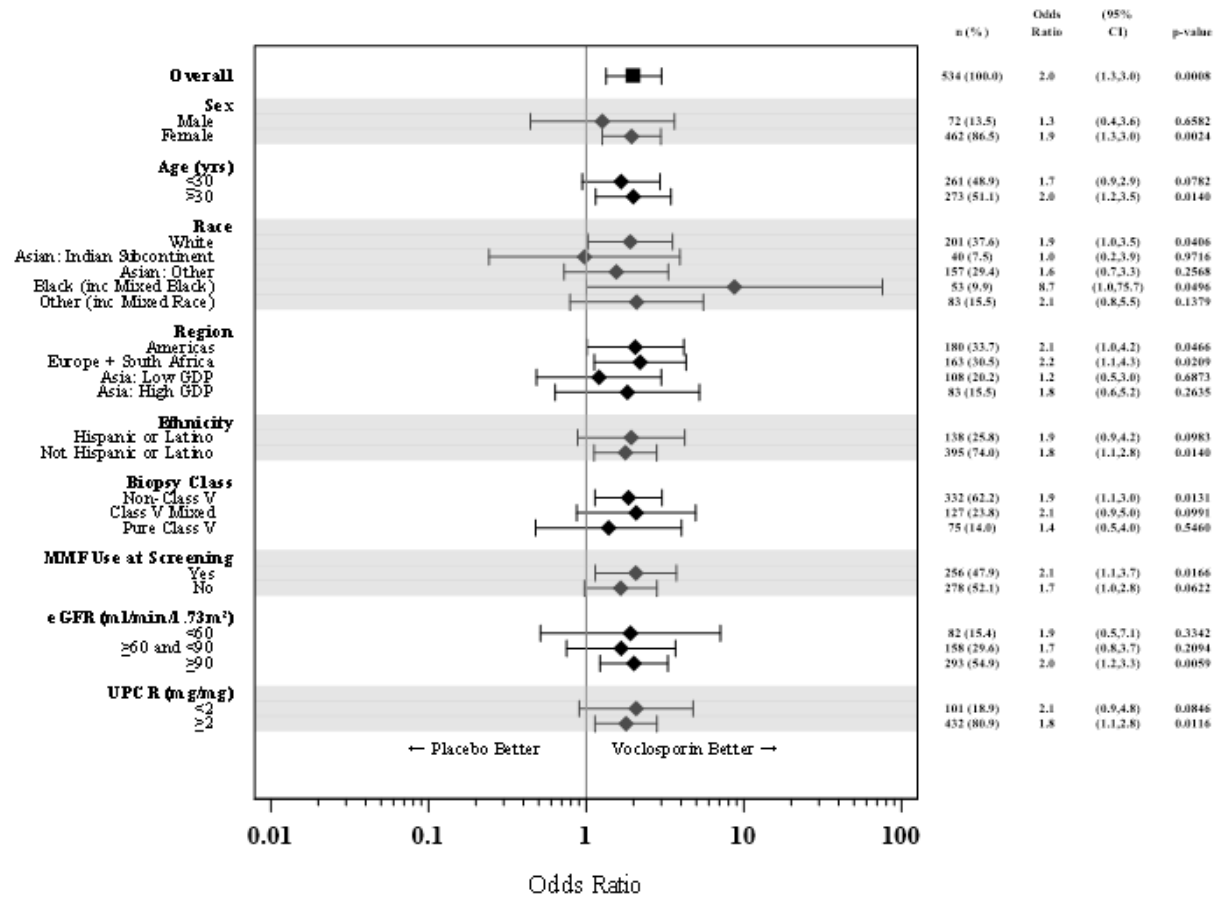
	1 Year			6 Months		
	Placebo (N=266) n (%)	Voclosporin 23.7 mg BID (N=268) n (%)	Odds Ratio 95% CI (vs placebo) p-value	Placebo (N=266) n (%)	Voclosporin 23.7 mg BID (N=268) n (%)	Odds Ratio 95% CI (vs placebo) p-value
Adjudicated Renal Response	62 (23.3)	117 (43.7)	2.76 (1.88, 4.05) <0.0001	54 (20.3)	85 (31.7)	2.01 (1.34, 3.01) 0.0008
Programmed Renal Response	60 (22.6)	110 (41.0)	2.61 (1.77, 3.84) <0.0001	52 (19.5)	87 (32.5)	2.16 (1.44, 3.25) 0.0002
Partial Renal Response	134 (50.6)	186 (69.4)	2.26 (1.58, 3.23) <0.0001	132 (49.8)	188 (70.1)	2.42 (1.68, 3.48) <0.0001
Programmed Renal Response with steroid taper (≤5 mg or ≤2.5 mg prednisone equivalent)						
Renal Response with ≤5 mg	57 (21.4)	105 (39.2)	2.57 (1.73, 3.80) <0.0001	52 (19.5)	80 (29.9)	1.90 (1.26, 2.87) 0.0021
Renal Response with ≤2.5 mg	53 (19.9)	101 (37.7)	2.58 (1.73, 3.84) <0.0001	26 (9.8)	49 (18.3)	2.28 (1.35, 3.84) 0.0019

Notes: Adjusted analysis used a logistic regression model with terms for study, treatment group, baseline UPCR, biopsy class, MMF use at screening, and region. Odds ratios greater than unity indicate benefit of voclosporin.
BID = twice daily; CI = confidence interval; LN ITT = lupus nephritis intent-to-treat; MMF = mycophenolate mofetil; UPCR = urine protein-creatinine ratio.

Figure 18 Forest Plot of Analysis Results of 1-Year Adjudicated Renal Response (Pooled LN ITT Population)



Notes: Analysis used a logistic regression model with terms for study, treatment group, sub-group, and treatment by sub-group interaction.
CI = confidence interval; eGFR = estimated glomerular filtration rate; GDP = Gross Domestic Product; ITT = intent-to-treat; LN = lupus nephritis; MMF = mycophenolate mofetil; UPCR = urine protein-creatinine ratio.



Notes: Analysis used a logistic regression model with terms for study, treatment group, sub-group, and treatment by sub-group interaction.
CI = confidence interval; eGFR = estimated glomerular filtration rate; GDP = Gross Domestic Product; ITT = intent-to-treat; LN = lupus nephritis; MMF = mycophenolate mofetil; UPCR = urine protein-creatinine ratio.

Figure 19 Forest Plot of Analysis Results of 6-Month Adjudicated Renal Response (Pooled LN ITT Population)

Clinical studies in special populations

Table 50 Overview of the Elderly Subjects Included in the Phase 2 and 3 Clinical Trials of Voclosporin (Safety Populations)

Trial	Age 65-74		Age 75-84		Age 85+	
	Voclosporin	Overall	Voclosporin	Overall	Voclosporin	Overall
CONTROLLED TRIALS						
Lupus Nephritis						
AURORA 1	0/178	2/356	0/178	0/356	0/178	0/356
AURA-LV	2/177	3/265	0/177	0/265	0/177	0/265
LN Total	2/355	5/621	0/355	0/621	0/355	0/621
Plaque Psoriasis						
ISA04-03	2/434	2/451	0/434	0/451	0/434	0/451
ISA05-25	24/490	36/642	4/490	5/642	0/490	0/642
Psoriasis Total	26/924	38/1093	4/924	5/1093	0/924	0/1093
Uveitis						
LX211-01	6/189	6/217	1/189	1/217	0/189	0/217
LX211-02	9/199	10/230	4/199	4/230	0/199	0/230
LX211-03	2/94	2/108	0/94	0/108	0/94	0/108
LX211-11	4/79	5/155	1/79	1/155	0/79	0/155
Uveitis Total	21/561	23/710	6/561	6/710	0/561	0/710
Renal Transplant						

ISA05-01	17/248	22/334	0/248	0/334	0/248	0/334
NONCONTROLLED TRIALS						
Lupus Nephritis						
AURION	0/10	0/10	0/10	0/10	0/10	0/10
Overall Total	66/2098	88/2768	10/2098	11/2768	0/2098	0/2768

Subjects randomised to placebo in ISA04-03 and ISA05-25 received placebo for 12 weeks and then were switched to 0.3 mg/kg BID voclosporin for the remainder of the trial.
The AURORA 2 and ISA05-02 trials are not included as these are extension studies and subjects are
already counted in the original trials (AURORA 1 and ISA04-03, respectively).

2.5.5.4. Supportive study(ies)

Data from the ongoing **AURORA 2** continuation study, as of 01 April 2021 were initially provided. Study AUR-VCS-2016-02 (AURORA 2) is now completed and the final CSR, the CSP and the SAP have been provided, as well as all other documentation.

Study Population and Disposition

Subjects who completed 52 weeks of treatment in the AURORA 1 study were eligible to continue with their randomised treatment for up to a further 24 months in the AURORA 2 continuation study (i.e., up to 36 months total exposure).

Of the 357 subjects who entered AURORA 1, a total of 216 subjects (60.5%) continued to receive blinded treatment beyond 12 months in the AURORA 2 study: 116/179 subjects (64.8%) from the voclosporin arm and 100/178 subjects (56.2%) from the placebo arm.

Of the other 141 subjects who entered AURORA 1, 46 subjects withdrew prematurely from the study (15 from the voclosporin arm and 31 from the placebo arm), and 28 subjects in each arm who completed the AURORA 1 study had permanently discontinued study treatment and thus were not eligible to participate in AURORA 2. A further 18 subjects did not enter AURORA 2 for administrative reasons (such as health authority approval not received in time or a decision taken that the site or country would not participate) and 7 subjects did not give consent as they were planning a pregnancy or were moving out of the area. The reasons for non-participation for the remaining 14 subjects who were potentially eligible but did not enter AURORA 2 were not captured.

Table 51 Summary of Demographics for AURORA 1 Subjects Enrolled or Not Enrolled into AURORA 2 (ITT)

Parameter	AURORA 2 Placebo (N=100)	AURORA 2 23.7 mg BID (N=116)	AURORA 2 Overall (N=216)	AURORA 1 Only Placebo (N=78)	AURORA 1 Only 23.7 mg BID (N=63)	AURORA 1 Only Overall (N=141)
Age (years)						
Mean (SD)	35.4 (11.64)	32.3 (10.31)	33.7 (11.03)	31.4 (9.75)	33.7 (12.03)	32.3 (10.85)
Median	33.0	30.0	31.0	29.0	31.0	30.0
Min, Max	18, 72	18, 59	18, 72	18, 68	19, 62	18, 68
Sex n (%)						
Male	12 (12.0)	11 (9.5)	23 (10.6)	14 (17.9)	7 (11.1)	21 (14.9)
Female	88 (88.0)	105 (90.5)	193 (89.4)	64 (82.1)	56 (88.9)	119 (85.1)
Race n (%)						
White	40 (40.0)	44 (37.9)	84 (38.9)	21 (26.9)	24 (38.1)	45 (31.9)
Asian	30 (30.0)	30 (25.9)	60 (27.8)	26 (33.3)	23 (36.5)	49 (34.8)
Black	7 (7.0)	18 (15.5)	25 (11.6)	12 (15.4)	8 (12.7)	20 (14.2)
Other	23 (23.0)	24 (20.7)	47 (21.8)	19 (24.4)	8 (12.7)	27 (19.1)
Ethnicity n (%)						
Hispanic or Latino	33 (33.0)	39 (33.6)	72 (33.3)	26 (33.3)	18 (28.6)	44 (31.2)
Not Hispanic or Latino	67 (67.0)	77 (66.4)	144 (66.7)	51 (65.4)	45 (71.4)	96 (68.1)
Unknown	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.3)	0 (0.0)	1 (0.7)
Region n (%)						
Americas	36 (36.0)	49 (42.2)	85 (39.4)	38 (48.7)	26 (41.3)	64 (45.4)
Europe + S. Africa	37 (37.0)	38 (32.8)	75 (34.7)	15 (19.2)	14 (22.2)	29 (20.6)
Asia	27 (27.0)	29 (25.0)	56 (25.9)	25 (32.1)	23 (36.5)	48 (34.0)
Weight (kg)						
Mean (SD)	65.2 (14.65)	66.6 (16.24)	65.9 (15.51)	68.3 (17.75)	66.3 (18.65)	67.4 (18.12)
Median	64.2	65.2	64.6	63.5	60.4	62.5
Min, Max	36, 114	37, 121	36, 121	41, 138	36, 142	36, 142

Note Black race includes mixed race where black is recorded. All other mixed race codes to Other.
BID = twice daily; ITT = intent-to-treat; SD = standard deviation.

The two treatment arms in AURORA 2 were balanced with respect to SLE history and comorbidities. The mean time since SLE diagnosis was approximately 7 years (range <1 to 38 years), and the majority of subjects reported mucocutaneous, musculoskeletal, and haematological involvement. As in the full AURORA 1 population, hypertension and hyperlipidemia were the most common comorbidities, affecting 69% and 48% of subjects, respectively, with the majority of cases considered related to SLE.

The mean time since first proteinuria and mean time since LN diagnosis were slightly higher in subjects entering AURORA 2 (4.8 years and 4.9 years, respectively) than for the full AURORA 1 population (4.7 years and 4.6 years, respectively)

Table 52 Summary of Renal History (Prior to First Dose in AURORA 1)

Parameter	Placebo (N = 100)	Voclosporin (N = 116)	Overall (N = 216)
Number of years since the 1st instance of a significant proteinuria (>500 mg/day)			
n	87	103	190
Mean (SD)	4.7 (4.49)	5.0 (5.15)	4.8 (4.85)
Median	3.0	3.0	3.0
Min [1], Max	1, 23	1, 26	1, 26
Number of years since the first diagnosis of LN			
n	100	116	216
Mean (SD)	5.0 (5.23)	4.8 (5.27)	4.9 (5.24)
Median	3.0	2.0	2.5
Min [1], Max	1, 28	1, 26	1, 28
Any previous dialysis, n (%)			
Yes	1 (1.0)	1 (0.9)	2 (0.9)
No	99 (99.0)	115 (99.1)	214 (99.1)
Number of years since the last dialysis			
n	1	1	2
Mean (SD)	15.0 (NA)	2.0 (NA)	8.5 (9.19)
Median	15.0	2.0	8.5
Min, Max	15, 15	2, 2	2, 15

1 Durations of <1 year were rounded to 1 year.
Notes: Data collected prior to first dose in AURORA 1
LN = lupus nephritis; NA = not applicable; SD = standard deviation.

Table 53 Summary of Kidney Biopsy, UPCR and eGFR at Baseline (Prior to First Dose in AURORA 1

Parameter	Placebo (N = 100)	Voclosporin (N = 116)	Overall (N = 216)
UPCR (mg/mg)			
Mean (SD)	3.868 (2.4764)	3.941 (2.5766)	3.907 (2.5251)
Median	2.963	2.811	2.921
Min, Max	0.79, 14.47	0.22, 13.11	0.22, 14.47
eGFR (mL/min/1.73m^2)			
Mean (SD)	92.0 (28.04)	94.1 (31.36)	93.2 (29.82)
Median	99.0	92.5	97.0
Min, Max	25, 140	39, 168	25, 168
KIDNEY BIOPSY CLASS [1], n (%)			
Pure CLASS III	21 (21.0)	13 (11.2)	34 (15.7)
Pure CLASS IV	37 (37.0)	64 (55.2)	101 (46.8)
Pure CLASS V	14 (14.0)	17 (14.7)	31 (14.4)
CLASS III and CLASS V Only	12 (12.0)	11 (9.5)	23 (10.6)
CLASS IV and CLASS V Only	16 (16.0)	10 (8.6)	26 (12.0)

1 One subject in the voclosporin arm was reported to be Class IIIA and Class IV-S, A and was not included in the biopsy class summary.
Notes: Baseline UPCR is defined as the average of the latest 2 pre-randomization values.
Data collected prior to the first dose in AURORA 1.
eGFR = estimated glomerular filtration rate; SD = standard deviation; UPCR = urine protein creatinine ratio.

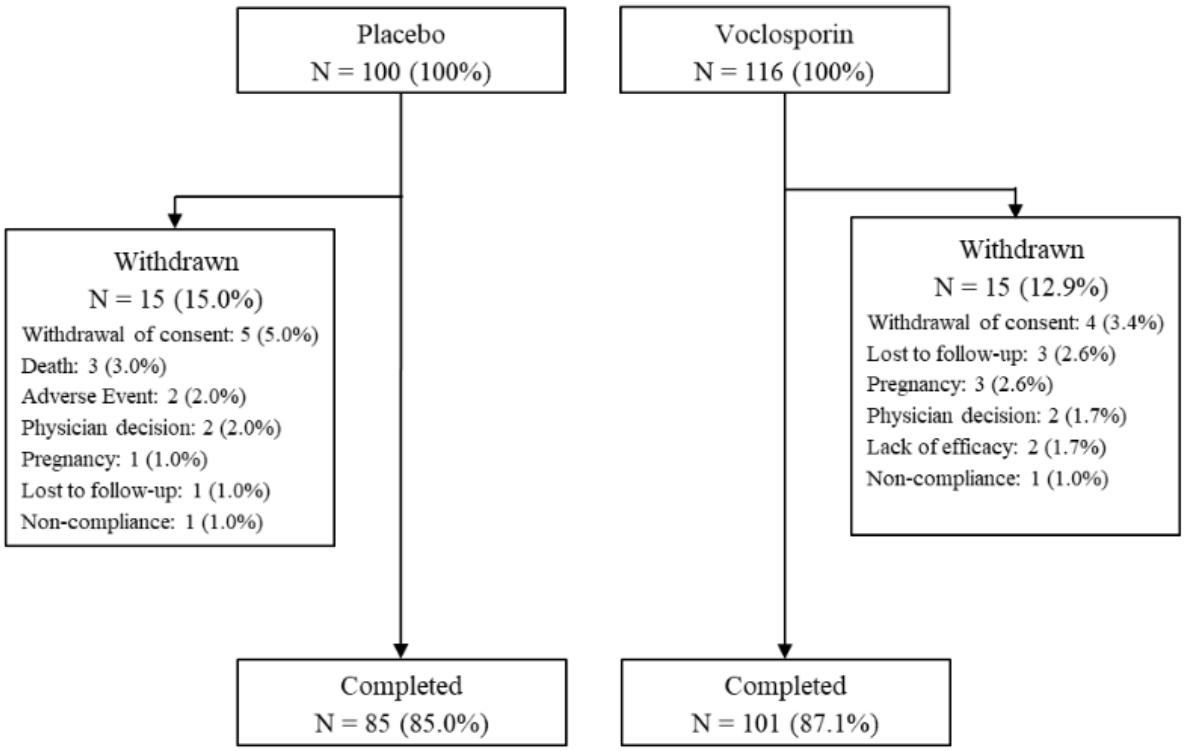


Figure 20 Subject Disposition – AURORA 2

Table 54 Summary of study drug discontinuation in AURORA 2

Parameter	Placebo (N = 100)	Voclosporin (N = 116)	Overall (N = 216)
Discontinuation from Study Medication	27 (27.0)	24 (20.7)	51 (23.6)
Primary reasons for early permanent withdrawals			
Intolerable adverse event	14 (14.0)	7 (6.0)	21 (9.7)
Death	1 (1.0)	0	1 (0.5)
Lost to follow up	1 (1.0)	3 (2.6)	4 (1.9)
Physician decision	0	2 (1.7)	2 (0.9)
Prohibited medication required	3 (3.0)	0	3 (1.4)
Pregnancy	0	3 (2.6)	3 (1.4)
Protocol non-compliance	0	1 (0.9)	1 (0.5)
Withdrawal of consent	3 (3.0)	3 (2.6)	6 (2.8)
Lack of efficacy	1 (1.0)	5 (4.3)	6 (2.8)
Other	4 (4.0)	0	4 (1.9)

As in AURORA 1, decreases in eGFR and increases in blood pressure were managed by dose modifications per protocol guidance. Across the total treatment duration (up to 3 years), more subjects in the voclosporin arm than the placebo arm had their dose of study drug modified (decreased): 39.7% of voclosporin subjects recorded no dose changes compared with 58.0% of placebo subjects. The proportion of subjects with no dose changes increased year on year in the voclosporin arm, from 55.2% in Year 1 to 78.4% in Year 3. In the placebo arm, 74% of subjects had no dose changes in Year 1, rising to 87.1% in Year 3. In years 2 and 3 of treatment, 42.2% of voclosporin subjects and 25.0% of placebo subjects recorded dose decreases and a higher proportion of subjects in both treatment groups consistently received the target dose of 47.4 mg per day (49.1% and 69.0%, respectively)

There were no notable differences in MMF or corticosteroid dosing between the two groups. The majority of dose changes in the voclosporin arm were due to changes in eGFR levels.

The AURORA 2 protocol allowed the investigator to reduce the dose of voclosporin or placebo to 2 capsules BID after 24 months of treatment in a subject whose UPCR was well controlled In practice, few investigators acted upon this, and only 3 placebo subjects and 6 voclosporin subjects had their dose reduced at 2 years (12 month in AURORA 2) as permitted. Fewer subjects in the voclosporin arm (78.4%) than the placebo arm (91.0%) were taking the full dose of 3 capsules BID of study treatment at the end of AURORA 1. This proportion dropped in both arms over the next two years to 49.1% and 64%, respectively, at the end of the AURORA 2 study.

The majority of subjects (at least 85% in each arm) were taking ≤2.5 mg/day prednisone (or equivalent) at the end of AURORA 1 (Month 12). Over the 2 years of the AURORA 2 study, this reduced slightly to approximately 80%, and at Month 36, 78% of placebo subjects and 76% of voclosporin subjects were on 2.5 mg or less per day.

Table 55 Logistic Regression Analysis of Renal Response by Visit

		Placebo (N = 100)	Voclosporin (N = 116)	Odds Ratio vs Placebo (95% CI)	p-value
Month 6 (AURORA 1)					
Yes	n (%)	26 (26.0)	47 (40.5)	2.19 (1.19, 4.04)	0.012
No	n (%)	74 (74.0)	69 (59.5)		
Month 12 (End of AURORA 1)					
Yes	n (%)	34 (34.0)	61 (52.6)	2.30 (1.30, 4.05)	0.004
No	n (%)	66 (66.0)	55 (47.4)		
Month 18 (AURORA 2)					
Yes	n (%)	46 (46.0)	74 (63.8)	2.19 (1.25, 3.83)	0.006
No	n (%)	54 (54.0)	42 (36.2)		
Month 24 (AURORA 2)					
Yes	n (%)	43 (43.0)	65 (56.0)	1.81 (1.04, 3.16)	0.035
No	n (%)	57 (57.0)	51 (44.0)		
Month 30 (AURORA 2)					
Yes	n (%)	42 (42.0)	69 (59.5)	2.24 (1.28, 3.92)	0.005
No	n (%)	58 (58.0)	47 (40.5)		
Month 36 (End of AURORA 2)					
Yes	n (%)	39 (39.0)	59 (50.9)	1.74 (1.00, 3.03)	0.051
No	n (%)	61 (61.0)	57 (49.1)		

Notes: The model is based on a logistic regression with terms for treatment, baseline UPCR, biopsy class, MMF use at baseline and region.
Subjects who withdrew from the study prior to the visit assessments and thus provide insufficient visit data were defined as non-responders.
CI = confidence interval; MMF = mycophenolate mofetil; UPCR = urine protein creatinine ratio.

Renal flares:

The CEC adjudicated adequate renal response, renal flares and recovery of renal flares from the start of treatment in AURORA 1 for all 216 subjects who entered AURORA 2. In order to experience a renal flare, a patient must have achieved an adequate response to treatment as judged by the CEC. A sustained reduction in UPCR to ≤0.7 mg/mg was considered an adequate response, based on clinical judgement and allowing for small inherent fluctuations. A patient could experience a flare from the

point they achieved a response (or recovery). Renal flares were judged according to the following criteria:

- A reproducible increase to UPCR >1 mg/mg from a post-response baseline of <0.2 mg/mg or
- an increase to UPCR >2 mg/mg from a post-response baseline between 0.2 to 1.0 mg/mg or
- a doubling of UPCR for baseline values of UPCR >1 mg/mg

Table 56 Adjudicated renal flares (AURORA 1 and AURORA 2)

	Placebo (N = 100) n (%)	Voclosporin (N = 116) n (%)	Odds Ratio vs Placebo (95% CI)	p-value
Overall				
Number of Subjects with Adequate Response	73 (73.0)	101 (87.1)		
Number of Subjects with Renal Flares	19 (26.0)	24 (23.8)	0.85 (0.42, 1.73)	0.662
Year 1 (Study Days 1-365)				
Number of Subjects with Adequate Response	62 (62.0)	93 (80.2)		
Number of Subjects with Renal Flares	9 (14.5)	6 (6.5)	0.35 (0.11, 1.07)	0.066
Year 2 (Study Days 366-730)				
Number of Subjects with Adequate Response	68 (68.0)	98 (84.5)		
Number of Subjects with Renal Flares	8 (11.8)	12 (12.2)	1.00 (0.38, 2.64)	0.995
Year 3 (Study Days 731 -->)				
Number of Subjects with Adequate Response	73 (73.0)	101 (87.1)		
Number of Subjects with Renal Flares	6 (8.2)	12 (11.9)	1.43 (0.50, 4.08)	0.504

Notes: An odds ratio < unity indicates benefit of voclosporin.
Subjects are defined as responders / non-responders as per CEC adjudication.
Percentages for subjects who responded are based on the number subjects in AURORA 2 Population.
Percentages for subjects with flares are based on the number subjects who responded prior to the visit.
The model is based on a logistic regression with terms for treatment, baseline UPCR, biopsy class, MMF use at baseline and region.

The CEC adjudicated 4 placebo subjects and 5 voclosporin subjects as having severe renal flares.

A further analysis was performed looking at the proportion of subjects who achieved an adequate response and did not have a renal flare. These subjects can be considered to have a positive renal outcome. Using these criteria, more voclosporin subjects than placebo subjects achieved a good outcome (66.4% vs 54.0%; OR 0.56; 95% CI 0.32, 0.99; p=0.045)

Table 57 Adjudicated Good Renal Outcome (AURORA 1 and AURORA 2)

	Placebo (N = 100) n (%)	Voclosporin (N = 116) n (%)	Odds Ratio vs Placebo (95% CI)	p-value
Overall				
Number of Subjects without Adequate Response or with Flares	46 (46.0)	39 (33.6)		
Number of Subjects with Adequate Response and without Flares	54 (54.0)	77 (66.4)	0.56 (0.32, 0.99)	0.045
Year 1 (Study Days 1-365)				
Number of Subjects without Adequate Response or with Flares	47 (47.0)	29 (25.0)		
Number of Subjects with Adequate Response and without Flares	53 (53.0)	87 (75.0)	0.33 (0.18, 0.60)	<.001
Year 2 (Study Days 366-730)				
Number of Subjects without Adequate Response or with Flares	40 (40.0)	30 (25.9)		
Number of Subjects with Adequate Response and without Flares	60 (60.0)	86 (74.1)	0.49 (0.27, 0.88)	0.017
Year 3 (Study Days 731 -->)				
Number of Subjects without Adequate Response or with Flares	33 (33.0)	27 (23.3)		
Number of Subjects with Adequate Response and without Flares	67 (67.0)	89 (76.7)	0.58 (0.31, 1.07)	0.079

Notes: An odds ratio < unity indicates benefit of voclosporin.
Good renal outcome is defined as with adequate response and without flare.
The model is based on a logistic regression with terms for treatment, baseline UPCR, biopsy class, MMF use at baseline and region.
CI = confidence interval; MMF = mycophenolate mofetil; UPCR = urine protein creatinine ratio.

AURION (AUR-VCS-2014-01)

This study was an open label study conducted at 2 sites in Malaysia and enrolled 10 Asian, female subjects with LN. The subjects were aged between 23 and 36 years at the start of the study, with a median duration of LN of 5.5 years (range 2 to 12 years). Subjects received 23.7 mg BID for 48 weeks with a background therapy of MMF 2 g daily and IV and oral corticosteroids. Complete remission was achieved in a total of 7/10 (70.0%) subjects at Week 24 and 4/8 (50.0%) subjects at Week 48. Improvements from baseline in UPCR, urine protein, and serum albumin levels were observed across all visits, with median changes from baseline to Week 48 of -0.55 mg/mg, -0.09 g/L, and 3.0 g/L, respectively. However, also increases in serum creatinine levels from baseline were observed (median increase of 15.5 µmol/L to Week 48). The small sample size and lack of control group mean that it is not possible to draw firm conclusions from this study.

2.5.6. Discussion on clinical efficacy

The applicant applied for the following indication:

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

Four clinical studies are included for efficacy analysis in this application. Two phase 2 studies (AURION and AURA-LV), one pivotal phase 3 study (AURORA 1) and final results from the AURORA 1 continuation study (AURORA 2).

Dose selection

Dose selection for the phase 2 AURA-LV study was based on previous experience with VCS in studies in healthy subjects and in other autoimmune indications (i.e., renal transplant, plaque psoriasis, and non-infectious uveitis). In these autoimmune indications, subjects were administered VCS at doses ranging from 0.2 mg/kg BID to 0.8 mg/kg BID. In consideration of the efficacy and safety of VCS in these studies, doses equivalent to approximately 0.3 to 0.4 mg/kg BID (low-dose) and 0.5 to 0.6 mg/kg BID (high-dose) were selected for the AURA-LV study, i.e., 23.7 mg BID (three capsules BID) and 39.5 mg BID (five capsules BID).

AURA-LV was a phase II randomised controlled double-blind study comparing the Efficacy and Safety of two doses of Voclosporin (23.7 mg BID or 39.5 mg BID) with Placebo in Achieving renal remission in patients with Active Lupus Nephritis. The length of the study was 48 weeks with primary endpoint assessed at 24 weeks. Inclusion and exclusion criteria were in line with the pivotal phase 3 AURORA 1 study (see below), with some minor difference that do not influence the ability to compare the result from the two studies. Study treatments were administered in 4 treatment arms: low-dose Voclosporin (3 capsules, 23.7 mg BID), low-dose placebo (3 capsules BID), high-dose Voclosporin (5 capsules, 39.5 mg BID) and high dose placebo (5 capsules BID). Thus, there was no blinding regarding dose levels of active treatment (high vs low), only to placebo. All participants received background SoC with corticosteroids and MMF. The primary efficacy endpoint was the number of subjects showing so called complete remission at Week 24 and secondary efficacy endpoints include complete remission at Week 48. It should be noted that although the term "complete remission" was used for the primary composite endpoint in the AURA-LV study, it was similar to the endpoint "renal response" used in the AURORA-1 study. Lack of multiplicity adjustment in this study leads to an increased possibility of observing a statistically significant result purely by chance.

A total of 265 subjects were randomised (88 to the placebo group (low/high placebo-dose combined), 89 to the low-dose Voclosporin (23.7 mg BID) group, and 88 to the high-dose Voclosporin (39.5 mg BID) group. Of these, 223 (84.2%) subjects completed the study, 70 (79.5%) subjects in the placebo group, 73 (82.0%) in the low-dose VCS group, and 80 (90.9%) in the high-dose VCS group. A total of 185 (69.8%) subjects completed 48 weeks of treatment with the study drug, with similar proportions in each treatment group. There were however more deaths in the low dose VSC group 10 (11.5%) compared with the high dose VCS group 2 (2.3%) and placebo 1 (1.1%). There were several notable differences in the composition of the treatment groups. More participants from Asia were randomised to the low dose VCS group and the low dose VCS group also consisted of patients with a longer disease duration and a more severe kidney disease at baseline. The low dose VSC group also had more haematological SLE involvement at baseline. Investigation of this difference revealed that there was a local imbalance in randomisation with subjects from low gross domestic product (GDP) countries (Bangladesh, Sri Lanka, Philippines) over-represented in the 23.7 mg voclosporin arm: 47.2% of subjects in the 23.7 mg voclosporin group were recruited from low GDP countries compared with 37.5% of subjects in the 39.5 mg group and 31.8% in the placebo group. This difference between the 23.7 mg group and the placebo group was statistically significant (p=0.0365). It could be agreed that this could explain difference in other baseline characteristics and also the discrepancies in deaths seen between the groups. However, regarding the local imbalance in randomisation, the applicant was asked to provide further details on this issue, including a description of steps undertaken to minimise selection bias in AURA-LV study. The CHMP considered that the described processes appear robust, and the described steps seems adequate to minimize the risk of selection bias.

The AURA-LV study met its primary endpoint. At Week 24, complete remission was achieved by a higher proportion of subjects in both the low-dose (32.6%) and high-dose (27.3%) voclosporin groups compared to the placebo group (difference 19.3%, OR=2.03; 95% CI: 1.01, 4.05; p=0.045 low dose vs placebo). At Week 48, complete remission was achieved by a higher proportion of subjects in both the low-dose (49.4%) and high dose (39.8%) voclosporin groups compared to the placebo group (23.9%). There was no formal comparison between the two doses and no clear dose-response connection was apparent in the AURA-LV study, but slightly more AEs with the higher dose and thus the lower dose was chosen to the phase 3 AURORA-1 study. This was considered acceptable by the CHMP.

Design and conduct of clinical studies

The applicant received a Scientific Advise (EMEA/H/SA/3483/1/2017/SME/III) in March 2017. Some recommendations were incorporated in the pivotal study AURORA 1 (e.g primary efficacy endpoint at week 52 instead of 24, inclusion of UPCR ≤0.5 instead of ≤0.7 and agreement to run a continuation study for 24 months after completion of AURORA 1 to allow a further assessment of the sustained long-term effect of voclosporin under double-blind, placebo-controlled conditions). However, there were also several points that diverged from the EMA advice, the major related to the definition of stable renal function in the composite primary endpoint "renal response". This, and other deviation from the recommendation will be discussed later in the report.

Pivotal Phase 3 study AURORA 1

AURORA 1 was a phase 3, randomised, double-blind, parallel-group, placebo-controlled, multicentre, 2-arm study of voclosporin versus matching placebo. Voclosporin at a dose of 23.7 mg BID or matching placebo were administered for 52 weeks with a background therapy of MMF and corticosteroids with a tapering schedule. The double blind, parallel group, randomised trial design with placebo given in add-on to standard of care therapy is in line with the EMA SLE/Lupus nephritis guideline. However, as pointed out in the GL, the 52-week trial design seems too short for the claimed indication "treatment", which are supposed to include both induction and maintenance therapy. To address comments in the previous Scientific Advice (SA), the applicant agreed to conduct a double-blind follow up study (AURORA 2), and initially an interim analysis from that study was provided. Study AUR-VCS-2016-02 (AURORA 2) is now completed and the final CSR, the CSP and the SAP have been provided, as well as all other documentation.

Eligible subjects in the study were 18-75 years old with SLE and active, biopsy-proven lupus nephritis Class III, IV or V (or V in combination with III or IV). According to the GL, "*active nephritis should be properly documented by increments in the total protein to creatinine ratio (UPCR), the presence of sediment and/or a significant decrease in renal function"*. It is noted that in the inclusion criteria, activity is only defined by the level of proteinuria (in relation to the biopsy results) with no requirement for significant decrease in renal function or presence of sediment. However, the patient should also be, in the opinion of the investigator, in need of high-dose corticosteroids and immunosuppressive therapy. Therefore, it could be agreed that the patient had active disease at baseline and upon request from the CHMP the applicant agreed to revise the wording of the indication to reflect that the treatment is indicated in LN patients with **active** disease.

It is noted that the time period for a kidney biopsy prior to screening was extended from 6 months in AURA-LV to 2 years in the AURORA 1 study. To ensure active disease, subjects with a biopsy between 6 months and 2 years prior to screening were additionally required to have had at least a 50% increase in UPCR within the last 6 months. In addition, data for any subject with a biopsy performed

more than 6 months prior to screening were reviewed by the Medical Monitor to ensure eligibility for treatment with systemic immunosuppression. This approach is acceptable to CHMP. However, it should be noted that it is not uncommon for patients to switch from one biopsy class to another after treatment, making it difficult to fully classify this group.

Voclosporin was orally administered at a dose of 23.7 mg BID given as three 7.9 mg soft gel capsules per dose for 52 weeks. Dose adjustments were allowed based on eGFR and blood pressure elevation. All patients received background therapy with corticosteroids and MMF.

Corticosteroids were given intravenous 1 g Day 1 and/or Day 2 combined (0.5 g in subjects who weighed <45 kg) followed by 20 mg/day for subjects <45 kg and 25 mg/day for subjects ≥45 kg. The dose was reduced according to a protocol-specified tapering schedule. The aim was for all subjects to have their steroid dose reduced to 2.5 mg/day by the end of Week 16.

Subjects with a lack of response were allowed one 4-week interval without dose reduction or one dose escalation to the previous dose for 2 weeks at any time during the study. Lack of response was defined as no or minimal change in UPCR per Investigator judgment over 3 visits or deterioration in UPCR not meeting the criteria for withdrawal. Additional information provided by the applicant upon CHMP request showed that there was no notable difference between dose groups in the proportion of subjects recording an increase in corticosteroid dose during the first 16 weeks of the trial (placebo: 14.6% of subjects; voclosporin: 12.8% of subjects). No information regarding any dose escalation later in the study was provided; however, since >80 % of the patients were able to decrease their steroid doses to 2.5 mg/day or less at week 16, a small, short increase in corticosteroid dose would not have any major impact on the result.

Subjects who were receiving MMF prior to randomisation continued without interruption. Subjects on azathioprine or mycophenolate sodium at screening were switched to MMF at baseline (Day 1). For subjects who were not already taking prescribed MMF prior to randomisation, the dosing of MMF started at 0.5 g BID for a total daily dose of 1 g/day for the first week, increasing to 1 g BID for a total daily dose of 2 g/day for the second and subsequent weeks (i.e., beginning on Day 8). Regarding the MMF dose, the applicant states *"Approval by the Medical Monitor is required for subjects taking a dose other than 2 g/day MMF from randomization onwards (e.g., total daily dose of 1 or 3 g/day)"*. However, it was unclear if a pre-defined criteria based on lack of response for increasing the dose of MMF to 3 g/d was defined, as suggested in the SA. Upon CHMP request, the applicant clarified that there were no predefined criteria for increasing the dose of MMF in AURORA 1 trial; investigators could adjust the MMF dose according to their professional judgement. However, the investigators were blinded and the overall exposure to MMF in g/day was comparable in both treatment arms (mean (SD) were 1.960 (0.3779) in placebo compared to 1.875 (0.4005) in voclosporin). Therefore, the CHMP concluded that the lack of a pre-defined criteria did not seem to impact study results.

All patients received MMF as "*background immunosuppressive therapie*s", and no other immunosuppressive therapy were allowed. This was a major concern during the assessment that the risk of infections and nephrotoxicity could be elevated when combined with other immunosuppressants, especially cyclophosphamide. Thus, at the CHMP's request, the applicant has submitted a revised product information and revised their claimed indication to combination with mycophenolate mofetil only.

The primary endpoint renal response is a combined endpoint. To achieve the primary endpoint "renal response" the patient must have urine protein to creatine ration (UPCR) ≤0.5, an eGFR ≥60 mL/min/1.73 m2 or no confirmed decrease from baseline in eGFR of >20% and not have received any rescue treatment or more than 10 mg prednisone for ≥3 consecutive days or for ≥7 days in total during Weeks 44-52. The primary endpoint is not fully in line with the EMA GL, especially with respect to the eGFR value used.

According to the EMA GL, "*Studies conducted in patients with lupus nephritis should be aimed for the control of renal activity. It is expected that primary endpoints should be contextualised by reference to clinically meaningful values for major/complete response, such as normalisation/return to baseline of measured GFR or proteinuria of <0.5 g/24-h. A partial response, i.e. not full recovery but renal response able to maintain an eGFR within pre-specified margins with respect to baseline values, could only be accepted as primary endpoint if prospectively defined and relevance is well justified*".

It should be noted that according to the applicant's definition of stable renal function (*an eGFR ≥60 mL/min/1.73 m2 or no confirmed decrease from baseline in eGFR of >20%)*, a patient will be regarded as having a stable renal function even if the eGFR will drop from >90 to 61 or from 60 to 40. It is not fully clear why the applicant kept this definition, despite the strong recommendation against using it.

In the EMA SA it was suggested using a stricter endpoint, not allowing a decrease of eGFR more than 10-15% regardless of eGFR values. The applicant has however included this endpoint in complementary analysis

The endpoint chosen by the applicant includes a strict definition regarding the amount of proteinuria allowed to be a responder (i.e UPCR ≤0.5). The CHMP considers that it is a clinically relevant measurement since a reduction in proteinuria to levels below 0.5-0.7 has been associated with improved renal survival. Also the key secondary endpoints reflect different aspects of reducing proteinuria.

Considering the above and the fact that the presented results are considered as robust and are supporting a clinically relevant effect, this issue of the choice of the primary endpoint was not further pursued by the CHMP.

The primary efficacy outcome was adjudicated, i.e., blinded data were reviewed by a Clinical Endpoints Committee (CEC), a group of external experts consisting of a chairperson along with two nephrologists and two rheumatologists. Each case was reviewed separately by one nephrologist and one rheumatologist, who each recorded their adjudicated outcome. The Chair then reviewed each case. Where the three outcomes were not unanimous, the CEC met to agree on the adjudicated outcome. The applicant provided additional information regarding this and disagreement within the CEC in adjudicating the primary outcome in AURORA 1 occurred in 16 cases. This amounts to approximately 4.5% of the total randomised participants, which is a rather small proportion of all randomised participants. In the majority of cases, the final adjudication was that the subject had achieved renal response (12/16, i.e. 75%). In voclosporin arm 9/11 (≈82%) subjects were finally adjudicated as achieving response while in placebo arm 3/5 (=60%) subjects were finally adjudicated as achieving response. Due to small numbers (particularly in placebo arm), no conclusions can be made regarding this imbalance in positive adjudication.

The five key secondary endpoints, renal response at week 24, partial renal response at week 52 and at week 24, time (days) to UPC of ≤5 and time (days) to 50 % reduction in UPCR from baseline all reflected aspects of the primary endpoint, where proteinuria is the main feature. It is acknowledged that the data in the scientific literature indicates that reduction in proteinuria at 12 months represents the best single predictor for long- term renal outcome (ie, risk for end- stage kidney disease (ESKD) or doubling of serum creatine after 10 years). Specifically, proteinuria reduction to 0.5- 0.7 g/day in response to treatment is associated with increased long-term kidney survival and is recommended as a treatment target in LN (2019 EULAR/ERA-EDTA recommendation for the management for lupus nephritis). According to that recommendation, evidence of improvement in proteinuria (with GFR normalisation/stabilisation) should be noted by 3 months, and at least 50% reduction in proteinuria by 6 months. Thus, the key secondary endpoints are considered relevant.

Other endpoints evaluated duration of the response, change from baseline in serology, change from baseline in eGFR, SLE activity index and HRQoL parameters and also renal response in patients on low-dose corticosteroids. However, to be in line with the GL and as pointed out in the SA, the incidence, severity, and type of renal flares throughout induction and maintenance phases should be assessed, and upon request the applicant provided this information, see further below in the report.

The CHMP guideline (EMA/CHMP/51230/2013) states that "*If patients with SLE are included, it should be ensured that any benefit in renal functioning is not offset by a deleterious effect on other organs. Therefore, this should be assessed either as a component of a co-primary endpoint or as a key secondary endpoint.*" During the discussion meeting the applicant proposed "Change from baseline in the SELENA-SLEDAI Index score at Weeks 24 and 52" as a secondary endpoint. The SA recommended inclusion of the BILAG score as well; this advice was not followed. The applicant was asked to discuss measures taken to ensure that the benefit in renal functioning is not offset by a deleterious effect on other organs. The applicant confirmed that baseline non-renal SELENA-SLEDAI score was low, with a median score of 4 points, showing that the majority of subjects had few extrarenal symptoms. This was not unexpected since the inclusion criteria was based on LN symptoms and did not specify a minimum SELENA-SLEDAI score. Voclosporin treatment resulted in a difference from baseline of -3.4 in renal score and – 2.4 in non-renal score. In the placebo group, the difference from baseline were -2.8 in renal score and -2.7 in non-renal score. No additional information with regards to different organ system were provided by the applicant; a more thorough evaluation of disease activity could have been gained if both indices (SELENA-SLEDAI and BILAG) had been used. However, although it could not be claimed that voclosporin does not have deleterious effects on other organs, in patients with active LN and little extrarenal activity, voclosporin did not seem to be associated with a worsening of other SLE symptoms, assessed with SELENA-SLEDAI score.

One protocol amendment was made during the study with some changes regarding the timing of the primary endpoint. It was not clear why the endpoint "Proportion of subjects experiencing a confirmed >30% decrease from baseline in eGFR at each time point" were removed as a key secondary outcome and upon request the applicant clarified that the inclusion of this endpoint as a key secondary endpoint instead of an" other" secondary endpoint was an error. The first statistical analysis plan and all subsequent versions of the SAP correctly included this endpoint as an " other" secondary endpoint, thus this error does not evoke any further concerns.

Statistical/methodological considerations

The statistical considerations with regard to the planned analyses and study design were found to be acceptable. The sample sise estimation was informed by phase 2 outcomes. All statistical analyses were performed at study closure; there were no interim analyses planned and none was performed. Database lock has been reported to have occurred on 01 November 2019 and the submitted SAP (version 5.0) was dated 21 October 2019. The included SAP amendment history covered all SAP versions; most of the changes/clarifications and what seemingly were the most significant were implemented with version 2.0 (July 2018 and September 2018). There appears hence to have been two version 2.0. This raises no serious concern per se more than to add to other minor unclarities. Several of the SAP revisions pertained to "regulatory agency feedback", they and others are overall supported. One exception, as discussed above, was the removal of one endpoint from the list of key secondary endpoints due to that it was not clear when or why.

Multiplicity was accounted for by proceeding to secondary endpoints only if the principal analysis of the primary efficacy endpoint reached statistical significance at the 5% level. Key secondary outcomes were tested using the Hochberg step-up procedure to adjust for multiple comparisons and maintain the overall type 1 error rate of 5%.

The primary endpoint was a composite responder endpoint; for a subject to be classified as responder all components had to be achieved. Subjects lacking week 52 data were classified as non-responders. Upon request, the applicant clarified non-responder imputation was used for 14/179 (7.8%) and 25/178 (14.0%) subjects in the voclosporin and placebo arm, respectively. For most non-responders, a subject's status could be calculated owing to that sufficient data was available at week 52.

The primary estimand was defined while the study was already ongoing (SAP version 3.0, March 2019). Regarding the intercurrent events (IEs), a combination of a composite strategy (study discontinuation, intake of rescue medication and death) and a treatment policy strategy (treatment discontinuation for any reason) was applied; in case of the latter, expectations were that they were to remain in the study. From the table as requested summarising the distribution of intercurrent events by treatment arm, it is clear that more subjects in the placebo than in the voclosporin arm, discontinued study treatment, discontinued the study, and received rescue medication. Although, the differences between treatment arms were <10% irrespective of intercurrent event, their direction support voclosporin efficacy.

Few subjects seemingly needed rescue medications with a not that dissimilar number of subjects comparing randomised arms; 24/178 (13.5%): placebo and 16/179 (8.9%): voclosporin. Being part of the primary endpoint definition, rescue use disqualified a subject from being a responder. Instead, it could have been considered to also handle intake of rescue medication using a treatment policy strategy. Upon request, an analysis ignoring intake of rescue medication and using available week 52 data in the responder/non-responder decision was performed. The difference compared with the protocol-defined primary endpoint analysis was however small since most of those receiving rescue were shown to be non-responders for other reasons. Actually, it was only 2 subjects, both in the voclosporin arm, who switched from being a non-responder to being responder, rather strengthening the renal response outcome in favour of voclosporin (OR 2.72 (95% CI: 1.69, 4.36; $p < 0.0001$) compared with an OR of 2.65 for the protocol-defined primary endpoint).

Several additional analyses of the primary endpoint were planned; a number of them for sensitivity purpose while others had been denoted supplementary. What regards the sensitivity analyses, they were rather performed to challenge the primary analysis model and, the supplementary analyses are considered more valuable for the understanding of the primary endpoint outcome. In addition, the planned Tipping point analysis is appreciated and is agreed to support the primary endpoint conclusion. Among the supplementary analyses were separate analyses of the primary endpoint components. As will be further discussed below, while the composite primary endpoint was statistically significant, the difference in favour of voclosporin versus placebo was driven by the difference in one component alone (UPCR).

The supplementary analysis using the programmed counterpart of renal response week 52 supported the primary (adjudicated) although the difference between voclosporin and placebo was slightly decreased. Separate analyses of the primary endpoint components were performed also for the programmed renal response confirming the treatment difference based on the UCPR component, although it is noted that in this analysis there was also a difference regarding eGFR success contrary to the adjudicated response. Based on information in the SAP (added in version 2.0, July 2018), renal response week 24 was initially only to be derived programmatically. When it was decided that also the week 24 renal response was to be adjudicated by the CEC is unclear. There is, however, no objection to the adjudication per se, and analyses of both the adjudicated and programmed response were provided. Despite that the number of responder/non-responders were identical, the estimated treatment difference slightly differed. This was clarified by the applicant to pertain to that the individual responding subjects differed concerning a total of six subjects all in the voclosporin arm. The difference in subjects led to a different covariate pattern which explains the slightly different estimates.

Regarding the primary endpoint, the applicant was strongly recommended (CHMP scientific advice) to change the definition of stable renal function. This advice was not followed. Instead, a number of post-hoc analyses were provided. These support the primary endpoint analysis although indicate that the voclosporin effect may be smaller. In the analysis using the strictest definition (confirmed % reduction in eGFR <10%), the estimated difference between treatment arms was decreased but was still nominally statistically significant. This should be explained by that the impact of the eGFR component on the overall outcome was small.

Subgroup analyses largely support internal consistency.

The submitted AURORA 1 CEC Charter was version Draft V2 dated 03 July 2019. The changes made compared to any earlier version or, why there seemingly did not exist a final version was not clear. According to the charter, CEC was to review blinded data for individually completed subjects on an ongoing basis. The applicant clarified that renal response was to be reviewed once a subject had completed the study. This was expected to occur between July 2019 and the database lock in November 2019, but as has been explained, the actual CEC review did not start before mid-October. With this clarification along with the confirmation that the CEC charter dated 03 Jul 2019 is the final version, the concern that CEC adjudications could have been performed based on different documented instructions and patient data has been alleviated.

It was recommended (CHMP scientific advice) that the incidence of renal flares should be assessed. According to the applicant, renal flares was to be addressed as part of the final analysis of the long-term AURORA 2 study. (AUR-VCS-2016-02). AURORA 2 was still ongoing at the time of the submission but was expected to complete in October 2021. Neither the CSP nor the SAP had been submitted. Eligible to enter AURORA 2 was subjects who completed AURORA 1 while still on study drug. AURORA 2 implied that subjects could continue on randomised treatment for an additional 24 months. AURORA 2 is now completed and the final CSR, the CSP and the SAP, as well as all other documentation, have been provided. According to the SAP, interim analyses were planned to enable that authorities could be provided with the most up to date information available. This is acknowledged. According to the SAP, timing of the interim analyses ranged from 3 months post the final subject final visit of the AURORA 1 study up to 6 months prior to the end of AURORA 2, i.e., when the last subject had reached Month 30. The latter time-point being in line with the data cut 01 April 2021 used for the reporting of outcomes provided with the initial submission. However, the submitted SAP (version 1.0) was dated 11 May 2021, i.e., after the above-mentioned data cut. To potentially mitigate any concerns regarding unplanned analyses it has been stated that the proposed analyses were based on the contents of the final version of the protocol (Amendment 2, dated 21 Dec 2018). However, according to the CSP, there was to be one unblinded, interim analysis expected to occur 3 months post the final subject final visit of the AURORA 1 study. Thereby is the SAP wording considered to be a post-construction. No randomisation was performed in this study and the sample sise was decided by the number of AURORA 1 subjects eligible and willing to continue. Efficacy was a secondary objective and there was no type I error control. Further, it is unavoidable that there has been a selection of subjects entering and thereby that AURORA 2 does no longer offer a truly randomised comparison and thus, efficacy data can at most be viewed as descriptive. A total of 216 subjects entered the AURORA 2 study: 116/179 subjects (64.8%) from the voclosporin arm and 100/178 subjects (56.2%) from the placebo arm whereof a similar proportion of subjects in the two arms completed the study: 85.0% (85/100) (placebo) and 87.1% (101/116) (voclosporin).

Efficacy data and additional analyses

A total of 357 eligible subjects were randomised into the study AURORA 1: 178 to the placebo arm and 179 to the voclosporin arm. Overall, 309 subjects (86.6%) completed the study, with more subjects in the voclosporin arm (162 subjects [90.5%]) than the placebo arm (147 subjects [82.6%]) reaching

Week 52. More subjects withdrew from the placebo arm (17.4%) than the voclosporin arm (8.9%). The most common reason for early withdrawal from the study was withdrawal of consent which accounted for nearly half of all withdrawals in both arms. Study treatment was discontinued in 59 subjects (33.1%) in the placebo arm and 43 subjects (24.0%) in the voclosporin arm. The most common reason for study treatment discontinuation was intolerable AE.

The demographic characteristics of subjects in the study were balanced across the two treatment arms and representative for the population intended for the indication. The mean age was 33 years (range 18 to 72 years) and the majority of subjects were female (87.7%). Most participant were white (36.1%) or Asian (30.5%), only 9.5% were black. The mean time since SLE diagnosis was 6.7 years (range <1 to 38 years), and the majority of subjects reported mucocutaneous, musculoskeletal, and haematological involvement. Mean time since diagnosis of LN was just under 5 years (range <1 to 28 years) in both groups and only 3 subjects in each arm had previously received dialysis. In both populations mean and median UPCR was > 3 mg/mg at baseline and mean and median eGFR values were > 90 (range 25 to 136) suggesting a patient population with nearly nephrotic range proteinuria but with rather preserved kidney function. Although the range of the values at baseline includes values not allowed for inclusion (e.g eGFR <45) the applicant states that all subjects met the eligibility criteria for UPCR and eGFR levels at screening. The applicant clarified that if a subject had eGFR > 45 at screening but was then found to have eGFR of ≤ 45 at baseline, the subject was still eligible to remain in the trial. All subjects had to demonstrate at least one eGFR value of > 45 to be eligible for trial entry. Approximately 5% of subjects in each group recorded a minimum baseline eGFR of < 45 prior to the first dose of study treatment. This is acceptable.

Given that the median number of years since diagnosis of LN was 2 years, half of the included study population was diagnosed within 2 years prior to enrolment. As the likelihood of successful initial outcome is greater if therapy for LN is started early in the course of the disease, inclusion of relatively recently diagnosed subjects might result in more favourable outcomes compared to the general LN population. Upon request the applicant provided a post-hoc analysis showing that the benefit of voclosporin treatment compared to placebo seems to be greater in patients diagnosed with LN within 2 years of enrolment compared to patients diagnosed with LN more than 2 years of enrolment. However, a larger proportion of responders treated with voclosporin compared to placebo is observed even for patients diagnosed with LN more than 2 years of enrolment (29.8% vs 18.4%, respectively). Adequate information regarding the mean and median duration of LN in AURORA-1 population (alongside other main characteristics of the studied population) is included in the SmPC 5.1.

The most common kidney biopsy class was pure Class IV (77 [43.3%] of placebo subjects and 91 [50.8%] of voclosporin subjects); 25 subjects (14.0%) in each arm were recorded as having pure Class V LN. Around 25% in both groups had a combined pattern of Class V + III or IV.

A total of 39 subjects (11%) had a biopsy more than 6 months prior to screening; of these subjects, the majority had a biopsy between 6 and 12 months prior with 12 (3%) having a biopsy more than 12 months prior to screening. The timing of biopsies taken more than 6 months prior to screening was balanced between treatment groups). Thus, any misclassification regarding biopsy class in this group are not supposed to affect the results.

Almost all patients had received previous treatments for LN (taken at any time prior to first dose of study treatment) and these treatments were well balanced across the treatment arms. The most common previous LN treatments in both groups were corticosteroids, antimalarials and MMF, which were taken by 94%, 67% and 63%, respectively, of all subjects. Cyclophosphamide and Azathioprine were taken by 34.6% and 30.1%, respectively. It was not clear whether there were any treatment naïve patients (patients who never had received any treatment for a LN flare) included in the study. It also not clear whether the patients included in the study had a previous response with Soc treatment

and then relapsed, or if they never received a response on SoC treatment (i.e. refractory patients). Upon CHMP request, the applicant clarified that data on subjects' responses or relapses with prior LN treatments were not collected in the study. In addition, only a few patients (4 subjects in the placebo arm and 3 subjects in the voclosporin arm) recorded no previous treatment for LN, although the applicant's definition of treatment naïve seems stricter than necessary, excluding patients on antimalarials and methotrexate. The numbers are too small to draw any conclusion regarding efficacy in this group. One may argue that the lack of data on treatment naïve patients could imply that Lupkynis should be used as second line therapy on top of SoC in patients who failed to achieve a response with SoC treatment only. However, the treatment is intended for active LN in combination with SoC (MMF), and it is anticipated that a response, with decrease of proteinuria and a similar safety profile will be achieved also when treating a first active LN episode. At CHMP's request, information regarding previous LN treatment (Cyclophosphamide, MMF) and the small number of treatment naïve patients has been included in the SmPC.

Additional information provided by the applicant assured that treatment groups were well balanced with regards to use of important concomitant medications at study start also in respect of doses of corticosteroids and MMF. The only exception is a slightly higher proportion of patients on calcium channel blocker in the placebo group (around 33% vs 22%) but this is not expected to have any important impact on the results.

Also, upon request, concomitant medications taken after study commencement were presented cut-off of ≥2% subjects instead of a cut-off of ≥10%. The most common concomitant medications started or subjected to a dose change during the trial were antihypertensive medications. Other concomitant medications in reflect the higher incidence of infections, gastrointestinal disorders, cough, and anaemia seen in the voclosporin arm than the placebo arm.

Efficacy analysis: The proportion of subjects achieving renal response was significantly higher in the voclosporin arm than in the placebo arm (40.8% vs 22.5%). The odds of responding were 2.65 times greater for subjects treated with voclosporin than placebo (OR 2.65; 95% CI: 1.64, 4.27; p<0.001). The absolute risk reduction observed with voclosporin is 18.3%. The results of the primary efficacy analysis are both statistically significant and clinically relevant.

Similar results were seen for supplementary analyses i.e., for the PP population, programmed renal response and for sensitivity analyses including only a term for treatment and omitting the regional covariate. A tipping point analyses showed that if all voclosporin withdrawals were truly non-responders, 65% of placebo assumed non-responders would have to be truly responders in order for statistical significance to be lost. The applicant concludes that this is an unlikely scenario given the observed placebo response was 22.5%, and this conclusion is supported.

However, when analysing the different components included in the combined endpoint "renal response" (UPCR ≤0.5 mg/mg, eGFR success, no rescue medication and not more than 10 mg prednisone during Weeks 44-52), it is clear that the main component driving the response is the reduction of proteinuria. No significant differences between Voclosporin and Placebo were seen in the other components. For UPCR≤0.5 mg/mg, the response was 23% in the placebo group and 45.3% in the voclosporin group (OR 3.11, CI 1.99, 5.0 p<0.001). For eGFR success the response was 75.8 % in the placebo group and 82.1 % in the voclosporin group (OR 1.50, CI 0.89, 2.52, p=0.129). Rescue medications were given to 13.5% in the placebo group and 8.9% in the voclosporin group and only 14.6% in the placebo group and 12.8% in the voclosporin group did receive steroids above 10 mg during the last 8 weeks before week 52.

Reducing proteinuria is important in the treatment of lupus nephritis, since sustained proteinuria is associated with a worse prognosis, however the main goal is still to prevent kidney damage and in the end kidney failure. Thus, it is crucial that the beneficial effect seen in renal response regarding

proteinuria is not counterbalanced by a detrimental effect in eGFR. It is noted that a patient could be a responder with an eGFR≤60 and a decrease of >20% if there was a non-treatment related AE in close relation to the measured value that could affect the eGFR. Only a few patients were responders in relation to that criterion (6 patients in the placebo group and 7 patients in the voclosporin group). Upon request, the applicant provided additional information regarding this topic that did not evoke any further concerns.

The applicant has also provided some complementary analysis with stricter eGFR definition of stable renal function. When "no confirmed decrease from baseline of >10% in corrected eGFR" were used, 62/179 (34.6%) in the voclosporin group and 38/178 (21.3%) in the placebo group achieved a renal response (OR 2.11 CI 1.3, 3.43, p=0.0026). This is reassuring, but it is noticed that the response in the voclosporin group seems to be affected more (contributing to a lesser response) than the placebo group with this stricter definition. To evaluate the contribution of this stricter definition to the total score, the applicant provided some additional information which showed, as expected, that a decrease in GFR was apparent in more patient treated with Voclosporin, than patients with SoC treatment. This is further discussed in the safety section (see 2.5.8.).

Consistent with the primary endpoint, the proportion of subjects achieving the key secondary outcomes were all in favour of voclosporin. Adjudicated renal response at Week 24 was significantly higher in the voclosporin arm than the placebo arm (32.4% vs 19.7%; OR 2.23; 95% CI: 1.34, 3.72; p=0.002). This result is in line with the results from the AURA LV study, where renal response at week 24 was the primary endpoint (32.6% vs 19.3%, OR=2.03; 95% CI: 1.01, 4.05; p=0.045). More subjects in the voclosporin arm achieved a partial renal response (defined as a 50% reduction from baseline in UPCR) at Week 24 and Week 52. In the majority of subjects who responded, partial renal response was achieved already at week 24. Of the subjects who achieved a partial response at Week 24, a higher proportion of subjects in the voclosporin group than in the placebo group were adjudicated to have a renal response at Week 52 (52.4% vs 39.3%). In addition, of the patients who did not achieve a renal or partial response at week 24, a numerical higher proportion of patients in voclosporin group than placebo group achieved a partial or renal response at week 52 (around 40% vs 28%). Upon CHMP request, the applicant also provided information that verified that, due to the wide individual fluctuation, it would be difficult to set a cut-off value for UPCR at 12- or 24-weeks which would accurately identify subjects who will not benefit with continued treatment. Thus, no additional stopping rules are suggested and decision to continue treatment beyond Week 24 in patients who may not have experienced a notable improvement in their disease after 6 months of treatment, are left to the treating physician's judgement. This gives support for continuing treatment also in patients who do not fully respond at week 24 and since no additional stopping rules were identified (such as level of proteinuria), the decision to continue treatment beyond Week 24 in patients who may not have experienced a notable improvement in their disease after 6 months of treatment, are left to the treating physician's judgement.

The time to UPCR ≤0.5 mg/mg was also significantly shorter for voclosporin treatment (median time: 169 days vs 372 days for placebo treatment; HR 2.02; 95% CI: 1.51, 2.70; p<0.001). Also, the time taken to reach a 50% reduction in UPCR was significantly shorter for the voclosporin arm than the placebo arm (HR 2.05; 95% CI: 1.62, 2.60; p<0.001). Median time to 50% reduction in UPCR was 29 days for voclosporin versus 63 days for placebo. These results confirms that voclosporin together with MMF + corticosteroid reduce proteinuria faster and more effectively (i.e to a lower level) than MMF+ corticosteroids alone.

Almost half of the patients who achieved UPCR <0.5 in both groups had a secondary occurrence of UPCR > 0.5 (47.4 % in the placebo group and 45.7% in the voclosporin group). This implies that the reduction of proteinuria may not sustain for a significant number of patients. In addition, a total of 18 subjects (10%) in each arm recorded a confirmed decrease of >30% from baseline in corrected eGFR

during the study. More occurrences were reported during the second half of the treatment period. Both these finding could imply a progression/relapse in disease activity with a similar number in both treatment group. Upon request additional information were provided by the applicant, including the final report of the AURORA 2 study. The proportions of subjects with a second occurrence of UPCR > 0.5 were derived programmatically based on any incursion above 0.5 (including values of 0.51) and as the applicant points out, such fluctuations in UPCR are expected, and do not necessarily indicate that the reductions in proteinuria are not sustained or that all these subjects relapsed. Based on data from the AURORA 2 study, the difference between the arms in the proportion of subjects with UPCR < 0.5 seems to be maintained across a further 2 years. In the AURORA 1 trial, 72.6% of subjects in the voclosporin arm achieved an adequate response (i.e a reduction in UPCR to ≤ 0.7 mg/mg) compared with 51.1% of subjects in the placebo arm. The incidence of renal flares in the responders were 10% in the voclosporin arm and 19.8% the placebo arm. For those patients who continued to AURORA 2 a similar proportion in both arms were adjudicated as having a renal flare (placebo 26.0%, voclosporin 23.8%) and 4 placebo subjects and 5 voclosporin subjects were considered to have severe renal flare. Thus, the frequency of flares did not seem to differ between the two groups, and it is noted that no definition with respect to mild, moderate or severe flares were provided. A good renal outcome, based on adequate renal response (UPCR ≤0.7) and no renal flare, was achieved by 66.4% of subjects treated with voclosporin compared with 54.0% of placebo subjects indicating a beneficial efficacy of voclosporin over placebo also in a longer perspective. This is reassuring to the CHMP even though, as stated above, efficacy data from Aurora 2 can at most be viewed as descriptive.

Mean corrected eGFR values at baseline were similar in both arms (78.3 mL/min/1.73m2 in the voclosporin arm and 77.4 mL/min/1.73m2 in the placebo arm). At Week 2, the mean corrected eGFR had decreased slightly in the voclosporin arm while the mean value in the placebo arm instead showed a small increase.

A >30% decrease in eGFR was reported for each time point. A total of 18 subjects (10%) in each arm recorded a confirmed decrease of >30% from baseline in the AUrORA-1 study . The applicant states there were no notable differences between two treatment arms at any time point. However, this statement is not agreed as from week 16 onwards at each time point numerically more >30% decreases in eGFR were recorded in voclosporin compared to placebo. The total number of occurrences of >30% decrease in eGFR was 61 for voclosporin compared to 43 in placebo arm. Given that the total number of subjects experiencing these decreases is the same both treatment arms, these findings may suggest a more protracted pattern of >30% decreases in eGFR in voclosporin compared to the placebo arm. The effect on eGFR is thoroughly discussed in the safety section (see 2.5.8.).

A reduction of the SELENA/SLEDAI index score and improvement of HRQoL were seen in both groups but there was no difference between the treatment groups. There were no apparent differences between the two treatment arms in health resource utilisation at baseline or during the study.

The study protocol requested a rather fast corticosteroid tapering schedule with a reduction to ≤2.5 mg at week 16. A majority of the patients in both groups were able to reduce their steroids to these levels (81.1% in the voclosporin group and 80.7% in the placebo group). In addition, 74.7% of the voclosporin group and 73.5% of the placebo group were still on that dose at week 52. Taken into account the adverse effects of long-term glucocorticoid treatment it is an important finding that the renal response at week 52 in patients with a low corticosteroid dose were also favouring voclosporin, with a response of 35.8% in the voclosporin group and 20.2% in the placebo group. Corticosteroid duration of exposure and mg/day exposure were similar in the groups with slightly lower corticosteroid dose in the voclosporin group. The mean cumulative oral steroid dose across the whole 12 months was slightly higher for the placebo arm (2549 mg) than the voclosporin arm (2374 mg).

A dose reduction or temporary interruption of treatment drug was done for slightly over half of the patients in the Voclosporin group (51.1%) and for 27.5% of the placebo patients. In most subjects, study treatment was resumed once the event resulting in a dose decrease/interruption had resolved. In the Voclosporin group, 57.2% of the patients did not resume to the full dose (28.6% stayed on 7.9 mg and 28.6% stayed on 15.8 mg). It was not clear whether these patients still achieved a renal response, and the applicant was asked to present renal response in this subpopulation. In subjects with no dose decreases, the response rate in the voclosporin arm was twice that in the placebo arm (around 46% vs 23%). Similar response rates were observed in subjects who finished the trial on the full dose of three capsules BID after a dose decrease or interruption (41% vs 22%). The response rates were lower in voclosporin subjects who ended the trial on 2 capsules (9/26, 34%) or 1 capsule (7/26, 27%) BID. Thus, a temporary decrease in dose does not seems to affect the results, but for the patients that continued with a lower dose, efficacy is reduced, although a response is still seen in some of the patients.

A treatment benefit of voclosporin was also seen across all pre specified subgroups. Especially in the patients who were already on MMF, Voclosporin seems to provide a robust renal response. This indicates a good efficacy in patients with a flare despite MMF. It is however unclear whether these patients had failed MMF therapy or if the patients suffered a renal flare responsive to MMF (i.e., not responding vs. responding to higher MMF dosage). The applicant was asked to clarify, however data on subjects' responses or relapses with prior MMF treatments were not collected in the study. There are some discrepancies between efficacy outcome in the subgroups with MMF at baseline or without MMF at baseline in the AURA-LV study and the AURORA-1 study and additional information regarding this was requested during the assessment. The applicant states that random variation was the only explanation for the differences seen in response rate between the groups in the two studies. This was considered acceptable by the CHMP.

Regarding the subgroups, the 95% CI of OR for voclosporin vs placebo crosses the line of null effect in several subgroups (White, pure Class V, Europe + South Africa, North America, no MMF at screening and maximum MMF dose >2 g). The sise of some of those subgroups (pure Class V, North America, maximum MMF dose >2 g) is small, providing a possible explanation for level of uncertainty around the effect sise. However, the sise of subgroups White, Europe + South Africa and no MMF at screening is considerable and the 95%CI is not very wide. Therefore, subgroup sise seems unlikely to be the only explanation for the 95% CI crossing the value of no difference between treatments in subgroups White, Europe + South Africa and no MMF at screening. Upon CHMP request, the applicant provided additional explanations and concluded that a high placebo response rate was observed in the selected subgroups, while the response to voclosporin was similar to that in the overall population. The CHMP concluded that a treatment benefit of voclosporin was seen across all pre-specified subgroups, including black participants, males and participants with Class V LN in the pivotal study.

Upon request, the applicant provided the final protocol from the AURORA 2 study. The proportion of patients in renal response month 36 among those who continued in AURORA 2 was 51% (59/116) in the voclosporin group and 39% (39/100) in the placebo group. When including the whole ITT-population from AURORA 1, the proportion of patients in renal response month 36 (AURORA 1 and AURORA 2) was 33% (59/179) in the voclosporin group and 22% (39/178) in the placebo group.

At the start of AURORA 2, 34/100 (34%) placebo subjects and 61/116 (52.6%) voclosporin subjects were in renal response. At month 36, 22/34 (64.7%) of the placebo subjects and 44/61 (72.1%) voclosporin subjects were still in renal response, indicating sustained remission for the majority of the patients in both groups. For patients with partial renal response, around 50% of the patients achieved a renal response at week 36 in both groups.

A description regarding the AURORA 2 study is considered informative for the prescriber to be included in the SmPC.

2.5.7. Conclusions on the clinical efficacy

AURA-LV was a phase II randomised controlled double-blind study comparing the Efficacy and Safety of two doses of Voclosporin (23.7 mg BID or 39.5 mg BID) with Placebo in Achieving renal remission in patients with Active Lupus Nephritis. The AURA-LV study met its primary endpoint. There was no formal comparison between the two doses and no clear dose-response connection was apparent in the AURA-LV study, but slightly more AEs with the higher dose. Hence, the lower dose (23.7 mg BID) was chosen to the phase 3 AURORA-1 study. This was considered acceptable by the CHMP.

The pivotal study AURORA 1 was a phase 3, randomised, double-blind, parallel-group, placebo controlled, multicenter, 2 arm study of voclosporin versus matching placebo. Voclosporin at a dose of 23.7 mg BID or matching placebo were administered for 52 weeks with a background therapy of MMF and corticosteroids with a tapering schedule.

Patients that completed the AURORA 1 study could continue in a 2-year continuation study (AURORA 2).

A better response for Voclosporin was seen in the primary endpoint and all key secondary endpoint, suggesting that voclosporin, together with MMF + corticosteroid, reduces proteinuria faster and more effectively (i.e. to a lower level) than MMF+ corticosteroids alone.

The study protocol requested a rather fast corticosteroid tapering schedule with a reduction to ≤2.5 mg at week 16. A majority of the patients in both groups were able to reduce their steroids to these levels. Taken into account the well-known adverse effects of long-term glucocorticoid treatment, it is an important finding that the rate of renal response at week 52 in patients with a low corticosteroid dose were also favouring voclosporin.

At the CHMP's request, the applicant accepted to revised their claimed indication to reflect that the treatment is indicated in LN patients with active disease and that voclosporin should only be used in combination with combination with mycophenolate mofetil as all patients in AURORA 1 received MMF as "background immunosuppressive therapies", and no other immunosuppressive therapy were allowed.

The CHMP concluded that the data submitted supported the following dosing recommendations and indication:

"*Lupkynis is indicated in combination with mycophenolate mofetil for the treatment of adult patients with active class III, IV or V (including mixed class III/V and IV/V) lupus nephritis (LN)*."

The recommended dose is 23.7 mg (three 7.9 mg soft capsules), twice daily.

2.5.8. Clinical safety

Voclosporin, a novel calcineurin inhibitor (CNI), is according to the applicant structurally similar to cyclosporine A (CsA) except for a modification to the amino acid-1 region. According to the applicant, this alteration has changed the binding of voclosporin to calcineurin, increasing the potency by 2- to 4-fold compared to CsA, and has shifted metabolism away from amino acid-1, the major site of metabolism for CsA, thus altering the metabolic profile.

Increased blood pressure and acute renal vasomotor effects are well-known potential toxicities of CNIs that are dose-related, reversible, and responsive to dose reduction or temporary interruption of

treatment [Wiseman 2016]. Other adverse effects associated with current CNIs include neurotoxicity (psychosis, speech apraxia, dysesthesias, anxiety, sleep disturbances, reversible posterior leukoencephalopathy syndrome), electrolyte disturbances, impaired glucose tolerance and new-onset diabetes mellitus, and, like all immunosuppressants, infections and malignancies [Sketris 1995].

2.5.8.1. Patient exposure

The application included safety data from 2,666 subjects exposed to voclosporin (any dose or duration) in clinical trials. The number of subjects with LN who have been exposed to voclosporin (any dose or duration) is 365 (Table 58-Table 59).

Table 58 Number of Study Subjects Exposed to Voclosporin or Placebo

Population	Placebo (N)	Voclosporin (Any Dose, N)	Total (N)
All Lupus Nephritis (LN) [1]	266	365	631
Pooled LN [2]	266	267	533
AURORA 2 [3]	100	116	216
Psoriasis/Uveitis (PsU) [4]	392	1,485	1,674
Phase 2b Renal Transplant	0	248	248
Phase 1	148	568	688
Total Unique Subjects [4]	806	2,666	3,241

1 Includes subjects from AURORA 1, AURORA 2 (not unique subjects), AURA-LV (placebo, 23.7 mg twice daily (BID), and 39.5 mg BID voclosporin groups), and AURION
2 Includes subjects from AURORA 1 and AURA-LV (placebo and 23.7 mg BID voclosporin groups) with exposure up to 1 year
3 Includes subjects from AURORA 1 who consented to participate in the ongoing AURORA 2 study with exposure >12 months and up to 36 months
4 Some placebo subjects in this population crossed over to active voclosporin treatment, therefore counts of placebo + voclosporin will not be additive

Table 59 Exposure to Voclosporin or Placebo (Pooled LN Safety Population, N=533)

	Placebo (N=266)	23.7 mg BID (N=267)
Mean Daily Dose (mg)		
n	266	267
Mean (SD)	49.9 (11.89)	40.6 (9.87)
Median	47.4	46.7
Min, Max	21.3, 77.8	6.0, 47.4
(IQR)	(47.4, 47.4)	(36.5, 47.4)
Mean Daily Dose Category		
≤15.8 mg	0 (0.0)	7 (2.6)
>15.8 and ≤31.6 mg	9 (3.4)	41 (15.4)
>31.6 and <47.4 mg	52 (19.5)	94 (35.2)
47.4 mg	163 (61.3)	125 (46.8)
>47.4 mg [1]	42 (15.8)	0 (0.0)
Dose Decreases (Subjects (%) / Decreases)	67 (25.2) / 88	142 (53.2) / 258
Dose Increases (Subjects (%) / Increases)	99 (37.2) / 144	123 (46.1) / 265
Days on Treatment [2]		
n	266	267
Mean (SD)	295.8 (105.80)	300.3 (110.82)
Median	343.0	357.0
Min, Max	1.0, 384.0	1.0, 384.0
(IQR)	(250.0, 366.0)	(304.0, 367.0)
Mean Days on Treatment [2]		
Up to 3 months	23 (8.6)	23 (8.6)
>3 to 6 months	30 (11.3)	31 (11.6)
>6 to 9 months	18 (6.8)	8 (3.0)
>9 to 12 months	183 (68.8)	188 (70.4)
>12 months [3]	12 (4.5)	17 (6.4)

1 Placebo control subjects for the high-dose (5 capsules BID) arm in AURA-LV.
2 Days on treatment calculated as the sum of all prescription record durations up to the last non-zero prescribing record.
3 Subjects who attended the Week 52 visit after the protocol-specified window of Day 364±10 days; subjects with 365 to 374 days of study treatment are counted in the category of >9 to 12 months because this is within the visit window.
Notes: BID = twice daily; IQR = interquartile range; SD = standard deviation.

Within the pooled LN population, the mean daily dose of voclosporin was higher in the AURORA 1 study (41.3 mg) compared with the AURA-LV study (34.6 mg). The guidance for dose modification or interruption was similar between the AURA-LV and AURORA 1 study protocols; however, a more cautious approach was used in the AURA-LV study given that it was conducted earlier in the LN development programme, with less safety information available. In AURA-LV, dose reductions were implemented based on a fixed percentage decrease from baseline (even if eGFR continued to be normal) and there was greater caution for returning to or near the prescribed study treatment dosing regimen.

The disposition and exposure in AURORA 2 are summarised below.

Table 60 Summary of Subject Disposition: Analysis Populations AURORA 2 ITT Population

Parameter	Statistic	Placebo (N = 100)	Voclosporin (N = 116)	Overall (N = 216)
AURORA 1 Intent-to-Treat Population	n	178	179	357
AURORA 1 Safety Population	n	178	178	356
AURORA 1 Safety Population Not Continuing into Extension	n	78	62	140
AURORA 2 Intent-to-Treat Population	n (%)	100 (100.0)	116 (100.0)	216 (100.0)
AURORA 2 Safety Population	n (%)	100 (100.0)	116 (100.0)	216 (100.0)
Completed Month 12	n (%)	100 (100.0)	116 (100.0)	216 (100.0)
Completed Month 18	n (%)	96 (96.0)	114 (98.3)	210 (97.2)
Completed Month 24	n (%)	88 (88.0)	111 (95.7)	199 (92.1)
Completed Month 30	n (%)	89 (89.0)	102 (87.9)	191 (88.4)
Completed Month 36	n (%)	85 (85.0)	101 (87.1)	186 (86.1)

Baseline demographic and disease characteristics are shown below:

Lupus nephritis studies

Pooled LN population:

Table 61 Demographic Characteristics (Pooled LN safety population, N=533)

Parameter	Statistic	Category	Placebo (N=266)	23.7 mg BID (N=267)	Overall (N=533)
Age (years)	n		266	267	533
	Mean (SD)		33.5 (10.67)	32.2 (11.15)	32.9 (10.92)
	Median		32.0	30.0	31.0
	Min, Max		18, 72	18, 66	18, 72
	(IQR)		(25.0, 40.0)	(24.0, 38.0)	(24.0, 40.0)
Sex	n (%)	Male	41 (15.4)	31 (11.6)	72 (13.5)
		Female	225 (84.6)	236 (88.4)	461 (86.5)
Race	n (%)	White	103 (38.7)	98 (36.7)	201 (37.7)
		Asian: Indian Subcontinent	18 (6.8)	22 (8.2)	40 (7.5)
		Asian: Other	74 (27.8)	83 (31.1)	157 (29.5)
		Black (inc. mixed black)	24 (9.0)	29 (10.9)	53 (9.9)
		Other (inc. mixed race)	47 (17.7)	35 (13.1)	82 (15.4)
Weight (kg)	n		265	266	531
	Mean (SD)		65.98 (16.127)	65.24 (16.946)	65.61 (16.531)
	Median		63.50	62.40	63.30
	Min, Max		36.0, 138.2	36.0, 142.0	36.0, 142.0
	(95% CI)		(64.03, 67.93)	(63.19, 67.28)	(64.20, 67.02)
Time since initial LN diagnosis (years)	n		266	267	533
	Mean (SD)		4.51 (4.608)	4.68 (5.085)	4.59 (4.849)
	Median		2.20	2.21	2.21
	Min, Max		0.6, 28.0	0.6, 32.3	0.6, 32.3
	(IQR)		(1.27, 6.82)	(1.26, 6.57)	(1.27, 6.61)
Biopsy Class, n (%)	Non-Class V		165 (62.0)	167 (62.3)	332 (62.2)
	Class V Mixed		63 (23.7)	64 (23.9)	126 (23.6)
	Pure Class V		38 (14.3)	37 (13.8)	75 (14.0)
MMF use at screening, n (%)	Yes		127 (47.7)	128 (47.9)	255 (47.8)
	No		139 (52.3)	139 (52.1)	278 (52.2)
Baseline eGFR (mL/min/1.73 m^2)	n		266	267	533
	Mean (SD)		93.62 (28.621)	93.18 (29.694)	93.40 (29.137)
	Median		98.00	92.00	95.00
	Min, Max		25.0, 153.0	39.0, 168.0	25.0, 168.0
	(95% CI)		(90.16, 97.07)	(89.60, 96.76)	(90.92, 95.88)
Baseline eGFR (mL/min/1.73 m^2), n(%)	≥15 and <30		1 (0.4)	0 (0.0)	1 (0.2)
	≥30 and <45		7 (2.6)	10 (3.7)	17 (3.2)
	≥45 and <60		33 (12.4)	31 (11.6)	64 (12.0)
	≥60 and <90		75 (28.2)	83 (31.1)	158 (29.6)
	≥90		150 (56.4)	143 (53.6)	293 (55.0)
Baseline UPCR (mg/mg)	n		266	267	533
	Mean (SD)		4.05 (2.823)	4.48 (3.290)	4.26 (3.071)
	Median		3.10	3.54	3.31
	Min, Max		0.8, 19.3	0.2, 29.7	0.2, 29.7
	(95% CI)		(3.71, 4.39)	(4.08, 4.88)	(4.00, 4.52)

Table 62 Summary of demographics for AURORA 1 subjects enrolled or not enrolled into AURORA 2 (ITT)

	AURORA 2			AURORA 1 Only		
Parameter	Placebo (N=100)	23.7 mg BID (N=116)	Overall (N=216)	Placebo (N=78)	23.7 mg BID (N=63)	Overall (N=141)
Age (years)						
Mean (SD)	35.4 (11.64)	32.3 (10.31)	33.7 (11.03)	31.4 (9.75)	33.7 (12.03)	32.3 (10.85)
Median	33.0	30.0	31.0	29.0	31.0	30.0
Min, Max	18, 72	18, 59	18, 72	18, 68	19, 62	18, 68
Sex n (%)						
Male	12 (12.0)	11 (9.5)	23 (10.6)	14 (17.9)	7 (11.1)	21 (14.9)
Female	88 (88.0)	105 (90.5)	193 (89.4)	64 (82.1)	56 (88.9)	119 (85.1)
Race n (%)						
White	40 (40.0)	44 (37.9)	84 (38.9)	21 (26.9)	24 (38.1)	45 (31.9)
Asian	30 (30.0)	30 (25.9)	60 (27.8)	26 (33.3)	23 (36.5)	49 (34.8)
Black	7 (7.0)	18 (15.5)	25 (11.6)	12 (15.4)	8 (12.7)	20 (14.2)
Other	23 (23.0)	24 (20.7)	47 (21.8)	19 (24.4)	8 (12.7)	27 (19.1)
Ethnicity n (%)						
Hispanic or Latino	33 (33.0)	39 (33.6)	72 (33.3)	26 (33.3)	18 (28.6)	44 (31.2)
Not Hispanic or Latino	67 (67.0)	77 (66.4)	144 (66.7)	51 (65.4)	45 (71.4)	96 (68.1)
Unknown	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.3)	0 (0.0)	1 (0.7)
Region n (%)						
Americas	36 (36.0)	49 (42.2)	85 (39.4)	38 (48.7)	26 (41.3)	64 (45.4)
Europe + S. Africa	37 (37.0)	38 (32.8)	75 (34.7)	15 (19.2)	14 (22.2)	29 (20.6)
Asia	27 (27.0)	29 (25.0)	56 (25.9)	25 (32.1)	23 (36.5)	48 (34.0)
Weight (kg)						
Mean (SD)	65.2 (14.65)	66.6 (16.24)	65.9 (15.51)	68.3 (17.75)	66.3 (18.65)	67.4 (18.12)
Median	64.2	65.2	64.6	63.5	60.4	62.5
Min, Max	36, 114	37, 121	36, 121	41, 138	36, 142	36, 142

Note Black race includes mixed race where black is recorded. All other mixed race codes to Other.
BID = twice daily; ITT = intent-to-treat; SD = standard deviation.

AURA-LV study (39.5 mg BID arm): There was local imbalance in randomisation between the treatment groups with respect to region (47.2% of subjects of the 23.7 mg BID voclosporin group was from low-GDP countries compared to 37.5% in 39.5 mg BID voclosporin and 31.8% in placebo group), which reflected with poorer safety outcomes in the 23.7 mg BID group.

AURION study: Contrary to other LN studies, all included subjects were female.

Renal Transplant Study

The subjects were primarily Caucasian (61.9%) and male (66.1%) with a median age of 46 to 50 years and received de novo kidney transplants within 24 hours prior to randomisation into the study with a history of dialysis for median duration of 19 to 23 months.

Clinical Pharmacology Studies

In the 13 Phase 1 studies were included healthy volunteers, primarily young (ranging from 18 to 45 years), majority Caucasians in most of these studies.

Subjects in the Phase 1 studies of renal or hepatic impairment were older compared to LN population (mean age of 62 years and 50 years) and majority were Caucasian. More males than females were included in the study of hepatic impairment.

SLE subjects were aged between 26 and 65 years (30% had history of LN) and most subjects were white and female.

2.5.8.2. Adverse events

This section presents the analysis of AEs and TEAEs in the pooled LN population, which includes subjects who were treated with placebo or voclosporin 23.7 mg BID for up to 12 months in the AURA-LV or AURORA 1 studies. Final results from the AURORA 2 study are also presented.

Overview of adverse events

The incidence of AEs in the pooled LN safety population is summarised in Table 63.

The following definition of treatment-emergent was used:

- Any AE that had an onset on or after the first dose of study drug within a given regimen up to 30 days following the last dose of study drug within the regimen.
- For subjects who moved into the continuation study on the same active treatment (i.e., from AURORA 1 to AURORA 2), the 30-day window after last dose was reduced to end of day prior to the start of the continuation study.

TEAEs leading to dose modification occurred more often in voclosporin-treated subjects (46%) than placebo-treated subjects (25%) (Table 63). However, the incidence of TEAEs leading to permanent study drug discontinuation was similar between placebo and voclosporin treatment groups (13.2% vs 13.5%). Treatment-related TEAEs leading to dose modification or permanent study drug discontinuation occurred in more voclosporin-treated subjects than placebo-treated subjects (dose modification: 28% vs 7%; permanent discontinuation: 7.5% vs 2.6). The study protocols included close monitoring of eGFR with prespecified guidance for dose modification or temporary interruption in the event of eGFR decreases; therefore, dose modification was not unexpected in these study groups.

Table 63 Overview of Adverse Events (Pooled LN Safety Population, N=533)

Event Category	Placebo (N=266) n (%) E [w%]	23.7 mg BID (N=267) n (%) E [w%]
Any AE	234 (88.0) 1,301 [88.0]	244 (91.4) 1,750 [91.4]
Any TEAE	232 (87.2) 1,197 [87.2]	244 (91.4) 1,662 [91.4]
Any Treatment-Related TEAE	60 (22.6) 106 [22.5]	125 (46.8) 306 [46.8]
Any Serious TEAE	50 (18.8) 73 [18.8]	61 (22.8) 99 [22.8]
Any Treatment-Related Serious TEAE	9 (3.4) 10 [3.4]	12 (4.5) 15 [4.5]
Any Severe TEAE	37 (13.9) 56 [13.9]	53 (19.9) 91 [19.8]
TEAE Leading to Dose Modification	67 (25.2) 90 [25.2]	123 (46.1) 223 [46.1]
Treatment-Related TEAE Leading to Dose Modification	19 (7.1) 22 [7.1]	75 (28.1) 117 [28.1]
TEAE Leading to Drug Discontinuation	35 (13.2) 40 [13.2]	36 (13.5) 45 [13.5]
Treatment-Related TEAE Leading to Drug Discontinuation	7 (2.6) 7 [2.6]	20 (7.5) 23 [7.5]
TEAE Leading to Death	4 (1.5) 5 [1.5]	8 (3.0) 8 [3.0]
Treatment-Related TEAE Leading to Death	0 (0.0) 0 [0.0]	0 (0.0) 0 [0.0]

Notes: AE = adverse event (any event on or after first dose of study treatment); E = events; TEAE = treatment-emergent adverse event (any event on or after first dose of study treatment until 30 days post-dose); w% = weighted incidence.

Common adverse events

In the pooled LN safety population (N=533), Infections and Infestations were the most frequently reported types of TEAEs and occurred in more voclosporin subjects (62.2%) than placebo-treated subjects (54.9%). Gastrointestinal (GI) Disorders were the second-most frequent type of TEAEs, reported in 45.3% and 35.3% of voclosporin and placebo subjects, respectively. While there was a higher incidence of GI Disorders in the voclosporin group, gastrointestinal events are also expected with MMF therapy.

Table 64 Incidence of Treatment-Emergent Adverse Events by System Organ Class (≥5% Incidence in Any Group, Pooled LN Safety Population, N=533)

System Organ Class	Placebo (N=266) n (%) E [w%]	23.7 mg BID (N=267) n (%) E [w%]
Any TEAE	232 (87.2) 1,197 [87.2]	244 (91.4) 1,662 [91.4]
INFECTIONS AND INFESTATIONS	146 (54.9) 295 [54.9]	166 (62.2) 359 [62.2]
GASTROINTESTINAL DISORDERS	94 (35.3) 174 [35.3]	121 (45.3) 253 [45.3]
INVESTIGATIONS	46 (17.3) 62 [17.3]	95 (35.6) 164 [35.6]
NERVOUS SYSTEM DISORDERS	44 (16.5) 61 [16.5]	74 (27.7) 114 [27.7]
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	65 (24.4) 98 [24.4]	68 (25.5) 104 [25.5]
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	52 (19.5) 72 [19.6]	66 (24.7) 95 [24.7]
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	49 (18.4) 63 [18.4]	64 (24.0) 93 [24.0]
BLOOD AND LYMPHATIC SYSTEM DISORDERS	42 (15.8) 55 [15.8]	54 (20.2) 78 [20.2]
VASCULAR DISORDERS	36 (13.5) 46 [13.5]	55 (20.6) 65 [20.6]
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	25 (9.4) 34 [9.4]	54 (20.2) 87 [20.2]
METABOLISM AND NUTRITION DISORDERS	57 (21.4) 75 [21.4]	49 (18.4) 72 [18.3]
RENAL AND URINARY DISORDERS	46 (17.3) 52 [17.3]	34 (12.7) 43 [12.7]
EYE DISORDERS	13 (4.9) 17 [4.9]	25 (9.4) 31 [9.4]
CARDIAC DISORDERS	14 (5.3) 15 [5.3]	20 (7.5) 28 [7.5]
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	17 (6.4) 18 [6.4]	17 (6.4) 18 [6.4]
PSYCHIATRIC DISORDERS	14 (5.3) 16 [5.3]	15 (5.6) 19 [5.6]
REPRODUCTIVE SYSTEM AND BREAST DISORDERS	15 (5.6) 21 [5.6]	11 (4.1) 13 [4.1]

Notes: BID = twice daily; E = events; TEAE = treatment-emergent adverse event; w% = weighted incidence.

GFR decreased was the most frequently reported TEAE in voclosporin-treated subjects (26.2%, compared with 9.4% placebo) followed by hypertension (19.1%, compared with 8.6% placebo) (Table 65).

Table 65 All Treatment-Emergent Adverse Events by Preferred Term with Incidence in the Voclosporin Group ≥2% Higher Than Placebo (Pooled LN Safety Population, N=533)

Preferred Term	Placebo (N=266) n (%) E [w%]	23.7 mg BID (N=267) n (%) E [w%]
GLOMERULAR FILTRATION RATE DECREASED	25 (9.4) 32 [9.4]	70 (26.2) 112 [26.2]
HYPERTENSION	23 (8.6) 27 [8.6]	51 (19.1) 58 [19.1]
DIARRHOEA	35 (13.2) 37 [13.2]	50 (18.7) 62 [18.7]
HEADACHE	22 (8.3) 29 [8.3]	40 (15.0) 47 [15.0]
ANAEMIA	16 (6.0) 18 [6.0]	33 (12.4) 36 [12.4]
COUGH	6 (2.3) 6 [2.3]	29 (10.9) 29 [10.8]
URINARY TRACT INFECTION	17 (6.4) 21 [6.4]	26 (9.7) 35 [9.7]
ABDOMINAL PAIN UPPER	6 (2.3) 7 [2.3]	19 (7.1) 19 [7.1]
ALOPECIA	7 (2.6) 7 [2.6]	17 (6.4) 17 [6.4]
DYSPEPSIA	7 (2.6) 7 [2.6]	16 (6.0) 16 [6.0]
RENAL IMPAIRMENT	7 (2.6) 8 [2.6]	15 (5.6) 18 [5.6]
ABDOMINAL PAIN	5 (1.9) 7 [1.9]	14 (5.2) 16 [5.2]
MOUTH ULCERATION	3 (1.1) 3 [1.1]	11 (4.1) 13 [4.1]
FATIGUE	3 (1.1) 3 [1.1]	10 (3.7) 12 [3.7]
TREMOR	2 (0.8) 2 [0.8]	9 (3.4) 10 [3.4]
ACUTE KIDNEY INJURY	2 (0.8) 2 [0.8]	9 (3.4) 10 [3.4]
DECREASED APPETITE	3 (1.1) 3 [1.1]	9 (3.4) 9 [3.4]
GINGIVITIS	0 (0.0) 0 [0.0]	6 (2.2) 6 [2.2]
HYPERTRICHOSIS	0 (0.0) 0 [0.0]	6 (2.2) 6 [2.2]

In the final CSR from the AURORA 2 study, AEs were reported in 86% of subjects in the voclosporin group and 80% of subjects in the placebo group (Table 66-*Table 67*).

Table 66 Overall Summary of Adverse Events (AURORA 2)

	Placebo (N = 100)		Voclosporin (N = 116)	
	Subjects n (%)	Events n	Subjects n (%)	Events n
Any TEAE	80 (80.0)	291	100 (86.2)	488
Treatment-Related TEAE	21 (21.0)	34	28 (24.1)	46
Serious TEAE	23 (23.0)	34	21 (18.1)	22
Treatment-Related Serious TEAE	2 (2.0)	2	1 (0.9)	1
TEAE Leading to Voclosporin/Placebo Discontinuation	17 (17.0)	18	11 (9.5)	11
TEAE Leading to Death	3 (3.0)	3	0	
Treatment-Related TEAE Leading to Death	0		0	
Disease-Related TEAE	34 (34.0)	69	50 (43.1)	93
Disease-Related Serious TEAE	11 (11.0)	14	7 (6.0)	7

Notes: TEAE = treatment-emergent adverse event.

Table 67 Summary of selected TEAEs reported in AURORA 2

SYSTEM ORGAN CLASS Preferred Term	Placebo (N = 100) Subjects n(%)	Events n	Voclosporin (N = 116) Subjects n(%)	Events n
Any TEAE	80 (80.0)	291	100 (86.2)	488
INFECTIONS AND INFESTATIONS	43 (43.0)	82	57 (49.1)	132
INVESTIGATIONS	16 (16.0)	20	24 (20.7)	35
Glomerular filtration rate decreased	5 (5.0)	5	12 (10.3)	15
Neutrophil count decreased	3 (3.0)	3	2 (1.7)	2
RENAL AND URINARY DISORDERS	10 (10.0)	14	21 (18.1)	25
Lupus nephritis	4 (4.0)	4	10 (8.6)	11
Proteinuria	1 (1.0)	2	4 (3.4)	6
Renal impairment	2 (2.0)	2	4 (3.4)	4
VASCULAR DISORDERS	13 (13.0)	13	10 (8.6)	11
Hypertension	7 (7.0)	7	10 (8.6)	10

Three subjects died as a result of TEAEs during the study, all from the placebo group; two deaths were due to SARS-CoV-2 coronavirus infection (COVID-19), and one death was the result of a pulmonary embolism.

Adverse events of special interest

Summaries for certain subsets of TEAEs of particular interest in LN patients and/or the CNI class of drug were prepared based on the pooled LN (N=533) and AURORA 2 (N=216) populations.

Acute renal failure

Overall, in the pooled LN population, 33.3% of voclosporin-treated subjects compared with 17.7% of placebo-treated subjects experienced a TEAE in this SMQ during the first year of study treatment, but the majority of these subjects had GFR decreases (26.2% in the voclosporin group and 9.4% in the placebo group) that were managed effectively with dose interruption or modification.

According to the applicant, in summary, the majority of the TEAEs identified using the Acute Renal Failure SMQ appear to be related to the small, transient, pharmacological effect of voclosporin on eGFR that resolves following dose reduction or interruption, or were due to underlying disease, and do not indicate a clinically meaningful acute adverse effect of voclosporin on the kidney.

In response to day 120 LoQ, the applicant also presented long-term renal data from the AURORA 2 trial:

Acute Renal Failure and Chronic Kidney Disease in the Long-Term AURORA 2 Trial

Overall, the proportion of subjects in AURORA 2 who experienced acute renal failure events (defined using SMQ20000003) or CKD events (defined using SMQ20000213) and including eGFR decreases was 27.6% in the voclosporin group and 17.0% in the placebo group. Excluding eGFR decreases, 18.1% of voclosporin treated subjects and 12.0% of placebo subjects had a TEAE in the acute renal failure SMQ and the CKD SMQ. The proportion of subjects with serious adverse events (SAEs) was lower in the voclosporin group compared with the placebo group (1.7% vs 5.0%) while the proportions with TEAEs leading to dose modification or dose discontinuation were similar across the treatment groups.

Table 68 Overview of TEAEs in the Acute Renal Failure SMQ and the CKD SMQ Excluding GFR Decreased: AURORA 2

	Placebo (N = 100)			23.7 mg BID (N = 116)		
Preferred Term	**n**	**(%)**	**E**	**n**	**(%)**	**E**
Any TEAE	12	(12.0)	16	21	(18.1)	26
TEAEs leading to dose modification	2	(2.0)	2	4	(3.4)	4
TEAEs leading to permanent study drug discontinuation	6	(6.0)	6	7	(6.0)	7
Serious TEAE	5	(5.0)	5	2	(1.7)	2

Renal toxicity is defined as acute renal failure (SMQ20000003 [Broad]) or CKD (SMQ20000213 [Broad]) omitting PT of GFR decreased. Adverse events are coded using MedDRA v20.0. A TEAE is an AE that occurred on or after the first dose of AURORA 2 study drug up to the last dose of study drug + 30 days.

Lupus nephritis and proteinuria were reported at a higher frequency in the voclosporin group compared with the placebo group.

Table 69 Treatment-Emergent Adverse Events Occurring in ≥ 2 Subjects in Any Group in the Acute Renal Failure SMQ and the CKD SMQ Excluding GFR Decreased: AURORA 2

	Placebo (N=100)			23.7 mg BID (N=116)		
Preferred Term	**n**	**(%)**	**E**	**n**	**(%)**	**E**
Any renal toxicity	12	(12.0)	16	21	(18.1)	26
Lupus nephritis	4	(4.0)	4	10	(8.6)	11
Renal impairment	2	(2.0)	2	4	(3.4)	4
Proteinuria	1	(1.0)	2	4	(3.4)	6
Nephrotic syndrome	2	(2.0)	3	0	(0.0)	0

Renal toxicity is defined as acute renal failure (SMQ20000003 [Broad]) or CKD (SMQ20000213 [Broad]) omitting PT of GFR decreased. Adverse events are coded using MedDRA v20.0. A TEAE is an AE that occurred on or after the first dose of AURORA 2 study drug up to the last dose of study drug + 30 days.

Chronic kidney disease

Overall, 30.0% of voclosporin-treated subjects compared with 22.9% of placebo-treated subjects experienced a TEAE in this SMQ during the first year of study treatment; this includes a large number

of subjects that had temporary GFR decreases (26.2% in the voclosporin group and 9.4% in the placebo group) that were managed with dose interruption or modification.

The applicant concludes that the majority of the TEAEs in the Chronic Kidney Disease SMQ appear to be related to the small, transient, pharmacological effect of voclosporin on eGFR or due to underlying disease, and do not indicate any chronic adverse effect of voclosporin on the kidney or development of CKD meeting KDIGO definitions.

Also in the long-term AURORA 2 study (interim data submitted in the original application), a higher proportion of of voclosporin subjects (22.4%) than placebo subjects (13.0%) of in AURORA 2 have reported a TEAE in the Chronic Kidney Disease SMQ during the second or third year of study treatment. Most of these TEAEs were not considered related to study treatment (23 out of 33 TEAEs in the voclosporin group and 13 out of 16 TEAEs in the placebo group). GFR decreases (10.3% voclosporin vs 4.0% placebo), lupus nephritis (7.8% voclosporin and 3.0% placebo), and proteinuria (2.6% voclosporin vs 1.0% placebo) are the most frequently reported TEAEs in this SMQ.

Hypertension

Overall, in the pooled LN population (N=533), a total of 69 events were identified by this SMQ in 56 subjects in the voclosporin group (21.0%) and 37 events in 28 subjects in the placebo group (10.5%).

Serious TEAEs were reported in 6 subjects (2.2%) in voclosporin group, which included 5 events of hypertension in 5 subjects and 1 event of hypertensive crisis in 1 subject. The exposure-adjusted incidence of hypertension was highest in the first 4 weeks of treatment and declined over time in both groups. The treatment difference between voclosporin and placebo group gradually decreased until the incidence was the same in both groups after 26 weeks.

Calcineurin inhibitor-related adverse events

Overall, in the pooled LN population (N=533), 32.2% of voclosporin-treated subjects and 22.9% of placebo subjects experienced TEAEs that are recognised effects of CNIs (Table 70).

Table 70 Calcineurin-Inhibitor-Related Treatment-Emergent Adverse Events (≥1% Incidence in Any Group, Pooled LN Safety Population, N=533)

System Organ Class Preferred Term	Placebo (N=266) n (%) E [w%]	23.7 mg BID (N=267) n (%) E [w%]
Any TEAE	61 (22.9) 77 [22.9]	86 (32.2) 122 [32.2]
VASCULAR DISORDERS	24 (9.0) 32 [9.0]	52 (19.5) 60 [19.5]
HYPERTENSION	23 (8.6) 27 [8.6]	51 (19.1) 58 [19.1]
HYPERTENSIVE CRISIS	3 (1.1) 4 [1.1]	1 (0.4) 1 [0.4]
INVESTIGATIONS	7 (2.6) 8 [2.6]	14 (5.2) 17 [5.2]
WEIGHT DECREASED	1 (0.4) 1 [0.4]	6 (2.2) 6 [2.2]
BLOOD PRESSURE INCREASED	3 (1.1) 4 [1.1]	5 (1.9) 6 [1.9]
METABOLISM AND NUTRITION DISORDERS	21 (7.9) 23 [7.9]	12 (4.5) 14 [4.5]
HYPERLIPIDAEMIA	6 (2.3) 6 [2.3]	7 (2.6) 7 [2.6]
HYPERGLYCAEMIA	4 (1.5) 6 [1.5]	2 (0.7) 3 [0.7]
HYPERTRIGLYCERIDAEMIA	7 (2.6) 7 [2.6]	1 (0.4) 1 [0.4]
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	0 (0.0) 0 [0.0]	11 (4.1) 11 [4.1]
HYPERTRICHOSIS	0 (0.0) 0 [0.0]	6 (2.2) 6 [2.2]
HIRSUTISM	0 (0.0) 0 [0.0]	4 (1.5) 4 [1.5]
NERVOUS SYSTEM DISORDERS	2 (0.8) 2 [0.8]	9 (3.4) 10 [3.4]
TREMOR	2 (0.8) 2 [0.8]	9 (3.4) 10 [3.4]
GASTROINTESTINAL DISORDERS	0 (0.0) 0 [0.0]	5 (1.9) 8 [1.9]
GINGIVAL HYPERTROPHY	0 (0.0) 0 [0.0]	5 (1.9) 8 [1.9]
RENAL AND URINARY DISORDERS	11 (4.1) 11 [4.1]	2 (0.7) 2 [0.8]
PROTEINURIA	10 (3.8) 10 [3.8]	0 (0.0) 0 [0.0]

Notes: BID = twice daily; E = events; TEAE = treatment-emergent adverse event; w% = weighted incidence.

Infections

The overall incidence of infections in the pooled LN population was 62.2% in the voclosporin group and 54.9% in the placebo group. Infections occurring in at least 5% of patients receiving voclosporin and at least 1% more frequently than patients receiving placebo were urinary tract infection, viral upper respiratory tract infection, herpes zoster and gastroenteritis.

Table 71 Treatment-Emergent Adverse Events Occurring at an Incidence of ≥ 5% in the Infections and Infestations System Organ Class by Preferred Term: Pooled LN Population

System Organ Class Preferred Term	Placebo (N=266) n (%) E [w%]	23.7 mg BID (N=267) n (%) E [w%]
INFECTIONS AND INFESTATIONS	146 (54.9) 295 [54.9]	166 (62.2) 359 [62.2]
Upper respiratory tract infection	40 (15.0) 56 [15.0]	42 (15.7) 65 [15.7]
Urinary tract infection	17 (6.4) 21 [6.4]	26 (9.7) 35 [9.7]
Viral upper respiratory tract infection	20 (7.5) 23 [7.5]	24 (9.0) 30 [9.0]
Herpes zoster	14 (5.3) 15 [5.3]	18 (6.7) 18 [6.7]
Gastroenteritis	12 (4.5) 12 [4.5]	15 (5.6) 19 [5.6]
Pneumonia	13 (4.9) 14 [4.9]	15 (5.6) 18 [5.6]
Influenza	11 (4.1) 13 [4.1]	14 (5.2) 17 [5.2]

n = subjects; w% = weighted incidence adjusted for study sise.
Adverse Events are coded using MedDRA v20.0. A TEAE is an AE that occurred on or after the first
dose of study drug up to the last dose of study drug + 30 days.

Opportunistic infections

Overall, in the pooled LN population (N=533), the incidence was similar between the voclosporin (1.1%) and placebo (0.8%) groups with 5 subjects reporting an Opportunistic Infection. The types of infections included cutaneous/disseminated or ophthalmic manifestations of cytomegalovirus or the herpes family of viruses. Only 1 subject, in the placebo group, had a serious opportunistic infection (herpes zoster disseminated). All of the opportunistic infections observed are a known complication of MMF, which was part of the study treatment regimen for both voclosporin and placebo groups. According to the applicant, these results indicate that in subjects with LN, who are also using corticosteroids and MMF, the risk of opportunistic infection and serious opportunistic infection does not increase by the addition of voclosporin treatment.

Malignancies

A total of 4 subjects in the pooled LN population reported a TEAE in this SMQ, all of whom were in the voclosporin group (1.5%). These TEAEs included a wide variety of preferred terms, with only single occurrences reported for each TEAE (stage 0 cervical carcinoma, skin neoplasm, pyoderma gangrenosum, and breast tumour excision). The only serious TEAE was cervical carcinoma.

No malignancies were reported in the AURORA 2 study.

MACE

The exposure-adjusted incidence rate of MACE in the pooled LN population was lower in the voclosporin group (1.7 E/100 PYs) than in the placebo group (2.1 E/100 PYs).

Adverse events after drug discontinuation

In AURORA 1 the patients that did not participate in the continuation study, were followed-up for 4 Weeks (+/-10 days). Post-treatment AEs were defined as events occurring more than 30 days post-last dose. That is deemed as an appropriate follow-up period.

Overall incidence of any post-treatment AE was 14% (25/178 subjects) in each study group, with 72 events in voclosporin and 69 events in placebo group. Most common were those pertaining to SOC Infections and infestations, but other SOCs with CNI class related AEs were represented (SOC Renal and urinary disorders, SOC Respiratory, thoracic and mediastinal disorders, SOC Blood and lymphatic system disorders, SOC Nervous system disorders and so on). Except of pneumonia events (4 vs 5 events) and SLE (4 vs 1 event), other occurred in 1-2 cases.

There were post-treatment SAEs observed: 6.2% (N=11, 17 events) in voclosporin vs 4.5% (N=8, 17 events) in placebo group. Same SOCs were represented, with pneumonia being most frequent (3 vs 2 events) and other events occurring individually. Three of these events resulted in death - 1 voclosporin subject and 2 placebo subjects (please refer to section "Deaths" below).

According to available data, post-treatment eGFR values suggest resolution of voclosporin effect on eGFR decrease. This effect was rather small and in accordance with analysis of eGFR over time (please refer to section "Laboratory findings" below).

2.5.8.3. Serious adverse event/deaths/other significant events

Serious adverse events

In the pooled LN population, serious TEAEs occurred in 22.8% of voclosporin-treated subjects and 18.8% of placebo-treated subjects (*Table 72*). The exposure-adjusted incidence of serious TEAEs in the voclosporin and placebo groups, respectively, was 28.3 and 23.2 events per 100 years of exposure.

Table 72 Incidence of Serious Treatment-Emergent Adverse Events by System Organ Class and Preferred Term (≥1% of Subjects in Any Group; Pooled LN Safety Population, N=533)

System Organ Class Preferred Term		Placebo (N=266) n (%) E [w%]	23.7 mg BID (N=267) n (%) E [w%]
Any Serious TEAE		50 (18.8) 73 [18.8]	61 (22.8) 99 [22.8]
	MILD	0 (0.0)	1 (0.4)
	MODERATE	27 (10.2)	23 (8.6)
	SEVERE	23 (8.6)	37 (13.9)
INFECTIONS AND INFESTATIONS		27 (10.2) 32 [10.1]	27 (10.1) 36 [10.1]
PNEUMONIA		10 (3.8) 11 [3.8]	11 (4.1) 13 [4.1]
GASTROENTERITIS		1 (0.4) 1 [0.4]	4 (1.5) 5 [1.5]
URINARY TRACT INFECTION		1 (0.4) 1 [0.4]	3 (1.1) 3 [1.1]
RENAL AND URINARY DISORDERS		9 (3.4) 9 [3.4]	13 (4.9) 14 [4.9]
ACUTE KIDNEY INJURY		2 (0.8) 2 [0.8]	8 (3.0) 9 [3.0]
RENAL IMPAIRMENT		1 (0.4) 1 [0.4]	3 (1.1) 3 [1.1]
LUPUS NEPHRITIS		4 (1.5) 4 [1.5]	1 (0.4) 1 [0.4]
NERVOUS SYSTEM DISORDERS		2 (0.8) 2 [0.8]	9 (3.4) 9 [3.4]
VASCULAR DISORDERS		3 (1.1) 4 [1.1]	6 (2.2) 6 [2.2]
HYPERTENSION		1 (0.4) 1 [0.4]	5 (1.9) 5 [1.9]
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS		2 (0.8) 3 [0.8]	6 (2.2) 6 [2.2]
BLOOD AND LYMPHATIC SYSTEM DISORDERS		1 (0.4) 1 [0.4]	5 (1.9) 6 [1.9]
ANAEMIA		1 (0.4) 1 [0.4]	3 (1.1) 4 [1.1]
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS		5 (1.9) 5 [1.9]	4 (1.5) 4 [1.5]
SYSTEMIC LUPUS ERYTHEMATOSUS		4 (1.5) 4 [1.5]	4 (1.5) 4 [1.5]
GASTROINTESTINAL DISORDERS		4 (1.5) 5 [1.5]	3 (1.1) 3 [1.1]
CARDIAC DISORDERS		3 (1.1) 3 [1.1]	3 (1.1) 5 [1.1]

Notes: BID = twice daily; E = events; TEAE = treatment-emergent adverse event; w% = weighted incidence.

A summary of serious adverse events in the AURORA 2 study is shown below.

Table 73 Summary of Serious TEAEs Occurring in >1% of Subjects in Either Arm (AURORA 2)

SYSTEM ORGAN CLASS Preferred Term	Placebo (N = 100) Subjects n(%)	Events n	Voclosporin (N = 116) Subjects n(%)	Events n
Any Serious TEAE	23 (23.0)	34	21 (18.1)	22
INFECTIONS AND INFESTATIONS	8 (8.0)	10	8 (6.9)	9
Corona virus infection	5 (5.0)	5	2 (1.7)	2
Urinary tract infection	0	0	2 (1.7)	2
Pneumonia viral	2 (2.0)	2	0	0
Disseminated tuberculosis	1 (1.0)	1	0	0
RENAL AND URINARY DISORDERS	5 (5.0)	5	2 (1.7)	2
Lupus nephritis	3 (3.0)	3	2 (1.7)	2
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	6 (6.0)	8	1 (0.9)	1
Systemic lupus erythematosus	3 (3.0)	3	1 (0.9)	1
Osteonecrosis	2 (2.0)	2	0	0

Notes: TEAE = treatment-emergent adverse event.

Deaths

In total, including the final AURORA 2 data, 23 subjects died in the LN trials (10 placebo subjects and 13 voclosporin subjects). Exposure-adjusted incidence rates are shown below for all AEs leading to death in AURA-LV (including the 39.5 mg group), AURORA 1 and AURORA 2 (final data).

Table 74 Exposure-Adjusted Incidence Rates and Treatment Comparisons for AEs Leading to Death: AURA-LV (including the 39.5 mg group), AURORA 1 and AURORA 2

System Organ Class Preferred Term	Statistic	Placebo (N=266)	Voclosporin (N=355)	Treatment Difference 95% CI
Any Fatal AE	n / Exp EAIR	10 / 436.80 2.3	13 / 555.89 2.3	[-0.4] (-2.1,1.3)

Treatment Difference = study adjusted treatment difference [active - placebo]. Exposure calculated as
time at risk of first event [time until the first of: event or last contact]. Adverse events are coded using
MedDRA v20.0. An AE is an event that occurs on or after the first dose of study drug.

The proportion of subjects in the 23.7 mg BID group in the AURA-LV study who died was higher than expected. The majority of deaths occurred in subjects from low-GDP countries (Bangladesh, Sri Lanka, Philippines), who also had more severe baseline disease characteristics. An imbalance in regional randomisation was subsequently identified, where the 23.7 mg BID group had a higher proportion of subjects enrolled from these low-GDP countries, and this is believed to have introduced a bias towards poorer safety outcomes in this group. Additionally, there was no greater proportion of deaths in the high-dose 39.5 mg BID voclosporin group and other safety indices from the AURA-LV study were similar between treatment groups (incidence of TEAEs and serious TEAEs). Supplementary analyses identified region and several baseline disease characteristics as significant factors contributing to death independent of treatment assignment. Furthermore, the incidence of death in subjects treated with 23.7 mg BID voclosporin in the AURORA 1 study was low (0.6%). According to the applicant, the

totality of data suggests that the imbalance of deaths in subjects treated with 23.7 mg BID voclosporin in the AURA-LV study was associated with additional factors independent of voclosporin treatments.

Of all deaths across the LN studies, none were considered to be treatment-related. An examination of mortality across all subjects with LN in the voclosporin studies indicated that the causes of death were multifactorial including sepsis, infection, and other lupus-related complications. Five deaths in the pooled LN population occurred >30 days after last dose of study drug. All subjects who died, along with the events leading to death, are listed below.

Table 75 Summary of All AEs Resulting in Death in AURORA 1

Treatment	Adverse Event	Day of Onset	Time Since Last Dose	TEAE (Yes/No)	Related to Treatment	Related to LN
Placebo						
	Pneumonia	Day 11	10 days	Yes	No	No
	Lupus nephritis	Day 240	21 days	Yes	No	Yes
	Pulmonary embolism	Day 110	36 days	No	No	Yes
	Pneumonia	Day 81	15 days	Yes	No	Yes
	Septic shock	Day 81	15 days	Yes	No	Yes
	Acute respiratory failure	Day 274	54 days	No	No	Yes
Voclosporin						
	Pneumonia	Day 350	79 days	No	No	Yes

Table 76 Listing of Subjects Who Had TEAEs Leading to Death in AURA-LV

	Gender	TEAE Preferred Term	Infection Y/N	Event Start (Study Day)	Death (Study Day)
Placebo					
	Female	Cerebrovascular accident	N	6	6
Low-Dose Voclosporin (23.7 mg BID)					
	Female	Multi-organ failure	Y[(1)]	43	43
	Female	Cardiac tamponade	N	237	237
	Male	Acute respiratory distress syndrome	Y[(1)]	165	168
	Female	Pericarditis tuberculous	Y	40	47
	Female	Acute respiratory distress syndrome	Y[(1)]	119	120
	Female	Pneumonia	Y	21[(3)]	41
	Male	Pulmonary embolism	N	28	29
	Female	Pneumonia	Y	57	59
	Female	Pulmonary alveolar haemorrhage	N	169	170
	Female	Pulmonary embolism	N	22	22
High-Dose Voclosporin (39.5 mg BID)					
	Female	Sepsis	Y	16	32
	Female	Pulmonary embolism	N	26	26

1 Deaths with an infectious component.

3 Subject : Onset date for leading non-serious pneumonia started Day 21 with event deemed serious from Day 32.
Notes: BID=Twice daily; N=No; No.=Number; SAE=Serious adverse event; TEAE=Treatment-emergent adverse event; Y=Yes.

In the final CSR from the AURORA 2 study, 3 placebo subjects have had TEAEs leading to death: coronavirus infection (2 subjects) and pulmonary embolism (1 subject). None of these TEAEs were considered treatment-related by the Investigators, who remain blinded to study treatment. There were no deaths in voclosporin-treated subjects in AURORA 2.

The weighted incidence of all-cause mortality or renal failure was 4.2% in the placebo group, 6.4% in the voclosporin 23.7 mg group and 3.4% in the voclosporin 39.5 mg group (Table 77).

Table 77 All Fatal or Renal Failure AEs Occurring in AURORA 1 and AURA-LV (including the 39.5 mg dose group)

System Organ Class Preferred Term	Placebo (N=266) n (%) E [w%]	23.7 mg BID (N=267) n (%) E [w%]	39.5 mg BID (N=88) n (%) E [w%]
All-Cause Mortality or Renal Failure	11 (4.1) 14 [4.2]	15 (5.6) 17 [6.4]	3 (3.4) 3 [3.4]

The incidence of all-cause mortality or renal failure in the long-term AURORA 2 trial was lower in the voclosporin group (0.9%) compared with the placebo group (4.0%) (Table 78).

Table 78 All Fatal or Renal Failure AEs Occurring in AURORA 2 by SOC and PT

System Organ Class Preferred Term	Placebo (N=100) n (%) E	23.7 mg BID (N=116) n (%) E
All-Cause Mortality or Renal Failure	4 (4.0) 4	1 (0.9) 1

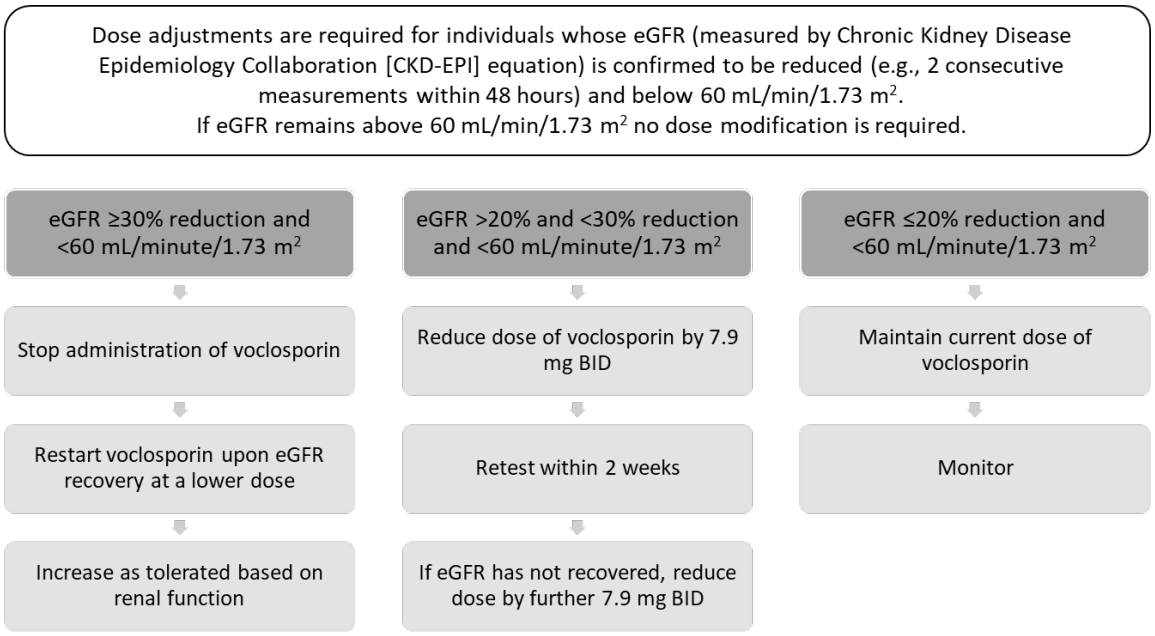
2.5.8.4. Laboratory findings

Renal function

Estimated glomerular filtration rate (eGFR)

The following dose adjustment recommendations based on GFR were applied in the LN studies:

Figure 21 Recommended Voclosporin Dose Adjustments in Response to eGFR



Note: Individuals requiring a decrease in dose should be reassessed for eGFR recovery within 2 weeks. For patients that had a decrease in dose due to eGFR reduction, consider increasing the dose by 7.9 mg BID for each eGFR measurement that is ≥80% of baseline; do not exceed the starting dose.

Analysis of the change in eGFR over time was calculated with both raw eGFR values (as reported by the central laboratory) and corrected values (all values >90 mL/min/1.73 m2 were rounded to 90 mL/min/1.73 m2 as requested by the Data and Safety Monitoring Board). In the pooled LN population, mean baseline corrected eGFR was similar between treatment groups (mean±SD of 79.0±15.44 mL/min/1.73 m2 in the voclosporin group and 79.1±15.86 mL/min/1.73 m2 in the placebo group). The maximum mean decrease from baseline in corrected eGFR in the voclosporin group occurred at Week 4 and was -3.4 mL/min/1.73 m2; in comparison, the placebo group had a mean increase of 2.2 mL/min/1.73 m2 at Week 4 (for a mean difference of -5.6 mL/min/1.73 m2, p <0.0001.

In the final CSR from the AURORA 2 continuation study, mean corrected eGFR values during Years 2 and 3 of study treatment are similar to the mean eGFR values observed over the first year of study treatment in this same group of subjects (Figure 21).

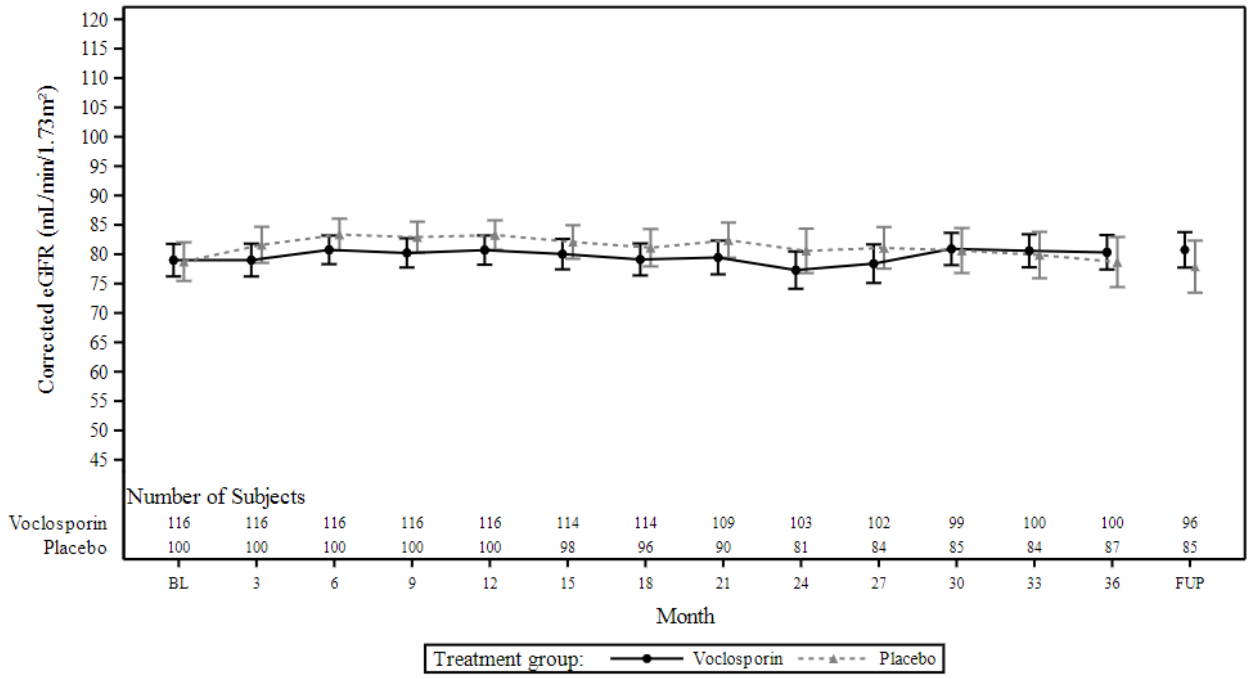


Figure 22. Mean (±95% CI) Corrected eGFR (mL/min/1.73 m2) by Visit (AURORA 1 and AURORA 2)

The reversibility of renal events was discussed in response to day 120 LoQ:

An analysis of the reversibility of TEAEs of acute renal failure or chronic kidney disease or a confirmed eGFR decrease of ≥ 30% is provided below for AURORA 1 together with an analysis of subjects with a ≥ 20% decrease in eGFR.

Recovery was defined as an increase in eGFR to within 20% of baseline. This is in line with the AURORA 1 protocol which stated that: *"subjects experiencing a decrease in eGFR with resultant decrease in dose should be reassessed for recovery of renal function. If the repeated eGFR is >80% of baseline, the dose should be increased by 1 capsule BID and eGFR assessed within 2 weeks."* It also reflects the proposed SmPC wording (SmPC Section 4.2) which states that the current dose of voclosporin should be maintained for a ≤ 20% reduction in eGFR.

Acute renal failure, chronic kidney disease or confirmed eGFR decreases of ≥ 30%

In total, 65 voclosporin subjects (36.5%) and 55 placebo subjects (30.9%) had at least 1 of the following events:

Acute renal failure defined using SMQ20000003.

CKD event defined using SMQ20000213.

eGFR decreases ≥ 30% defined as 2 consecutive measures showing at least a 30% drop from baseline.

Of these subjects, the proportion of voclosporin treated subjects who recovered was 92.3% (Table 79).

Table 79 Summary of Subjects with a Confirmed eGFR Decrease of ≥ 30% by Subsequent eGFR Recovery: AURORA 1

Parameter	Placebo (N = 178)	23.7 mg BID (N = 178)
Subjects with event[a], n (%)	55 (30.9)	65 (36.5)
Subjects with event who recovered, n (%)	42 (76.4)	60 (92.3)
Subjects with event who did not recover, n (%)	13 (23.6)	5 (7.7)

[a] Event = At least 1 of the following events: acute renal failure Events defined using SMQ20000003, CKD events defined using

SMQ20000213, or GFR decrease defined as 2 consecutive measures showing at least a 30% reduction from baseline. Recovery following event defined as a return to within 20% of baseline.

Of the 5 subjects in the voclosporin group who did not recover to within 20% of the baseline eGFR, 4 had clear disease progression/LN flare and 1 subject had a partial recovery in eGFR levels, although recovery was to less than 20% of baseline.

Confirmed eGFR decreases of ≥ 20%

More voclosporin subjects than placebo subjects had a confirmed decrease of ≥ 20% in eGFR (25.8% vs 18.5%). Among these, 73.9% of subjects in the voclosporin group recovered (Table 80).

Table 80 Summary of Subjects with a Confirmed eGFR Decrease of ≥ 20% by Subsequent eGFR Recovery: AURORA 1

Parameter	Placebo (N = 178)	23.7 mg BID (N = 178)
Subjects with event[a], n (%)	33 (18.5)	46 (25.8)
Subjects with event who recovered, n (%)	19 (57.6)	34 (73.9)
Subjects with event who did not recover, n (%)	14 (42.4)	12 (26.1)

[a] Event = eGFR decrease defined as 2 consecutive measures showing at least a 20% reduction from baseline. Recovery following event defined as a return to within 20% of baseline. Dose Change = any study medication dose increase or decrease following event in question.
Discontinuation = permanently stopping study medication following event in question.

Of the 12 subjects in the voclosporin group who did not recover, 5 were discussed above (=had eGFR decrease of ≥ 30%). Of the remaining 7 subjects who did not recover, disease progression was a factor in 6 subjects and 1 had partial recovery in eGFR levels although recovery was to less than 20% of baseline.

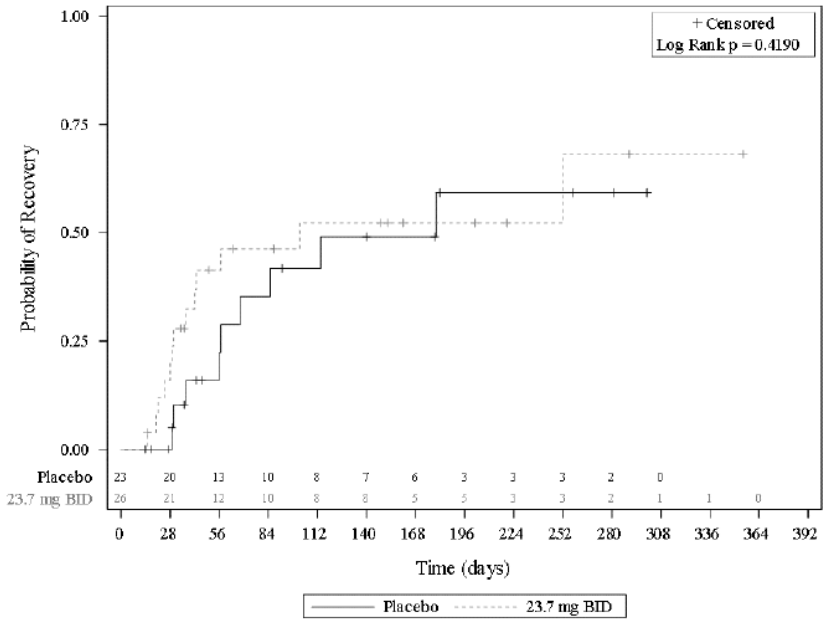


Figure 23. Kaplan-Meier plot of time to recovery in subjects with eGFR decrease of ≥30% in AURORA 1

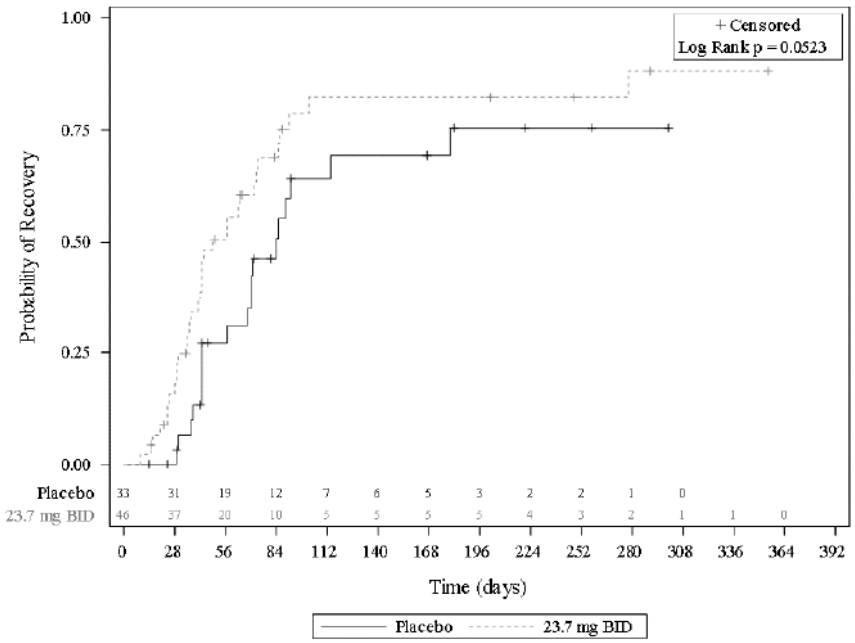


Figure 24. Kaplan-Meier plot of time to recovery in subjects with eGFR decrease of ≥20% in AURORA 1

Further, in response to day 180 LoQ, the applicant presented details on the reversibility of renal events from the AURORA 2 study.

During the second and third years of treatment, fewer subjects in both arms experienced events of acute renal failure, chronic kidney disease (CKD), or eGFR decrease of ≥ 30% from AURORA 1 baseline than in the first 12 months. As in the first year of treatment in AURORA 1, more events were recorded in the voclosporin arm than the placebo arm (30.2% vs 20.0%); however, the recovery rate was higher in the voclosporin arm (85.7% vs 55.0%).

Table 81 Summary of subjects with renal events and their recovery in AURORA 2

Parameter	Placebo (N = 100)	23.7 mg BID (N = 116)
Subjects with event[a], n (%)	20 (20.0)	35 (30.2)
n (%) of subjects with event who recovered	11 (55.0)	30 (85.7)
n (%) of subjects with event who did not recover	9 (45.0)	5 (14.3)

[a]Event = At least 1 of the following events: acute renal failure events defined using SMQ20000003, CKD events defined using SMQ20000213, or GFR decrease defined as 2 consecutive measures showing at least a 30% reduction from baseline that occurred on or after the first dose of AURORA 2 study drug up to the last dose of study drug + 30 days.
Recovery following event defined as a return to within 20% of AURORA 1 baseline.

Similarly, more voclosporin subjects than placebo subjects had a confirmed decrease of ≥ 20% in eGFR (19.8% vs 12.0%), but the proportion of subjects who recovered was higher in the voclosporin group compared with the placebo group (69.6% vs 41.7%). This shows that even after long-term treatment with voclosporin (beyond 12 months), the majority of subjects recover from the CNI-induced decrease in eGFR.

Table 82 Summary of subjects with eGFR decrease by ≥20% and their recovery in AURORA 2

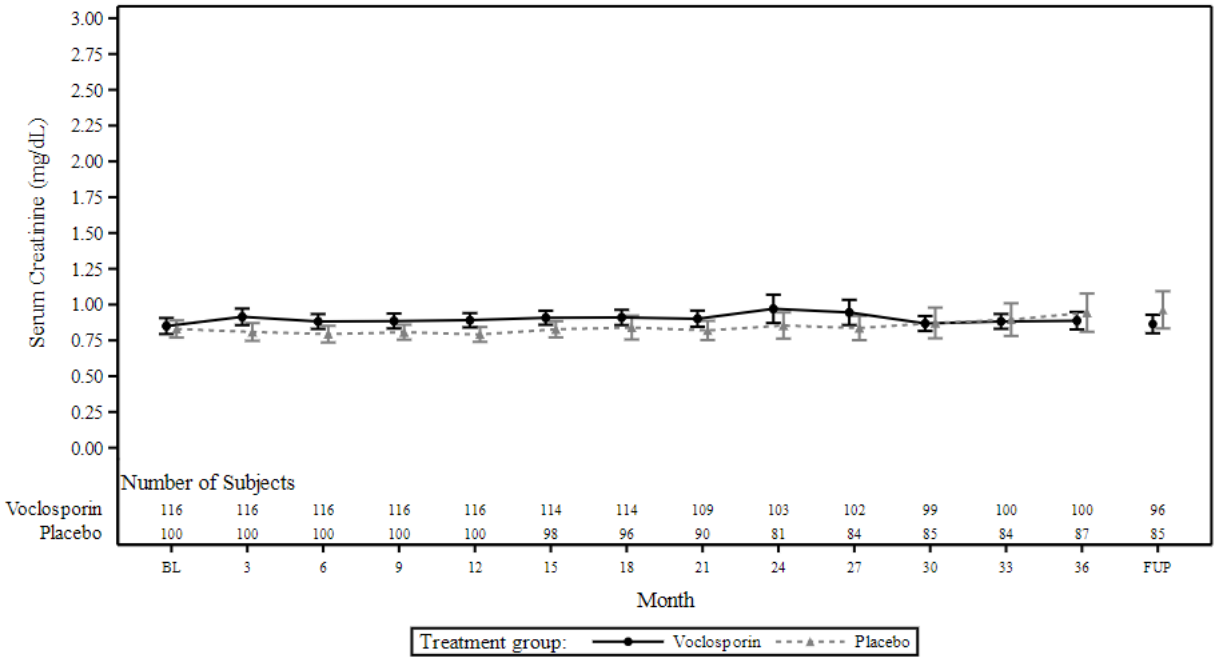
Parameter	Placebo (N = 178)	23.7 mg BID (N = 178)
Subjects with event[a], n (%)	12 (12.0)	23 (19.8)
Subjects with event who recovered, n (%)	5 (41.7)	16 (69.6)
Subjects with event who did not recover, n (%)	7 (58.3)	7 (30.4)

[a] Event = eGFR decrease defined as 2 consecutive measures showing at least a 20% reduction from baseline that occurred on or after the first dose of AURORA 2 study drug up to the last dose of study drug + 30 days.

Recovery following event defined as a return to within 20% of AURORA 1 baseline.

Serum creatinine

In the pooled LN population, mean baseline serum creatinine was similar between treatment groups (0.82 mg/dL in the voclosporin group and 0.80 mg/dL in the placebo group). Mean serum creatinine levels are shown below.



Notes: BL = baseline; CI = confidence interval; FUP = follow-up.

Figure 25. Mean (±95% CI) Observed Serum Creatinine (mg/dL) by Visit (AURORA 1 and AURORA 2)

No subjects in the voclosporin group had any Grade 3 or 4 serum creatinine increases during study treatment and in the placebo group, there were 2 subjects with increases in serum creatinine to Grade 3 or 4. Shifts to Grade 2 serum creatinine occurred in 34 subjects in the voclosporin group and 17 subjects in the placebo group.

Other renal function parameters

In the pooled LN population, mean baseline albumin levels were below normal (range of 3.5 to 5.5 g/dL) in both the voclosporin (2.87±0.757 g/dL) and placebo (2.98±0.711) groups, which is expected given that the subjects had pronounced proteinuria. Albumin levels gradually improved throughout study treatment in both groups and reached the normal range by Week 12 in the voclosporin group and by Week 24 in the placebo group.

Liver function

In the pooled LN population, alkaline phosphatase gradually increased from baseline in the voclosporin group, whereas the placebo group experienced sporadic changes. Mean values remained within the normal range (37 to 116 U/L) at all time points.

Mean bilirubin values were within normal ranges (0.1 to 1.1 mg/dL) at all time points in both groups.

Aspartate aminotransferase (AST), alanine aminotransferase (ALT), and gamma-glutamyl transpeptidase (GGT) were within normal ranges and there were no meaningful differences between treatment groups). There was no difference in the percentages of subjects with shifts from baseline representing a Grade 1 or 2 worsening of ALT or AST (no subjects in either group had Grade 3 or 4 shifts).

There was 1 subject in the voclosporin group with changes in both aminotransferases and bilirubin that met biochemical criteria for Hy's Law. This subject had increases in ALT (>5x upper limit of normal [ULN]), AST (>5x ULN), and bilirubin (>2x ULN) on Day 31; however, study treatment had been previously discontinued on Day 23 following several TEAEs, including drug-induced liver injury that was reported as hepatotoxicity secondary to anti-tuberculosis medication and was considered by the Investigator to be unrelated to study treatment. The subject was taking multiple concomitant medications, including rifampicin (known to have hepatotoxic adverse effects), and had other comorbidities, including pulmonary tuberculosis starting on Day 22 and pericarditis tuberculous leading to death on Day 40. There were no other subjects with changes in transaminases and bilirubin suggestive of liver injury, nor any other TEAEs of drug-induced liver injury in the LN population.

Other blood chemistry parameters

Serum electrolytes

Mean calcium levels were below normal range (8.5 to 10.5 mg/dL) in the voclosporin group at baseline but increased to within the normal range during study treatment (8.38±0.650 mg/dL at baseline and 8.95±0.517 mg/dL Week 52. Shifts from normal to below normal or from below normal to a more severe category of below normal at any time during study treatment occurred in both voclosporin and placebo groups at similar frequencies. Furthermore, the incidence of hypocalcemia as a TEAE was similar between treatment groups (0.4% voclosporin and 0.8% placebo)

The changes from baseline in potassium were significantly different between treatment groups at every visit ($p \leq 0.002$), but mean values remained within the normal range (3.5 to 5.0 mmol/L) in both groups at all time points. According to the applicant, there was no meaningful difference between treatment groups in TEAE incidence of hypokalemia (5.6% voclosporin vs 6.8% placebo) and hyperkalemia (1.9% voclosporin vs 0.8% placebo).

Haematology and coagulation

In the pooled LN population, mean and median values for haematocrit, haemoglobin, and red blood cells (RBCs) were near or below the lower limit of the respective normal ranges in both placebo and voclosporin groups at all time points, including baseline. Both placebo and voclosporin groups experienced small decreases from baseline in mean haematocrit, haemoglobin, and RBC values throughout study treatment at most time points. These decreases were larger in the voclosporin group than placebo group at each time point.

Leukocytes, lymphocytes, and neutrophils initially increased from baseline at Week 4 in both treatment groups, with larger increases from baseline in the voclosporin group than the placebo group; however, absolute counts were within the normal range. After Week 4, mean leukocyte counts were lower than baseline in both treatment groups with no differences between treatments, and mean values continued

to remain within normal ranges at all time points. A lower percentage of voclosporin-treated subjects (3.1%) shifted to Grade 3 or 4 lymphocytes compared with placebo-treated subjects (6.5%). Neutrophils remained normal in most subjects in both treatment groups overall, with shifts to Grade 3 or 4 neutrophils occurring at a low, similar frequency between groups (2.3% of voclosporin and 1.5% of placebo).

Lipids and glucose

Hyperlipidemia is a common comorbidity in subjects with LN and was observed frequently in the medical history of the study populations. As such, mean baseline values for total cholesterol, low-density lipoprotein (LDL), and triglycerides were above the respective normal ranges in both placebo and voclosporin groups. Overall, lipid profiles improved in both treatment groups throughout the study periods.

Mean glucose levels were within normal range (60 to 115 mg/dL) at all time points in both treatment groups, according to the applicant with no meaningful change over the study treatment periods. A similar number of subjects experienced a shift above normal in the placebo (13 subjects, 4.9%) and voclosporin groups (10 subjects, 3.8%); shifts to Grade 3 hyperglycemia were observed in 2 voclosporin subjects and 0 placebo subjects. The Grade 3 shifts in glucose in the voclosporin group occurred in different subjects at sporadic visits (Week 8 and 20) and were not sustained. The absence of any long-term changes in glucose is supported by the HbA1c results, as mean levels were within normal range (4% to 6%) at all time points in both treatment groups and there were no meaningful changes from baseline during treatment. New-onset diabetes is an important recognised adverse effect of CNI inhibitors, but an examination of TEAEs related to diabetes and glycemic control indicate that there is no increase in these types of events with voclosporin treatment.

Urinalysis

In general, urinalysis parameters improved in both the placebo and voclosporin groups. Improvements include a reduction in the percentage of subjects exhibiting any amount of blood in the urine (voclosporin: 78.7% at baseline and 42.9% at Week 52; placebo: 74.4% at baseline and 49.2%; results for urinary RBCs were similar) and, in those subjects with results available, increases in the percentage of subjects with no or occasional granular casts present (voclosporin: 27.0% at baseline [n=63] and 42.1% at Week 52 [n=19]; placebo: 26.5% at baseline [n=68] and 55.6% at Week 52 [n=18]).

Improvements in urinary protein were also observed throughout study treatment. At baseline most subjects had ≥300 mg/dL (79% voclosporin and 80.1% placebo). By Week 52, the proportion of subjects with ≥300 mg/dL protein decreased to 23.7% in the voclosporin group and 49.2% in the placebo group.

Vital signs and physical findings

Dedicated QT studies

The effect of voclosporin on the QT interval were explored in the single-dose (Study ISA03-11) and multiple-dose (Study ISA05-03) studies in healthy subjects. According to the applicant, these studies were designed in accordance with the ICH E14 guidance "Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs" and primarily included supratherapeutic doses (from 0.5 to 4.5 mg/kg single dose and 0.3 to 1.5 mg/kg multiple dose for 6 days). According to the ICH Topic E 14, "The Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs":

"The positive control should have an effect on the mean QT/QTc interval of about 5 ms (i.e., an effect that is close to the QT/QTc effect that represents the threshold of regulatory concern, around 5 ms)".

"A negative 'thorough QT/QTc study' is one in which the upper bound of the 95% one-sided confidence interval for the largest time-matched meaneffect of the drug on the QTc interval excludes 10 ms."

Study ISA03-11 showed that after a single dose of 0.5 mg/kg, the mean maximum difference from placebo on the QTcF interval was **6.4 msec** (upper bound of the 95% CI **11.6 msec)**. In Study ISA05-03, voclosporin did not prolong the QTcF interval after multiple doses of 1.5 mg/kg BID (supratherapeutic dose) nor 0.3 or 0.5 mg/kg BID dosing (closer to therapeutic LN dose) relative to placebo.

ECG findings in phase 2/3 studies

In the AURA-LV study, TEAEs of QT prolongation were observed in one subject treated with 23.7 mg BID voclosporin and one subject treated with 39.5 mg BID voclosporin. According to the applicant, a detailed, independent analysis of ECG data from the AURA-LV study in subjects with LN showed no evidence of ECG-related safety concerns. Mean values for heart rate and PR, QRS, and QTcF intervals were stable across visits with only nominal differences between treatment groups. Furthermore, a regression analysis of change of QTcF from baseline (adjusted for placebo) showed a minimally negative slope that was not statistically different from a slope of 0. As a result of these conclusions from the AURA-LV study, it was determined that the ECG monitoring (12-lead) requirements could be reduced for the subsequent AURORA 1 study (i.e., less frequent and without triplicate readings or central monitoring, except for subjects who met prespecified criteria).

According to the applicant, in the AURORA1 study there were no clinically meaningful changes from baseline or differences between treatment groups in ECG parameters. No subject recorded a QTcF of >500 msec. Two TEAEs of QT prolongation were recorded in one subject (increases of 92 msec and 53 msec from baseline) and this subject discontinued voclosporin treatment following the second event. QTcF prolongation (an increase from baseline of 76 msec) was confirmed in a second subject who had discontinued study treatment 22 days earlier, but not recorded as a TEAE. Both subjects were asymptomatic and continued follow-up in the study. An independent review of ECG interval changes from AURORA 1 was also performed and concluded that there were no meaningful signs of delayed cardiac repolarisation.

In the final CSR from AURORA 2 (01 April 2021), 3 subjects in the placebo group were reported to have prolonged QT time. No TEAEs of QT prolongation have been reported in the voclosporin group.

2.5.8.5. Safety in special populations

Age

As per the inclusion criterion in the AURA-LV and AURORA 1 studies, all patients were aged 18-75 years. A summary of the safety outcome by age is presented below.

Table 83 Summary of Treatment-Emergent Adverse Events in the Voclosporin Group by Age Group: Lupus Nephritis Trials AURORA 1 and AURA-LV (Including the 39.5 mg Voclosporin Group): Safety Population

MedDRA Terms	Age <65 n (%)	Age 65-74 n (%)	Age 75-84 n (%)	Age 85+ n (%)
	N = 353	N = 2	N = 0	N = 0
Total TEAEs	327 (92.6)	2 (100)	-	-
Serious TEAEs – Total	82 (23.2)	0	-	-
Fatal	10 (2.8)	0	-	-
Hospitalisation/prolong existing hospitalisation	75 (21.2)	0	-	-
Life-threatening	13 (3.7)	0	-	-
Disability/incapacity	6 (1.7)	0	-	-
Other (medically significant)	20 (5.7)	0	-	-
TEAE leading to discontinuation	50 (14.2)	0	-	-
Psychiatric disorders	23 (6.5)	0	-	-
Nervous system disorders	97 (27.5)	1 (50)	-	
Accidents and injuries	19 (5.4)	0	-	-
Cardiac disorders	28 (7.9)	0	-	-
Vascular disorders	75 (21.2)	0	-	-
Cerebrovascular disorder	0	0	-	-
Infections and infestations	224 (63.5)	0	-	-
Anticholinergic syndrome	41 (11.6)	0	-	-
Quality of life decreased	0	0	-	-
Sum of postural hypotension, falls, black outs, syncope, dizziness, ataxia, fractures	17 (4.8)	0	-	-
Other AE appearing more frequently in older patients	0		-	-

Number of TEAEs in Psychiatric disorders, Nervous system disorders, Cardiac disorders, Vascular disorders, Infections and Infestations include all TEAEs within the relevant SOC; Cerebrovascular disorder includes any TEAE with a preferred term of cerebrovascular disorder; Accidents and injuries includes all TEAEs within the Accidents and Injuries SMQ; Anticholinergic syndrome includes all TEAEs within the Anticholinergic syndrome SMQ; Quality of life decreased includes all TEAEs with a preferred term of quality of life decreased.

Renal impairment

Adverse events by baseline eGFR

The incidence of TEAEs was comparable between voclosporin and placebo treatment groups in the subgroups of subjects with higher baseline eGFR (i.e., ≥60 and <90 or ≥90 mL/min/1.73 m^2), but in the lowest baseline eGFR subgroup (<60 mL/min/1.73 m^2), the voclosporin group had a higher incidence of TEAEs (97.5%) than placebo (87.3%) (Table 84). The incidence of serious TEAEs was highest in the subgroup of subjects with the worst baseline eGFR levels and lowest in the subgroup of subjects with the highest baseline eGFR, reflecting an increasingly greater incidence of serious TEAEs

as baseline disease increased in severity, with similar incidences between voclosporin and placebo, except in the lowest eGFR subgroup (38.2% voclosporin vs 28.8% placebo).

Table 84 Overview of Treatment-Emergent Adverse Event and Serious Treatment-Emergent Adverse Event Incidence By Baseline eGFR (Pooled LN Safety Population, N=533)

Subgroup Parameter	Placebo n (%) E [w%]	23.7 mg BID n (%) E [w%]
<60 mL/min/1.73 m^2		
N	41	41
Any TEAE	36 (87.8) 165 [87.3]	40 (97.6) 221 [97.5]
Any Serious TEAE	12 (29.3) 18 [28.8]	16 (39.0) 29 [38.2]
≥60 and <90 mL/min/1.73 m^2		
N	75	83
Any TEAE	64 (85.3) 324 [85.4]	74 (89.2) 471 [89.2]
Any Serious TEAE	18 (24.0) 27 [24.1]	19 (22.9) 30 [22.9]
≥90 mL/min/1.73 m^2		
N	150	143
Any TEAE	132 (88.0) 708 [88.0]	130 (90.9) 970 [90.9]
Any Serious TEAE	20 (13.3) 28 [13.3]	26 (18.2) 40 [18.2]

Notes: BID = twice daily; E = events; TEAE = treatment-emergent adverse event; w% = weighted percent.

Hepatic impairment

According to the applicant, voclosporin is metabolised in the liver, primarily through the cytochrome P450 (CYP) enzyme CYP3A4/5, and is predominantly eliminated through biliary excretion. The hepatic impairment study ISA07-09 was conducted to determine the pharmacokinetic and pharmacodynamic profile of voclosporin and its metabolites in subjects with hepatic impairment after single or multiple doses. Safety parameters of AEs, vital signs, ECGs, and clinical laboratory parameters were also examined.

The applicant states that single and multiple doses of voclosporin 0.4 mg/kg were well tolerated in healthy volunteer subjects and in subjects with mild hepatic impairment, as were single doses in subjects with moderate hepatic impairment. No deaths and no SAEs were reported during the study, and no subjects discontinued due to an AE.

The applicant concludes that administration of 0.4 mg/kg voclosporin to subjects with mild (Child-Pugh A) to moderate (Child-Pugh B) hepatic impairment resulted in an approximately 1.5-fold to 2-fold increase in voclosporin exposure after single doses. Furthermore, that single and multiple doses of voclosporin were well tolerated with regard to AEs, vital signs, ECG findings and laboratory findings in subjects with hepatic impairment and in normal subjects. Thus, voclosporin dose reductions may be required in subjects with mild to moderate hepatic impairment, similar to the manner recommended for subjects with reduced eGFR. The use of voclosporin in subjects with severe hepatic impairment (Child-Pugh C) has not been evaluated.

Use in pregnancy and lactation

In nonclinical studies, voclosporin was not teratogenic in animal studies at doses that caused maternal toxicity. The maternal effects included changes in body weight and/or swollen mammary glands, and fetal effects consisted of a slight reduction in body weights and related skeletal developmental variations.

There are no adequate well-controlled studies with voclosporin in pregnant women. A study of placental transfer and lacteal excretion in rats demonstrated that radiolabeled voclosporin was present in fetal tissues, suggesting that dose-related material had crossed the placental barrier. Dose-related material was observed in the milk of lactating females, and in the stomach contents and carcasses of male and female pups, suggesting that voclosporin administered to pregnant female rats was transferred to the pups via the milk and subsequently absorbed from the GI tract of the pups. These results suggest that voclosporin might also cross the placental barrier in humans.

In clinical trials with voclosporin, across all indications, there were 16 reports of pregnancy in subjects treated with voclosporin or their partners (Table 85). It is important to note that subjects with LN were also taking MMF as part of the study treatment regimen, which is known to be teratogenic; therefore any adverse effects on pregnancy outcomes in voclosporin-treated subjects with LN will be confounded by the use of this background medication.

Table 85 Outcomes of Pregnancies Reported in Subjects Treated with Voclosporin

Population	Pregnancies in a Female Study Subject (n=7)	Pregnancies in a Female Partner of a Male Study Subject (n=7)
LN [(1)]	1 pregnancy ended with induced abortion 1 pregnancy resulted in delivery of a healthy infant	None
PsU	4 pregnancies resulted in delivery of healthy infant 1 pregnancy ended (unknown)	2 pregnancies resulted in delivery of healthy infant 1 pregnancy ended spontaneously 1 pregnancy ended with induced abortion 3 pregnancy outcomes unknown
Renal transplant	None	1 pregnancy ended spontaneously 1 pregnancy outcome unknown

1 Includes all studies of subjects with LN: AURION, AURA-LV, AURORA 1, and ongoing AURORA 2.

In summary, from the information available, no adverse maternal or foetal effects were identified due to voclosporin exposure at the doses used in these clinical studies. There are no adequate or well-controlled studies of voclosporin in pregnant women. Available data on use of voclosporin in pregnant women are insufficient to determine whether there is a drug-associated risk for major birth defects or miscarriage. There are risks to the mother and fetus associated with SLE.

A placental transfer and lacteal excretion study in rats indicated that voclosporin was secreted in rat breast milk; therefore, it is likely to be excreted in human milk. No information is available on the presence of voclosporin in human milk, the effects of voclosporin on the breastfed infant, or the effects of voclosporin on milk production.

2.5.8.6. Immunological events

No immunogenicity is expected for a small molecule.

2.5.8.7. Safety related to drug-drug interactions and other interactions

In vitro data demonstrate that CYP3A4 is the major enzyme responsible for voclosporin metabolism and voclosporin is a substrate for P-glycoprotein (P-gp). Based on the results from *in vitro* studies, clinical PK drug-drug interaction studies were conducted with ketoconazole (strong CYP3A4 and/or P-

gp inhibitor), verapamil (moderate CYP3A4 and strong P-gp inhibitor), and rifampin (strong CYP3A4 and P-gp inducer, OATP1B1/3 inhibitor) to evaluate the potential for voclosporin to be a victim for interactions. In addition, clinical studies were conducted to evaluate the effect of voclosporin as a perpetrator of drug-drug interactions with midazolam (CYP3A4 substrate) and digoxin (P-gp substrate). Furthermore, as voclosporin is to be administered with MMF as background therapy, a clinical drug-drug interaction study was performed in subjects with SLE (with or without LN) to evaluate the effect on plasma concentrations of mycophenolic acid (MPA) and mycophenolic acid glucuronide (MPAG).

The results from these studies are discussed in detail in the PK section (see 2.5.2.).

Approximately one-third of subjects in the AURA-LV and AURORA 1 studies received concomitant treatment with statins. There was no consistent imbalance in TEAEs reflective of clinical manifestations of statin toxicity in voclosporin-treated subjects on statins compared with not receiving statins. A dedicated statin study is planned for (see 2.5.4.).

2.5.8.8. Discontinuation due to adverse events

The percentage of subjects in the pooled LN population who experienced TEAEs resulting in permanent study drug discontinuation was the same between the voclosporin (13.5%) and placebo (13.2%) groups (*Table 65*). Although there was a similar overall incidence between treatment groups, an examination of the specific TEAEs that led to study drug discontinuation shows some differences. In the voclosporin group, TEAEs resulting in study drug discontinuation were most often due to GFR decreased (10 subjects, 3.7%), a recognised effect of CNIs. In contrast, only 5 placebo-treated subjects (1.9%) had this TEAE resulting in study drug discontinuation. The next most frequent TEAEs resulting in study drug discontinuation in the voclosporin group were renal impairment (5 subjects) and pneumonia (3 subjects), which occurred in similar numbers of placebo subjects (4 subjects and 2 subjects, respectively).

In the placebo group, the most frequent TEAE resulting in study drug discontinuation was lupus nephritis (6 subjects, 2.3%), which occurred in only 2 voclosporin-treated subjects (0.7%). The incidences of proteinuria and SLE leading to discontinuation were also higher in the placebo group (5 and 3 subjects, respectively) than in the voclosporin group (0 subjects and 1 subject, respectively). As these events are part of the underlying disease, this pattern of TEAE-related discontinuations indicates that disease activity remained higher in the placebo group.

Overdose

In the AURORA 1 study, one accidental overdose occurred in the voclosporin group; the subject accidentally dosed more than prescribed on some mornings for a total of 12 extra capsules over a 4-week period. The TEAE was considered mild and intermittent and was not associated with any medical intervention or ongoing sequelae. A second voclosporin-treated subject in the AURORA 1 trial had an intentional multidrug overdose, which did not involve an overdose of voclosporin: the subject consumed an estimated 20 tablets each of atorvastatin, sulfamethoxazole / trimethoprim, and MMF.

In the AURORA 2 trial, one TEAE of accidental overdose was reported in a voclosporin-treated subject, which was classified as mild and non-serious. Following a 1-week interruption in study treatment (from 30 Aug 2019 to 05 Sep 2019) due to a decrease in eGFR, the subject was restarted on a dose of 2 capsules (15.8 mg) BID on 06 Sep 2019 (Day 382). Over the next 73 days (between this date and the Month 15 visit on 18 Nov 2019 [Day 455]), the subject took 67 capsules more than prescribed (equivalent to less than one additional capsule per day above their prescribed dose of 2 capsules BID). Therefore, the subject is not thought to have exceeded the proposed therapeutic dose of 3 capsules

BID. No symptoms were reported relating to the misdosing of voclosporin, and the subject did not require or receive treatment for the overdose and recovered without sequalae.

Additional information on potential adverse effects of voclosporin overdose can be drawn from Study LX211-06, in which coadministration of ketoconazole and voclosporin resulted in an 18-fold increase in voclosporin exposure in healthy volunteers. Increases in serum creatinine, decreases in serum magnesium, and increases in blood pressure were observed in these subjects, which were considered to be effects directly related to the large increase in voclosporin exposure.

2.5.8.9. Post marketing experience

Voclosporin (Lupkynis) was approved in the United States on 22 January 2021. As of 21 April 2021, an estimated patients in the United States have been prescribed Lupkynis as part of their medical care (based on the number of patients who have had a prescription dispensed). According to the applicant, preliminary reports from postmarketing use of Lupkynis indicate that the safety profile remains consistent with that observed in clinical trials and there continues to be a favorable benefit / risk in patients with LN.

The most frequently reported ADRs pertained to SOC Gastrointestinal disorders (24 cases, 42 events), followed by SOC Nervous system disorders (17 cases, 18 events), SOC General disorders and administration site conditions (12 cases, 16 events), SOC Injury, poisoning and procedural complications (8 cases, 10 events), SOC Vascular disorders (8 cases, 8 events). The most frequently reported ADRs were nausea (N=12), headache (N=9), diarrhoea (N=8), hypertension (N=7).

2.5.9. Discussion on clinical safety

Voclosporin is a calcineurin-inhibitor immunosuppressant proposed for treatment of lupus nephritis. Calcineurin is a calcium/calmodulin-dependent phosphatase whose activity is required for the induction of T-cell lymphokine production and proliferation.

According to the applicant, voclosporin is structurally similar to cyclosporine A (CsA) except for a modification to the amino acid-1 region which is proposed to alter the metabolic profile.

Increased blood pressure and acute renal vasomotor effects are well-known potential toxicities of CNIs. Other adverse effects associated with current CNIs include neurotoxicity, electrolyte disturbances, impaired glucose tolerance and new-onset diabetes mellitus, and, like all immunosuppressants, infections and malignancies.

Voclosporin was approved in the US for treatment of lupus nephritis in January 2021.

<u>Exposure</u>

The total exposure to voclosporin is 2,666 subjects, including 365 patients with LN whereof 116 have been exposed for >1 year. Across all indications (including also psoriasis and uveitis), a total of 385 subjects have been exposed for more than 1 year.

The current application is based primarily on pooled data from the phase 2 AURA-LV and phase 3 AURORA 1 study up to 1 year of treatment exposure. The final CSR from the long-term extension phase of AURORA 1 (AURORA 2) was submitted in response to day 120 LoQ. In this study, 101 voclosporin-treated patients were exposed for >36 months.

The following exclusion criteria with impact on safety were used in the AURA-LV and AURORA 1 studies:

Estimated glomerular filtration rate (eGFR) as calculated by the Chronic Kidney Disease Epidemiology Collaboration equation of ≤45 mL/min/1.73 m^2 at screening
Information on this is available in the SmPC section 4.2.

Taking medications listed as prohibited in the protocol
In response to day 120 LoQ it was clarified in the section 4.4 that there are no data on concomitant use with cyclophosphamide.

Requiring dialysis

Previous or planned kidney transplant

History of congenital or acquired immunodeficiency, malignancy, lymphoproliferative disease or previous total lymphoid irradiation, severe viral infection requiring antiviral therapy, active tuberculosis, or known history of tuberculosis/evidence of old tuberculosis if not taking prophylaxis with isoniazid

Active medical conditions such as severe cardiovascular disease, liver dysfunction, chronic obstructive pulmonary disease or asthma requiring oral steroids, bone marrow insufficiency, active bleeding disorders, or current infection requiring intravenous (IV) antibiotics.

At the CHMP's request, the Section 4.4 SmPC text was updated to reflect the common warnings about serious infections.

Baseline demographic and disease characteristics

The baseline demographic and disease characteristics of the pooled LN safety population were well balanced between voclosporin and placebo groups, and are deemed representative of the target population. Background medications use, i.e. MMF and corticosteroids (iv and peroral), was generally balanced between the groups in the pooled LN safety population. However, it is impossible to distinguish possible interaction of voclosporin with MMF. The assessment of voclosporin's clinical safety profile is further hampered by extensive additional concomitant treatment (e.g. angiotensin receptor blockers or angiotensin-converting enzyme inhibitors, lipid modifying agents, anti-anaemic agents, calcium channel blockers, beta blockers, antimalarials). For details on concomitant medications, please refer to the efficacy section (See 2.5.5.).

Integrated analyses present demographic baseline characteristics of LN patients combining the European and South-African regions, representing 28.8% of analysed LN safety population. European sites were generally located in eastern countries, outside EU. As part of day 120 LoQ, the applicant was invited to elaborate whether LN studied population is representative of the EU-population taking possible differences in medical practices into consideration too (please refer to the ICH E5 and Reflection paper CHMP/EWP/692702/08). In their response, the applicant provided a justification that the studied population is representative of the EU-population, which was agreed by the CHMP.

Adverse events

In the pooled LN population, the incidences were similar for adverse events (AEs) (91% and 88%) and TEAEs (treatment-emergent adverse events) (91% and 87%, defined as occurring on-treatment or up to 30 days post-treatment) in the voclosporin and placebo groups, respectively. On the other hand, treatment-related TEAEs were more frequently observed in voclosporin-treated subjects (47%) than placebo-treated subjects (23%). Serious TEAEs occurred in 23% of voclosporin-treated subjects and 19% of placebo-treated subjects.

TEAEs leading to dose modification occurred more often in voclosporin-treated subjects (46%) than placebo-treated subjects (25%). However, the incidence of TEAEs leading to permanent study drug discontinuation was similar between voclosporin and placebo treatment groups (13.5% vs 13.2%).

Infections and Infestations were the most frequently reported SOC for TEAEs and were more frequent among voclosporin-treated subjects (62.2%) than among placebo-treated subjects (54.9%). Also in the AURORA 2 study, infections and infestations were the most frequently reported types of TEAEs. Gastrointestinal (GI) disorders were the second-most frequent SOC for TEAEs, reported in 45.3% and 35.3% of voclosporin and placebo subjects, respectively.

Among TEAEs, GFR decreased was the most frequently reported TEAE in voclosporin-treated subjects (26.2%, compared with 9.4% placebo) followed by hypertension (19.1%, compared with 8.6% placebo). Although these are known and expected side effects of CNIs, it is problematic in a disease manifesting with these symptoms since this might complicate monitoring of disease activity. This is discussed in detail below.

Other TEAEs occurring in ≥10% in voclosporin group were: diarrhoea (18.7%), headache (15.0%), anaemia (12.4%), cough (10.9%) and urinary tract infection (9.7%).

In the final CSR from the AURORA 2 study, AEs were reported in 86% of subjects in the voclosporin group and 80% of subjects in the placebo group.

Serious adverse events and deaths

Approximately half of the subjects who experienced serious TEAEs had a serious Infection or Infestation, with similar incidence across treatment groups (10.1% of subjects in each group). Serious TEAEs more common in the voclosporin than in the placebo group were acute kidney injury, renal impairment, nervous system disorders, hypertension, respirator, thoracic and mediastinal disorders, and anaemia.

A total of 23 subjects died in the LN studies, 13/365 voclosporin-treated patients (3.6%) and 10/266 placebo-treated patients (3.8%). Infections, acute respiratory distress syndrome and pulmonary embolism were the most frequent causes of death.

It is noteworthy that there was a higher number of deaths in the voclosporin group than in the placebo group in the AURA-LV study. According to the applicant, this might be due to differences in baseline characteristics between the groups with a higher proportion of subjects in the voclosporin group enrolled from low-GDP countries, which is believed to have introduced a bias towards poorer safety outcomes in this group. Although this can only be hypothesised, it is reassuring that the same pattern was not observed in the AURORA 1 or AURORA 2 studies, where the frequency of death was higher among placebo-treated subjects. In total, the frequency of death is comparable between the treatment groups. Further, reassuringly, there was a low number of deaths in higher dose voclosporin 39.5 BID group in the AURA-LV study.

There were two deaths among voclosporin-treated patients in the psoriasis/uveitis population, one accident and one case of bile duct cancer, the latter possibly related to voclosporin. In response to day 120 LoQ, details were presented on this case. The applicant clarified that the case of death due to bile duct cancer in the plaque psoriasis study occurred 56 days from start of voclosporin treatment, which is considered too short to suspect causality. Further, that the case was confounded by previous treatment with other immunosuppressive drugs. Causality with voclosporin is thus unlikely.

As noted in the "Guideline on the clinical investigation of medicinal products to prevent development/slow progression of chronic renal insufficiency", the composite of all-cause mortality and renal failure should always be reported. This was reported in response to day 120 LoQ: The incidence of all-cause mortality or renal failure in the AURA-LV and AURORA 1 studies was 4.2% in the placebo

group, 6.4% in the voclosporin 23.7 mg group and 3.4% in the voclosporin 39.5 mg group. Although this is of some concern, data from the AURORA 2 study are reassuring where the incidence was 4.0% in the placebo group and 0.9% in the voclosporin group.

Adverse events of special interest

Adverse events of particular interest in LN patients and/or the CNI class of drug were acute renal failure, chronic kidney disease, hypertension, calcineurin-inhibitor-related adverse events, opportunistic infections, and malignancies.

Serious Infections including opportunistic infections is listed as an important identified risk in the RMP. MACEs, Neurotoxicity, Nephrotoxicity (acute and chronic), Malignancies (including lymphomas) associated with long term use are listed as important potential risks in the RMP.

Acute renal failure occurred in 33.3% of voclosporin-treated subjects compared with 17.7% of placebo-treated subjects during the first year of study treatment. Of these, the large majority had decreased GFR, 26.2% in the voclosporin group and 9.4% in the placebo group, that according to the applicant were managed effectively with dose interruption or modification.

Chronic kidney disease occurred in 30.0% of voclosporin-treated subjects compared with 22.9% of placebo-treated subjects during the first year of study treatment.

The maximum mean decrease from baseline in corrected eGFR in the voclosporin group occurred at Week 4 and was -3.4 mL/min/1.73 m^2. Mean GFR levels remained stable thereafter, and there were no signs of decreasing mean GFR levels over time in the AURORA 2 study up to 36 months treatment.

The reversibility of the observed decreases in GFR and renal adverse events were discussed in response to day 120 and 180 LoQs. The applicant clarified that the increased risk for acute renal failure observed for voclosporin compared to placebo was mainly due to a reversible decrease in GFR. In total, 65 voclosporin subjects (36.5%) and 55 placebo subjects (30.9%) had at least 1 of the following events: acute renal failure, CKD, or eGFR decreases $\geq$ 30%. Of these subjects, 92.3% of voclosporin-treated subjects recovered. Of the 5 subjects in the voclosporin group who did not recover to within 20% of the baseline eGFR, 4 had clear disease progression/LN flare and 1 subject had a partial recovery in eGFR levels, although recovery was to less than 20% of baseline. There are no indications on a chronic nephrotoxic effect of voclosporin. The risk for acute renal failure is considered possible to handle through careful monitoring of GFR, and dose modification or discontinuation of therapy in case of decreased GFR. The monitoring guidelines and dose recommendation are based on what was used in the AURORA 1 study (please refer to *Figure 21*) and is considered acceptable.

When comparing AEs by GFR subgroups, in all subgroups AEs were slightly more frequent for voclosporin than for placebo, but the difference was most prominent in patients with eGFR<60 mL/min/1.73 m^2. Patients with GFR<45 were excluded from the clinical studies. The safety in patients with renal impairment was discussed in response to day 120 LoQ. The applicant clarified that seventeen subjects (9 voclosporin, 8 placebo) enrolled into the AURORA 1 clinical trial had an eGFR value ≤ 45 mL/min/1.73 m2 at screening or baseline visits. Of these patients, 8 voclosporin-treated patients completed AURORA 1 and 5 of these entered the AURORA 2 study. According to the applicant, the dedicated renal impairment study suggests that there is no significant effect of mild or moderate renal impairment on voclosporin exposure and that severe renal impairment may result in a 1.46- and 1.74-fold increase in Cmax and AUC0-48 a after a single dose. Voclosporin and metabolites are in 2% excreted by the kidney.

Although on one hand these patients with GFR<45 can be considered to represent those with the most serious disease and are likely to be in most need of effective treatment, on the other hand these are the most fragile patients with limited reserves to handle potential CNI-induced renal toxicity. It is

agreed that in certain patients with severe disease, use of Lupkynis might be justified despite GFR<45 and adequate dosing recommendations in these patients are available in Section 4.2 of the SmPC:

"Lupkynis has not been studied in patients with severe renal impairment (eGFR < 30 mL/min/1.73 m^2) and is not recommended in these patients unless the benefit outweighs the risk. If used, the recommended starting dose is 15.8 mg twice daily (see section 5.2)."

A small increase in mean serum creatinine levels was observed in the voclosporin group from week 4, with stable levels thereafter.

Adequate information on the risk of renal toxicity and monitoring of the GFR levels have been included in the SmPC:

"As with other calcineurin-inhibitors, adverse reactions of acute worsening of renal function or eGFR decreases have been seen in patients treated with voclosporin. In the first four weeks of treatment with voclosporin, haemodynamic reductions in eGFR have been observed. This can be managed by dose adjustments. Regular monitoring of eGFR levels is recommended."

"It is recommended to establish a baseline estimated glomerular filtration rate (eGFR) before starting treatment with voclosporin, and assess every two weeks for the first month, and every four weeks thereafter."

AURORA 2 includes a biopsy substudy, in which 18 voclosporin subjects and 15 placebo subjects had second biopsies taken. Although the results were requested, no biopsy results could be provided because of a delay in the interpretation of the biopsies due to the COVID-19 pandemic. According to the AURORA 2 CSR these biopsies should have been performed 6 months after entry in the AURORA 2 study. Of the 216 patients who entered the AURORA 2 study, the majority (186/216 patients) had completed 36 months of treatment (i.e. had completed 24 months in the AURORA 2 study). Therefore, most of these biopsies should have been performed >18 months ago. Although it is understandable if all analyses (such as gene expression and immune markers) might be time consuming, at least preliminary histological results should be available. However, the CHMP agreed to receive the final results in December 2022, . The AURORA 2 biopsy substudy is included as a category 3 study in the RMP.

Hypertension occurred in 56 subjects in the voclosporin group (21.0%) and 28 subjects in the placebo group (10.5%). Hypertension is a known CNI effect and is an expected AE also for voclosporin. This AE is adequately reflected in section 4.8 of the SmPC Furthermore, a warning is included in section 4.4, along with recommendations for management in case hypertension occurs:

"Voclosporin can cause or worsen systemic hypertension. Blood pressure should be monitored every two weeks for the first month after initiating voclosporin, and as clinically indicated thereafter. In the event of clinically concerning elevated blood pressure, the recommendations in table below should be followed.

Blood pressure	**Recommendation**
Systolic pressure > 130 and ≤ 165 mmHg and Diastolic pressure > 80 and ≤ 105 mmHg	Antihypertensive therapy may be initiated/adjusted

Blood pressure	Recommendation
Blood pressure > 165/105 mmHg, with symptoms of hypertension	Stop administration of voclosporin and initiate/adjust antihypertensive therapy

Calcineurin inhibitor-related adverse events that were reported more frequently in the voclosporin group (at least 2% higher incidence) compared with placebo were hypertension, tremor, and hypertrichosis.

In the pooled LN population, 32.2% of voclosporin-treated subjects and 22.9% of placebo subjects experienced CNI-related TEAEs. Hypertrichosis, hirsutism and gingival hypertrophy were observed exclusively in the voclosporin group.

This information is adequately reflected in the SmPC.

Due to limited long-term follow-up, it is still not clear whether voclosporin like other calcineurin inhibitors is associated with a risk for renal fibrosis after many years of treatment. To date, there are no indications on irreversible renal damage caused by voclosporin but this will be an important issue to follow through post-approval data collection (PSUR and PASS).

Opportunistic infections were rare but more frequent in the voclosporin group, 10.9% compared to 6.4% in placebo group. Serious opportunistic infections were recorded in 1.1% (3 participants) in voclosporin group and in 0.8% (2 participants) in placebo group. One opportunistic infection, pericarditis tuberculous, in the voclosporin group led to death. Incidences of opportunistic infections in AURORA 2 study were higher in voclosporin group compared to placebo group (5.2% vs 0.8%). This is adequately described in the SmPC.

Malignancies occurred in 4 subjects in the pooled LN population, all of whom were in the voclosporin group (1.5%). Due to the rarity and diversity of observed malignancy cases, it is not possible to draw conclusions. Information on the risk for malignancy is included in section 4.4 of the SmPC.

The exposure-adjusted incidence rate of MACE in the pooled LN population was lower in the voclosporin group (1.7 E/100 PYs) than in the placebo group (2.1 E/100 PYs).

At the CHMP's request, the applicant will conduct a PASS to further characterise potential risks: malignancy, neurotoxicity, and chronic nephrotoxicity. The applicant is currently undertaking a feasibility assessment to determine the most appropriate design for this study in order to meet the required objectives. The duration of recruitment to the study will be determined by the market uptake of Lupkynis in Europe. It is planned to obtain up to 6 years of data from patients from the time of their initiating Lupkynis. A study protocol will be submitted to the EMA 3 months after the granting of MA for Lupkynis in the EU. This study is listed as a category 3 study in the RMP.

Laboratory findings

Renal parameters are discussed above.

Regarding liver function, voclosporin is metabolised in the liver, primarily through the cytochrome P450 (CYP) enzyme CYP3A4/5, and is predominantly eliminated through biliary. In the hepatic impairment study, voclosporin C_{max} and AUC_{0-48} increased by 1.5-fold and 2.0-fold, respectively, in patients with mild and moderate hepatic impairment. In clinical studies, there seems to be minor effects of voclosporin on liver parameters. Although 1 patient in the voclosporin group met criteria for Hy´s Law, this patient was on concomitant hepatotoxic drugs (rifampicin) and causality with voclosporin seems

less likely. In patients with mild and moderate hepatic impairment (Child-Pugh Class A and B, respectively), the recommended starting dose is 15.8 mg twice daily. The effect of voclosporin in patients with severe hepatic impairment (Child-Pugh Class C) has not been assessed and is not recommended in this patient population. Relevant information is included in sections 4.2, 4.4 and 5.2 of the SmPC.

Among serum electrolytes, hyperkalaemia was observed with a higher frequency among voclosporin-treated patients than among patients treated with placebo. This is reflected in the SmPC.

Among haematological parameters, a higher proportion of patients in the voclosporin group was reported with anaemia as an AE, and anaemia is proposed for inclusion in the SmPC section 4.8.

Although diabetes is a class effect of the CNIs, mean increase from baseline to follow-up in glucose levels was lower in the voclosporin than in the placebo group.

QT prolongation is a class effect of CNIs. The single dose finding QT study was positive, though steady-state findings were negative. Also in the non-clinical and clinical studies, there have been signs of QT prolongation for voclosporin. This is reflected in the SmPC.

Safety in special populations

Pregnancy and lactation

Lupkynis is not recommended during pregnancy.

Preclinical studies have shown excretion of voclosporin/metabolites in milk. It is unknown whether voclosporin/metabolites are excreted in human milk (see also discussions in 2.4.). Since voclosporin in LN is intended for use in combination with MMF, which is contraindicated during lactation, voclosporin is not expected to be used during breast-feeding unless MMF is discontinued.

Section 4.6 of the SmPC states that:

"Lupkynis is not recommended during pregnancy and in women of childbearing potential not using contraception."

"A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from Lupkynis therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman."

Use in pregnancy is listed as missing information in the RMP.

Interactions

Voclosporin is metabolised by CYP3A4, is an inhibitor of P-gp and an OATP1B1 inhibitor. Based on DDI studies and safety data, there are restrictions in use of voclosporin with other inhibitors/ inducers/ substrates of respective enzyme or cell membrane protein/ transporter. Please refer to section 2.5.2. .

Voclosporin is contraindicated in combination with strong CYP3A4 inhibitors. A warning is also proposed for inclusion in section 4.4 of the SmPC.

Voclosporin should not be used in combination with cyclophosphamide, since there are no data to support such a combination. This is adequately reflected in Section 4.2 of the SmPC.

An interaction study with statins is planned for (see recommendation in Section 2.5.4.). Approximately one-third of subjects in the AURA-LV and AURORA 1 studies received concomitant treatment with statins and in these patients, there were no safety signals observed.

Age

There were only 2 subjects in the voclosporin group in the LN trials aged ≥ 65 years and no subjects aged 75 years or over. No conclusions can be drawn from this due to the very limited number of patients. In the plaque psoriasis and uveitis clinical programme, 47 subjects were aged 65 to 74 years and 10 subjects were aged 75 years and over. According to the applicant, the safety profile of voclosporin in subjects aged 65 years and over was consistent with that in the younger age groups and no new AEs of concern were seen. This is agreed by the CHMP.

Overdose

In response to day 120 LoQ, the wording in Section 4.9 of the SmPC was revised to distinguish overdose symptoms observed in voclosporin trials from other CNI class effects and to provide more detail around the treatment of overdose.

From the safety database all the adverse reactions reported in clinical trials have been included in the Summary of Product Characteristics.

2.5.10. Conclusions on the clinical safety

The safety of voclosporin seems consistent with other calcineurin inhibitors, with predominantly infections, renal impairment and hypertension. Renal adverse events were observed more frequently in voclosporin-treated patients, than in patients treated with placebo. This is of concern because patients with LN are already at risk for development of renal failure, where an additive effect of LN and drug toxicity might enhance this risk. Furthermore, it can be difficult to distinguish between voclosporin-caused toxicity and treatment failure. At the CHMP's request, the applicant clarified that these renal adverse events were mostly due to decreases in GFR. Although this is still of concern, it is somewhat reassuring that these events were generally reversible. To date, there are no indications on irreversible renal damage caused by voclosporin. The risk for acute nephrotoxicity is considered possible to handle through careful monitoring of GFR, and dose reduction or treatment discontinuation if GFR is decreased. Adequate warnings and guidance on the monitoring have been included in the SmPC.

At the CHMP's request, the applicant has accepted to conduct an observational PASS in EU to further characterise and quantify long-term safety profile of Lupkynis to address the uncertainties regarding long term safety and more particularly the risks of Malignancy, Neurotoxicity and Nephrotoxicity. This study is included in the RMP as a category 3 study.

2.6. Risk Management Plan

2.6.1. Safety concerns

Important identified risks	Serious Infections including opportunistic infections
Important potential risks	MACEs Neurotoxicity Nephrotoxicity (acute and chronic) Malignancies (including lymphomas) associated with long term use
Missing information	Use in pregnancy

2.6.2. Pharmacovigilance plan

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation (key to benefit risk)				
None				
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances (key to benefit risk)				
None				
Category 3 - Required additional pharmacovigilance activities (by the competent authority)				
AURORA 2 Biopsy sub-study	Information on renal status	Nephrotoxicity	Study report	Dec 2022
An observational PASS in EU to further characterise and quantify long-term safety profile of Lupkynis	Long term safety	Malignancy Neurotoxicity Nephrotoxicity	Final protocol	3 months after European Commission Approval

2.6.3. Risk minimisation measures

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Important Identified Risks		
Serious Infections including opportunistic infections	**Routine risk minimisation measures**: SmPC Section 4.4, 4.8. PL Section 2, 4 Legal status: Prescription only medicine **Additional risk minimisation measures**: None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection**: None **Additional pharmacovigilance activities**: None
Important Potential Risks		
MACEs	**Routine risk minimisation measures**: SmPC Section 4.4, 4.8 PL Section 2, 4 Legal status: Prescription only medicine **Additional risk minimisation measures**: None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection**: None **Additional pharmacovigilance activities**: None
Neurotoxicity	**Routine risk minimisation measures**: SmPC Section 4.4, 4.8 PL Section 2, 4 Legal status: Prescription only medicine **Additional risk minimisation measures**: None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection**: None **Additional pharmacovigilance activities**: An observational PASS in EU to further characterise and quantify long-term safety profile of Lupkynis

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Nephrotoxicity (acute and chronic)	**Routine risk minimisation measures**: SmPC Section 4.2, 4.4, 4.8 PL Section 2, 4 Legal status: Prescription only medicine **Additional risk minimisation measures**: None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection**: None **Additional pharmacovigilance activities**: An observational PASS in EU to further characterise and quantify long-term safety profile of Lupkynis AURORA 2 biopsy sub-study
Malignancies (including lymphomas) associated with long term use	**Routine risk minimisation measures**: SmPC Section 4.4, 4.8, 5.3. PL Section 2 Legal status: Prescription only medicine **Additional risk minimisation measures**: None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection**: None **Additional pharmacovigilance activities**: An observational PASS in EU to further characterise and quantify long-term safety profile of Lupkynis
Missing Information		
Use in pregnancy	**Routine risk minimisation measures**: SmPC Section 4.6, 5.3. PL Section 2 Legal status: Prescription only medicine **Additional risk minimisation measures**: None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection**: None **Additional pharmacovigilance activities**: None

2.6.4. Conclusion

The CHMP considers that the risk management plan version 1.0 is acceptable.

2.7. Pharmacovigilance

2.7.1. Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.7.2. Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. The applicant did request alignment of the PSUR cycle with the international birth date (IBD). The IBD is 22.01.2021. The new EURD list entry will therefore use the IBD to determine the forthcoming Data Lock Points.

2.8. Product information

2.8.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

2.8.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Lupkynis (voclosporin) is included in the additional monitoring list as it contains a new active substance which, on 1 January 2011, was not contained in any medicinal product authorised in the EU.

Therefore the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

Voclosporin is a novel calcineurin inhibitor which is structurally similar to cyclosporine A except for the modification of a functional group on amino acid-1 of the molecule. The immunosuppressant activity results in inhibition of lymphocyte proliferation, T-cell cytokine production, and expression of T-cell activation surface antigens.

The applicant applied for the following indication is "Lupkynis is indicated in combination with background immunosuppressive therapies for the treatment of adult patients with active class III, IV or V (including mixed class III/V and IV/V) lupus nephritis (LN)".

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease which primarily affects women between the ages of 20 and 40 years. LN is the most common serious manifestation of SLE and is a debilitating and potentially life-threatening condition.

LN is divided into different classes (I-VI) according to the International Society of Nephrology and the Renal Pathology Society (ISN/RPS) 2003 Classification of LN [Weening et al 2004].

In patients with LN, renal damage results in proteinuria and/or hematuria and a decrease in renal function as evidenced by reduced creatinine clearance and estimated glomerular filtration rate (eGFR).

It is estimated that 10%-30% of patients with LN will develop end-stage renal disease (ESRD), the presence of which has been associated with a 26-fold increase in mortality risk compared with a demographically matched general population [Almaani et al 2017, Costenbader et al 2011, Tektonidou et al 2016, Yap et al 2012].

Proteinuria is the defining aspect of LN and indicates damage to the kidney; if not resolved this damage becomes permanent. A rapid reduction in proteinuria is, therefore, an important goal of treatment in LN [Fanouriakis et al 2020].

The overall aim of treatment is to achieve remission, in order to prevent future renal failure.

3.1.2. Available therapies and unmet medical need

Treatment of LN is based in large part on the histopathological classification. The proliferative classes (III and IV) require aggressive treatment with corticosteroids and immunosuppressive agents. Class V (membranous LN) is treated similarly to Classes III/IV if it is associated with nephrotic range proteinuria. In contrast, Classes I and II generally do not require immunosuppressive therapy and patients with Class VI LN are considered to be candidates for renal transplant [Fanouriakis et al 2020, Hahn et al 2012].

Initial treatment with immunosuppressive agents (mycophenolate mofetil [MMF 2 3 g/day] or intravenous low-dose cyclophosphamide [500 mg every 2 weeks for a total of 6 doses]) in combination with corticosteroids are recommended for Class III (±Class V) and Class IV (±Class V) LN, with similar recommendations for pure Class V LN where it is associated with nephrotic range proteinuria. If improvement after initial treatment is achieved, subsequent immunosuppression is recommended with either MMF (1 2 g/day) or azathioprine (2 mg/kg/day). Although the EULAR guidelines were published prior to the approval of belimumab, they state that belimumab may be considered as add on treatment.

Despite current treatment regimens, a significant proportion of LN patients develops end-stage renal disease. This, in combination with the toxicity of available treatment options, implies that there is an unmet medical need for new treatments in LN.

3.1.3. Main clinical studies

Four clinical studies are included for efficacy analysis in this application. Two phase 2 studies (AURION and AURA-LV), one pivotal phase 3 study (AURORA 1) and one long-term AURORA 1 continuation study (AURORA 2).

Study ID/Name (Phase)	Study Design	Patient Population	Dose, Route, and Regimen	No. of Subjects
AUR-VCS-2016-01 / AURORA 1 (Phase 3)	Prospective, randomised, placebo-controlled, double-blind, parallel-group, 52-week, international, multicenter, 2-arm comparison study of voclosporin versus matching placebo	SLE patients aged 18-75 with LN class III, IV-G, IV-S (confirmed UPCR ≥1.5 mg/mg) or Class V (UPCR ≥2.0 mg/mg)	Voclosporin 23.7 mg BID or placebo BID for 52 weeks All subjects also received background therapy with MMF and an initial treatment with IV methylprednisolone, followed by a reducing taper of oral corticosteroids	357 23.7 mg BID: 179 Placebo: 178

Study ID/Name (Phase)	Study Design	Patient Population	Dose, Route, and Regimen	No. of Subjects
AUR-VCS-2012-01 / AURA-LV (Phase 2)	Prospective, randomised, placebo-controlled, double-blind, parallel-group, international, multicenter, 3-arm comparison study of voclosporin versus matching placebo	SLE patients aged 18-75 with LN class III, IV-G, IV-S (confirmed proteinuria ≥1,500 mg/24 hours / UPCR ≥1.5 mg/mg) or Class V (confirmed proteinuria ≥2,000 mg/24 hours / UPCR ≥2.0 mg/mg)	Voclosporin 23.7 mg BID or 39.5 mg BID or placebo BID for 48 weeks All subjects also received background therapy with MMF and an initial treatment with IV methylprednisolone, followed by a reducing taper of oral corticosteroids	265 23.7 mg BID: 89 39.5 mg BID: 88 Placebo: 88
AUR-VCS-2014-01 / AURION (Phase 2)	Prospective, single-arm, open-label, pilot study of voclosporin combined with standard of care	SLE patients aged 18-75 with LN class III, IV-G, IV-S (confirmed proteinuria ≥1,000 mg/24 hours / UPCR ≥1.0 mg/mg) or Class V (confirmed proteinuria ≥1,500 mg/24 hours / UPCR ≥1.5 mg/mg)	Voclosporin 23.7 mg BID for 48 weeks All subjects also received background therapy with MMF and an initial treatment with IV methylprednisolone, followed by a reducing taper of oral corticosteroids	10
AUR-VCS-2016-02 / AURORA 2 (Phase 3)	Prospective, placebo-controlled, double-blind, parallel-group, 24-month continuation study to AURORA 1	SLE patients with LN who completed 52 weeks of treatment in Study AURORA 1	As assigned in AURORA 1 (voclosporin 23.7 mg BID or placebo BID) for up to a further 24 months On entry, all subjects continued to receive background therapy with MMF and oral corticosteroids at the same dose as at the end of AURORA 1.	216 23.7 mg BID: 116 Placebo: 100

The pivotal study AURORA 1 was a phase 3, randomised, double-blind, parallel-group, placebo-controlled, multicenter, 2-arm study of voclosporin versus matching placebo. Voclosporin at a dose of 23.7 mg BID or matching placebo were administered for 52 weeks with a background therapy of MMF and corticosteroids with a tapering schedule. Eligible subjects in the study were 18-75 years old with SLE and active, biopsy-proven lupus nephritis Class III, IV or V (or V in combination with III or IV). Primary efficacy endpoint was adjudicated renal response, a combined endpoint. To achieve the primary endpoint "renal response" the patient must have urine protein to creatine ration (UPCR) ≤0.5, eGFR ≥60 mL/min/1.73 m^2 or no confirmed decrease from baseline in eGFR of >20% and not have received any rescue treatment or more than 10 mg prednisone for ≥3 consecutive days or for ≥7 days in total during Weeks 44-52. A total of 375 patients were included in the study, 179 in the voclosporin group and 178 in the placebo group.

3.2. Favourable effects

The primary endpoint, adjudicated renal response at week 52, was achieved by 73/179 (40.8%) in the voclosporin group and 40/178 (22.5%) in the placebo group (OR 2.65; 95% CI: 1.64, 4.27; p<0.001).

The results of the primary efficacy analysis are supported by two pre-specified sensitivity analyses (including only a term for treatment and omitting the regional covariate) and by two supplemental analyses (for the PP population and for the programmed renal response).

A tipping point analyses showed that if all voclosporin withdrawals were truly non-responders, 65% of placebo assumed non-responders would have to be truly responders in order for statistical significance to be lost.

Consistent with the primary endpoint, the proportions of subjects achieving the key secondary outcomes (adjudicated renal response at Week 24, partial renal response at Week 24 and Week 52. time to UPCR ≤0.5 mg/mg and time to a 50% reduction in UPCR) were all in favour of voclosporin. Adjudicated renal response at Week 24 was achieved by 58/179 (32.4%) in the voclosporin group and 35/178 (19.7%) in the placebo group (OR 2.23; 95% CI: 1.34, 3.72; p=0.002).

Partial renal response (defined as a 50% reduction from baseline in UPCR) at Week 52 was achieved by 125/179 (69.8%) in the voclosporin group and 92/178 (51.7%) in the placebo group (OR 2.26; 95% CI: 1.45, 3.51; p<0.001).

Partial renal response at week 24 was achieved by 126/179 (70.4%) in the voclosporin group and 89/179 (50%) in the placebo group (OR 2.43; 95% CI: 1.56, 3.79; p<0.001).

The median time to UPCR ≤0.5 mg/mg was 169 days for voclosporin and 372 days for placebo (HR 2.02; 95% CI: 1.51, 2.70; p<0.001).

The median time to reach 50% reduction in UPCR was 29 days for voclosporin versus 63 days for placebo (HR 2.05; 95% CI: 1.62, 2.60; p<0.001).

Proportion of subjects on low dose steroids achieving renal response was higher in voclosporin arm compared to placebo arm at both Week 24 (OR 2.44, 95%CI 1.26, 4.71, p 0.008) and Week 52 (OR 2.44, 95%CI 1.48, 4.00, p <.001).

3.3. Uncertainties and limitations about favourable effects

The primary endpoint renal response is a combined endpoint. The primary endpoint is not fully in line with the EMA GL, especially with respect to the eGFR value used to define "eGFR success" (or stable renal function). However, the presented results are considered as robust and are supporting a clinically relevant effect.

More subjects in the voclosporin arm achieved a partial renal response at Week 24 and Week 52. Of the subjects who achieved a partial response at Week 24, a higher proportion of subjects in the voclosporin group than in the placebo group were adjudicated to have a renal response at Week 52 (52.4% vs 39.3%). In addition, of the patients who did not achieve a renal or partial response at week 24, a numerical higher proportion of patients in voclosporin group than placebo group achieved a partial or renal response at week 52 (around 40% vs 28%). This gives support for continuing treatment also in patients who do not fully respond at week 24 and since no additional stopping rules were identified (such as level of proteinuria), the decision to continue treatment beyond Week 24 in patients who may not have experienced a notable improvement in their disease after 6 months of treatment, are left to the treating physician's judgement.

A dose reduction or temporary interruption of treatment drug was done for patients 51.1% and for 27.5% in the voclosporin and placebo groups, respectively. In most subjects, study treatment was resumed once the event resulting in a dose decrease/interruption had resolved. In the Voclosporin group, 57.2% of the patients did not resume to the full dose (28.6% stayed on 7.9 mg and 28.6% stayed on 15.8 mg). The response rates were lower in voclosporin subjects who ended the trial on 2 capsules (9/26, 34%) or 1 capsule (7/26, 27%) BID.

Almost half of the patients who achieved UPCR <0.5 in both groups had a secondary occurrence of UPCR > 0.5 (47.4 % in the placebo group and 45.7% in the voclosporin group). This implies that the

reduction of proteinuria will not sustain for a significant number of patients. In addition, a total of 18 subjects (10%) in each arm recorded a confirmed decrease of >30% from baseline in corrected eGFR during the study. More occurrences were reported during the second half of the treatment period. In the ITT-population from AURORA 1, the proportion of patients in renal response month 36 (AURORA 1 and AURORA 2) was 33% (59/179) in the voclosporin group and 22% (39/178) in the placebo group.

At the start of AURORA 2, 34/100 (34%) placebo subjects and 61/116 (52.6%) voclosporin subjects were in renal response. At month 36, 22/34 (64.7%) of the placebo subjects and 44/61 (72.1%) voclosporin subjects were still in renal response, indicating sustained remission (response both at the start of AURORA 2 and month 36) for the majority of the patients in both groups.

An important issue is whether the benefit in renal functioning could be offset by a deleterious effect on other organs affected by the SLE disease. Only limited information with regards to the potential effects on different non-renal organ systems were provided by the applicant. Thus, it is uncertain whether the drug can have deleterious effects on other SLE target organs. However, based on the available data, it can be concluded that in patients with active LN and little extrarenal activity, voclosporin does not seem to be associated with a worsening of other SLE symptoms, as assessed with SELENA-SLEDAI score.

3.4. Unfavourable effects

The total exposure to voclosporin is 2,666 subjects, including 365 patients with LN. Of these, 116 patients were exposed for 1 year in AURORA 1. In the follow up study, 101 of these patients were exposed to voclosporin for 36 months.

Adverse events

In the pooled LN population, the overall incidences of TEAEs were 91.4 vs 87.2% in voclosporin and placebo group, respectively. Serious AEs occurred in 22.8% voclosporin-treated participants compared to 18.8% in placebo group.

The most commonly (≥10%) TEAEs reported in voclosporin group in the pooled LN population were GFR decreased (26.2% vs 9.4%), hypertension (19.1% vs 8.6%), diarrhoea (18.7% vs 13.2%), headache (15.0% vs 8.3%), anaemia (12.4% vs 6.0%), cough (10.9% vs 2.3%) and urinary tract infection (9.7% vs 6.4%).

Adverse events leading to dose modification or temporary interruption and study treatment discontinuation

The incidences of TEAEs that led to dose modification or temporary interruption were 46.1% in voclosporin group compared to 25.2% in placebo group. The incidences of TEAEs that led to study treatment discontinuation were 13.5% in voclosporin and 13.2% in placebo group.

Deaths

There were in total 23 deaths in the LN clinical studies (N=631), with exposure-adjusted incidences of 2.3 E/100PYs in both the voclosporin and placebo groups. When looking at all TEAEs leading to death in pooled LN safety population (N=17/533), none of TEAEs stands out.

Adverse events of special interest

Adverse events of particular interest in LN patients and/or the CNI class of drug were acute renal failure, chronic kidney disease, hypertension, calcineurin-inhibitor-related adverse events, opportunistic infections, and malignancies.

Acute renal failure occurred in 33.3% of voclosporin-treated subjects compared with 17.7% of placebo-treated subjects during the first year of study treatment. According to the applicant, of these, 26.2% in the voclosporin group and 9.4% in the placebo group were managed effectively with dose interruption or modification.

In total, 65 voclosporin subjects (36.5%) and 55 placebo subjects (30.9%) had at least 1 of the following events:

Acute renal failure

CKD event

eGFR decreases ≥ 30% defined as 2 consecutive measures showing at least a 30% drop from baseline

Of these subjects, 92.3% of voclosporin treated subjects recovered compared with 76.4% in the placebo group.

The maximum mean decrease from baseline in corrected eGFR in the voclosporin group occurred at Week 4 and was -3.4 mL/min/1.73 m^2. Mean GFR levels remained stable thereafter, and there were no signs of decreasing mean GFR levels over time in the AURORA 2 study up to 36 months.

Hypertension occurred in 56 subjects in the voclosporin group (21.0%) and 28 subjects in the placebo group (10.5%).

Malignancies occurred in 4 subjects in the pooled LN population, all of whom were in the voclosporin group (1.5%). No specific patter was observed with regards to malignancy type.

The incidence of opportunistic infections was similar in the voclosporin (1.1%, 3 subjects) and placebo group (0.8%, 2 subjects) in the pooled LN population. Those were sporadic cases of cytomegalovirus (CMV chorioretinitis, CMV infection) and herpes virus family infections (herpes zoster cutaneous disseminated, herpes zoster disseminated, ophthalmic HSV).

All those adverse events are adequately reflected in the SmPC. When relevant, appropriate guidance on how to handle them is provided.

Safety in special populations

Lupkynis is not recommended during pregnancy and in women of childbearing potential not using contraception.

Voclosporin is contraindicated in combination with strong CYP3A4 inhibitors.

Dose reduction is proposed in patients with mild and moderate impairment, and voclosporin is not recommended in patients with severe hepatic impairment.

There are limited data in patients with impaired renal function (GFR<45 mL/min/1.73 m^2). However, it is agreed that in certain patients with severe disease, use of Lupkynis might be justified despite GFR<45 with adequate monitoring and dose adjustments.

All the information above is adequately reflected in the SmPC.

3.5. Uncertainties and limitations about unfavourable effects

Important potential long-term risks are renal toxicity, malignancy and neurotoxicity. Other important uncertainties pertain to adverse events with low frequency, given the rarity of the disease and the limited sise of the clinical studies. Even if 100 patients have been exposed for 36 months, some uncertainties remain with respect to long term safety. At the CHMP's request, the applicant has

accepted to conduct an observational PASS in EU to further characterise and quantify long-term safety profile of Lupkynis to address the uncertainties regarding long term safety and more particularly the risks of Malignancy, Neurotoxicity and Nephrotoxicity. This study is included in the RMP as a category 3 study.

Renal adverse events were observed more frequently in voclosporin-treated patients, than in patients treated with placebo. This is of concern because patients with LN are already at risk for development of renal failure and the additive effect of LN and drug toxicity might enhance this risk. Furthermore, it can be difficult to distinguish between voclosporin-caused toxicity and LN treatment failure. In response to day 120 LoQ, the applicant clarified that these renal adverse events were mostly due to early decreases in GFR. Although this is still of concern, it is reassuring that these events were generally reversible. It is noted that of the 65 voclosporin-treated subjects with at least 1 of the following events: acute renal failure, CKD, or eGFR decreases $\geq$ 30%, 92.3% recovered. Of the 5 subjects who did not recover to within 20% of the baseline eGFR, 4 had clear disease progression/LN flare and 1 subject had a partial recovery in eGFR levels, although recovery was to less than 20% of baseline. Thus, it is agreed that this safety issue can be handled through careful monitoring of GFR, and dose reduction or treatment discontinuation if GFR is decreased. Adequate warning and recommendations have been included in the SmPC.

AURORA 2 includes a biopsy substudy, in which 18 voclosporin subjects and 15 placebo subjects had second biopsies taken. Although the results were requested, no biopsy results could be provided because of a delay in the interpretation of the biopsies due to the COVID-19 pandemic. According to the AURORA 2 CSR these biopsies should have been performed 6 months after entry in the AURORA 2 study. Of the 216 patients who entered the AURORA 2 study, the majority (186/216 patients) had completed 36 months of treatment (i.e. had completed 24 months in the AURORA 2 study). Therefore, most of these biopsies should have been performed >18 months ago. Although it is understandable if all analyses (such as gene expression and immune markers) might be time consuming, at least preliminary histological results should be available. to the applicant will present the final results in December 2022. The AURORA 2 biopsy substudy is included as a category 3 study in the RMP.

Due to limited long-term follow-up, it is still not clear whether voclosporin like other calcineurin inhibitors is associated with a risk for renal fibrosis after many years of treatment. To date, there are no indications on irreversible renal damage caused by voclosporin but this will be an important issue to follow through post-approval data collection (PSUR and PASS).

There are no clinical data on pregnancy or lactation. Voclosporin is proposed with concomitant MMF with a known teratogenic effect, limiting the possibilities to gain further data.

Repeated-dose animal studies have shown neurohistological findings of gliosis and perivascular infiltrates in the brain and spinal cord in rats, but not in dogs or monkeys. Data in human is too limited for a reliable assessment of this risk. This finding is adequately reflected in Section 5.3 of the SmPC.

3.6. Effects Table

Table 86 Effects Table for Lupkynis and lupus nephritis (data cut-off: 1 April 2021).

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
Favourable Effects						
Renal Response at Week 52	Adjudicated RR At week 52	N (%)	73/179 (40.8%)	40/178 (22.5%)	p<0.001 OR 2.65 95% CI 1.64, 4.27	AURORA-1
Renal Response at Week 24	Adjudicated RR at week 24	N (%)	58/179 (32.4%)	35/178 (19.7%)	P=0.002 OR 2.23 95% CI 1.34, 3.72	AURORA-1
Partial RR at Week 52	Partial renal response, defined as 50% reduction from baseline in UPCR, at Week 52	N (%)	125/179 (69.8%)	92/178 (51.7%)	p<0.001 OR 2.26 95% CI 1.45, 3.51	AURORA-1
Partial RR at Week 24	Partial renal response, defined as 50% reduction from baseline in UPCR, at Week 24	N (%)	126 (70.4%)	89 (50.0%)	p<0.001 OR 2.43 95% CI 1.56, 3.79	AURORA-1
Time to UPCR ≤ 0.5	Median time to UPCR ≤0.5 mg/mg (days)	days	169	372	p<0.001 Hazard Ratio 2.02 95% CI 1.51, 2.70	AURORA-1
Time to 50% reduction in UPCR from baseline	Median time to 50% reduction in UPCR	days	29	63	P<0.001 Hazard Ratio 2.05 95% CI 1.62, 2.60	AURORA-1
Unfavourable Effects						
Adverse event (AE)	Any adverse event	N (%)	244/267 (91.4)	234/266 (88.0)		Pooled data from AURA-LV and AURORA 1 studies, ISS
Serious TEAE	Any serious treatment-emergent AE (any event on or after first dose of study treatment until 30 days post-dose)	N (%)	61/267 (22.8%)	50/266 (18.8)		ISS
Infections and infestations		N (%)	166/267 (62.2)	146/266 (54.9)		ISS
GFR decreased		N (%)	70/267 (26.2)	25/266 (9.4)		ISS

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
Acute renal failure	All Preferred Terms Appearing in the Acute Renal Failure SMQ	N (%)	89/267 (33.3)	47/266 (17.7)		ISS
Chronic kidney disease	All Preferred Terms Appearing in the Chronic Kidney Disease SMQ	N (%)	80/267 (30.0)	61/266 (22.9)		ISS
Deaths	Summary of All Deaths in Subjects with LN by Study and Treatment Group (AURION N=10, AURA-LV N=265, AURORA 1 N=356, AURORA 2, N=216)	N (E/100 PYs))	13/355 (2.3)	10/266 (2.3)		Table 74

Abbreviations: RR=renal response (Adjudicated based on blinded data by the CEC based on meeting the following criteria: UPCR≤0.5 mg/mg and eGFR ≥60 mL/min/1.73 m2 or no confirmed decrease from baseline in eGFR of >20%, and received no rescue medication for LN, and did not receive more than 10 mg prednisone for ≥3 consecutive days or for ≥7 days in total during Weeks 44-52.)

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Importance of favourable effects

LN is the most common serious manifestation of SLE and is a debilitating and potentially life-threatening condition. Proteinuria is the defining aspect of LN and indicates damage to the kidney; if not resolved this damage becomes permanent. A rapid reduction in proteinuria is, therefore, an important goal of treatment in LN.

The pivotal phase 3 AURORA 1 used a composite primary endpoint, renal response at week 52. This endpoint includes a strict definition regarding the amount of proteinuria allowed to be a responder (i.e UPCR ≤0.5). This is a clinically relevant measurement since a reduction in proteinuria to levels below 0.5-0.7 has been associated with improved renal survival. Also the key secondary endpoints reflect different aspects of reducing proteinuria.

In the AURORA 1 study, the results seen for the primary endpoint and all secondary endpoints were highly significant and robustly showed that voclosporin together with MMF+ corticosteroid reduce proteinuria faster and more effectively (i.e to a lower level) than MMF+ corticosteroids alone. Also, when renal response was analysed with a stricter eGFR definition of stable renal function "no confirmed decrease from baseline of >10% in corrected eGFR", 34.6% in the voclosporin group and 21.3% in the placebo group achieved a renal response. Although based on a complementary analyse, this finding is reassuring and provide additional information that a response is seen also when aiming for complete renal remission.

The study protocol requested a rather fast corticosteroid tapering schedule with a reduction to ≤2.5 mg at week 16. A majority of the patients in both groups were able to reduce their steroids to these levels. Taken into account the well-known adverse effects of long-term glucocorticoid treatment, it is an important finding that the rate of renal response at week 52 in patients with a low corticosteroid dose were also favouring voclosporin.

A treatment benefit of voclosporin was seen across all pre-specified subgroups, including black participants, males and participants with Class V LN in the pivotal study. There were however only a few treatment-naive patients included and detailed clinical data regarding refractory or relapsing patients were not collected in the study, making an evaluation of efficacy in these patients difficult. However, it is anticipated that a response, with decrease of proteinuria and a similar safety profile will be achieved also when treating a first active LN episode.

Voclosporin was not studied in combination with other immunosuppressive therapies than MMF. There is a major concern that the risk of infections and nephrotoxicity could be elevated when combined with other immunosuppressants, especially cyclophosphamide. Thus, the indication is restricted to combination with mycophenolate mofetil only. At the CHMP's request, the applicant also accepted to revised their claimed indication to reflect that the treatment is indicated in LN patients with active disease.

Importance of unfavourable effects

Class effects of calcineurin inhibitors include increased blood pressure, acute renal vasomotor effects and renal fibrosis. Other adverse effects associated with CNIs include neurotoxicity, electrolyte disturbances, impaired glucose tolerance and new-onset diabetes mellitus, and, like all immunosuppressants, infections and malignancies.

The safety of voclosporin seems consistent with other calcineurin inhibitors, with predominantly infections, renal impairment and hypertension. These are considered possible to handle through information in the SmPC. This information is included in the SmPC.

It is worth noting that the risk of malignancy, infection and cardiovascular events is already increased in SLE patients.

The most important safety concern is the risk for nephrotoxicity. Acute and chronic renal toxicity are known risks associated with calcineurin inhibitors. The efficacy of voclosporin is mainly driven by a reduction in proteinuria, which is acknowledged as a predictor of preserved long-term renal function. However, the nephrotoxic effect of voclosporin might negatively affect the long-term prognosis. A mean decrease in GFR was noted from baseline in the voclosporin group. Although this decrease was small on a group level it might be serious in individual cases and have a significant impact, especially if the decrease is persistent. Furthermore, adverse events of acute and chronic renal failure were observed more frequently in voclosporin-treated patients, than in patients treated with placebo. Patients with LN are already at risk for development of renal failure and an additive effect of LN and drug toxicity might enhance this risk. Another aspect is that it will be difficult to distinguish between voclosporin-caused toxicity and treatment failure, which is important because of different treatment approaches.

At the CHMP's request, the applicant clarified that these renal adverse events were mostly due to early decreases in GFR. Although this is still of concern, it is somewhat reassuring that these events were generally reversible. The CHMP agreed that this safety issue can be handled through careful monitoring of GFR, and dose reduction or treatment discontinuation if GFR is decreased. Adequate information the risk and recommendations for monitoring have been included in the SmPC.

Long-term safety data are limited, and the potential long-term risks associated with voclosporin use, mainly nephrotoxicity, neurotoxicity, and malignancy, needs to be further characterised post approval. At the CHMP's request, the applicant has accepted to conduct an observational PASS in EU to further characterise and quantify long-term safety profile of Lupkynis to address the uncertainties regarding long term safety and more particularly the risks of Malignancy, Neurotoxicity and Nephrotoxicity. This study is included in the RMP as a category 3 study. A feasibility assessment and updated protocol will be submitted after approval.

3.7.2. Balance of benefits and risks

Overall, statistically significant and clinically relevant efficacy results show superiority of voclosporin 23.7 mg BID to matching placebo for 52 weeks with a background therapy of MMF and corticosteroids in adult patients diagnosed with LN. Efficacy results are robust. Internal validity of the main study appears to be high.

Voclosporin safety profile can be characterised as serious and complex. An extensive monitoring of patients is required, and dose modifications due to ADRs are needed. The most important safety concern for voclosporin is the risk for nephrotoxicity, which is considered possible to handle through careful monitoring of GFR, and dose reduction or treatment discontinuation if GFR is decreased. Adequate information on risks and recommendations for monitoring have been included in the SmPC. In addition, at the CHMP's request, the applicant has accepted to conduct an observational PASS in EU to further characterise and quantify long-term safety profile of Lupkynis.

3.8. Conclusions

The overall benefit/risk balance of Lupkynis is positive.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Lupkynis is favourable in the following indication(s):

Lupkynis is indicated in combination with mycophenolate mofetil for the treatment of adult patients with active class III, IV or V (including mixed class III/V and IV/V) lupus nephritis (LN).

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2.)

In accordance with Article 114 Directive 2001/83/EC, the official batch release will be undertaken by a state laboratory or a laboratory designated for that purpose.

Other conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive

2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Risk Management Plan (RMP)

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

At the request of the European Medicines Agency;

Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

New Active Substance Status

Based on the CHMP review of the available data, the CHMP considers that voclosporin is to be qualified as a new active substance in itself as it is not a constituent of a medicinal product previously authorised within the European Union.