European Union (EU) Risk Management Plan (RMP) for Lupkynis™ (voclosporin)

RMP version to be assessed as part of this application:

RMP Version number	5.0 (Final date 27 November 2023)
Data lock point (DLP) for this RMP	5 November 2021: Clinical data 22 January 2022: Module SV Post-marketing experience 5 October 2022: Drug-drug interaction study to investigate effects of voclosporin on pharmacokinetics of simvastatin. 14 June 2023: Kidney biopsy sub-study to study AUR-VCS-2016-02 (AURORA 2). 20 June 2023: Study to evaluate the amount of voclosporin excreted in breast milk following oral administration of a single dose in healthy, lactating, female volunteers.
Date of final sign off	
Rationale for submitting an updated RMP	Completion of drug -drug interaction study, kidney biopsy sub study and lactation study.
Summary of significant changes in this RMP	**SII** Addition of summary of drug-drug interaction study and lactation study **SVII.3.1, Part VI.II.B** Addition of a summary of results of Kidney Biopsy Sub Study. **III.2, III.3, V.3, Part VI II. B, Part VI II.C.2, Annex 3:** Removal of Kidney Biopsy Sub Study **Part VI.** Correction to place "An observational PASS in the EU to further characterise and quantify long term safety profile of Lupkynis" as an Additional Pharmacovigilance Activity and remove from Additional Risk Minimisation.

Other RMP versions under evaluation:

Version number of RMP under evaluation:	Not applicable
Submitted on:	Not applicable
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Details of the currently approved RMP:

Version number:	4.0
Approved with procedure:	EMEA/H/C/005256/IB/0006

EU Qualified Person for Pharmacovigilance (QPPV)

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List of Abbreviations

Abbreviation	Definition
AE	Adverse event
ATC	Anatomical therapeutic chemical
AUC	Area under the concentration-time curve
BCRP	Breast cancer resistance protein
BID	Twice daily
CI	Confidence interval
C_{max}	Maximum concentration
CNI	Calcineurin inhibitor
CsA	Cyclosporine A
CSR	Clinical Study Report
C trough	Pre-dose Trough concentration
CYP	Cytochrome P450
DLP	Data lock point
dsDNA	Double stranded deoxyribonucleic acid
E	Event
EAIRs	Exposure adjusted incidence rates
ECG	Electrocardiogram
EEA	European economic area
eGFR	Estimated glomerular filtration rate
EMA	European Medicines Agency
E_{max}	Maximum calcineurin inhibition levels
EPAR	European public assessment report
ESRD	End-stage renal disease
EU	European Union
F	Fatal
F_1	First generation
FDA	Food and Drug Administration
GFR	Glomerular filtration rate
hERG	Human ether-a-go-go-related gene
HIV	Human immunodeficiency virus
IC_{20}	20% inhibitory concentration
IC_{50}	50% inhibitory concentration
ICH	International Council for Harmonisation
IgA	Immunoglobulin type A
IgG	Immunoglobulin type G
INN	International nonproprietary name
IV	Intravenous
KDIGO	Kidney disease improving global outcomes
LN	Lupus nephritis
MACE	Major Adverse Cardiovascular Event
MedDRA	Medical dictionary for regulatory activities
Mil	Mild
MMF	Mycophenolate mofetil
Mod	Moderate
MPA	Mycophenolic acid
NA	Not applicable
NO	Nitric oxide
NOAEL	No-observed-adverse-effect level
OATP	Organic-anion-transporting polypeptide
PASS	Post-Authorisation Safety Study
Pgp	P glycoprotein
PK	Pharmacokinetics
PL	Patient leaflet
PR	Electrocardiogram PR interval
PRES	Posterior Reversible Encephalopathy Syndrome

PSUR	Periodic safety update report
PT	Preferred term
QPPV	Qualified person for pharmacovigilance
QRS	Electrocardiogram combination of the Q wave, R wave and S wave, the "QRS complex".
QT	QT interval
QTc	Corrected QT interval
QTcF	Corrected QT interval using Fridericia's formula
Rel	Related
Res	Resolved
RID	Relative infant dose
RMP	Risk management plan
RR	Electrocardiogram RR interval
RSq	Resolved with sequelae
Sev	Severe
SLE	Systemic lupus erythematosus
SmPC	Summary of product characteristics
SMQ	Standardised medical dictionary for regulatory activities query
SOC	System organ class
SPS-1	Sucrose-phosphate synthase-1
TEAE	Treatment emergent adverse events
T_{regs}	Regulatory T cells
UK	United Kingdom
UPCR	Urine Protein/Creatinine Ratio
US	United States
UV	Ultraviolet

Part I: Product overview

Active substance(s) (international nonproprietary name [INN] or common name)	Voclosporin
Pharmacotherapeutic group(s) (anatomical therapeutic chemical [ATC] Code)	Immunosuppressants, calcineurin inhibitor (CNI) (L04AD03)
Marketing Authorisation Holder	Otsuka Pharmaceutical Netherlands B.V.
Medicinal products to which this RMP refers	Voclosporin
Invented name(s) in the European Economic Area (EEA)	Lupkynis
Marketing authorisation procedure	Centralised: EMEA/H/C/005256
Brief description of the product	**Chemical class**: Voclosporin, a novel CNI, is structurally similar to cyclosporine A (CsA) except for a modification to the amino acid-1 region.
	Summary of mode of action: Voclosporin is a CNI 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.
	Important information about its composition: None
Hyperlink to the Product Information	Module 1.3.1
Indication(s) in the EEA	Current : 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).
	Proposed : Not applicable (NA)
Dosage in the EEA	Current : The recommended dose is 23.7 mg (three 7.9 mg soft capsules), twice daily
	Proposed: NA
Pharmaceutical form(s) and strengths	Current : Soft capsule, 7.9 mg voclosporin Pink/orange oval soft capsules measuring approximately 13 mm x 6 mm
	Proposed : NA
Is/will the product be subject to additional monitoring in the EU?	Yes

Part II: Safety specification

Part II: Module SI - Epidemiology of the indication(s) and target population(s)

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) LN.

LN is one of the most serious manifestations of systemic lupus erythematosus (SLE). It usually arises within 5 years of diagnosis, and its prevalence varies, according to published studies, from 30 to 90% (Schieppati et al, 2009).

Incidence and Prevalence:

The prevalence of LN was calculated as ranging between 0.44 and 1.4 per 10,000 (Table 1).

Table 1. Incidence and Prevalence of LN in European Countries

Country	LN Incidence Per 10,000 Per Year	LN Prevalence Per 10,000	Period	Reference
United Kingdom (UK)	0.040	0.44	2001	(Patel et al, 2006)
Norway	0.07	0.7	1978-1995(1)	(Eilertsen et al, 2011)
	0.045	1.4	1996-2006(2)	
Denmark	0.045	0.64 (3)	2004-2011	(Hermansen et al, 2016)

1. Results for a cohort which enrolled subjects between 1978-1995.
2. Results for a cohort which enrolled subjects between 1996-2006.
3. Point prevalence for 2011

Notes: Incidence and prevalence rates per 10,000 were derived from rates reported per 100,000 in the original study reports. LN=Lupus nephritis

Estimates of incidence and prevalence based on studies looking specifically at patients diagnosed with LN are limited (Table 1). Therefore, the incidence and prevalence were calculated based on the prevalence of SLE and the estimated proportion of patients diagnosed with SLE who go on to develop LN. The calculation is based on the racial mix in the UK and was extrapolated to the EU. This calculation resulted in that the total proportion of EU patients with SLE who will develop LN is estimated to be 25.3%. The estimated prevalence of LN ranged from 0.63 to 2.28 per 10,000 persons (Table 2).

Table 2. Estimated Incidence and Prevalence of LN in Europe Calculated from Data Reported for SLE

Region	SLE Incidence Per 10,000 Per Year	Estimated LN Incidence per 10,000 (Calculated)	Reported SLE Prevalence Per 10,000 Per Year	Estimated LN Prevalence per 10,000 (Calculated)	Period	References
Europe[1]	0.33-0.50	0.08 – 0.13	2.54–9.10	0.63-2.28	1975-2004	(Danchenko et al, 2006)
Other individual studies conducted across the EU	NA	NA	1.62-12.3	0.41-3.08	1999-2013	(Alamanos et al, 2003; Alonso et al, 2011; Arnaud et al, 2014; Benucci et al, 2005; Brinks et al, 2014; Dadoniene et al, 2006; Eaton et al, 2010; Eilertsen et al, 2009; EPISER 2001, 2001; Gergianaki et al, 2017; Gómez et al, 2006; Govoni et al, 2006; Hermansen et al, 2016; Ingvarsson et al, 2016; Laustrup et al, 2009; Lerang et al, 2012; López et al, 2003; Otsa et al, 2017; Rees et al, 2016; Sardu et al, 2012; Simard et al, 2014; Tsioni et al, 2015)

1. Incidence data was reported for France, Iceland, Spain, Sweden, and the UK; and prevalence data was reported for Finland, France, Germany, Iceland, Italy, Northern Ireland, Spain, Sweden, and the UK. Incidence and prevalence rates per 10,000 for SLE were derived from rates reported per 100,000 in the original study report. Incidence and prevalence rates per 10,000 for LN were estimated by extrapolation based on the assumption of 25% of SLE patients manifesting LN. Ranges reported in this table are based on data for "whole populations", rather than data reported for sub-groups according to individual ethnic group. LN=Lupus nephritis; SLE=Systemic lupus erythematosus.

A systematic literature review showed a worldwide variation, with the highest incidence reported in North America (23.2/100,000 person-years, 95% confidence interval [CI]: 22.4, 24.0) and the lowest incidences reported in Africa (0.3/100,000 person-years) and Ukraine (0.3/100,000 person-years, 95% CI: 0.0, 1.5). In general, European countries had a lower incidence of SLE, whereas Asia, Australia and the Americas had a higher incidence (Rees et al, 2017).

The prevalence of LN derived from SLE studies was found to be 0.63-2.28/10,000 based on the Danchenko et al, 2006 review (Danchenko et al, 2006) and 0.41-3.08/10,000 based on 23 individual studies conducted across the EU (Table 2). This is of a similar order to the three studies which examined the prevalence of LN directly where the range was 0.44-1.40/10,000 (Table 1).

A recent meta-analysis showed that the prevalence rate of biopsy-proven LN among patients with SLE ranged from 16.9% to 42.8% (Wang et al, 2017).

Demographics of the population in the proposed indication – age, gender, racial and/or ethnic origin and risk factors for the disease:

Age and Gender

SLE

SLE prevalence is highest among females, with a female to male ratio ranging between 1.2:1 and 15:1. The peak age of prevalence is between 45 and 69 years for females and between 40 and 89 years for males (Rees et al, 2017).

LN

A meta-analysis designed to determine the prevalence of biopsy-proven LN showed that biopsy-proven LN developed in about 29% of SLE patients; the mean age of patients with SLE at renal biopsy was approximately 30 years and 85% of patients with biopsy-proven LN were female. The sex distribution and ages of patients with biopsy-proven LN varied with geography and ethnicity. In Pakistan, the percentage

of female patients with biopsy-proven LN was 51.4%, compared with 84.6% in Northwest England. Among Afro-Caribbean and Chinese females, the prevalence rate of LN was highest in those aged 20-39 years, whereas among white and Indo-Asian females, it was highest in those aged 40-59 years (Wang et al, 2017).

Racial and/or ethnic origin

Hanly and colleagues studied a large (N=1,827) multi-ethnic cohort of patients with SLE across the EU, United States (US), Canada, Mexico and Asia (Hanly et al, 2016). SLE was diagnosed according to American College of Rheumatology criteria and LN was defined by the International Society of Nephrology and the Renal Pathology Society 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).

In a US-based study of 353 patients with SLE, Bastian and colleagues also reported that the rate of occurrence of LN was dependent on race/ethnicity: LN occurred in 14.3% of patients of Caucasian origin, 43.1% Hispanic and 50.5% African-American (Bastian et al, 2002).

Similar findings were reported by Patel and colleagues in a UK-based study of the prevalence of biopsy proven LN in the UK: 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).

Risk factors

Distinct genetic factors were associated with the risk of LN in SLE patients of different ethnicities. Gene-based analyses showed significant associations between variation in single-nucleotide polymorphisms in genes like *ZNF546*, *TRIM15*, and *TRIMI0* and LN among South Europeans, and *TTC34* was significantly associated with LN among Hispanics (Lanata et al, 2018).

Risk factors for the development of LN include clinical features like malar rash, pericarditis, arterial hypertension, anaemia, low levels of serum complements, and raised anti-double stranded deoxyribonucleic acid (dsDNA). Additional risk factors are male gender and younger age of disease onset (Burling et al, 2007; Faezi, 2017; Galindo-Izquierdo et al, 2016).

The main existing treatment options:

The Joint European League Against Rheumatism and European Renal Association–European Dialysis and Transplant Association recommends immunosuppressive treatment and hydroxychloroquine (Bertsias et al, 2012). In active proliferative LN, initial treatment with mycophenolate mofetil (MMF) (2–3 g/day or mycophenolic acid (MPA) at equivalent dose) or low-dose intravenous cyclophosphamide (500 mg×6 biweekly doses), both combined with glucocorticoids (pulses of intravenous methylprednisolone, then oral prednisone 0.3–0.5 mg/kg/day) is recommended. MMF/CNI (especially tacrolimus) combination and high-dose cyclophosphamide are alternatives for patients with nephrotic-range proteinuria and adverse prognostic factors (Fanouriakis et al, 2020).

Subsequent long-term treatment with MMF or azathioprine should follow, with no or low-dose (<7.5 mg/day) glucocorticoids (Fanouriakis et al, 2020).

In non-responding disease, switch of immunosuppressants or use of rituximab are recommended. In pure membranous LN with nephrotic-range proteinuria or proteinuria >1 g/24 hours despite renin–angiotensin–aldosterone blockade, MMF in combination with glucocorticoids is preferred (Fanouriakis et al, 2020).

Belimumab has been approved by the Food and Drug Administration (FDA) and recently by European Medicines Agency (EMA) on 30 April 2021 for LN. Voclosporin was approved by the FDA for the treatment of LN on 22 Jan 2021. All other treatments as described in Table 3 are used off label.

Table 3. The Main Treatment Options for LN

Drug class	Drug	Main risks
B-lymphocyte stimulator	Belimumab	Hypersensitivity, infections, depression and suicidality, progressive multifocal leukoencephalopathy, malignancies and lymphoproliferative disorders, concomitant use with B cell targeted therapy, cyclophosphamide or vaccines, use in the following patient groups: severe active central nervous system lupus, severe active LN, human immunodeficiency virus (HIV), a history of, or current, hepatitis B or C, hypogammaglobulinaemia (immunoglobulin type G [IgG] <400 mg/dL) or immunoglobulin type A (IgA) deficiency (IgA <10 mg/dL), a history of major organ transplant or hematopoietic stem cell/marrow transplant or renal transplant (Benlysta SmPC).
Alkylating agents	Cyclophosphamide	Anaphylactic reactions, cross-sensitivity with other alkylating agents, myelosuppression, immunosuppression, infections, urinary tract and renal toxicity, cardiotoxicity, pulmonary toxicity, secondary malignancies, veno-occlusive liver disease, genotoxicity, and impairment of wound healing (Cyclophosphamide SmPC).
Antimalarial	Hydroxychloroquine	Retinopathy, hypoglycaemia, cardiomyopathy, chronic cardiac toxicity, and prolongation of corrected QT interval (QTc) interval, extrapyramidal disorders, use in patients with hepatic or renal disease, severe gastrointestinal, neurological or blood disorders, drug-drug interactions (Hydroxychloroquine SmPC).
CNIs	CsA	Lymphomas and other malignancies, infections, renal toxicity, hepatotoxicity, hypertension, blood lipids increased, hyperkalaemia, hypomagnesaemia, hyperuricaemia, and vaccinations may be less effective (Sandimmun Neoral SmPC).
	Tacrolimus	Gastrointestinal disorders, cardiac disorders, lymphomas and other malignancies, infections including opportunistic infections, posterior reversible encephalopathy syndrome, eye disorders, pure red cell aplasia, and vaccinations may be less effective (Advagraf SmPC).
Glucocorticoids	Prednisolone/prednisone	Psychiatric adverse reactions, tumorigenicity, calciphylaxis, adrenocortical insufficiency, infections, exposure to chickenpox, herpes zoster and measles, administration of live vaccines, ocular effects (e.g., cataract, glaucoma, use in ocular herpes simplex, retinal detachment), Cushing's disease, raised intracranial pressure, Scleroderma renal crisis, use in the elderly, growth retardation in infancy, childhood and adolescence. Co-administration in patients with the following conditions: tuberculosis, inflammatory bowel disease, Crohn's disease, hypertension, congestive heart failure, liver failure, hepatic disease, renal insufficiency, diabetes mellitus, osteoporosis, a history of severe affective disorders and particularly those with a previous history of steroid-induced psychoses, existing emotional instability or psychotic tendencies, epilepsy, and/or seizure disorders, peptic ulceration, previous steroid myopathy, myasthenia gravis receiving anticholinesterase therapy, patients with thromboembolic disorders, and Duchenne muscular dystrophy (Prednisolone SmPC).
Other immunosuppressants	MMF/MPA	Neoplasms, infections, neutropenia, pure red cell aplasia, gastrointestinal tract ulceration, haemorrhage and perforation, teratogenic effects (spontaneous abortions and congenital

Drug class	Drug	Main risks
		malformations) and drug-drug interactions as well as lessened efficacy of vaccinations (CellCept SmPC).
	Azathioprine	Lymphoproliferative disorders and other malignancies, infections, macrophage activation syndrome, and photosensitivity (Azathioprine SmPC).
	Rituximab	Infusion related reactions, cardiac disorders, haematological toxicities, infections (including progressive multifocal leukoencephalopathy), skin reactions and vaccines may be less effective (MabThera SmPC).

Natural history of the indicated condition in the untreated and treated population, including mortality and morbidity:

LN is the most common serious manifestation of SLE and is a cause of renal failure and mortality (Schieppati et al, 2009). LN manifests as diverse patterns of immune-complex mediated renal disease affecting glomerular, tubulointerstitial and vascular compartments. In patients with LN, renal damage results in proteinuria and/or haematuria and a decrease in renal function as evidenced by reduced creatinine clearance and estimated glomerular filtration rate (eGFR), and can lead to permanent and irreversible tissue damage within the kidney, resulting in end-stage renal disease (ESRD), i.e., the need for long-term dialysis or transplantation.

LN is divided into different classes as shown in Table 4.

Table 4. LN Classes

Classification category	Clinical Features
Class I: minimal mesangial	Normal/minimal proteinuria, normal creatinine. Earliest and mildest form of glomerular involvement.
Class II: mesangial proliferative	Microscopic haematuria ± proteinuria. Hypertension uncommon and nephrotic syndrome plus renal insufficiency rarely seen.
Class III: focal LN	Haematuria, proteinuria, hypertension, reduced eGFR ± nephrotic syndrome.
Class IV: diffuse LN	Most common and severe form of LN. Clinical features as for class III but also significantly low complement 3 and high dsDNA, especially in active disease.
Class V: membranous nephropathy	Nephrotic syndrome, microscopic haematuria, hypertension, normal/high creatinine. Can present without other clinical or serological manifestations of SLE but electron microscopy features will distinguish it from the idiopathic form.
Class VI: advanced sclerosing lupus	Slowly progressive renal failure with proteinuria and bland urine sediment.
Adapted from Bomback AS, Appel GB. Lupus nephritis: Diagnosis and classification. UpToDate 2020 (Bomback & Appel, 2021).	

In the US, approximately 35% of adults with SLE have LN at the time of diagnosis with an estimated 50%-60% developing LN during the first 10 years of the disease (Hahn et al, 2012); the figures from Europe are not available. It is estimated that 10%-30% of patients with LN will develop ESRD (Almaani et al, 2017; Costenbader et al, 2011; Tektonidou et al, 2016); the risk varies with histologic class and is highest in patients with Class III and IV proliferative LN. The development of ESRD in LN patients has

been associated with a 26-fold increase in mortality risk compared with a demographically matched general population (Yap et al, 2012).

The overall 5-, 10-, and 20-year survival rates for patients with biopsy-proven LN were 94%, 86% and 71%, respectively. Class IV nephritis, present in 40% of patients with biopsy-proven LN, was a risk factor for renal failure that contributed to poor prognosis in patients with SLE (Wang et al, 2017).

Important co-morbidities:

Patients with SLE and LN are frequently burdened with a variety of comorbidities like cardiovascular disease (mainly hypertension), atherosclerosis, dyslipidaemia, diabetes, obesity, infections, anaemia, malignancies, osteoporosis, atopic dermatitis, asthma, chronic obstructive pulmonary disease, depression, and anxiety (Gergianaki & Bertsias, 2018; Tzavara et al, 2013). The prevalence of posterior reversible encephalopathy syndrome (PRES) among patients with SLE ranges from 0.7% to 1.4% with recurrence in up to 15% of cases and risk factors include SLE activity, hypertension, haematologic and renal disease (Valdez-Lopez 2021).

Part II: Module SII - Non-clinical part of the safety specification

Key safety findings from non-clinical studies and relevance to human usage is described in Table 5. The safety concerns from non-clinical data are summarised in Table 6.

Table 5. Key safety findings from non-clinical studies with voclosporin and relevance to human usage

Key safety findings from non-clinical studies	Relevance to human usage
Toxicity	
Key issues identified from acute or repeat-dose toxicity studies	
Single-Dose Toxicology Single intravenous doses of voclosporin up to 2.5 mg/kg, the highest dose tested, were well tolerated in Sprague Dawley rats. In Beagle dogs, emesis was the only effect noted with single oral doses of mix-ISA247 (isomeric mixture of voclosporin[1]) up to 75 mg/kg.	No safety concern relevant to human use has arisen from these non-clinical data.
Repeat-Dose Toxicology In the rat, cataract formation, renal effects and neuro-histological findings were the primary adverse effects. Cataract formation is considered to be a species-specific, class related effect, which is also observed with CsA (Avery et al, 1991; Bernauer et al, 1991; Cruz et al, 1996; O'Riordan et al, 1994).	**Cataract**: Cataract is considered to be species specific and is not considered to be a safety concern relevant to human use.
Renal effects included increases in blood urea nitrogen and creatinine, tubular basophilia and degeneration/regeneration, and corticomedullary mineralization. These findings generally occurred in chronic repeat-dose studies at dose levels of ≥2.5 mg/kg/day. It is unclear whether all of the renal findings are directly treatment-related or whether exposure to mix-ISA247, voclosporin or CsA produced an exacerbation of a normal biological response since the spectrum of observed microscopic renal changes can arise spontaneously in the kidneys of male rats, especially as they age.	**Renal effect**s: Nephrotoxicity (Acute and chronic) is considered an **Important Potential Risk**.
The neuro-histological effects included gliosis and perivascular infiltrates in the brain and spinal cord. The observed neuro-histopathological changes in rats were confirmed to be dose-dependent and are thought to be a species-specific effect, as they were not observed in repeat-dose toxicology studies of mix-ISA247 in dogs or monkeys. CsA was associated with the same neuro-histopathological findings in the 13-week bridging study in rats in which CsA was included as a comparator control. The proposed therapeutic dose of voclosporin for LN of 23.7 mg BID (approximately 0.4 mg/kg BID) is less than the dose of CsA typically used in transplant patients (1.5 to 3.0 mg/kg BID) (Serkova et al, 2004), the population in which CsA-related neurologic signs occur.	**Neurological effects**: The observed neuro-histopathological changes in rats were not observed in repeat-dose toxicology studies of mix-ISA247 in other species. In rats, neuro-histopathological findings related to voclosporin have also been shown to be dose dependent. The proposed therapeutic dose of voclosporin for lupus nephritis (23.7 mg BID), corresponding to 0.4 mg/kg BID for a typical 60 kg patient) is less than the dose of CsA typically used (eg, 1.5 to 3.0 mg/kg BID) (Serkova et al, 2004 in which CsA-related neurologic signs occur. Given the lack of inter- and intra-patient variability with voclosporin, physicians will be able to maintain patients with the correct dosage in lupus nephritis. Hypomagnesemia has not been seen with

[1] Voclosporin (90 to 95% trans-isomer) is the active ingredient in Lupkynis. Animal reproductive studies were primarily conducted with an approximate 50:50 mixture of voclosporin and its cis-isomer (mix-ISA247). Similarity of the toxicity effects of the 50:50 mixture and voclosporin was demonstrated in comparative toxicity studies with adult rats. Interconversion between cis and trans isomers was not detected with in vitro or in vivo studies.

Key safety findings from non-clinical studies	Relevance to human usage
In the 39-week chronic monkey study, lymphosarcoma was one of the main toxicological findings in the high-dose animals (1 male and 4 females given mix-ISA247 at a dose level of 150 mg/kg/day). No lymphosarcomas were observed in the mid- or low-dose animals. In this study, calcineurin inhibition data confirmed that the mid- and high-dose monkeys had a high level of immunosuppression where calcineurin inhibition was in excess (>80%), well in excess for the treatment of autoimmune diseases such as LN. The Sponsor believes that this also applies to the treatment of other autoimmune diseases such as LN. Immunosuppressed monkeys are especially at risk of developing viral-related malignancies. In particular, several literature reports have shown that development of lymphosarcomas in non-human primates is markedly increased with immunosuppressive therapy (Gaschen & Schuurman, 2001; McInnes et al, 2002; Schmidtko et al, 2002). The increase in incidence of lymphoma is considered to be a class effect of immunosuppressive agents (CsA and tacrolimus product information feature this observation). Taking the above into consideration, the finding of lymphosarcoma in the monkey is not unexpected and does not raise additional concern. Likewise, findings of splenic hyperplasia and gingival hyperplasia observed at the mix-ISA247 dose levels of 75 and 150 mg/kg/day were considered to be related to pharmacologic activity.	voclosporin, discounting one of the proposed mechanisms of potential neurotoxicity. **Lymphomas and malignancies:** Malignancies (including lymphomas) associated with long term use is considered an **Important Potential Risk**.
Reproductive/developmental toxicity	
The no-observed-adverse-effect level (NOAEL) for voclosporin in pregnant rabbits was determined to be 1 mg/kg/day and foetal toxicity (reduced foetal body weights and skeletal variations) was only observed at doses associated with maternal toxicity (based on swollen mammary glands, reduced body weights, clinical observations and food consumption effects). Voclosporin was not considered teratogenic. Fertility studies were conducted with mix-ISA247 in rats with no treatment-related changes in fertility, mating parameters, sperm evaluations, embryonic viability or in the number and location of implantation sites or observations on placentae. No general behavioural, reproductive or developmental toxicities were noted in the first generation (F_1) generation. No fertility or early embryonic developmental toxicity studies have been conducted with voclosporin. However, as voclosporin is more bioavailable than the cis-isomer, it is reasonable to assume that the fertility or early embryonic developmental toxicity of voclosporin is comparable to that of mix-ISA247. A placental and milk transfer study with [^{14}C]-voclosporin in rats indicated that transfer of radioactivity across the placental barrier was slow and limited, while transfer into milk was relatively rapid, but systemic absorption by the pups was slow and limited.	Use in pregnancy will be considered **Missing Information**. In Study AUR-VCS-2021-04 to evaluate the amount of voclosporin excreted in breast milk, following a single oral dose of 23.7 mg voclosporin in healthy lactating female volunteers, the mean total amount of voclosporin excreted in breast milk was 0.00472 mg. Approximately 80% of the total amount was excreted within the first 12 hours after dosing. The relative infant dose (RID) was 0.688% or 0.917% calculated based on the infant ingesting 150 or 200 mL/kg/day, respectively, of breast milk. Using individual subject data, the highest estimated RID was 1.41%. Adverse effects on the breastfed infant have not been reported. There are no data on the effects of the drug on milk production. The estimated RID indicates that use of voclosporin in lactating women results in low exposure to the breastfed infant. It is recommended that a decision 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.

Key safety findings from non-clinical studies	Relevance to human usage
The toxicity profile of voclosporin in juvenile rats was similar to that seen in conventional studies in adult rats, with similar changes observed in the thymus, kidney, brain and sciatic nerve.	
Genotoxicity	
Voclosporin was not mutagenic in the Ames test or in a chromosomal aberration study, with and without metabolic activation. Mix-ISA247 showed no genotoxic potential in the standard International Council for Harmonisation (ICH) battery of genotoxicity assays: Ames, chromosomal aberration with and without metabolic activation, and the in vivo rat micronucleus assay. Additionally, the in-silico assessment of 20 voclosporin-related substances concluded that these compounds did not show evidence of genotoxic potential.	No safety concern relevant to human use has arisen from these non-clinical data.
Carcinogenicity	
In a 2-year mouse carcinogenicity study, administration of voclosporin at oral doses of 3, 10, or 30 mg/kg/day resulted in an increased incidence of malignant lymphoma in high dose females and a dose-responsive trend for increase in malignant lymphoma in males. Malignant lymphoma was considered drug related in mice. In a 2-year rat carcinogenicity study, oral administration of voclosporin at doses up to 1.25 mg/kg/day in males and 2.5 mg/kg/day in females (doses that result in approximately similar drug exposures in rats) resulted in no statistically significant increases of tumour incidences. In a 39-week oral toxicology study with monkeys, malignant lymphomas occurred at a dose of 150 mg/kg/day. At this dose, monkeys experienced high levels of immunosuppression as indicated by maximum calcineurin inhibition levels (E_{max}) of greater than 80%.	Malignancies (including lymphomas) associated with long term use is considered an **Important Potential Risk.**
Safety pharmacology	
Cardiovascular system, including potential effect on the QT interval	
The results of a human ether-a-go-go-related gene (hERG) assay in Chinese Hamster Ovary cells indicated that mix-ISA247 and voclosporin inhibited repolarizing currents through hERG K^+ channels in vitro at 20% inhibitory concentration (IC_{20}) values of approximately 6-18 µM (approximately 7,000-22,000 ng/mL). However, these concentrations are well in excess of the estimated clinical maximum concentration (C_{max}) of 0.1 µM (approximately 120 ng/mL). Furthermore, in a rabbit Purkinje fibre assay, mix-ISA247 was not associated with the induction of arrhythmias at the concentration range tested (nominally 0.01-10 µM). In vivo, voclosporin and/or mix ISA247 lengthened QT and QTc intervals at a dose level of 200 mg/kg, the highest dose tested, in cardiovascular safety pharmacology studies in conscious monkeys, but had no effect at lower doses. In these studies, no effects on heart rate were observed and the electrocardiogram (ECG) waveforms showed no effect on RR, PR and QRS complex duration. Exposure to voclosporin at a dose level of 200 mg/kg in monkeys was approximately 8-fold and 5-fold higher than the estimated therapeutic exposure based on area under the concentration-time curve (AUC) and C_{max}, respectively. No drug-related ECG abnormalities were observed in any other non-rodent toxicology study	Clinical data do not show a signal for an increased risk of arrhythmias in patients with LN at a voclosporin dose level of 23.7 mg BID. The SmPC Section 4.4 provides information allowing the prescriber to identify circumstances which may increase the risk of QT prolongation. QT prolongation and arrhythmias are not considered to be an important risk for voclosporin

Key safety findings from non-clinical studies	Relevance to human usage
including 14-day dog, 13-week dog, 13-week monkey and 39-week monkey studies.	
Nervous system	
Voclosporin did not have any effect on neuropharmacological signs in rats at doses up to 25 mg/kg.	No safety concern relevant to human use has arisen from these non-clinical data.
Respiratory system	
At a dose of 25 mg/kg (estimated clinical exposure multiple of 35-fold), the highest dose tested, voclosporin was associated with a slight transient decrease in respiration rate in rats, without an increase in tidal volume.	No safety concern relevant to human use has arisen from these non-clinical data.
Renal system	
The only acute effect of voclosporin in a rat renal study was a marginal decrease in urine volume at a dose of 25 mg/kg, the highest dose tested.	**Renal effect**s: Nephrotoxicity (acute and chronic) is considered an **Important Potential Risk**.
Other toxicity-related information or data	
Drug-Drug Interaction	
A 13-week combination toxicity study with voclosporin and prednisone was conducted in rats. There were no new toxic effects that occurred in rats administered voclosporin and prednisone in combination, compared to administration of each test article separately. The incidence of cataract formation was similar whether voclosporin was administered alone or in combination with prednisone. Small, but toxicologically insignificant, differences in temporal onset were observed.	No safety concern relevant to human use has arisen from these non-clinical data.
Cytochrome P450 (CYP)3A4/5 is the primary enzyme involved in the Phase 1 metabolism of voclosporin. A clinical drug interaction study with ketoconazole confirmed that voclosporin was a substrate for CYP3A4/5.	Section 4.5 of the SmPC provides sufficient information regarding potential interactions such that interactions between voclosporin and medicinal products or herbal remedies known to inhibit or induce CYP3A4 do not constitute a safety concern for human use.
In vitro drug interaction studies have shown that voclosporin is a competitive inhibitor of CYP3A4/5 without time-dependent or metabolism-dependent inhibition.	Multiple administrations of voclosporin orally (0.4 mg/kg BID) had no clinically relevant effect on the pharmacokinetics (PK) if the sensitive CYP3A4 substrate midazolam. There is no safety concern for human use.
In vitro studies have suggested that voclosporin may be a potential P-glycoprotein (P-gp) inhibitor at high concentrations (4 µM) and a potential substrate.	Section 4.5 of the SmPC provides sufficient information regarding co-administration of voclosporin with sensitive P-gp substrates such that these interactions do not constitute a safety concern for human use.
Voclosporin interacted with human transporters organic-anion-transporting polypeptide (OATP)1B1, breast cancer resistance protein (BCRP) and OATP1B3. The results of the in vitro transporter studies suggest that voclosporin may cause pharmacokinetic (PK) drug-drug interactions when co-administered with other drugs that are substrates of the OATP1B1 and OATP1B3 transporters.	In study AUR-VCS-2021-02 (Statin DDI), following administration of simvastatin 40 mg with voclosporin 23.7 mg BID, simvastatin C_{max} was increased 1.60-fold, while $AUC_{0\text{-}inf}$ was comparable (treatment ratio of 0.94) with administration of simvastatin alone. Exposure to the metabolite simvastatin acid was increased in the presence of voclosporin by 3.10-fold for C_{max} and 1.84-fold for $AUC_{0\text{-}inf}$. Based on these results, voclosporin is considered an inhibitor of OATP1B1. Section 4.5 of the SmPC provides sufficient information regarding the need to monitor for adverse events when OATP1B1 and OATP1B3 substrates are used concomitantly with voclosporin and when voclosporin is used with BCRP
Although voclosporin was shown to interact with the BCRP transporter in the BCRP-mediated vesicular transport inhibition assay, the calculated 50% inhibitory concentration (IC_{50}) value was greater than 10 µM, the highest concentration investigated.	

Key safety findings from non-clinical studies	Relevance to human usage
	substrates. Accordingly, these interactions do not constitute a safety concern.

Table 6. Safety concerns from non-clinical studies with voclosporin

Important identified risks	None
Important potential risks	▪ Malignancies (including lymphomas) associated with long term use ▪ Nephrotoxicity
Missing information	▪ Use in pregnancy

Part II: Module SIII - Clinical trial exposure

The clinical development program of voclosporin includes studies in four indications: LN, plaque psoriasis, non-infectious uveitis, and renal transplant.

The LN clinical program was designed to investigate the efficacy and safety of voclosporin when added to standard of care therapy with MMF (2 mg/day) and initial intravenous methylprednisolone pulse followed by oral prednisone at a daily dose of up to 25 mg which was then tapered to 2.5 mg over a period of 16 weeks. When clinically indicated, patients could be completely titrated off oral corticosteroids. The entire clinical development program of voclosporin for all indications is described in Table 7.

The exposure for the indication of LN in Studies AURA-LV and AURORA 1 (Safety population) is described in Table 8, Table 9, Table 10, and Table 11. This represents pooled LN data for 12 months of 267 subjects in the voclosporin group and 266 subjects in the placebo group.

AURORA 2 was a 2 year continuation study of AURORA 1 to assess the long-term safety and efficacy of 116 subjects in the voclosporin group and 100 subjects in the placebo group. Table 12, Table 13, Table 14, and Table 15 present exposure data for AURORA 1 and AURORA 2 from Month 0 to Month 36. All studies are completed. Safety data is reported separately for AURORA 2 for the period Month 12 to 36.

Table 7. Overview of the Clinical Development Program

Indication	Clinical development program	Number of patients		
		Placebo	Voclosporin	Total
LN	The LN clinical program comprises four studies: ▪ Two double-blind, placebo-controlled studies were conducted in 36 countries across the Americas (including the US), Asia, Europe and South Africa: o AUR-VCS-2016-01 (AURORA 1) o AUR-VCS-2012-01 (AURA-LV). ▪ A double-blind, placebo-controlled continuation study, AUR-VCS-2016-02 (AURORA 2), enrolled eligible patients who completed AURORA 1 and provides long-term safety and efficacy data in LN. ▪ A small open-label exploratory study, AUR-VCS-2014-01 (AURION), was conducted at two sites in Malaysia and provides supportive efficacy and safety data.	266	365	631
Plaque psoriasis*	Three Phase 3 studies (including one extension study)	392	1,485	1,674
Non-infectious uveitis	Four Phase 2/3 studies			
Renal transplant	One Phase 2b study	0	248	248

Indication	Clinical development program	Number of patients		
		Placebo	Voclosporin	Total
Other*	16 Phase 1 studies in healthy volunteers, subjects with hepatic or renal impairment, and patients with SLE.	148	568	688
Total unique subjects*		**806**	**2,666**	**3,241**
*Some placebo patients crossed over to active voclosporin treatment, therefore counts of placebo + voclosporin will not be additive				

Table 8. Duration of Exposure in Studies AURA-LV and AURORA 1 (Safety population [N=533])

Duration of Exposure	Statistic	Placebo (N=266)	Voclosporin 23.7 mg BID (N=267)
≥1 day	Subjects (n)	266	267
	Subject-Years exposure	215.6	219.7
≥1 Month	Subjects (n)	257	251
	Subject-Years exposure	215.4	218.9
≥3 Months	Subjects (n)	243	244
	Subject-Years exposure	212.6	217.8
≥6 Months	Subjects (n)	213	213
	Subject-Years exposure	200.4	205.9
≥12 Months	Subjects (n)	88	96
	Subject-Years exposure	89.3	97.5
Total	Subjects (n)	266	267
	Subject-Years exposure	215.6	219.7
Exposure calculated as the sum of all prescription record durations up to the last non-zero prescribing record. Subject-Years exposure = total exposure for all subjects achieving given duration. Source: Table T30EX.1.1.10.8.1			

Table 9. Exposure by Age Group and Gender in Studies AURA-LV and AURORA 1 (Safety population [N=533])

Age group	Statistic	Placebo (N=266)		Voclosporin 23.7 mg BID (N=267)	
		Male	Female	Male	Female
18 to 64	Subjects (n)	40	223	29	236
	Subject-Years exposure	32.3	180.8	22.9	194.9
≥65	Subjects (n)	1	2	2	0
	Subject-Years exposure	1.0	1.5	1.9	0
Total	Subjects (n)	41	225	31	236
	Subject-Years exposure	33.3	182.3	24.8	194.9
≤30	Subjects (n)	20	100	13	128
	Subject-Years exposure	14.8	78.2	11.1	104.6
>30	Subjects (n)	21	125	18	108
	Subject-Years exposure	18.5	104.1	13.7	90.4
Total	Subjects (n)	41	225	31	236
	Subject-Years exposure	33.3	182.3	24.8	194.9
Exposure calculated as the sum of all prescription record durations up to the last non-zero prescribing record. Source: Table T30EX.1.1.10.8.2.1 and Table T30EX.1.1.10.8.2.2					

Table 10. Exposure by Dose in Studies AURA-LV and AURORA 1 (Safety population [N=533])

Mean daily dose	Statistic	Placebo (N=266)	Voclosporin 23.7 mg BID (N=267)
≤15.8 mg	Subjects (n)	0	7
	Subject-Years exposure	0	5.6
>15.8 and ≤31.6 mg	Subjects (n)	9	41
	Subject-Years exposure	8.8	34.1
>31.6 and ≤47.4 mg	Subjects (n)	215	219
	Subject-Years exposure	174.1	180.0
>47.4 mg*	Subjects (n)	42	0
	Subject-Years exposure	32.7	0
Total	Subjects (n)	266	267
	Subject-Years exposure	215.6	219.7

Exposure calculated as the sum of all prescription record durations up to the last non-zero prescribing record.
* Only placebo subjects in the AURA-LV study who were matched to the high-dose voclosporin group were prescribed >47.4 mg per day.
Source: Table T30EX.1.1.10.8.3

Table 11. Exposure by Race and Ethnic Origin in Studies AURA-LV and AURORA 1 (Safety population [N=533])

Race	Statistic	Placebo (N=266)	Voclosporin 23.7 mg BID (N=267)
White	Subjects (n)	103	98
	Subject-Years exposure	82.6	83.1
Asian: Indian Subcontinent	Subjects (n)	18	22
	Subject-Years exposure	15.5	14.6
Asian: Other	Subjects (n)	74	83
	Subject-Years exposure	62.3	65.5
Black (including mixed black)	Subjects (n)	24	29
	Subject-Years exposure	15.6	23.5
Other (including mixed race)	Subjects (n)	47	35
	Subject-Years exposure	39.7	32.9
Total	Subjects (n)	266	267
	Subject-Years exposure	215.6	219.7
Ethnicity			
Hispanic or Latino	Subjects (n)	72	65
	Subject-Years exposure	59.5	57.3
Not Hispanic or Latino	Subjects (n)	193	202
	Subject-Years exposure	155.1	162.4
Unknown	Subjects (n)	1	0
	Subject-Years exposure	1.0	0
Total	Subjects (n)	266	267
	Subject-Years exposure	215.6	219.7

Exposure calculated as the sum of all prescription record durations up to the last non-zero prescribing record.
Source: Table T30EX.1.1.10.8.4 and Table T30EX.1.1.10.8.5

Table 12. Duration of Exposure in Studies AURORA 1 and AURORA 2 (AURORA 2 Safety population [N=216])

Duration of Exposure	Statistic	Placebo (N=100)	Voclosporin 23.7 mg BID (N=116)
≥1 day	Subjects (n)	100	116
	Subject-Years exposure	271.0	318.6
≥1 Month	Subjects (n)	100	116
	Subject-Years exposure	271.0	318.6
≥3 Months	Subjects (n)	100	116
	Subject-Years exposure	271.0	318.6
≥6 Months	Subjects (n)	100	116
	Subject-Years exposure	271.0	318.6
≥12 Months	Subjects (n)	100	115
	Subject-Years exposure	271.0	317.6
≥18 Months	Subjects (n)	95	111
	Subject-Years exposure	264.9	313.0
≥24 Months	Subjects (n)	85	102
	Subject-Years exposure	247.4	297.3
≥30 Months	Subjects (n)	79	94
	Subject-Years exposure	233.9	279.4
≥36 Months	Subjects (n)	7	11
	Subject-Years exposure	21.1	33.3
Total	Subjects (n)	100	116
	Subject-Years exposure	271.0	318.6

Exposure calculated as the sum of all AURORA 1 and AURORA 2 prescription record durations up to the last non-zero prescribing record.
Subject-Years exposure = total exposure for all subjects achieving given duration.
Source: Table T30EX.0201.10.08.01.00 26 Jan 2022

164 subjects completed the study on treatment, 92 in the voclosporin group on treatment and 72 in the placebo group. It should be noted that subjects who attended the Month 36 visit not within the protocol defined window of ±10 days from Day 1095 were not included in the ≥36 months of exposure but were summarised as having ≥ 30 months of exposure.

Table 13. Exposure by Age Group and Gender in Studies AURORA 1 and AURORA 2 (AURORA 2 Safety population [N=216])

Age group	Statistic	Placebo (N=100)		Voclosporin 23.7 mg BID (N=116)	
		Male	Female	Male	Female
18 to 64	Subjects (n)	11	88	11	105
	Subject-Years exposure	31.5	237.5	29.4	289.2
≥65	Subjects (n)	1	0	0	0
	Subject-Years exposure	2.1	0	0	0
Total	Subjects (n)	12	88	11	105
	Subject-Years exposure	33.6	237.5	29.4	289.2
≤30	Subjects (n)	2	35	6	54
	Subject-Years exposure	4.7	94.4	15.5	147.8
>30	Subjects (n)	10	53	5	51
	Subject-Years exposure	28.9	143.1	13.9	141.4
Total	Subjects (n)	12	88	11	105
	Subject-Years exposure	33.6	237.5	29.4	289.2

Exposure calculated as the sum of all prescription record durations up to the last non-zero prescribing record
Source: Table T30EX 0201.10.08.02.01 and Table T30EX.0201.10.08.02.02 26 Jan 2022

Table 14. Exposure by Dose in Studies AURORA 1 and AURORA 2 (AURORA 2 Safety population [N=216])

Mean daily dose	Statistic	Placebo (N=100)	Voclosporin 23.7 mg BID (N=116)
≤15.8 mg	Subjects (n)	0	3
	Subject-Years exposure	0	9.0
>15.8 and ≤31.6 mg	Subjects (n)	5	19
	Subject-Years exposure	13.6	49.2
>31.6 and ≤47.4 mg	Subjects (n)	95	94
	Subject-Years exposure	257.4	260.4
Total	Subjects (n)	100	116
	Subject-Years exposure	271.0	318.6

Exposure calculated as the sum of all AURORA 1 and AURORA 2 prescription record durations up to the last non-zero prescribing record.
Source: Table T30EX. 0201.10.08.03.00 26 Jan 2022

Table 15. Exposure by Race and Ethnic Origin in Studies AURORA 1 and AURORA 2 (AURORA 2 Safety population [N=216])

Race	Statistic	Placebo (N=100)	Voclosporin 23.7 mg BID (N=116)
White	Subjects (n)	40	44
	Subject-Years exposure	110.7	120.8
Asian: Other	Subjects (n)	30	30
	Subject-Years exposure	79.7	87.9
Black (including mixed black)	Subjects (n)	7	18
	Subject-Years exposure	17.3	49.1
Other (including mixed race)	Subjects (n)	23	24
	Subject-Years exposure	63.3	60.8
Total	Subjects (n)	100	116
	Subject-Years exposure	271.0	318.6
Ethnicity			
Hispanic or Latino	Subjects (n)	33	39
	Subject-Years exposure	88.6	100.6
Not Hispanic or Latino	Subjects (n)	67	77
	Subject-Years exposure	182.5	218.0
Total	Subjects (n)	100	116
	Subject-Years exposure	271.0	318.6

Exposure calculated as the sum of all AURORA 1 and AURORA 2 prescription record durations up to the last non-zero prescribing record.
Source: Table T30EX.0201.10.08.04.00 and Table T30EX.0201.10.08.05.00 26 Jan 2022

Part II: Module SIV - Populations not studied in clinical trials

SIV.1 Exclusion criteria in pivotal clinical studies within the development programme

Criterion	Reason for exclusion	Is it considered to be included as missing information?	Rationale
eGFR as calculated by the Chronic Kidney Disease Epidemiology Collaboration equation of ≤45 mL/min/1.73 m^2 at screening (Visit 1) (AURA-LV and AURORA 1).	To avoid confounding evaluation of efficacy and safety outcomes as voclosporin can reduce renal function.	No	'The risk of nephrotoxicity (acute and chronic)' is considered an important potential risk.
Serum potassium >5.5 mmol/L at screening, confirmed before randomization (AURA-LV).	To avoid confounding evaluation of efficacy and safety outcomes voclosporin.	No	Use of voclosporin in this condition is very unlikely, because treatment can be postponed until the patient is medically controlled and stabilised.
Was currently requiring renal dialysis (haemodialysis or peritoneal dialysis) or was expected to require dialysis during the study period (AURA-LV and AURORA 1).	To avoid confounding evaluation of efficacy and safety outcomes.	No	Such patients are unlikely to be treated in the post marketing setting.
A previous kidney transplant or planned transplant within study treatment period (AURA-LV and AURORA 1).	To avoid confounding evaluation of efficacy and safety outcomes.	No	Such patients are unlikely to be treated in the post marketing setting.
Any known hypersensitivity or contraindication to MMF, MPA, CsA, corticosteroids or any components of these drug products (AURA-LV and AURORA 1).	A safety concern.	No	Voclosporin is contraindicated in patients with hypersensitivity to any component of the product. Thus, use in this population in the post-marketing period is not anticipated.
Had current or medical history of pancreatitis or gastrointestinal haemorrhage within 6 months prior to screening (AURA-LV).	To avoid confounding evaluation of safety and efficacy due to study treatment and reduce occurrence of complications of other treatments.	No	Use of voclosporin in this condition is very unlikely, because treatment can be postponed until the patient is medically controlled and stabilised.
Had current or medical history of active unhealed peptic ulcer within 3 months prior to screening. If an ulcer had healed and the subject was on adequate therapy, the subject could be randomised (AURA-LV).	To avoid confounding evaluation of safety and efficacy due to study treatment and reduce occurrence of complications of other treatments.	No	Use of voclosporin in this condition is very unlikely, because treatment can be postponed until the patient is medically controlled and stabilised.

Criterion	Reason for exclusion	Is it considered to be included as missing information?	Rationale
Had current or medical history of congenital or acquired immunodeficiency (AURA-LV and AURORA 1).	These patients will have increased risk of significant and serious infections. To avoid confounding evaluation of safety and efficacy due to study treatment and reduce occurrence of complications of other treatments.	No	The risk would be recognised by clinicians and studies in this patient population would not be justified. Therefore, it is not considered missing information.
In the opinion of the Investigator, clinically significant drug, or alcohol abuse 2 years prior to screening (AURA-LV and AURORA 1).	Patients would be at increased risk of infection or liver damage. To avoid confounding evaluation of efficacy and safety outcomes.	No	The known safety profile is not expected to be affected by drug and alcohol abuse.
Had current or medical history of malignancy within 5 years of screening, with the exception of basal and squamous cell carcinomas treated by complete excision. Patients with cervical dysplasia that was cervical intraepithelial neoplasia 1 but had been treated with conization or loop electrosurgical excision procedure and had a normal repeat Pap smear were allowed (AURA-LV).	To avoid confounding evaluation of safety outcomes.	No	The risk of 'Malignancies (including lymphomas) associated with long term use' is considered an important potential risk.
Had current or medical history of lymphoproliferative disease or previous total lymphoid irradiation (AURA-LV and AURORA 1).	To avoid confounding evaluation of safety outcomes.	No	The risk of 'Malignancies (including lymphomas) associated with long term use' is considered an important potential risk.
Had current or medical history of severe viral infection (such as cytomegalovirus, hepatitis B virus, hepatitis C virus) within 3 months of screening; or known HIV infection. (Note: severe viral infection was defined as active disease requiring antiviral therapy) (AURA-LV and AURORA 1)	To avoid confounding evaluation of safety outcomes.	No	The risk of 'Serious infections including opportunistic infections' is considered an important identified risk.
Had current or medical history of active tuberculosis or known history of tuberculosis/evidence of old tuberculosis if not taking prophylaxis with isoniazid (AURA-LV and AURORA 1).	To avoid confounding evaluation of safety outcomes.	No	The safety profile in patients with active tuberculosis or known history of tuberculosis is not expected to differ from the known safety profile.

Criterion	Reason for exclusion	Is it considered to be included as missing information?	Rationale
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. Corrected QT interval using Friderica's formula (QTcF) exceeding 480 msec in the presence of a normal QRS interval (<110 msec) at time of screening resulted in exclusion (AURA-LV and AURORA 1).	To avoid confounding evaluation of safety outcomes and reduce occurrence of complications of other treatments.	No	There is no evidence of significant ECG safety concerns. Major Adverse Cardiovascular Events (MACEs) is considered to be an important potential risk. Studies in patients with severe cardiovascular disease would not be justified.
Other known clinically significant active medical conditions, such as liver dysfunction (aspartate aminotransferase, alanine aminotransferase, or bilirubin greater than 2.5 times the upper limit of normal) at screening and confirmed before randomization (AURA-LV and AURORA 1).	To avoid confounding evaluation of safety outcomes and reduce occurrence of complications of other treatments.	No	The SmPC Section 4.2 advises that in patients with mild and moderate hepatic impairment (Child-Pugh Class A and B, respectively), the recommended starting dose is 15.8 mg BID. The effect of voclosporin in patients with severe hepatic impairment (Child Pugh Class C) has not been assessed and voclosporin is not recommended in this patient population. Studies in patients with severe hepatic impairment would not be justified.
Other known clinically significant active medical conditions, such as chronic obstructive pulmonary disease or asthma requiring oral steroids (AURA-LV and AURORA 1).	To avoid confounding evaluation of safety outcomes and reduce occurrence of complications of other treatments.	No	The safety profile in patients with chronic obstructive pulmonary disease or asthma requiring oral steroids is not expected to differ from the known safety profile.
Other known clinically significant active medical conditions, such as bone marrow insufficiency unrelated to active SLE (according to Investigator judgment) with white blood cell count <2,500/mm^3; absolute neutrophil count <1.3 × 10^3/μL; thrombocytopenia (platelet count <50,000/mm^3) (AURA-LV and AURORA 1).	To avoid confounding evaluation of safety outcomes and reduce occurrence of complications of other treatments.	No	Use of voclosporin in this condition is very unlikely, because treatment can be postponed until the patient is medically controlled and stabilised.
Other known clinically significant active medical conditions, such as active bleeding disorders (AURA-LV and AURORA 1).	To avoid confounding evaluation of safety outcomes and reduce occurrence of complications of other treatments.	No	The safety profile in patients with active bleeding disorders is not expected to differ from the known safety profile.

Criterion	Reason for exclusion	Is it considered to be included as missing information?	Rationale
Had current infection requiring IV antibiotics (AURA-LV and AURORA 1).	To avoid confounding evaluation of safety outcomes and reduce occurrence of complications of other treatments.	No	Use of voclosporin in this condition is very unlikely, because treatment can be postponed until the patient is medically controlled and stabilised.
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., Sjogren's syndrome) were not excluded (AURA-LV and AURORA 1).	To avoid confounding evaluation of efficacy and safety outcomes and reduce occurrence of complications of other treatments.	No	The safety profile in patients with overlapping autoimmune condition is not expected to differ from the known safety profile.
Other major physical or psychiatric illness or major traumatic injury within 6 months prior to screening (AURA-LV and AURORA 1).	To avoid confounding evaluation of efficacy and safety outcomes and reduce occurrence of complications of other treatments.	No	The safety profile in patients with major physical or psychiatric illness or major traumatic injury is not expected to differ from the known safety profile.
Patients who were pregnant, breast feeding or, if of childbearing potential, not using adequate contraceptive precautions. Patients had to agree to use adequate contraception (as defined in the protocol) during the study and for 1 month after the last dose of the study medication. • Two reliable forms of contraception were required to be used simultaneously unless abstinence was the chosen method. Effective contraception had to be used before beginning study medication, during study dosing, and 1 month following discontinuation of study dosing, even when there had been a history of infertility, unless due to hysterectomy (AURA-LV and AURORA 1).	Standard practice for clinical studies	Use in pregnancy is considered to be Missing Information	Not applicable

Criterion	Reason for exclusion	Is it considered to be included as missing information?	Rationale
No vaccines using live organisms, virus or bacterial, were allowed during screening and while taking the study treatment (AURORA 1).	Immunosuppressants may affect the response to vaccination and vaccination during treatment with voclosporin may be less effective.	No	The SmPC (Section 4.4) states that the use of live attenuated vaccines should be avoided.

SIV.2 Limitations to detect adverse reactions in clinical trial development programmes

From the clinical development programme adverse drug reactions with a frequency greater than 1 in 889 would be detected if there were no background incidence.

A total of 92 (79.3%) subjects have completed the 36 months study on treatment with voclosporin. There were no new-onset adverse events (AEs) that could be correlated with prolonged exposure or long-latency.

PK analysis showed that there was no significant accumulation of voclosporin with repeated dosing.

SIV.3 Limitations in respect to populations typically under-represented in clinical trial development programmes

Exposure of special populations included or not in clinical trial development programmes

Type of special population	Exposure
Pregnant women	There have been 19 reports of pregnancy in the whole clinical development program (including all studies in other indications): • 9 in a female partner of a male patient exposed to voclosporin • 10 in female patients exposed to voclosporin Outcomes were 7 live births, 2 spontaneous abortions, 5 induced abortions and 5 unknown (lost to follow-up).
Breastfeeding women	Not included in the clinical development program.
Patients with relevant comorbidities:	
Patients with hepatic impairment	Patients with hepatic impairment (defined as aspartate aminotransferase, alanine aminotransferase, or bilirubin ≥2.5 times the upper limit of normal) were not included in the clinical development program. Study ISA07-09 included 6 subjects with mild hepatic impairment (Child-Pugh A), and 6 subjects with moderate hepatic impairment (Child-Pugh B).
Patients with severe renal impairment (Kidney disease improving global outcomes (KDIGO) chronic kidney disease grades 4 & 5)	Not included in the clinical development program.

<table>
<tr><th>Type of special population</th><th>Exposure</th></tr>
<tr><td>Patients with cardiovascular impairment</td><td>
Medical History in Study AURA-LV
Conditions Reported for >10% of patients by system organ class (SOC) and preferred term (PT)
<table>
<tr><th>SOC
PT</th><th>Placebo
(N=88)
n (%)</th><th>Voclosporin 23.7 mg
(N=89)
n (%)</th><th>Voclosporin 39.5 mg
(N=89)
n (%)</th></tr>
<tr><td>Vascular Disorders</td><td>61 (69.3)</td><td>58 (65.2)</td><td>65 (73.9)</td></tr>
<tr><td>Hypertension</td><td>55 (62.5)</td><td>51 (57.3)</td><td>60 (68.2)</td></tr>
<tr><td>Metabolism and Nutrition Disorders</td><td>46 (52.3)</td><td>29 (32.6)</td><td>47 (53.4)</td></tr>
<tr><td>Hyperlipidaemia</td><td>29 (33.0)</td><td>17 (19.1)</td><td>25 (28.4)</td></tr>
<tr><td>Dyslipidaemia</td><td>6 (6.8)</td><td>9 (10.1)</td><td>8 (9.1)</td></tr>
<tr><td>Cardiac Disorders</td><td>19 (21.6)</td><td>18 (20.2)</td><td>15 (17.0)</td></tr>
<tr><td colspan="4">Source: AURA-LV CSR Table 20</td></tr>
</table>
Medical History in Study AURORA 1
Conditions Reported for >10% of patients by SOC and PT
<table>
<tr><th>SOC
PT</th><th>Placebo
(N = 178)
n (%)</th><th>Voclosporin 23.7 mg
(N = 179)
n (%)</th></tr>
<tr><td>Vascular disorders</td><td>130 (73.0)</td><td>138 (77.1)</td></tr>
<tr><td>Hypertension</td><td>118 (66.3)</td><td>124 (69.3)</td></tr>
<tr><td>Raynaud's phenomenon</td><td>9 (5.1)</td><td>18 (10.1)</td></tr>
<tr><td>Metabolism and nutrition disorders</td><td>105 (59.0)</td><td>101 (56.4)</td></tr>
<tr><td>Hyperlipidaemia</td><td>52 (29.2)</td><td>51 (28.5)</td></tr>
<tr><td>Dyslipidaemia</td><td>29 (16.3)</td><td>25 (14.0)</td></tr>
<tr><td>Cardiac disorders</td><td>29 (16.3)</td><td>31 (17.3)</td></tr>
<tr><td colspan="3">Source: AURORA 1 CSR Table 18</td></tr>
</table>
</td></tr>
<tr><td>Patients with a disease severity different from inclusion criteria in clinical trials</td><td>Not included in the clinical development program.</td></tr>
<tr><td>Population with relevant different ethnic origin</td><td>
Exposure by Race and Ethnic Origin in Studies AURA-LV and AURORA 1 (Safety population [N=533])
<table>
<tr><th>Race</th><th>Placebo
(N = 266)
n (%)</th><th>Voclosporin 23.7 mg BID
(N=267)
n (%)</th></tr>
<tr><td>White</td><td>103 (38.7)</td><td>98 (36.7)</td></tr>
<tr><td>Asian: Indian Subcontinent</td><td>18 (6.7)</td><td>22 (8.2)</td></tr>
<tr><td>Asian: Other</td><td>74 (27.8)</td><td>83 (31.1)</td></tr>
<tr><td>Black (including mixed black)</td><td>24 (9.0)</td><td>29 (10.9)</td></tr>
<tr><td>Other (including mixed race)</td><td>47 (17.7)</td><td>35 (13.1)</td></tr>
<tr><td>Ethnicity</td><td></td><td></td></tr>
<tr><td>Hispanic or Latino</td><td>72 (27.1)</td><td>65 (24.3)</td></tr>
<tr><td>Not Hispanic or Latino</td><td>193 (72.6)</td><td>202 (75.7)</td></tr>
<tr><td>Unknown</td><td>1 (0.4)</td><td>0</td></tr>
<tr><td colspan="3">Source: Table T30EX.1.1.10.8.4 and Table T30EX.1.1.10.8.5</td></tr>
</table>
</td></tr>
<tr><td>Subpopulations carrying relevant genetic polymorphisms</td><td>Not applicable</td></tr>
</table>

Part II: Module SV - Post-authorisation experience

Voclosporin (Lupkynis™) was approved in the US on 22 January 2021. As of 22 January 2022, an estimated CCI patients in the US have been prescribed voclosporin as part of their medical care (based on the number of patients who have had a prescription dispensed). Preliminary reports from postmarketing use of voclosporin 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.

Part II: Module SVI – Additional EU requirements for the safety specification

Potential for misuse for illegal purposes

There are no properties of voclosporin that would make it attractive for misuse for illegal purposes.

Part II: Module SVII - Identified and potential risks

SVII.1 Identification of safety concerns in the initial RMP submission

SVII.1.1. Risks not considered important for inclusion in the list of safety concerns in the RMP

Risk	Reason for not considered an important risk
CNI class effect	Voclosporin is structurally similar to CsA except for the modification of a functional group on amino acid-1 of the molecule. Voclosporin exhibits some similar CNI class effects but is differentiated as a result of its higher potency and lower dose administration. Anaemia, and gingival hyperplasia are CNI class effects which occurred at a higher incidence in the voclosporin arm than the placebo arm. These treatment-emergent adverse events (TEAEs) had minimal clinical impact in relation to the severity of the indication, and a review of the seriousness, severity, treatment required, causality, plausibility and outcome did not support including these terms as important risks at this time. Diabetes and hyperglycaemia were not considered risks for voclosporin. Examination of TEAEs related to impaired glucose metabolism and diabetes indicates that there is no greater incidence of these types of events with voclosporin compared with placebo. TEAEs of diabetes (including exacerbation of pre-existing diabetes) were rare and occurred in both groups (2 events in placebo and 1 event in voclosporin, which was serious but considered unrelated to treatment). Hyperglycaemia was reported more often in the placebo group than the voclosporin group (1.5% vs 0.7% in the pooled LN population whilst in AURORA 2, it was reported in 0% in placebo v 0.9% in the voclosporin group. Diabetes and hyperglycaemia events are not considered an important risk for voclosporin. Clinical data do not show a signal for an increased risk of arrhythmias in patients with LN at a voclosporin dose level of 23.7 mg BID. After long term treatment with voclosporin in AURORA 2, the incidence of arrhythmias was lower in the voclosporin group compared with the placebo group. Section 5.1 of the SmPC provides information on two thorough QT studies. In addition, Section 4.4 of the SmPC provides information allowing the prescriber to identify circumstances which may increase the risk of QT prolongation. QT prolongation and arrhythmia are not considered to be important risks for voclosporin.
Hypersensitivity	Contraindication. The incidence of hypersensitivity was similar between voclosporin and placebo treated subjects in the pooled LN population (21.0% vs 16.5%). The most common hypersensitivity events (as defined by the hypersensitivity standardised medical dictionary for regulatory activities query [SMQ]) were mouth ulceration (4.1% in voclosporin vs 1.1% in placebo), rash (3.0% vs 1.9%), erythema (1.9% vs 0.8%) and pruritis (1.5% vs 1.1%). More than 75% of the events were mild and none were severe. Very few events were considered related to study treatment (7 events in voclosporin vs 3 events in placebo) none of which were considered serious. One serious event of hypersensitivity occurred in each treatment arm (both were generalised oedema). In AURORA 2, the incidence of hypersensitivity was 16.4% in the voclosporin group compared to 6.0% in the placebo group). The most common hypersensitivity events (as defined by the hypersensitivity SMQ) were dermatitis (3.4% in voclosporin vs 0% in placebo) and rash (2.6% vs 2.0%). There were no severe events in either arm. Only one event was considered related to study treatment. This was an event of conjunctivitis in the voclosporin group. There were no serious events of hypersensitivity in either treatment arm. In relation to the severity of the indication treated, hypersensitivity is not considered an important risk as this time.

SVII.1.2. Risks considered important for inclusion in the list of safety concerns in the RMP

Important Identified Risks	
Serious Infections including opportunistic infections	
Scientific evidence for risk to be added in the safety specification	**Clinical trials**: The incidence of serious infections including opportunistic infections was marginally higher in the voclosporin group compared to the placebo group in the pooled LN population, In AURORA 2, the incidence was lower and comparable, between the two treatment arms indicating that the frequency of serious infection including opportunistic infections was higher in the first 12 months of treatment. **Class effect**: Like other immunosuppressants, CNIs predispose patients to the development of a variety of bacterial, fungal, parasitic, and viral infections, often with opportunistic pathogens.
Risk-benefit impact	Serious infections including opportunistic infections can have a significant impact on the patient. Section 4.4 of the SmPC states that immunosuppressants, including voclosporin, may increase the risk of developing bacterial, viral, fungal, and protozoal infections, including opportunistic infections which may be serious or fatal and that patients must be monitored closely for infections during treatment with voclosporin. If an infection occurs, the benefit of continuing voclosporin should be assessed in consideration of the risk of continued administration.
Important Potential Risks	
Major Adverse Cardiovascular Events (MACEs) (see Annex 7 for MedDRA terms)	
Scientific evidence for risk to be added in the safety specification	**Clinical trials**: In the pooled LN population, the number of subjects with MACE TEAEs or treatment-emergent fatal cardiovascular events was low across both treatment groups: 5 subjects in the placebo group had a TEAE meeting the MACE criteria compared with 4 subjects in the voclosporin group. An analysis of exposure adjusted incidence rates (EAIRs) of TEAEs did not show any statistically significant differences between treatment groups and the overall EAIR was higher in the placebo group compared with the voclosporin group. In AURORA 2 there were no MACE TEAEs in the voclosporin group and one MACE TEAE of pulmonary embolism in the placebo group. Hypertension is a risk factor for MACEs. In the pooled LN population, hypertension, including treatment related hypertension, occurred more frequently in the voclosporin group compared to placebo. In AURORA 2, the frequency was lower and comparable between the two groups indicating that the frequency of hypertension was higher in the first 12 months of treatment. The majority of events in the voclosporin and placebo groups in the pooled LN and AURORA 2 populations were mild or moderate. **Class effect**: As a class, CNIs induce hypertension which is a risk factor for MACEs.
Risk-benefit impact	MACEs can be serious and fatal if not treated. Routine pharmacovigilance activities will further monitor the risk of MACE with respect to number of reports, seriousness, outcome, and risk factors, including patient history. Advice on how to minimise the risk of hypertension, a risk factor for MACE, disseminated through routine risk minimisation measures and the appropriate labelling will provide information to ensure that the benefit-risk for the product remains positive.
Neurotoxicity (Nervous System Disorders SOC)	
Scientific evidence for risk to be added in the safety specification	**Clinical trials**: In the pooled LN population, TEAEs in the Nervous System Disorders SOC occurred at a higher rate in the voclosporin group than in the placebo group. However, the Nervous System Disorders SOC contains some terms which are not indicative of neurotoxicity. Six preferred terms occurred with an incidence in the voclosporin group ≥ 1% higher than placebo (headache, tremor, post-herpetic neuralgia, paraesthesia, hypoaesthesia and seizure); the remaining events occurred either at a lower incidence in voclosporin compared with placebo or occurred in only 1 or 2 subjects in any treatment group. In AURORA 2, Nervous System Disorder TEAEs occurred more frequently in the voclosporin treated patients compared to the placebo group. Three

	preferred terms occurred with an incidence in the voclosporin group ≥ 1% higher than placebo (headache, hypoaesthesia and dizziness) **Class effect**: CNIs have been associated with hypertensive encephalopathy and PRES (Farouk et al, 2020).
Risk-benefit impact	Neurotoxicity including PRES can be serious and fatal if not treated. Most cases of PRES resolve over days to weeks without complications, however, death and permanent neurologic disability can occur from cerebral oedema either from intracranial haemorrhage or the disease itself (Farouk et al, 2020). Routine pharmacovigilance activities will further monitor the risk of neurotoxicity with respect to number of reports, seriousness, outcome, and risk factors, including patient history. Advice on how to minimise the risk of neurotoxicity is disseminated through routine risk minimisation measures and the appropriate labelling will provide information to ensure that the benefit-risk for the product remains positive.
Nephrotoxicity (acute [Acute renal failure SMQ] and chronic [Chronic kidney disease SMQ])	
Scientific evidence for risk to be added in the safety specification	**Non-clinical:** In a single dose renal safety pharmacology study with voclosporin in rats, there was a marginal effect on renal function (i.e., a 25% decrease in urine volume at the highest dose tested, 25 mg/kg). In repeat-dose toxicity studies in rats, renal effects included increases in blood urea nitrogen and creatinine, tubular basophilia and degeneration/regeneration, and corticomedullary mineralization. It is unclear whether all of the renal findings are directly treatment-related or whether exposure to voclosporin or CsA exacerbated normal biological processes since the observed renal changes can arise spontaneously in male rats, especially as they age. In dogs, no renal effects were noted. **Clinical trials**: There has been no indication of true voclosporin-related events suggestive of nephrotoxicity in the clinical development program with treatment up to three years. LN causes a loss of renal function which is manifest by a decreasing eGFR and an increase in urine protein/creatinine ration (UPCR). In addition, voclosporin has a haemodynamic effect leading to a small decrease in eGFR which is reversible on stopping treatment. Data from the long-term AURORA 2 trial supports the lack of nephrotoxicity of voclosporin over a 3-year period. An assessment of eGFR levels over time from the start of AURORA 2 shows that mean eGFR levels were generally stable from Month 12 to Month 27 after which point the mean eGFR levels in the voclosporin group increased while those in the placebo group decreased, potentially reflecting a worsening of renal function relating to disease progression in some placebo subjects. **Class effect**: Renal toxicity, associated with CNIs, is reported most frequently in kidney transplant recipients (Issa et al, 2013; Naesens et al, 2009). While chronic nephrotoxicity has been observed at levels of CNI suppression needed in organ transplantation, the level of suppression at the voclosporin dose proposed for LN (23.7 mg BID) is lower than that generally required in transplantation. At a dose of voclosporin of 23.7 mg BID, calcineurin inhibition has been determined to be 15.7% at the pre-dose trough concentration (C_{trough}) and 58.1% at C_{max}. In contrast, the trough concentration of CNI suppression in patients treated with CsA undergoing renal transplant has been reported to be 68% (Halloran et al, 1999).
Risk-benefit impact	Based upon the clinical trial data of voclosporin treatment for up to 3 years, there is no indication of an association between voclosporin and acute or chronic nephrotoxicity. Reports are confounded by the indication and overall, there was an improvement in renal function in patients treated with voclosporin compared to placebo. Section 4.2 of the SmPC recommends establishing a baseline eGFR before starting treatment with voclosporin and assessing eGFR every two weeks for the first month, and every four weeks thereafter. Dose adjustments are required for those individuals whose eGFR is confirmed to be reduced (i.e., two consecutive assessments within 48 hours) and below 60 mL/min/1.73 m^2. Details of appropriate dose adjustments are provided in Section 4.2. If eGFR remains ≥60 mL/min/1.73 m^2 no dose modification is required.

	Section 4.4 of the SmPC explains that cases of acute and chronic renal toxicity have been reported in patients treated with other calcineurin-inhibitors. Adverse events of acute worsening of renal function or eGFR decreases have been seen in patients treated with voclosporin, which can be managed by dose modification. In the first four weeks of treatment with voclosporin, haemodynamic reductions in eGFR have been observed. Regular monitoring of eGFR levels is recommended. In addition, chronic nephrotoxicity has been observed at levels of CNI suppression needed in organ transplantation. The level of CNI suppression of voclosporin in LN is lower than that generally required in organ transplantation.
Malignancies (including lymphomas) associated with long term use (Malignancies SMQ)	
Scientific evidence for risk to be added in the safety specification	**Non-clinical:** Daily oral gavage of voclosporin for 60 to 89 weeks to mice was associated with higher incidences of malignant lymphoma in the high-dose males (30 mg/kg/day) when compared with the saline control, but not with the vehicle control, and in the high-dose females (30 mg/kg/day) when compared with the vehicle control, but not the saline control. **Clinical trials**: There has been no indication of malignancy events related to voclosporin in the clinical development program over the three -year period. **Class effect**: Like other immunosuppressants, CNIs increase the risk of developing lymphomas and other malignancies, particularly those of the skin.
Risk-benefit impact	Malignancies are serious conditions that can be life-threatening. However, there is insufficient evidence to confirm a causal association between voclosporin therapy and malignancies (including lymphoma). Section 4.4 of the SmPC provides a general statement that immunosuppressants increase the risk of developing lymphomas and other malignancies, particularly of the skin and patients should be advised to avoid or limit unprotected exposure to sunlight and ultraviolet (UV) light.
Missing Information	
Use in pregnancy	
Reason for missing information to be added in the safety specification	**Non-clinical:** Foetal toxicity (reduced foetal body weights and skeletal variations) was only observed at doses associated with maternal toxicity (based on swollen mammary glands, reduced body weights, clinical observations and food consumption effects). Voclosporin was not teratogenic. **Clinical trials**: Subjects who were pregnant were excluded from the clinical trials. However, there have been 19 reports of pregnancy in the whole clinical development program (including all studies in other indications): • 9 in a female partner of a male patient exposed to voclosporin • 10 in female patients exposed to voclosporin Outcomes were 7 live births, 2 spontaneous abortions, 5 induced abortions and 5 unknown (lost to follow-up). Use in pregnancy is considered as Missing Information due to the small amount of data on exposure in pregnancy.
Risk-benefit impact	Voclosporin is not teratogenic based on non-clinical data however, it was given with other medications that might induce embryofoetal toxicity. Available data on use of voclosporin in pregnant women are insufficient to determine whether there is a drug-associated embryofoetal toxicity. Section 4.6 of the SmPC states that there is no or limited amount of data (less than 300 pregnancy outcomes) from the use of voclosporin in pregnant women and animal studies have shown reproductive toxicity. Voclosporin is not recommended during pregnancy and in women of child-bearing potential not using contraception.

SVII.2 New safety concerns and reclassification with a submission of an updated RMP

Not applicable

SVII.3 Details of important identified risks, important potential risks, and missing information

SVII.3.1. Presentation of important identified risks and important potential risks

<table>
<tr><th colspan="2">Important identified risk: Serious Infections including opportunistic infections</th></tr>
<tr><td>Potential mechanism</td><td>Impairment of the immune system leading to infections that would not otherwise be seen in a healthy person (Fishman, 2017) based on immunosuppressive mode of action of class.</td></tr>
<tr><td>Evidence source and strength of evidence</td><td>Clinical trials: The incidence of serious infections including opportunistic infections was marginally higher in the voclosporin group compared to the placebo group in the pooled LN population, In AURORA 2, the incidence was lower and comparable, between the two treatment arms indicating that the frequency of serious infection including opportunistic infections was higher in the first 12 months of treatment.
Class effect: Like other immunosuppressants, CNIs predispose patients to the development of a variety of bacterial, fungal, parasitic, and viral infections, including opportunistic pathogens.</td></tr>
<tr><td>Characterisation of the risk: Frequency, relationship, and outcome</td><td><u>Studies AURA-LV and AURORA 1 (Safety population [N=533])</u>
Events of serious infections including opportunistic infections include all serious events in the Infections and Infestations SOC and a wide search criteria for opportunistic infections.
Events of serious infections including opportunistic infection occurred in 18.4% of the voclosporin treated patients compared to 15% in the placebo group (Table 16 and Table 17).
Of the 64 events that occurred in the voclosporin group:
21 were considered related to treatment
46 were resolved
26 led to dose modification
6 led to permanent discontinuation
Of the 49 events that occurred in the placebo group:
12 were considered related to treatment
39 were resolved.
19 led to dose modification
4 led to permanent discontinuation
Source: Tables T40AE.1.1.10.17.10.1; T40AE.1.1.10.17.10.4; T40AE.1.1.10.17.10.10; T40AE.1.1.10.17.10.11
Table 16. Serious Infections including Opportunistic Infections TEAEs and Relationship to Study Drug occurring in > 1 subject in either treatment arm in Studies AURA-LV and AURORA 1
<table>
<tr><th>PT</th><th colspan="3">Placebo (N=266)</th><th colspan="3">23.7 mg BID (N=267)</th></tr>
<tr><th></th><th>n (%) E</th><th>NR</th><th>Rel</th><th>n (%) E</th><th>NR</th><th>Rel</th></tr>
<tr><td>Any serious infection including opportunistic infection*</td><td>40 (15.0)
49</td><td>37</td><td>12</td><td>49 (18.4)
64</td><td>43</td><td>21</td></tr>
<tr><td>Herpes Zoster*</td><td>14 (5.3)
15</td><td>11</td><td>4</td><td>18 (6.7)
18</td><td>8</td><td>10</td></tr>
<tr><td>Pneumonia</td><td>10 (3.8)
11</td><td>9</td><td>2</td><td>11 (4.1)
13</td><td>11</td><td>2</td></tr>
<tr><td>Pulmonary tuberculosis*</td><td>0 (0.0) 0</td><td>0</td><td>0</td><td>4 (1.5) 4</td><td>3</td><td>1</td></tr>
<tr><td>Gastroenteritis</td><td>1 (0.4)
1</td><td>1</td><td>0</td><td>4 (1.5) 5</td><td>5</td><td>0</td></tr>
<tr><td>Herpes virus infection*</td><td>0 (0.0) 0</td><td>0</td><td>0</td><td>3 (1.1) 3</td><td>2</td><td>1</td></tr>
</table></td></tr>
</table>

Urinary tract infection	1 (0.4) 1	1	0	3 (1.1) 3	3	0
Bronchitis	3 (1.1) 3	2	1	0 (0.0) 0	0	0

*Denotes opportunistic infection
n: Subjects. E: Events. NR=Not Related events, Rel=Related events.
AE=Adverse Event TEAE=Treatment Emergent Adverse Event. 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.
Source: Table T40AE.1.1.10.17.10.1

In addition to the events in Table 16, there were:

- 5 events that occurred at a rate of one event per subject in both the voclosporin group and the placebo group
- 13 events that occurred at a rate of one event per subject in the voclosporin group only 13 events that occurred at a rate of one event per subject in the placebo group only.

Table 17. Serious Infections including Opportunistic Infections TEAEs and Outcome in > 1 subject in either treatment arm in Studies AURA-LV and AURORA 1

PT	Placebo (N=266)					23.7 mg BID (N=267)				
	n (%) E	Res	RSq	NR	F	n (%) E	Res	RSq	NR	F
Any serious infection including opportunistic infection*	40 (15.0) 49	39	4	3	3	49 (18.4) 64	46	6	10	2
Herpes Zoster*	14(5.3) 15	13	1	1	0	18 (6.7) 18	14	4	0	0
Pneumonia	10 (3.8) 11	7	1	1	2	11 (4.1) 13	11	0	1	1
Pulmonary tuberculosis*	0 (0) 0	0	0	0	0	4 (1.5) 4	1	0	3	0
Gastroenteritis	1 (0.4) 1	1	0	0	0	4 (1.5) 5	5	0	0	0
Urinary tract infection	1 (0.4) 1	1	0	0	0	3 (1.1) 3	2	0	1	0
Herpes virus infection*	0 (0) 0	0	0	0	0	3 (1.1)3	2	1	0	0
Bronchitis	3 (1.1)3	3	0	0	0	0 (0.0) 0	0	0	0	0

*Denotes opportunistic infection
n: Subjects. E: Events. Res=Resolved Events, RSq=Resolved with Sequelae events, NR=Not Resolved events, F=Fatal events. Not Resolved includes: Improved, Not Recovered/Not Resolved, Ongoing, Recovering/Resolving, Worsened, Unknown.
AE=Adverse Event, TEAE=Treatment Emergent Adverse Event. 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.
Source: Table T40AE.1.1.10.17.10.4

Treatment-related events of serious infections including opportunistic infections occurred in 6% of the voclosporin treated patients compared to 4.1% in the placebo group (Table 18).

Of the 21 treatment-related events that occurred in the voclosporin group:

- 12 were resolved
- 11 led to dose modification
- 2 led to permanent discontinuation

Of the 12 treatment-related events that occurred in the placebo group:

- 9 were resolved
- 5 led to dose modification
- 3 led to permanent discontinuation

Source: Tables 40AE.1.1.10.17.10.2; 40AE.1.1.10.17.10.3; 40AE.1.1.10.17.10.5

Table 18. Treatment-related Serious Infections including Opportunistic Infections TEAEs and Outcome in > 1 subject in either treatment arm in Studies AURA-LV and AURORA 1

PT	Placebo (N=266)					23.7 mg BID (N=267)				
	n (%) E	Res	RSq	NR	F	n (%) E	Res	RSq	NR	F
Any treatment related serious infection or opportunistic infection*	**11 (4.1) 12**	**9**	**3**	**0**	**0**	**16 (6.0) 21**	**12**	**4**	**5**	**0**
Herpes Zoster*	4(1.5) 4	3	1	0	0	10 (3.7) 10	7	3	0	0
Pneumonia	2 (0.8) 2	2	0	0	0	2 (0.7) 2	1	0	1	0

*Denotes opportunistic infection
n: Subjects. E: Events. Res=Resolved Events, RSq=Resolved with Sequelae events, NR=Not Resolved events, F=Fatal events. Not Resolved includes: Improved, Not Recovered/Not Resolved, Ongoing, Recovering/Resolving, Worsened, Unknown.
AE=Adverse Event, TEAE=Treatment Emergent Adverse Event. 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.
Source: Table T40AE.1.1.10.17.10.5

Study AURORA 2 (Safety population [N=216])

Events for serious infections including opportunistic infections include all serious events in the Infections and Infestations SOC and a wide search criteria for opportunistic infections.

Events of serious infections including opportunistic infection occurred in 12.1% of the voclosporin treated patients compared to 13% in the placebo group (Table 19 and Table 20).

Of the 15 events that occurred in the voclosporin group:

- 4 were considered related to treatment;
- 13 were resolved
- 7 led to dose modification
- 1 led to permanent study drug discontinuation.

Of the 19 events that occurred in the placebo group:

- 4 were considered related to treatment
- 13 were resolved
- 8 led to dose modification
- 4 led to permanent study drug discontinuation

Source: Tables: T40AE.0401.10.17.10.01; T40AE.0401.10.17.10.04; T40AE.0401.10.17.10.10; T40AE.0401.10.17.10.11.

Table 19. Serious Infections including Opportunistic Infections TEAEs and Relationship to Study Drug in > 1 subject in either treatment arm in AURORA 2

PT	Placebo (N=100)			23.7 mg BID (N=116)		
	n (%) E	NR	Rel	n (%) E	NR	Rel
Serious infections including opportunistic infection*	**13 (13.0) 19**	**15**	**4**	**14 (12.1) 15**	**11**	**4**
Herpes Zoster*	7 (7.0) 7	4	3	4 (3.4) 4	2	2
Corona Virus Infection	5 (5.0) 5	5	0	2 (1.7) 2	2	0
Urinary Tract Infection	0 (0.0) 0	0	0	2 (1.7) 2	2	0
Pneumonia Viral	2 (2.0) 2	2	0	0 (0.0) 0	0	0

*Denotes opportunistic infection
n: Subjects. E: Events. NR=Not Related events, Rel=Related events.
AE=Adverse Event TEAE=Treatment Emergent Adverse Event. 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.
Source: Table T40AE.0401.10.17.10.01

In addition to the events shown in Table 19, there were:

- One event that occurred equally at a rate of one event per subject in both the voclosporin group and the placebo group.
- One event occurred at a rate of 2 events in one subject in the voclosporin group and one event per subject in the placebo group
- 4 events that occurred at a rate of one event per subject in the voclosporin group only:
- 3 events that occurred at a rate of one event per subject in the placebo group only:

Table 20. Serious Infections including Opportunistic Infections TEAEs and Outcome in > 1 subject in either treatment arm in AURORA 2.

PT	Placebo (N=100)					23.7 mg BID (N=116)				
	n (%) E	Res	RSq	NR	F	n (%) E	Res	RSq	NR	F
Serious infections including opportunistic infection*	**13 (13.0) 19**	**13**	**1**	**3**	**2**	**14 (12.1)15**	**13**	**1**	**1**	**0**
Herpes Zoster*	7 (7.0) 7	7	0	0	0	4 (3.4) 4	4	0	0	0
Corona Virus Infection	5 (5.0) 5	3	0	0	2	2 (1.7) 2	1	1	0	0
Urinary Tract Infection	0 (0.0) 0	0	0	0	0	2 (1.7) 2	2	0	0	0
Pneumonia Viral	2 (2.0) 2	0	1	1	0	0 (0.0) 0	0	0	0	0

*Denotes opportunistic infection
n: Subjects. E: Events. Res=Resolved Events, RSq=Resolved with Sequelae events, NR=Not Resolved events, F=Fatal events. Not Resolved includes: Improved, Not Recovered/Not Resolved, Ongoing, Recovering/Resolving, Worsened, Unknown.
AE=Adverse Event, TEAE=Treatment Emergent Adverse Event. 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.
Source: Table T40AE.4.1.10.17.10.4

Treatment -related events

Treatment-related events of serious infections including opportunistic infections occurred in 3.4% of the voclosporin treated patients compared to 4.0% in the placebo group.

Of the 4 treatment-related events that occurred in the voclosporin group:

- 3 were resolved
- 2 led to dose modification
- 1 led to permanent study drug discontinuation

Of the 4 treatment-related events that occurred in the placebo group:

- 3 were resolved
- 2 led to dose modification
- 1 led to permanent study drug discontinuation

Herpes Zoster was the only treatment-related event occurring in more than one subject. There were 2 Herpes Zoster events in the voclosporin group, both of which resolved and 3 Herpes Zoster events in the placebo group, all of which resolved.

Source: Tables T40AE.0401.10.17.10.05; T40AE.0401.10.17.10.02; T40AE.0401.10.17.03

Characterisation of the risk: Seriousness and Outcome

Studies AURA-LV and AURORA 1 (Safety population [N=533])

In the following discussion, all serious infections are discussed which includes **serious** opportunistic infections only (Table 21). Previous presentations above have included **all** opportunistic infections.

The incidence of serious events was 10.1% and 10.2% in the voclosporin treated patients and placebo, respectively.

Of the 36 serious events in the voclosporin group, 28 resolved.

Of the 32 serious events in the placebo group, 24 resolved.

Table 21. Serious Infections including serious opportunistic infections TEAEs and Outcome in > 1 subject in either treatment arm in Studies AURA-LV and AURORA 1

PT	Placebo (N=266)					23.7 mg BID (N=267)				
	n (%) E	Res	RSq	NR	F	n (%) E	Res	RSq	NR	F
Serious infections including serious opportunistic infection	**27 (10.2) 32**	**24**	**3**	**2**	**3**	**27 (10.1) 36**	**28**	**2**	**4**	**2**
Pneumonia	10 (3.8) 11	7	1	1	2	11 (4.1) 13	11	0	1	1
Gastroenteritis	1 (0.4)1	1	0	0	0	4 (1.5) 5	5	0	0	0
Urinary Tract Infection	1 (0.4) 1	1	0	0	0	3 (1.1) 3	2	0	1	0
Bronchitis	3 (1.1)3	3	0	0	0	0 (0.0) 0	0	0	0	0

n: Subjects. E: Events. Res=Resolved Events, RSq=Resolved with Sequelae events, NR=Not Resolved events, F=Fatal events. Not Resolved includes: Improved, Not Recovered/Not Resolved, Ongoing, Recovering/Resolving, Worsened, Unknown.
AE=Adverse Event, TEAE=Treatment Emergent Adverse Event. 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.
Source: Table T40AE.1.1.10.17.10.6

Treatment-Related Serious Infections including serious opportunistic infections

The incidence of treatment-related serious events was 1.9% and 2.6% in the voclosporin treated patients and placebo, respectively.

Of the 7 events in the voclosporin group, 4 resolved.

Of the 7 events in the placebo group, 5 resolved.

There was only one event (pneumonia) that occurred in more than one subject. There were 2 events of pneumonia in the voclosporin group, one of which resolved and 2 events in the placebo group, both of which resolved.

Source: Table T40AE 1 1 10 17.10.7

Study AURORA 2 (Safety population [N=216])

The incidence of serious events was 6.9 % and 8.0 % in the voclosporin treated subjects and placebo, respectively.

Of the 9 serious events in the voclosporin group, 8 resolved.

Of the 10 serious events in the placebo group, 5 resolved.

Source: Table T40AE.0401 10 17.10.06

The incidence of treatment-related serious events was 0.9% and 1.0% in the voclosporin treated subjects and placebo, respectively. The one treatment related serious event in the voclosporin group was resolved. The one treatment related serious event in the placebo group was not resolved.

Source: Table T40AE.0401 10 17.10.07

Characterisation of the risk: Severity

Studies AURA-LV and AURORA 1 (Safety population [N=533])

In the voclosporin group, 41 events were mild or moderate and 23 were severe. In the placebo group, most were mild to moderate with 10 being severe (Table 22).

Table 22. Serious Infections including Opportunistic Infections TEAEs and Severity in > 1 subject in either treatment arm in Studies AURA-LV and AURORA 1

PT	Placebo (N=266)				23.7 mg BID (N=267)			
	n (%) E	Mil	Mod	Sev	n (%) E	Mil	Mod	Sev
Any serious infection or opportunistic infection	**40 (15.0) 49**	**8**	**31**	**10**	**49 (18.4) 64**	**12**	**29**	**23**
Herpes Zoster*	14 (5.3) 15	6	9	0	18 (6.7)18	3	15	0
Pneumonia	10 (3.8) 11	0	4	7	11 (4.1)13	1	4	8
Gastroenteritis	1 (0.4)1	0	1	0	4 (1.5) 5	1	1	3
Pulmonary tuberculosis*	0 (0.0) 0	0	0	0	4 (1.5)4	1	2	1
Urinary tract infection	1 (0.4) 1	0	1	0	3 (1.1) 3	1	2	0
Herpes virus infection*	0 (0.0) 0	0	0	0	3 (1.1) 3	2	1	0
Bronchitis	3 (1.1) 3	0	3	0	0 (0.0) 0	0	0	0

*Denotes opportunistic infection
n: Subjects. E: Events. Mil=Mild events, Mod=Moderate events, Sev=Severe events.
AE=Adverse Event TEAE=Treatment Emergent Adverse Event. 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.
Source: Table T40AE.1.1.10.17.10.8

In the voclosporin group, 14 of the treatment-related events were mild or moderate and 7 were severe. In the placebo group, 11 mild or moderate with one being severe (Table 23).

Table 23. Treatment-Related Serious Infections including Opportunistic Infections TEAEs and Severity in >1 subject in Studies AURA-LV and AURORA 1

PT	Placebo (N=266)				23.7 mg BID (N=267)			
	n (%) E	Mil	Mod	Sev	n (%) E	Mil	Mod	Sev
Any treatment related serious infection opportunistic infection*	**11 (4.1) 12**	**1**	**10**	**1**	**16 (6.0) 21**	**1**	**13**	**7**
Herpes Zoster*	4 (1.5) 4	1	3	0	10 (3.7) 10	0	10	0
Pneumonia	2 (0.8) 2	0	1	1	2 (0.7) 2	0	1	1

*Denotes opportunistic infection
n: Subjects. E: Events. Mil=Mild events, Mod=Moderate events, Sev=Severe events.
AE=Adverse Event TEAE=Treatment Emergent Adverse Event. 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.
Source: Table T40AE.1.1.10.17.10.9

Study AURORA 2 (Safety population [N=216])

All of the events in the voclosporin group were mild or moderate in severity.

Most of the events in the placebo group were mild or moderate with only 3 events being severe. There were no treatment-related severe events in either treatment arm.
Source: Table T40AE.0401 10 17.10.08

Risk factors and risk groups	Patients who are using immunosuppressive treatment of any kind have an increased risk of serious infections including opportunistic infection.
Preventability	Section 4.4 of SmPC states that immunosuppressants, including voclosporin, may increase the risk of developing bacterial, viral, fungal, and protozoal infections, including opportunistic infections which may be serious or fatal, and that patients must be monitored closely for infections during treatment with voclosporin. If an infection occurs, the benefit of continuing voclosporin should be assessed in consideration of the risk of continued administration.
Impact on the risk-benefit balance of the product	Serious infections including opportunistic infections in general can be serious and fatal if not treated. Routine pharmacovigilance activities will further monitor the risk of serious infections including opportunistic infections with respect to number of reports, seriousness, outcome, and risk factors, including patient history. Advice on how to minimise the risk of serious infections including opportunistic infections is disseminated through routine risk minimisation measures and the appropriate labelling will provide information to ensure that the benefit-risk for the product remains positive.
Public health impact	Minimal due to the limited number of patients with the specific indication and rarity of occurrence.

Important potential risk: MACE	
Potential mechanism	CNIs induce hypertension by vasoconstriction, sympathetic excitation and sodium retention by the kidney. The vasoconstrictive effects of CNIs are related to interference with the balance of vasoactive substances, including endothelin and nitric oxide (NO). CNIs increase the activity of the thiazide-sensitive sodium chloride cotransporter through an effect on the lysine deficient protein kinase 1 and sucrose-phosphase synthase-1 (SPS1)-related proline/alanine-rich kinase (Hoorn et al, 2012). Hypertension is a contributing factor in the development of MACEs.
Evidence source and strength of evidence	**Clinical trials**: In the pooled LN population, the number of subjects with MACE TEAEs or treatment-emergent fatal cardiovascular events was low across both treatment groups in the pooled LN population: 5 subjects in the placebo group had a TEAE meeting the MACE criteria compared with 4 subjects in the voclosporin group. An analysis of EAIRs of TEAEs did not show any statistically significant differences between treatment groups and the overall EAIR was higher in the placebo group compared with the voclosporin group. In AURORA 2 there were no MACE TEAEs in the voclosporin group and one MACE TEAE of pulmonary embolism in the placebo group. Hypertension is a risk factor for MACEs. In the pooled LN population, hypertension, including treatment related hypertension, occurred more frequently in the voclosporin group compared to placebo. In AURORA 2, the frequency was lower and comparable between the two groups indicating that the frequency of hypertension was higher in the first 12 months of treatment. The majority of events in the voclosporin and placebo groups in the pooled LN and AURORA 2 populations were mild or moderate. **Class effect**: As a class, CNIs induce hypertension which is a risk factor for MACEs.
Characterisation of the risk: Frequency, relationship, and outcome	**Studies AURA-LV and AURORA 1 (Safety population [N=533])** MedDRA search terms for MACEs were defined by clinical review of preferred terms with the addition of fatal pulmonary embolism and fatal cardiac disorder events. A full list of terms is provided in Annex 7. MACEs occurred in 1.5% of the voclosporin treated patients compared to 1.9% in the placebo group (Table 24 and Table 25). It should be noted that this includes 2 events

of cerebrovascular accident and 1 of haemorrhagic stroke, occurring in the placebo group and 1 event of cerebral infarction which occurred in the voclosporin group and which have also been included in the neurotoxicity analysis.

Of the 4 events that occurred in the voclosporin group:

- none were considered related to treatment
- 2 resolved and 2 were fatal
- none led to dose modification
- none led to permanent discontinuation

Of the 5 events that occurred in the placebo group:

- none were considered related to treatment
- 2 were resolved and 1 was fatal.
- 2 led to dose modification
- 1 led to permanent discontinuation

Source: Table Q180_33.1.1; Table Q180_33.1.4; Table Q180_33.1.10; Table Q180_33.1.11

Table 24. MACE TEAEs and Relationship to Study Drug in Studies AURA-LV and AURORA 1

PT	Placebo (N=266)			23.7 mg BID (N=267)		
	n (%) E	NR	Rel	n (%) E	NR	Rel
Any MACE Events	**5 (1.9) 5**	**5**	**0**	**4 (1.5) 4**	**4**	**0**
Pulmonary Embolism	0 (0.0) 0	0	0	2 (0.7) 2	2	0
Acute Coronary Syndrome	1 (0.4) 1	1	0	1 (0.4) 1	1	0
Cerebral Infarction	0 (0.0) 0	0	0	1 (0.4) 1	1	0
Cerebrovascular Accident	2 (0.8) 2	2	0	0 (0.0) 0	0	0
Acute Myocardial Infarction	1 (0.4) 1	1	0	0 (0.0) 0	0	0
Haemorrhagic Stroke	1 (0.4) 1	1	0	0 (0.0) 0	0	0

n: Subjects. E: Events. NR=Not Related events, Rel=Related events.
AE=Adverse Event , TEAE=Treatment Emergent Adverse Event. 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.
Source: Table Q180_33.1.1

Table 25. MACE TEAEs and Outcome in Studies AURA-LV and AURORA 1

PT	Placebo (N=266)					23.7 mg BID (N=267)				
	n (%) E	Res	RSq	NR	F	n (%) E	Res	RSq	NR	F
Any MACE Events	**5 (1.9) 5**	2	1	1	1	**4 (1.5) 4**	2	0	0	2
Pulmonary Embolism	0 (0.0) 0	0	0	0	0	2 (0.7) 2	0	0	0	2
Acute Coronary Syndrome	1 (0.4) 1	1	0	0	0	1 (0.4) 1	1	0	0	0
Cerebral Infarction	0 (0.0) 0	0	0	0	0	1 (0.4) 1	1	0	0	0
Cerebrovascular Accident	2 (0.8) 2	0	1	0	1	0 (0.0) 0	0	0	0	0
Haemorrhagic Stroke	1 (0.4) 1	0	0	1	0	0 (0.0) 0	0	0	0	0
Acute Myocardial Infarction	1 (0.4) 1	1	0	0	0	0 (0.0) 0	0	0	0	0

n: Subjects. E: Events. Res=Resolved Events, RSq=Resolved with Sequelae events, NR=Not Resolved events, F=Fatal events. Not Resolved includes: Improved, Not Recovered/Not Resolved, Ongoing, Recovering/Resolving, Worsened, Unknown.
AE=Adverse Event, TEAE=Treatment Emergent Adverse Event. 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.
Source: Table Q180_33.1.4

There were no treatment-related events of MACE in either the voclosporin or the placebo groups.

Source: Tables Q180_33.1.5

Study AURORA 2 (Safety population [N=216])

There were no MACE TEAEs in the voclosporin group in AURORA 2.

There was one MACE TEAE of pulmonary embolism in the placebo group which was not-related and which was fatal.

Source: Table Q180_33.2.1

Characterisation of the risk: Seriousness and Outcome

Studies AURA-LV and AURORA 1 (Safety population [N=533])

All of the MACE events in the voclosporin group discussed above were serious.

In the placebo group, there was one non-serious cerebrovascular accident. All other events were serious.

Source: Table Q180_33.1.6

Study AURORA 2 (Safety population [N=216])

The one MACE TEAE in the placebo group was fatal and hence serious.

Source: Table Q180_33.2.4; Table Q180_33.2.6

Characterisation of the risk: Severity

Studies AURA-LV and AURORA 1 (Safety population [N=533])

In the voclosporin group, 1 event was moderate and 3 were severe. In the placebo group, 1 was mild, 2 moderate and 2 severe (Table 26).

Table 26. MACE TEAEs and Severity in Studies AURA-LV and AURORA 1

PT	Placebo (N=266)				23.7 mg BID (N=267)			
	n (%) E	Mil	Mod	Sev	n (%) E	Mil	Mod	Sev
Any MACE Events	**5 (1.9) 5**	**1**	**2**	**2**	**4 (1.5) 4**	**0**	**1**	**3**
Pulmonary Embolism	0 (0.0) 0	0	0	0	2 (0.7) 2	0	0	2
Acute Coronary Syndrome	1 (0.4) 1	0	1	0	1 (0.4) 1	0	0	1
Cerebral Infarction	0 (0.0) 0	0	0	0	1 (0.4) 1	0	1	0
Cerebrovascular Accident	2 (0.8) 2	1	0	1	0 (0.0) 0	0	0	0
Haemorrhagic Stroke	1 (0.4) 1	0	0	1	0 (0.0) 0	0	0	0
Acute Myocardial Infarction	1 (0.4) 1	0	1	0	0 (0.0) 0	0	0	0

n: Subjects. E: Events. Mil=Mild events, Mod=Moderate events, Sev=Severe events.
AE=Adverse Event, TEAE=Treatment Emergent Adverse Event. 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.
Source: Table Q180_33.1.8

Study AURORA 2 (Safety population [N=216])

In AURORA 2, the only MACE TEAE was in the placebo group and was severe.

Source: Table Q180_33.2.8

Risk factors and risk groups	Patients with LN are a population at greater risk of experiencing cardiovascular AEs such as MACE due to inflammation, elevated blood lipids, antiphospholipid syndrome. Additionally, hypertension, obesity, smoking, diabetes, family history and lack of exercise are risk factors for MACE.
Preventability	Section 4.4 of the SmPC states that blood pressure should be monitored every two weeks for the first month after initiating voclosporin and as clinically indicated thereafter. Advice is also provided as to management of clinically concerning elevated blood pressure and when to stop administration of voclosporin.
Impact on the risk-benefit balance of the product	MACE can be serious and fatal if not treated. Routine pharmacovigilance activities will further monitor the risk of MACE with respect to number of reports, seriousness, outcome, and risk factors, including patient history. Advice on how to minimise the risk of hypertension, a risk factor for MACE, disseminated through routine risk minimisation measures and the appropriate labelling, will provide information to ensure that the benefit-risk for the product remains positive.
Public health impact	Minimal due to the limited number of patients with the specific indication and rarity of occurrence.

Important potential risk: Neurotoxicity	
Potential mechanism	The exact mechanism of CNI associated neurotoxicity is not completely understood as CNIs are highly lipophilic and do not readily cross the blood-brain barrier. Proposed mechanisms include altered Central Nervous System permeability due to increased endothelin production as well as increased production of toxic free radicals resulting from CNI-induced mitochondrial dysfunction (Farouk et al 2020).
Evidence source and strength of evidence	**Clinical trials**: In the pooled LN population, TEAEs in the Nervous System Disorders SOC occurred at a higher rate in the voclosporin group than in the placebo group. However, the Nervous System Disorders SOC contains some terms which are not indicative of neurotoxicity. Six preferred terms occurred with an incidence in the voclosporin group ≥ 1% higher than placebo (headache, tremor, post-herpetic neuralgia, paraesthesia, hypoaesthesia and seizure); the remaining events occurred either at a lower incidence in voclosporin compared with placebo or occurred in only 1 or 2 subjects in any treatment group. In AURORA 2, Nervous System Disorder TEAEs occurred more frequently in the voclosporin treated patients compared to the placebo group. Three preferred terms occurred with an incidence in the voclosporin group ≥ 1% higher than placebo (headache, hypoaesthesia and dizziness) **Class effect**: CNIs have been associated with hypertensive encephalopathy and PRES (Farouk et al 2020).
Characterisation of the risk: Frequency, relationship, and outcome	**Studies AURA-LV and AURORA 1 (Safety population [N=533])** The MedDRA SOC of Nervous System Disorders was used as the search term for neurotoxicity. Events of nervous system disorder occurred in 27.7 % of the voclosporin treated patients compared to 16.5% in the placebo group (Table 27 and Table 28). It should be noted that this includes 2 events of cerebrovascular accident and 1 of haemorrhagic stroke, occurring in the placebo group and an event of cerebral infarction which occurred in the voclosporin group and have also been included in the MACE analysis. Of the 114 events that occurred in the voclosporin group: • 20 were considered related to treatment • 85 were resolved • 6 led to dose modification • 5 led to permanent discontinuation Of the 61 events that occurred in the placebo group:

- 7 were considered related to treatment
- 48 were resolved
- 2 led to dose modification
- 1 led to permanent discontinuation

Source: Table q1354.1.1; Table q1354.1.4; Table q1354.1.10; Table q1354.1.11

Table 27. Nervous System Disorder TEAEs and Relationship to Study Drug occurring in > 1 subject in either treatment arm in Studies AURA-LV and AURORA 1

PT	Placebo (N=266)			23.7 mg BID (N=267)		
	n (%) E	NR	Rel	n (%) E	NR	Rel
Any Nervous System Disorder	**44 (16.5) 61**	**54**	**7**	**74 (27.7) 114**	**94**	**20**
Headache	22 (8.3) 29	27	2	40 (15.0) 47	39	8
Tremor	2 (0.8) 2	0	2	9 (3.4) 10	5	5
Dizziness	7 (2.6) 9	8	1	8 (3.0) 8	8	0
Post Herpetic Neuralgia	2 (0.8) 2	1	1	6 (2.2) 6	6	0
Migraine	3 (1.1) 3	3	0	5 (1.9) 7	5	2
Hypoaesthesia	0 (0.0) 0	0	0	4 (1.5) 4	2	2
Seizure	0 (0.0) 0	0	0	4 (1.5) 4	2	2
Paraesthesia	1 (0.4) 1	1	0	4 (1.5) 4	3	1
Tension Headache	2 (0.8) 2	2	0	2 (0.7) 3	3	0
Disturbance in Attention	0 (0.0) 0	0	0	2 (0.7) 2	2	0
Posterior Reversible Encephalopathy Syndrome	0 (0.0) 0	0	0	2 (0.7) 2	2	0
Cerebrovascular Accident	2 (0.8) 2	2	0	0 (0.0) 0	0	0

n: Subjects. E: Events. NR=Not Related events, Rel=Related events.
AE=Adverse Event ,TEAE=Treatment Emergent Adverse Event. 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.
Source: Table q1354.1.1

In addition to the events in Table 27, there were:

- 4 events that occurred at a rate of one event in one subject in both the voclosporin group and the placebo group
- 13 events that occurred at a rate of one event in one subject in the voclosporin group, and 7 events that occurred at a rate of one event per subject in the placebo group only.

Table 28. Nervous System Disorder TEAEs and Outcome in > 1 subject in either treatment arm in Studies AURA-LV and AURORA 1

PT	Placebo (N=266)					23.7 mg BID (N=267)				
	n (%) E	Res	RSq	NR	F	n (%) E	Res	RSq	NR	F
Any Nervous System Disorder	**44 (16.5) 61**	**48**	**1**	**11**	**1**	**74 (27.7) 114**	**85**	**1**	**28**	**0**
Headache	22 (8.3) 29	27	0	2	0	40 (15.0) 47	38	0	9	0
Tremor	2 (0.8) 2	2	0	0	0	9 (3.4) 10	9	0	1	0
Dizziness	7 (2.6) 9	7	0	2	0	8 (3.0) 8	6	0	2	0
Post Herpetic Neuralgia	2 (0.8) 2	0	0	2	0	6 (2.2) 6	5	0	1	0
Migraine	3 (1.1) 3	2	0	1	0	5 (1.9) 7	5	0	2	0
Paraesthesia	1 (0.4) 1	1	0	0	0	4 (1.5) 4	2	0	2	0
Hypoaesthesia	0 (0.0) 0	0	0	0	0	4 (1.5) 4	2	0	2	0
Seizure	0 (0.0) 0	0	0	0	0	4 (1.5) 4	4	0	0	0
Disturbance in Attention	0 (0.0) 0	0	0	0	0	2 (0.7) 2	1	0	1	0
Tension Headache	2 (0.8) 2	2	0	0	0	2 (0.7) 3	3	0	0	0
Posterior Reversible Encephalopathy Syndrome	0 (0.0) 0	0	0	0	0	2 (0.7) 2	2	0	0	0
Cerebrovascular Accident	2 (0.8) 2	0	1	0	1	0 (0.0) 0	0	0	0	0

n: Subjects. E: Events. Res=Resolved Events, RSq=Resolved with Sequelae events, NR=Not Resolved events, F=Fatal events. Not Resolved includes: Improved, Not Recovered/Not Resolved, Ongoing, Recovering/Resolving, Worsened, Unknown.
AE=Adverse Event, TEAE=Treatment Emergent Adverse Event. 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.
Source: Table q1354.1.4

Treatment-related events of nervous system disorders occurred in 6.0% of the voclosporin treated patients compared to 2.6 % in the placebo group (Table 29).

Of the 20 treatment-related events that occurred in the voclosporin group:

- 16 were resolved
- 3 led to dose modification
- 3 led to permanent discontinuation

Of the 7 treatment-related events that occurred in the placebo group:

- 6 were resolved
- None led to dose modification
- None led to permanent discontinuation

Source: Table q1354.1.5; Table q1354.1.2; Table q1354.1.3

Table 29. Treatment-related Nervous System Disorder TEAEs and Outcome in > 1 subject in either treatment arm in Studies AURA-LV and AURORA 1

PT	Placebo (N=266)					23.7 mg BID (N=267)				
	n (%) E	Res	RSq	NR	F	n (%) E	Res	RSq	NR	F
Any Nervous System Disorder	**7 (2.6) 7**	**6**	**0**	**1**	**0**	**16 (6.0) 20**	**16**	**0**	**4**	**0**
Headache	2 (0.8) 2	2	0	0	0	8 (3.0) 8	7	0	1	0
Tremor	2 (0.8) 2	2	0	0	0	4 (1.5) 5	5	0	0	0
Migraine	0 (0.0) 0	0	0	0	0	2 (0.7) 2	0	0	2	0
Hypoaesthesia	0 (0.0) 0	0	0	0	0	2 (0.7) 2	1	0	1	0
Seizure	0 (0.0) 0	0	0	0	0	2 (0.7) 2	2	0	0	0

n: Subjects. E: Events. Res=Resolved Events, RSq=Resolved with Sequelae events, NR=Not Resolved events, F=Fatal events. Not Resolved includes: Improved, Not Recovered/Not Resolved, Ongoing, Recovering/Resolving, Worsened, Unknown.
AE=Adverse Event, TEAE=Treatment Emergent Adverse Event. 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.
Source: Table q1354.1.5

Study AURORA 2 (Safety population [N=216])

Nervous System Disorder TEAEs occurred in 12.1% of the voclosporin treated patients compared to 8.0% in the placebo group (Table 30 and Table 31).

Of the 22 events that occurred in the voclosporin group:

- None were considered related to treatment
- 20 were resolved
- 1 led to dose modification
- None led to permanent study drug discontinuation.

Of the 10 events that occurred in the placebo group:

- None were considered related to treatment
- 8 were resolved
- None led to dose modification
- None led to permanent study drug discontinuation

Source: Table q1354.2.1; Table q1354.2.4; Table q1354.2.10; Table q1354.2.11

Table 30. Nervous System Disorder TEAEs and Relationship to Study Drug in > 1 subject in either treatment arm in AURORA 2

PT	Placebo (N=100)			23.7 mg BID (N=116)		
	n (%) E	NR	Rel	n (%) E	NR	Rel
Any Nervous System Disorder	**8 (8.0) 10**	**10**	**0**	**14 (12.1) 22**	**22**	**0**
Headache	5 (5.0) 6	6	0	8 (6.9) 12	12	0
Hypoaesthesia	0 (0.0) 0	0	0	3 (2.6) 3	3	0
Dizziness	1 (1.0) 1	1	0	2 (1.7) 2	2	0

n: Subjects. E: Events. NR=Not Related events, Rel=Related events.
AE=Adverse Event, TEAE=Treatment Emergent Adverse Event. 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.
Source: Table q1354.2.1

In addition to the events shown in Table 30, there were:

- 5 events that occurred at a rate of one event per subject in the voclosporin group only
- 3 events that occurred at a rate of one event per subject in the placebo group only

Table 31. Nervous System Disorder TEAEs and Outcome in > 1 subject in either treatment arm in AURORA 2.

PT	Placebo (N=100)					23.7 mg BID (N=116)				
	n (%) E	Res	RSq	NR	F	n (%) E	Res	RSq	NR	F
Any Nervous System Disorder	**8 (8.0) 10**	**8**	**0**	**2**	**0**	**14 (12.1) 22**	**20**	**0**	**2**	**0**
Headache	5 (5.0) 6	6	0	0	0	8 (6.9) 12	11	0	1	0
Hypoaesthesia	0 (0.0) 0	0	0	0	0	3 (2.6) 3	3	0	0	0
Dizziness	1 (1.0) 1	1	0	0	0	2 (1.7) 2	2	0	0	0

n: Subjects. E: Events. Res=Resolved Events, RSq=Resolved with Sequelae events, NR=Not Resolved events, F=Fatal events. Not Resolved includes: Improved, Not Recovered/Not Resolved, Ongoing, Recovering/Resolving, Worsened, Unknown.
AE=Adverse Event, TEAE=Treatment Emergent Adverse Event. 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.
Source: Table q1354.2.4

Treatment-related events

There were no treatment-related events in either group.

Source: Table q1354.2.5

Characterisation of the risk: Seriousness and Outcome

Studies AURA-LV and AURORA 1 (Safety population [N=533])

The incidence of serious events was 3.4 % and 0.8% in the voclosporin treated patients and placebo, respectively (Table 32).

Of the 9 serious events in the voclosporin group, 6 resolved and there were no fatal events.

Of the 2 serious events in the placebo group, none resolved and one was fatal.

Table 32. Serious Nervous System Disorder TEAEs and Outcome in > 1 subject in either treatment arm in Studies AURA-LV and AURORA 1

PT	Placebo (N=266)					23.7 mg BID (N=267)				
	n (%) E	Res	RSq	NR	F	n (%) E	Res	RSq	NR	F
Any Nervous System Disorder	**2 (0.8) 2**	**0**	**0**	**1**	**1**	**9 (3.4) 9**	**6**	**1**	**2**	**0**
Posterior Reversible Encephalopathy Syndrome	0 (0.0) 0	0	0	0	0	2 (0.7) 2	2	0	0	0

n: Subjects. E: Events. Res=Resolved Events, RSq=Resolved with Sequelae events, NR=Not Resolved events, F=Fatal events. Not Resolved includes: Improved, Not Recovered/Not Resolved, Ongoing, Recovering/Resolving, Worsened, Unknown.
AE=Adverse Event, TEAE=Treatment Emergent Adverse Event. 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.
Source: Table q1354.1.6

Serious Treatment-Related Nervous System Disorder TEAEs in Studies AURA-LV and Aurora 1

The incidence of serious treatment-related events was 0.4% and 0% in the voclosporin group and placebo, respectively.

The one serious treatment-related event in the voclosporin group was an event of seizure which resolved.

Source: Table q1354.1.7

Study AURORA 2 (Safety population [N=216])

The incidence of serious Nervous System Disorder events was 0% in the voclosporin group and 1.0% in the placebo.

The one serious event in the placebo group was an event of syncope which resolved.

Source: Table q1354.2.6

There were no serious treatment-related events in either arm.

Source: Table q1354.2.7

Characterisation of the risk: Severity

Studies AURA-LV and AURORA 1 (Safety population [N=533])

In the voclosporin group, 104 events were mild or moderate and 10 were severe. In the placebo group, 58 were mild to moderate with 3 being severe (Table 33).

Table 33. Nervous System Disorder TEAEs and Severity in > 1 subject in either treatment arm in Studies AURA-LV and AURORA 1

PT	Placebo (N=266)				23.7 mg BID (N=267)			
	n (%) E	Mil	Mod	Sev	n (%) E	Mil	Mod	Sev
Any Nervous System Disorder	**44 (16.5) 61**	**45**	**13**	**3**	**74 (27.7) 114**	**76**	**28**	**10**
Headache	22 (8.3) 29	22	7	0	40 (15.0) 47	32	11	4
Tremor	2 (0.8) 2	2	0	0	9 (3.4) 10	10	0	0
Dizziness	7 (2.6) 9	7	2	0	8 (3.0) 8	6	2	0
Post Herpetic Neuralgia	2 (0.8) 2	1	1	0	6 (2.2) 6	3	3	0
Migraine	3 (1.1) 3	2	1	0	5 (1.9) 7	0	6	1
Seizure	0 (0.0) 0	0	0	0	4 (1.5) 4	1	1	2
Hypoaesthesia	0 (0.0) 0	0	0	0	4 (1.5) 4	3	1	0
Parasthesia	1 (0.4) 1	1	0	0	4 (1.5) 4	4	0	0
Posterior Reversible Encephalopathy Syndrome	0 (0.0) 0	0	0	0	2 (0.7) 2	0	1	1
Tension Headache	2 (0.8) 2	2	0	0	2 (0.7) 3	3	0	0
Disturbance in Attention	0 (0.0) 0	0	0	0	2 (0.7) 2	2	0	0
Cerebrovascular accident	2 (0.8) 2	1	0	1	0 (0.0) 0	0	0	0

n: Subjects. E: Events. Mil=Mild events, Mod=Moderate events, Sev=Severe events.
AE=Adverse Event, TEAE=Treatment Emergent Adverse Event. 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.
Source: Table q1354.1.8

	In the voclosporin group, 19 of the treatment-related events were mild or moderate and 1 was severe. In the placebo group, 7 were mild or moderate with none being severe (Table 34). **Table 34. Treatment-Related Nervous System Disorder TEAEs and Severity in >1 subject in Studies AURA-LV and AURORA 1** **PT** | **Placebo (N=266)** | | | | **23.7 mg BID (N=267)** | | | | | **n (%) E** | **Mil** | **Mod** | **Sev** | **n (%) E** | **Mil** | **Mod** | **Sev** **Any treatment related nervous system disorder** | **7 (2.6) 7** | **6** | **1** | **0** | **16 (6.0) 20** | **11** | **8** | **1** Headache | 2 (0.8) 2 | 2 | 0 | 0 | 8 (3.0) 8 | 4 | 4 | 0 Tremor | 2 (0.8) 2 | 2 | 0 | 0 | 4 (1.5) 5 | 5 | 0 | 0 Seizure | 0 (0.0) 0 | 0 | 0 | 0 | 2 (0.7) 2 | 0 | 1 | 1 Migraine | 0 (0.0) 0 | 0 | 0 | 0 | 2 (0.7) 2 | 0 | 2 | 0 Hypoaesthesia | 0 (0.0) 0 | 0 | 0 | 0 | 2 (0.7) 2 | 1 | 1 | 0 n: Subjects. E: Events. Mil=Mild events, Mod=Moderate events, Sev=Severe events. AE=Adverse Event, TEAE=Treatment Emergent Adverse Event. 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. Source: Table q1354.1.9 **Study AURORA 2 (Safety population [N=216])** Of the 22 events in the voclosporin group and 10 events in the placebo group, all were mild or moderate in severity. Source: Table q1354.2.8
Risk factors and risk groups	There are no clear risk factors for neurotoxicity. However, the prevalence of PRES among patients with SLE ranges from 0.7% to 1.4% with recurrence in up to 15% of cases. Risk factors include SLE activity, hypertension, haematologic and renal disease (Valdez-Lopez 2021). Female gender, hypertension and exposure to immunosuppressive therapy and heroin consumption have been postulated as additional risk factors (Ansari 2021).
Preventability	Section 4.4 of SmPC states that patients receiving immunosuppressive therapies including voclosporin are at increased risk of neurotoxicity. Patients should be monitored for new-onset or worsening of neurological symptoms including seizures, tremors, or signs and symptoms suggestive of PRES and reduction or discontinuation of voclosporin should be considered if these occur.
Impact on the risk-benefit balance of the product	Neurotoxicity including PRES can be serious and fatal if not treated. Most cases of PRES resolve over days to weeks without complications, however, death and permanent neurologic disability can occur from cerebral oedema either from intracranial haemorrhage or the disease itself (Farouk 2020). Routine pharmacovigilance activities will further monitor the risk of neurotoxicity with respect to number of reports, seriousness, outcome, and risk factors, including patient history. An EU PASS study will further characterise the risk of neurotoxicity in the post-marketing setting. Advice on how to minimise the risk of neurotoxicity is disseminated through routine risk minimisation measures and the appropriate labelling will provide information to ensure that the benefit-risk for the product remains positive.
Public health impact	Minimal due to the limited number of patients with the specific indication and rarity of occurrence.

Important potential risk: Nephrotoxicity (acute [Acute renal failure SMQ] and chronic [Chronic kidney disease SMQ])	
Potential mechanism	CNIs lead to activation of the renin angiotensin and endothelin systems and to increase of sympathetic nerve activity. In addition, CNIs are known to inhibit NO synthesis and NO-mediated vasodilation, and also increase free radicals and superoxide production through vasoconstriction-associated hypoxia. Increased levels of intrarenal renin and angiotensin II induced by CNI are recognised as an important mechanism that contributes to nephrotoxicity. The direct effect of CNI on the tubular epithelial cells plays a major role in the development of interstitial fibrosis. Activation of renin-angiotensin system is not only important in terms of its haemodynamic contribution, but it also directly promotes renal interstitial fibrosis through profibrotic effect of transforming growth factor beta (Hošková et al, 2017).
Evidence source and strength of evidence	**Non-clinical:** Toxicity studies in rats showed renal effects including increases in blood urea nitrogen and creatinine, tubular basophilia and degeneration/regeneration, and corticomedullary mineralization. **Clinical trials**: There has been no indication of true voclosporin events of nephrotoxicity in the clinical development program with treatment up to three years. LN causes a loss of renal function which is manifest by a decreasing eGFR and an increase in UPCR. In addition, voclosporin has a haemodynamic effect leading to a small decrease in eGFR which is reversible on stopping treatment. Data from the long-term AURORA 2 trial supports the lack of nephrotoxicity of voclosporin over a 3-year period. An assessment of eGFR levels over time from the start of AURORA 2 shows that mean eGFR levels were generally stable from Month 12 to Month 27 after which point the mean eGFR levels in the voclosporin group increased while those in the placebo group decreased, potentially reflecting a worsening of renal function relating to disease progression in some placebo subjects. In the AURORA 2 Kidney Biopsy Substudy, assessments from two separate laboratories showed that there were no unique histological findings or changes with voclosporin compared to placebo. The mean chronicity scores remained generally stable in both arms from baseline to follow-up whilst mean activity scores decreased in both treatment arms. In this study, there was no indication of CNI-induced nephrotoxicity occurring in subjects treated with voclosporin for approximately 18 months. However, the interpretation of the histology results from this study is limited by the small sample size. **Class effect**: Renal toxicity is a known effect of CNIs seen most frequently in kidney transplant recipients.
Characterisation of the risk: Frequency, relationship, and outcome	**Studies AURA-LV and AURORA 1 (Safety population [N=533])** Nephrotoxicity is a very broad term which covers acute and chronic effects. Reversible decreases in eGFR are frequently seen in subjects treated with voclosporin due to the haemodynamic effect of the drug; these decreases in eGFR confound any assessment of renal toxicity using standardised MedDRA queries (SMQs), since changes in eGFR are the most common event that occurred in the search using the SMQs for Acute Renal Failure (SMQ20000003) and Chronic Kidney Disease (SMQ20000213). **Renal toxicity events including eGFR decreased.** Renal toxicity events, including GFR decreased, occurred in 35.6% of the voclosporin treated patients compared to 25.2 % in the placebo group (Table 35 and Table 36). Of the 160 renal toxicity events that occurred in the voclosporin group: • 90 were considered related to treatment • 92 were resolved • 106 led to dose modification • 21 led to permanent study drug discontinuation. Of the 85 events that occurred in the placebo group:

- 14 were considered related to treatment
- 31 were resolved
- 26 led to dose modification
- 23 led to permanent study drug discontinuation.

Source: Tables Q1301_0301; Q1301_0304; Q1301_0310; Q1301_0311

Table 35. Renal Toxicity TEAEs and Relationship to Study Drug in > 1 subject in either treatment arm in AURA-LV and AURORA 1

PT	Placebo (N=266)			23.7 mg BID (N=267)		
	n (%) E	NR	Rel	n (%) E	NR	Rel
Any renal toxicity event	**67 (25.2) 85**	**71**	**14**	**95 (35.6) 160**	**70**	**90**
GFR decreased	25 (9.4) 32	23	9	70 (26.2) 112	33	79
Renal impairment	7 (2.6) 8	5	3	15 (5.6) 18	11	7
Acute kidney injury	2 (0.8) 2	2	0	9 (3.4) 10	8	2
Hyperkalaemia	2 (0.8) 2	2	0	5 (1.9) 5	5	0
Lupus nephritis	15 (5.6) 15	15	0	2 (0.7) 2	1	1
Blood creatinine increased	2 (0.8) 2	1	1	2 (0.7) 2	2	0
Hypocalcaemia	2 (0.8) 2	2	0	1 (0.4) 1	1	0
Proteinuria	10 (3.8) 10	9	1	0 (0.0) 0	0	0
Hypoalbuminaemia	4 (1.5) 4	4	0	0 (0.0) 0	0	0

n: Subjects. E: Events. NR=Not Related events, Rel=Related events
AE=Adverse Event TEAE=Treatment Emergent Adverse Event. 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.
Source: Table Q1301_0301

Table 36. Renal Toxicity TEAEs and Outcome in > 1 subject in either treatment arm in AURA-LV and AURORA 1

PT	Placebo (N=266)					23.7 mg BID (N=267)				
	n (%) E	Res	RSq	NR	F	n (%) E	Res	RSq	NR	F
Any renal toxicity event	**67 (25.2) 85**	**31**	**5**	**48**	**1**	**95 (35.6) 160**	**92**	**9**	**59**	**0**
GFR decreased	25 (9.4) 32	16	4	12	0	70 (26.2) 112	66	7	39	0
Renal impairment	7 (2.6) 8	4	0	4	0	15 (5.6) 18	12	0	6	0
Acute kidney injury	2 (0.8) 2	0	0	2	0	9 (3.4) 10	6	1	3	0
Hyperkalaemia	2 (0.8) 2	2	0	0	0	5 (1.9) 5	4	0	1	0
Lupus nephritis	15 (5.6) 15	0	1	13	1	2 (0.7) 2	0	0	2	0
Blood creatinine increased	2 (0.8) 2	2	0	0	0	2 (0.7) 2	1	0	1	0
Hypocalcaemia	2 (0.8) 2	2	0	0	0	1 (0.4) 1	1	0	0	0
Proteinuria	10 (3.8) 10	1	0	9	0	0 (0.0) 0	0	0	0	0
Hypoalbuminaemia	4 (1.5) 4	1	0	3	0	0 (0.0) 0	0	0	0	0

n: Subjects. E: Events. Res=Resolved Events, RSq=Resolved with Sequelae events, NR=Not Resolved events, F=Fatal events. Not Resolved includes: Improved, Not Recovered/Not Resolved, Ongoing, Recovering/Resolving, Worsened, Unknown.
AE=Adverse Event TEAE=Treatment Emergent Adverse Event. 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.
Source: Table Q1301_0304

Treatment-related renal toxicity events, including GFR decreased, occurred in 22.1% of the voclosporin treated patients compared to 4.1% in the placebo group (Table 37).

Of the 90 treatment-related renal toxicity events that occurred in the voclosporin group:

- 54 were resolved
- 70 led to dose modification
- 10 events led to permanent study drug discontinuation

Of the 14 treatment-related renal toxicity events that occurred in the placebo group:

- 10 were resolved
- 8 led to dose modification
- 3 led to permanent study drug discontinuation

Source: Tables Q1301_0302; Q1301_0303; Q1301_0305

Table 37. Treatment-related Renal Toxicity TEAEs and Outcome in > 1 subject in either treatment arm in AURA-LV and AURORA 1

PT	Placebo (N=266)					23.7 mg BID (N=267)				
	n (%) E	Res	RSq	NR	F	n (%) E	Res	RSq	NR	F
Any treatment related renal toxicity event	**11 (4.1) 14**	**10**	**0**	**4**	**0**	**59 (22.1) 90**	**54**	**6**	**30**	**0**
GFR decreased	7 (2.6) 9	6	0	3	0	51 (19.1) 79	48	5	26	0
Renal impairment	2 (0.8) 3	3	0	0	0	6 (2.2) 7	5	0	2	0
Acute kidney injury	0 (0.0) 0	0	0	0	0	2 (0.7) 2	1	1	0	0

n: Subjects. E: Events. Res=Resolved Events, RSq=Resolved with Sequelae events, NR=Not Resolved events, F=Fatal events. Not Resolved includes: Improved, Not Recovered/Not Resolved, Ongoing, Recovering/Resolving, Worsened, Unknown.
AE=Adverse Event TEAE=Treatment Emergent Adverse Event. 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.
Source: Table Q1301_0305

Renal toxicity events excluding eGFR decreased.

In the pooled LN population (AURA-LV and AURORA 1), excluding eGFR decreases, the proportion of subjects who experienced renal toxicity events was lower in the voclosporin group than the placebo group: in the voclosporin group there were 36 subjects (13.5%) who experienced 48 events whilst the placebo group there were 42 subjects (15.8%) who experienced 53 events.

Thus, the apparent renal toxicity of voclosporin is predominantly driven by the changes in eGFR rather than a true toxicity effect.

Reversibility of renal toxicity events.

The reversibility of the eGFR decreases was assessed in subjects who had at least one event of acute renal failure, chronic kidney disease or a confirmed eGFR decrease of ≥30%. This analysis showed that although slightly more voclosporin subjects (36.5%) than placebo subjects (30.9%) had at least one event of acute renal failure, chronic kidney disease or confirmed eGFR decrease of ≥30%, the proportion of subjects who recovered was higher in the voclosporin group (92.3%) compared with the placebo group (76.4%). Of the 5 voclosporin subjects who did not recover, 4 were considered to be due to clear disease progression or LN flare and medication was discontinued in these subjects. This is not unexpected as, even with treatment, patients with LN progressively lose renal function over time.

Study AURORA 2 (Safety population [N=216])

Renal toxicity events including eGFR decreased.

Renal toxicity events including eGFR decreased occurred in 27.6% of the voclosporin treated patients compared to 17.0 % in the placebo group (Table 38 and Table 39).

Of the 41 renal toxicity events that occurred in the voclosporin group:

- 14 were considered related to treatment
- 23 were resolved
- 18 led to dose modification
- 8 led to permanent study drug discontinuation.

Of the 21 events that occurred in the placebo group:

- 4 were considered related to treatment
- 7 were resolved

- 4 led to dose modification
- 9 led to permanent study drug discontinuation.

Source: Tables Q1301_0401; Q1301_0404; Q1301_0410; Q1301_0411

Table 38. Renal Toxicity TEAEs and Relationship to Study Drug in > 1 subject in either treatment arm in AURORA 2

PT	Placebo (N=100)			23.7 mg BID (N=116)		
	n (%) E	NR	Rel	n (%) E	NR	Rel
Any renal toxicity event	17 (17.0) 21	17	4	32 (27.6) 41	27	14
GFR decreased	5 (5.0) 5	2	3	12 (10.3) 15	6	9
Lupus nephritis	4 (4.0) 4	4	0	10 (8.6) 11	10	1
Renal impairment	2 (2.0) 2	1	1	4 (3.4) 4	1	3
Proteinuria	1 (1.0) 2	2	0	4 (3.4) 6	6	0
Nephrotic syndrome	2 (2.0) 3	3	0	0 (0.0) 0	0	0

n: Subjects. E: Events. NR=Not Related events, Rel=Related events
AE=Adverse Event TEAE=Treatment Emergent Adverse Event. 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.
Source: Table Q1301_0401

Table 39. Renal Toxicity TEAEs and Outcome in > 1 subject in either treatment arm AURORA 2

PT	Placebo (N=100)					23.7 mg BID (N=116)				
	n (%) E	Res	RSq	NR	F	n (%) E	Res	RSq	NR	F
Any renal toxicity event	17 (17.0) 21	7	0	14	0	32 (27.6) 41	23	0	18	0
GFR decreased	5 (5.0) 5	1	0	4	0	12 (10.3) 15	11	0	4	0
Lupus nephritis	4 (4.0) 4	1	0	3	0	10 (8.6) 11	3	0	8	0
Renal impairment	2 (2.0) 2	1	0	1	0	4 (3.4) 4	1	0	3	0
Proteinuria	1 (1.0) 2	2	0	0	0	4 (3.4) 6	4	0	2	0
Nephrotic syndrome	2 (2.0) 3	0	0	3	0	0 (0.0) 0	0	0	0	0

n: Subjects. E: Events. Res=Resolved Events, RSq=Resolved with Sequelae events, NR=Not Resolved events, F=Fatal events. Not Resolved includes: Improved, Not Recovered/Not Resolved, Ongoing, Recovering/Resolving, Worsened, Unknown.
AE=Adverse Event TEAE=Treatment Emergent Adverse Event. 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.
Source: Table Q1301_0404

Treatment-related renal toxicity events including eGFR decreased occurred in 11.2% of the voclosporin treated patients compared to 4.0% in the placebo group (Table 40).

Of the 14 treatment-related renal toxicity events that occurred in the voclosporin group:

- 9 were resolved
- 11 led to dose modification
- 2 events led to permanent study drug discontinuation

Of the 4 treatment-related renal toxicity events that occurred in the placebo group:

- none were resolved
- 1 led to dose modification
- 3 led to permanent study drug discontinuation

Source: Tables Q1301_0402; Q1301_0403; Q1301_0405

Table 40. Treatment-related Renal Toxicity TEAEs and Outcome in > 1 subject in either treatment arm in AURORA 2

PT	Placebo (N=100)					23.7 mg BID (N=116)				
	n (%) E	Res	RSq	NR	F	n (%) E	Res	RSq	NR	F
Any treatment related renal toxicity event	4 (4.0) 4	0	0	4	0	13 (11.2) 14	9	0	5	0
GFR decreased	3 (3.0) 3	0	0	3	0	8 (6.9) 9	6	0	3	0
Renal impairment	1 (1.0) 1	0	0	1	0	3 (2.6) 3	1	0	2	0

n: Subjects. E: Events. Res=Resolved Events, RSq=Resolved with Sequelae events, NR=Not Resolved events, F=Fatal events. Not Resolved includes: Improved, Not Recovered/Not Resolved, Ongoing, Recovering/Resolving, Worsened, Unknown.
AE=Adverse Event TEAE=Treatment Emergent Adverse Event. 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.
Source: Table Q1301_0405

Renal toxicity events excluding eGFR decreased.

In AURORA 2, excluding eGFR decreases, the proportion of subjects who experienced renal toxicity events in the voclosporin group was 21 (18.1%) who experienced 26 events whilst in the placebo group there were 12 subjects (12.0%) who experienced 16 events.

Lupus nephritis and proteinuria were reported at a higher frequency in the voclosporin group compared with the placebo group. Ten subjects (8.6%) experienced 11 LN events in the voclosporin group compared to 4 (4.0%) experiencing 4 events in the placebo group. Four (3.4%) subjects experienced 6 events of proteinuria compared to 1 (1.0%) experiencing 2 events in placebo. It is likely that this reflects disease progression despite treatment. The apparent imbalance between the placebo and voclosporin groups reflects the fact that placebo subjects with LN or proteinuria were likely to have stopped treatment earlier in AURORA 1 and hence did not enter AURORA 2.

Characterisation of the risk: Seriousness and Outcome

Studies AURA-LV and AURORA 1 (Safety population [N=533])

Serious events of renal toxicity including eGFR decrease

The incidence of serious renal toxicity events including eGFR decrease events was 5.2% and 3.4% in the voclosporin treated patients and placebo, respectively (Table 41).

Six of these in the voclosporin group resolved and three in the placebo group resolved.

There was one serious event of eGFR decreased in both the voclosporin and the placebo arms.

Table 41. Serious Renal Toxicity TEAEs and Outcome in > 1 subject in either treatment arm in AURA-LV and AURORA 1

PT	Placebo (N=266)					23.7 mg BID (N=267)				
	n (%) E	Res	RSq	NR	F	n (%) E	Res	RSq	NR	F
Any serious renal toxicity event	**9 (3.4) 10**	**3**	**0**	**6**	**1**	**14 (5.2) 15**	**6**	**2**	**7**	**0**
Acute Kidney Injury	2 (0.8) 2	0	0	2	0	8 (3.0) 9	5	1	3	0
Renal Impairment	1 (0.4) 1	1	0	0	0	3 (1.1) 3	1	0	2	0
Lupus nephritis	4 (1.5) 4	0	0	3	1	1 (0.4) 1	0	0	1	0

n: Subjects. E: Events. Res=Resolved Events, RSq=Resolved with Sequelae events, NR=Not Resolved events, F=Fatal events. Not Resolved includes: Improved, Not Recovered/Not Resolved, Ongoing, Recovering/Resolving, Worsened, Unknown.
AE=Adverse Event TEAE=Treatment Emergent Adverse Event. 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.
Source: Table Q1301_0306

The incidence of serious treatment-related renal toxicity events including eGFR events was 1.1% and 0.4% in the voclosporin treated patients and placebo, respectively.

Of the 3 events in the voclosporin group, one resolved.

There was one event only in the placebo arm and this resolved.

Source: Table Q1301_0307

Serious renal toxicity events excluding eGFR decrease

The incidence of serious renal toxicity events excluding eGFR decrease events was 4.9% and 3.0% in the voclosporin treated patients and placebo, respectively.

Source: Table Q1301.1.6;.

Study AURORA 2 (Safety population [N=216])

The incidence of serious renal toxicity events was 2.6 % and 5.0 % in the voclosporin treated patients and placebo, respectively. Two of three serious events in the voclosporin group resolved and two of the five in the placebo group resolved.

There were no serious treatment-related renal toxicity events in either arm.

Source: Table Q1301_0406; Q1301_0407

Characterisation of the risk: Severity

Studies AURA-LV and AURORA 1 (Safety population [N=533])

Most of the renal toxicity events in the voclosporin and placebo groups were mild to moderate in severity with 21 out of 160 events in the voclosporin group and 16 out of 85 events in the placebo group being severe (Table 42).

Table 42. Renal Toxicity TEAEs and Severity in > 1 subject in either treatment arm AURA-LV and AURORA 1

PT	Placebo (N=266)				23.7 mg BID (N=267)			
	n (%) E	Mil	Mod	Sev	n (%) E	Mil	Mod	Sev
Any renal toxicity event	**67 (25.2) 85**	**23**	**46**	**16**	**95 (35.6) 160**	**70**	**69**	**21**
GFR decreased	25 (9.4) 32	12	14	6	70 (26.2) 112	53	50	9
Renal impairment	7 (2.6) 8	3	5	0	15 (5.6) 18	5	13	0
Acute kidney injury	2 (0.8) 2	0	0	2	9 (3.4) 10	2	2	6
Hyperkalaemia	2 (0.8) 2	0	2	0	5 (1.9) 5	4	1	0
Lupus nephritis	15 (5.6) 15	2	9	4	2 (0.7) 2	0	0	2
Blood creatinine increased	2 (0.8) 2	1	1	0	2 (0.7) 2	1	1	0
Hypocalcaemia	2 (0.8) 2	1	1	0	1 (0.4) 1	1	0	0
Proteinuria	10 (3.8) 10	1	8	1	0 (0.0) 0	0	0	0
Hypoalbuminaemia	4 (1.5) 4	2	2	0	0 (0.0) 0	0	0	0

n: Subjects. E: Events. Mil=Mild events, Mod=Moderate events, Sev=Severe events.
AE=Adverse Event TEAE=Treatment Emergent Adverse Event. 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.
Source: Table Q1301_0308

Most of the treatment-related renal toxicity events in the voclosporin group were mild or moderate with 6 out of 90 events being severe. All treatment- related renal toxicity events in the placebo arm were mild to moderate (Table 43).

Table 43. Treatment-Related Renal Toxicity TEAEs and Severity in > 1 subject in either treatment arm AURA-LV and AURORA 1

PT	Placebo (N=266)				23.7 mg BID (N=267)			
	n (%) E	Mil	Mod	Sev	n (%) E	Mil	Mod	Sev
Any treatment -related renal toxicity event	**11 (4.1) 14**	**8**	**6**	**0**	**59 (22.1) 90**	**44**	**40**	**6**
GFR decreased	7 (2.6) 9	5	4	0	51 (19.1) 79	40	36	3
Renal impairment	2 (0.8) 3	2	1	0	6 (2.2) 7	3	4	0
Acute kidney injury	0 (0.0) 0	0	0	0	2 (0.7) 2	0	0	2

n: Subjects. E: Events. Mil=Mild events, Mod=Moderate events, Sev=Severe events.
AE=Adverse Event TEAE=Treatment Emergent Adverse Event. 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.
Source: Table Q1301_0309

Study AURORA 2 (Safety population [N=216])

Most of the renal toxicity events in the voclosporin and placebo groups were mild to moderate in severity with 3 out of 41 events in the voclosporin group and 4 out of 21 events in the placebo group being severe (Table 44).

Table 44. Renal Toxicity TEAEs and Severity in > 1 subject in either treatment arm in AURORA 2

PT	Placebo (N=100)				23.7 mg BID (N=116)			
	n (%) E	Mil	Mod	Sev	n (%) E	Mil	Mod	Sev
Any renal toxicity event	17 (17.0) 21	6	11	4	32 (27.6) 41	19	19	3
GFR decreased	5 (5.0) 5	2	3	0	12 (10.3) 15	8	6	1
Lupus nephritis	4 (4.0) 4	0	2	2	10 (8.6) 11	1	9	1
Renal impairment	2 (2.0) 2	1	1	0	4 (3.4) 4	2	2	0
Proteinuria	1 (1.0) 2	1	1	0	4 (3.4) 6	5	1	0
Nephrotic syndrome	2 (2.0) 3	0	2	1	0 (0.0) 0	0	0	0

n: Subjects. E: Events. Mil=Mild events, Mod=Moderate events, Sev=Severe events.
AE=Adverse Event TEAE=Treatment Emergent Adverse Event. 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.
Source: Table Q1301_0408

All the treatment-related renal toxicity events were mild or moderate in both the voclosporin and placebo groups with no severe events.

Source: Table Q1301_0409

Risk factors and risk groups

Patients with LN by definition have renal disease. Patients will continue to show progression of disease despite treatment and it has been estimated that as many as 30% of LN patients will progress to end-stage renal disease (Almaani et al 2017, Costenbader et al 2011, Tektonidou et al 2016).

A cross-sectional observational study based on data from the Spanish Registry of Glomerulonephritis for the years 1994–2009 showed that risk factors associated with renal failure in patients with LN were older age, male gender, intensity of proteinuria, and presence of hypertension (Vozmediano et al, 2012).

Preventability

Section 4.2 of the SmPC recommends establishing a baseline eGFR before starting treatment with voclosporin and assessing eGFR every two weeks for the first month, and every four weeks thereafter. Dose adjustments are required for those individuals whose eGFR is confirmed to be reduced (i.e., two consecutive assessments within 48 hours) and below 60 mL/min/1.73 m^2.

Details of appropriate dose adjustments are provided in Section 4.2. If eGFR remains ≥ 60 mL/min/1.73 m^2 no dose modification is required.

Section 4.4 of the SmPC explains that as with other CNIs, 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 and this can be managed by dose adjustments. Regular monitoring of eGFR levels is recommended.

Impact on the risk-benefit balance of the product

If the drug-induced renal events are not diagnosed and treated rapidly and adequately, complications potentially resulting in a fatal outcome may occur.

Routine pharmacovigilance activities will further characterise the risk of renal effects with respect to number of reports, seriousness, outcome, and risk factors and whether experience in the post marketing setting is consistent with the information already known for this risk from clinical trial data.

An EU PASS study will further characterise the risk of chronic nephrotoxicity in the post-marketing setting.

Advice on how to minimise the risk of nephrotoxicity is disseminated through routine risk minimisation measures and the appropriate labelling will provide information to ensure that the benefit-risk for the product remains positive.

Public health impact	Minimal due to the limited number of patients with the specific indication and the ability to manage the risk via routine risk minimisation activities.

Important potential risk: Malignancies (including lymphomas) associated with long term use (Malignancies SMQ)	
Potential mechanism	Immunosuppression predisposes patients to a variety of viral infections that lead to malignant transformations of different tissues. In addition, they may also have direct tumorigenic effects. CNIs can promote tumour growth through transforming growth factor-β production or induce tumour growth through overexpression of the angiogenic cytokine vascular endothelial growth factor. In addition, CNIs may lead to the activation of the Ras-Raf proteins pathway (Datta et al, 2009). Both drug-induced immunosuppression and an increase in tumour-driven regulatory T cells (T_{regs}) (i.e., migration and expansion of naturally occurring T_{regs} or conversion and expansion of induced T_{regs}) contribute to impaired immune surveillance and responses against cancer cells (Ducloux, 2014).
Evidence source and strength of evidence	**Non-clinical:** Daily oral administration of voclosporin for 60 to 89 weeks to mice was associated with higher incidences of malignant lymphoma. **Clinical trials**: There has been no indication of malignancy events related to voclosporin in the clinical development program over the three-year period. **Class effect**: Like other immunosuppressants, CNIs increase the risk of developing lymphomas and other malignancies, particularly those of the skin.
Characterisation of the risk: Frequency, relationship, and outcome	**Studies AURA-LV and AURORA 1 (Safety population [N=533])** Malignancy events occurred in 1.5% of the voclosporin treated patients compared to 0% in the placebo group. The 4 events were breast tumour excision, cervix carcinoma Stage 0, neoplasm skin and pyoderma gangrenosum Of the 4 malignancy events that occurred in the voclosporin group: • none were considered related to treatment • 3 were resolved • none led to dose modification • 1 led to permanent study drug discontinuation Source: Table T40AE 1 1 10 17.4.1; T40AE.1.1.10.17.4.4; T40AE.1.1.10.17.4.11 **Study AURORA 2 (Safety population [N=216])** There were no events of malignancy in AURORA 2.
Characterisation of the risk: Seriousness and Outcome	**Studies AURA-LV and AURORA 1 (Safety population [N=533])** Of the 4 malignancy events in the voclosporin group, one was serious (cervix carcinoma Stage 0) and resolved. **Study AURORA 2 (Safety population [N=216])** Not applicable as there were no events of malignancy in AURORA 2.
Characterisation of the risk: Severity	**Studies AURA-LV and AURORA 1 (Safety population [N=533])** Of the 4 events of malignancy, 2 were mild (neoplasm skin and pyoderma gangrenosum) and 2 were moderate (breast tumour excision and cervix carcinoma stage 0). Source: Table T40AE 1 1 10 17.4.8 **Study AURORA 2 (Safety population [N=216])** Not applicable as there were no events of malignancy.
Risk factors and risk groups	Long-term immunosuppression.

Preventability	Section 4.4 of the SmPC states that immunosuppressants increase the risk of developing lymphomas and other malignancies, particularly of the skin and patients should be advised to avoid or limit unprotected exposure to sunlight and UV light.
Impact on the risk-benefit balance of the product	Lymphoma and malignancies in general are serious conditions that can be life-threatening. However, current data are insufficient to confirm or exclude the risk of malignancies associated with the use of voclosporin. All four malignancies were single occurrences and not considered related due to early onset in the short term study. Routine pharmacovigilance activities will further characterise the risk of lymphomas and malignancies associated with long term use with respect to number of reports, seriousness, outcome, and risk factors. An EU PASS study will further characterise the risk of malignancies in the post-marketing setting. Advice on how to minimise the risk of malignancies is disseminated through routine risk minimisation measures and the appropriate labelling will provide information to ensure that the benefit-risk for the product remains positive.
Public health impact	Minimal due to the limited number of patients with the specific indication and rarity of occurrence.

SVII.3.2. Presentation of the missing information

Use in pregnancy	
Evidence source	Pregnant subjects were excluded from clinical trials and thus there is no data regarding the safety profile in this population.
Population in need of further characterisation	The risk of use in pregnancy cannot be defined based on available data and thus the safety profile will be derived from routine pharmacovigilance activities.

Part II: Module SVIII - Summary of the safety concerns

Summary of safety concerns	
Important identified risks	▪ Serious Infections including opportunistic infections
Important potential risks	▪ Major Adverse Cardiovascular Events ▪ Neurotoxicity ▪ Nephrotoxicity (acute and chronic) ▪ Malignancies (including lymphomas) associated with long term use
Missing information	▪ Use in pregnancy

Part III: Pharmacovigilance Plan (including post-authorisation safety studies)

III.1 Routine pharmacovigilance activities

Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:

Specific adverse reaction follow-up questionnaires: None

Other forms of routine pharmacovigilance activities: None

III.2 Additional pharmacovigilance activities

1.Study short name and title: An observational PASS in EU to further characterise and quantify long-term safety profile of Lupkynis.

Rationale and study objectives

In the EU, Lupkynis is anticipated to be 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 Estimated prevalence of LN ranged from 0.63 to 2.28 per 10,000 persons. The Risk Management Plan for Lupkynis includes malignancy, neurotoxicity, and chronic nephrotoxicity as Important Potential Risks. The purpose of this PASS study is to assess the occurrence of these events in patients treated with Lupkynis in the real-world setting.

Study design:

The Market Authorisation Applicant is currently undertaking feasibility assessments to determine the most appropriate design for this study in order to meet the required objectives. The final design of this study will be determined once the results of feasibility assessments are available. The duration of recruitment to the study will be determined by 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.

Study population:

The study population will consist of patients who have been prescribed Lupkynis as per normal clinical practice. Country selection will be determined based upon anticipated market uptake of Lupkynis in Europe.

Milestones:

- Study protocol submission to the EMA: by 18 December 2023
- Further milestones will be provided in the full protocol once the results of the feasibility assessment are available.

III.3 Summary Table of additional Pharmacovigilance activities

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)				
An observational PASS in EU to further characterise and quantify long-term safety profile of Lupkynis	Long term safety	Malignancy Neurotoxicity Nephrotoxicity	PASS protocol Submission	31 March 2023

Part IV: Plans for post-authorisation efficacy studies

Not applicable

Part V: Risk minimisation measures (including evaluation of the effectiveness of risk minimisation activities)

V.1. Routine Risk Minimisation Measures

Safety concern	Routine risk minimisation activities
Important Identified Risks	
Serious Infections including opportunistic infections	**Routine risk communication**: SmPC Section 4.4, 4.8. PL Section 2, 4 **Routine risk minimisation activities recommending specific clinical measures to address the risk**: Instructions to monitor patients closely for infections during treatment with voclosporin are provided in SmPC Section 4.4. If an infection occurs, the benefit of continuing Lupkynis should be assessed in consideration of the risk of continued administration. PL Section 2 and 4 instructs patients to contact their doctor if they have any signs of infection, such as fever, chills or sore throat. **Other routine risk minimisation measures beyond the Product Information**: Legal status: Prescription only medicine
Important Potential Risks	
MACEs	**Routine risk communication**: (Hypertension) SmPC Section 4.4, 4.8 PL Section 2, 4 **Routine risk minimisation activities recommending specific clinical measures to address the risk**: SmPC Section 4.4: 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 as set out in the SmPC Section 4.4 should be followed. PL Section 2 informs patients that their blood pressure will be monitored. **Other routine risk minimisation measures beyond the Product Information**: Legal status: Prescription only medicine
Neurotoxicity	**Routine risk communication**: SmPC Section 4.4, 4.8 PL Section 2, 4 **Routine risk minimisation activities recommending specific clinical measures to address the risk**: SmPC Section 4.4: Patients should be monitored for new-onset or worsening of neurological symptoms including seizures, tremors or signs and symptoms suggestive of PRES. Reduction or discontinuation of voclosporin should be considered if these occur. **Other routine risk minimisation measures beyond the Product Information**: Legal status: Prescription only medicine
Nephrotoxicity (acute and chronic)	**Routine risk communication**: SmPC Section 4.2, 4.4, 4.8 PL Section 2, 4 **Routine risk minimisation activities recommending specific clinical measures to address the risk**:

	SmPC Section 4.2 advises that a baseline eGFR should be established before starting treatment with voclosporin,and assessed every two weeks for the first month and every four weeks thereafter. Dose adjustments should be done as recommended in the SmPC Section 4.2 and in individuals requiring a reduction in dose, reassessment of eGFR recovery should be done within 2 weeks **Other routine risk minimisation measures beyond the Product Information**: Legal status: Prescription only medicine
Malignancies (including lymphomas) associated with long term use	**Routine risk communication**: SmPC Section 4.4, 4.8, 5.3. PL Section 2 **Routine risk minimisation activities recommending specific clinical measures to address the risk**: Patients should be advised to avoid or limit unprotected exposure to sunlight and UV light (SmPC Section 4.4). PL Section 2 instructs patients to avoid or limit their exposure to sunlight and UV light by wearing appropriate protective clothing and frequently applying sunscreen with a high protection factor. **Other routine risk minimisation measures beyond the Product Information**: Legal status: Prescription only medicine
Missing Information	
Use in pregnancy	**Routine risk communication**: SmPC Section 4.6, 5.3. PL Section 2 **Routine risk minimisation activities recommending specific clinical measures to address the risk**: Section 4.6 of the SmPC states that voclosporin is not recommended during pregnancy and in women of child-bearing potential not using contraception. PL Section 2 advises patients to ask their doctor for advice before taking voclosporin if they are pregnant or planning to become pregnant. **Other routine risk minimisation measures beyond the Product Information**: Legal status: Prescription only medicine

V.2. Additional Risk Minimisation Measures

Routine risk minimisation activities as described in Part V.1 are sufficient to manage the safety concerns of the medicinal product.

V.3. Summary of 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
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
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

Part VI: Summary of the risk management plan

Summary of risk management plan for Lupkynis (voclosporin)

This is a summary of the risk management plan (RMP) for Lupkynis. The RMP details important risks of Lupkynis, how these risks can be minimised, and how more information will be obtained about Lupkynis's risks and uncertainties (missing information).

Lupkynis's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Lupkynis should be used.

This summary of the RMP for Lupkynis should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of Lupkynis's RMP.

I. The medicine and what it is used for

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) (see SmPC for the full indication). It contains voclosporin as the active substance and it is given by oral route.

Further information about the evaluation of Lupkynis’s benefits can be found in Lupkynis’s EPAR, including in its plain-language summary, available on the EMA website, under the medicine’s webpage.

II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of Lupkynis, together with measures to minimise such risks and the proposed studies for learning more about Lupkynis's risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine’s packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine’s legal status — the way a medicine is supplied to the patient (e.g., with or without prescription) can help to minimise its risks.

Together, these measures constitute *routine risk minimisation* measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including periodic safety update report (PSUR) assessment so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

If important information that may affect the safe use of Lupkynis is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of Lupkynis are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely taken. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Lupkynis. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g., on the long-term use of the medicine).

List of important risks and missing information	
Important identified risks	▪ Serious infections including opportunistic infections
Important potential risks	▪ Major adverse cardiovascular events (MACEs) ▪ Neurotoxicity ▪ Nephrotoxicity (acute and chronic) ▪ Malignancies (including lymphomas) associated with long term use
Missing information	▪ Use in pregnancy

II.B Summary of important risks

Important identified risk: Serious infections including opportunistic infections	
Evidence for linking the risk to the medicine	**Clinical trials**: The incidence of serious infections including opportunistic infections was marginally higher in the voclosporin group compared to the placebo group in the pooled LN population, In AURORA 2, the incidence was lower and comparable, between the two treatment arms indicating that the frequency of serious infection including opportunistic infections was higher in the first 12 months of treatment. **Class effect**: Like other immunosuppressants, CNIs predispose patients to the development of a variety of bacterial, fungal, parasitic, and viral infections, including opportunistic pathogens.
Risk factors and risk groups	Patients who are using immunosuppressive treatment of any kind have an increased risk of opportunistic infection.
Risk minimisation measures	**Routine risk minimisation measures**: SmPC Section 4.4, 4.8. PL Section 2, 4 Legal status: Prescription only medicine **Additional risk minimisation measures**: None

Important potential risk: MACEs	
Evidence for linking the risk to the medicine	**Clinical trials**: The number of subjects with MACE TEAEs or treatment-emergent fatal cardiovascular events was low across both treatment groups in the pooled LN population: 5 subjects in the placebo group had a TEAE meeting the MACE criteria compared with 4 subjects in the voclosporin group. An analysis of exposure adjusted incidence rates (EAIRs) of TEAEs did not show any statistically significant differences between treatment groups and the overall EAIR was higher in the placebo group compared

	with the voclosporin group. In AURORA 2 there were no MACE TEAEs in the voclosporin group and one MACE TEAE of pulmonary embolism in the placebo group. Hypertension is a risk factor for MACE. In the pooled LN population, hypertension, including treatment related hypertension, occurred more frequently in the voclosporin group compared to placebo. In AURORA 2, the frequency was lower and comparable between the two groups indicating that the frequency of hypertension was higher in the first 12 months of treatment. The majority of events in the voclosporin and placebo groups in the pooled LN and AURORA 2 populations were mild or moderate. **Class effect**: As a class, CNIs induce hypertension which is a risk factor for MACE.
Risk factors and risk groups	Patients with LN are a population at greater risk of experiencing cardiovascular AEs such as MACEs due to inflammation, elevated blood lipids, antiphospholipid syndrome. Additionally, hypertension, obesity, smoking, diabetes, family history and lack of exercise are risk factors for MACEs.
Risk minimisation measures	**Routine risk minimisation measures**: (hypertension) SmPC Section 4.4, 4.8 PL Section 2, 4 Legal status: Prescription only medicine **Additional risk minimisation measures**: None

Important potential risk: Neurotoxicity	
Evidence for linking the risk to the medicine	**Clinical trials**: In the pooled LN population, TEAEs in the Nervous System Disorders SOC occurred at a higher rate in the voclosporin group than in the placebo group. However, the Nervous System Disorders SOC contains some terms which are not indicative of neurotoxicity. Six preferred terms occurred with an incidence in the voclosporin group ≥ 1% higher than placebo (headache, tremor, post-herpetic neuralgia, paraesthesia, hypoaesthesia and seizure); the remaining events occurred either at a lower incidence in voclosporin compared with placebo or occurred in only 1 or 2 subjects in any treatment group. In AURORA 2, Nervous System Disorder TEAEs occurred more frequently in the voclosporin treated patients compared to the placebo group. Three preferred terms occurred with an incidence in the voclosporin group ≥ 1% higher than placebo (headache, hypoaesthesia and dizziness). **Class effect**: CNIs have been associated with hypertensive encephalopathy and posterior reversible encephalopathy syndrome (PRES) (Farouk et al 2020).
Risk factors and risk groups	There are no clear risk factors for neurotoxicity. However, the prevalence of PRES among patients with SLE ranges from 0.7% to 1.4% with recurrence in up to 15% of cases. Risk factors include SLE activity, hypertension, haematologic and renal disease (Valdez-Lopez 2021). Female gender, hypertension and exposure to immunosuppressive therapy and heroin consumption have been postulated as additional risk factors (Ansari 2021).
Risk minimisation measures	**Routine risk minimisation measures**: SmPC Section 4.4, 4.8 PL Section 2, 4 Legal status: Prescription only medicine

	Additional risk minimisation measures: None
Additional Pharmacovigilance Activities	An observational PASS in EU to further characterise and quantify long-term safety profile of Lupkynis

Important potential risk: Nephrotoxicity (acute and chronic)	
Evidence for linking the risk to the medicine	**Non-clinical:** Toxicity studies in rats showed renal effects including increases in blood urea nitrogen and creatinine, tubular basophilia and degeneration/regeneration, and corticomedullary mineralization. **Clinical trials**: There has been no indication of true voclosporin-related nephrotoxicity in the clinical development program with treatment up to three years. LN causes a loss of renal function which is manifest by a decreasing eGFR and an increase in UPCR. In addition, voclosporin has a haemodynamic effect leading to a small decrease in eGFR which is reversible on stopping treatment. Data from the long-term AURORA 2 trial supports the lack of nephrotoxicity of voclosporin over a 3-year period. An assessment of eGFR levels over time from the start of AURORA 2 shows that mean eGFR levels were generally stable from Month 12 to Month 27 after which point the mean eGFR levels in the voclosporin group increased while those in the placebo group decreased, potentially reflecting a worsening of renal function relating to disease progression in some placebo subjects. In the AURORA 2 Kidney Biopsy Substudy, assessments from two separate laboratories showed that there were no unique histological findings or changes with voclosporin compared to placebo. The mean chronicity scores remained generally stable in both arms from baseline to follow-up whilst mean activity scores decreased in both treatment arms. In this study, there was no indication of CNI-induced nephrotoxicity occurring in subjects treated with voclosporin for approximately 18 months. However, the interpretation of the histology results from this study is limited by the small sample size. **Class effect**: Renal toxicity is a known effect of CNIs seen most frequently in kidney transplant recipients.
Risk factors and risk groups	Patients with LN by definition have renal disease. A cross-sectional observational study based on data from the Spanish Registry of Glomerulonephritis for the years 1994–2009 showed that risk factors associated with renal failure in patients with LN were older age, male gender, intensity of proteinuria, and presence of hypertension.
Risk minimisation measures	**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
Additional Pharmacovigilance Activities	An observational PASS in EU to further characterise and quantify long-term safety profile of Lupkynis

Important potential risk: Malignancies (including lymphomas) associated with long term use	
Evidence for linking the risk to the medicine	**Non-clinical:** Daily oral administration of voclosporin for 60 to 89 weeks to mice was associated with higher incidences of malignant lymphoma. **Clinical trials**: There has been no indication of malignancy events related to voclosporin in the clinical development programme over the three year period. **Class effect**: Like other immunosuppressants, CNIs increase the risk of developing lymphomas and other malignancies, particularly those of the skin.
Risk factors and risk groups	Long-term immunosuppression.
Risk minimisation measures	**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
Additional Pharmacovigilance Activities	An observational PASS in EU to further characterise and quantify long-term safety profile of Lupkynis

Missing information: Use in pregnancy	
Risk minimisation measures	**Routine risk minimisation measures**: SmPC Section 4.6, 5.3. PL Section 2 Legal status: Prescription only medicine **Additional risk minimisation measures**: None

II.C Post-authorisation development plan

II.C.1 Studies which are conditions of the marketing authorisation

There are no studies which are conditions of the marketing authorisation or specific obligation of Lupkynis.

II.C.2 Other studies in post-authorisation development plan

1. Study short name and title: An observational PASS in EU to further characterise and quantify long-term safety profile of Lupkynis.

Rationale and study objectives

In the EU, Lupkynis is anticipated to be 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 Estimated prevalence of LN ranged from 0.63 to 2.28 per 10,000 persons. The Risk Management Plan for Lupkynis includes malignancy, neurotoxicity, and chronic nephrotoxicity as Important Potential Risks. The purpose of this PASS study is to assess the occurrence of these events in patients treated with Lupkynis in the real-world setting.

Annex 4 - Specific adverse drug reaction follow-up forms

Not applicable

Annex 6 - Details of proposed additional risk minimisation activities (if applicable)

Not applicable