Report on the Deliberation Results

September 3, 2024
Pharmaceutical Evaluation Division, Pharmaceutical Safety Bureau
Ministry of Health, Labour and Welfare

Brand Name	Lupkynis Capsules 7.9 mg
Non-proprietary Name	Voclosporin (JAN*)
Applicant	Otsuka Pharmaceutical Co., Ltd.
Date of Application	November 10, 2023

Results of Deliberation

In its meeting held on August 26, 2024, the First Committee on New Drugs concluded that the product may be approved and that this result should be presented to the Pharmaceutical Affairs Council.

The product is not classified as a biological product or a specified biological product. The re-examination period is 8 years. The drug product and its drug substance are both classified as powerful drugs.

Approval Condition

The applicant is required to develop and appropriately implement a risk management plan.

**Japanese Accepted Name (modified INN)*

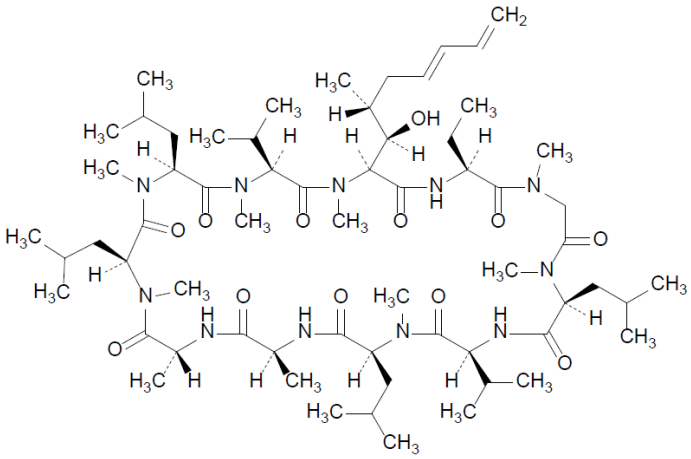
Review Report

August 9, 2024
Pharmaceuticals and Medical Devices Agency

The following are the results of the review of the following pharmaceutical product submitted for marketing approval conducted by the Pharmaceuticals and Medical Devices Agency (PMDA).

Brand Name	Lupkynis Capsules 7.9 mg
Non-proprietary Name	Voclosporin
Applicant	Otsuka Pharmaceutical Co., Ltd.
Date of Application	November 10, 2023
Dosage Form/Strength	Soft capsules: Each capsule contains 7.9 mg of voclosporin.
Application Classification	Prescription drug, (1) Drug with a new active ingredient

Chemical Structure



Molecular formula: $C_{63}H_{111}N_{11}O_{12}$

Molecular weight: 1,214.62

Chemical name: Cyclo{[(2S,3R,4R,6E)-3-hydroxy-4-methyl-2-(methylamino)nona-6,8-dienoyl]-L-2-aminobutanoyl-N-methylglycyl-N-methyl-L-leucyl-L-valyl-N-methyl-L-leucyl-Lalanyl-D-alanyl-N-methyl-L-leucyl-N-methyl-L-leucyl-N-methyl-L-valyl}

Items Warranting Special Mention

None

Reviewing Office Office of New Drug I

Results of Review

On the basis of the data submitted, PMDA has concluded that the product has efficacy in the treatment of lupus nephritis, and that the product has acceptable safety in view of its benefits (see Attachment).

As a result of its review, PMDA has concluded that the product may be approved for the indication and dosage and administration shown below, with the following condition.

Indication

Lupus nephritis

Dosage and Administration

The usual adult dosage is 23.7 mg of voclosporin administered orally twice daily. The dose may be reduced according to the patient's condition.

Approval Condition

The applicant is required to develop and appropriately implement a risk management plan.

Attachment

Review Report (1)

July 11, 2024

The following is an outline of the data submitted by the applicant and content of the review conducted by the Pharmaceuticals and Medical Devices Agency (PMDA).

Product Submitted for Approval

Brand Name	Lupkynis Capsules 7.9 mg
Non-proprietary Name	Voclosporin
Applicant	Otsuka Pharmaceutical Co., Ltd.
Date of Application	November 10, 2023
Dosage Form/Strength	Soft capsules: Each capsule contains 7.9 mg of voclosporin.

Proposed Indication

Lupus nephritis

Proposed Dosage and Administration

The usual adult dosage is 23.7 mg of voclosporin administered orally twice daily.

Table of Contents

List of Abbreviations

See Appendix.

1. Origin or History of Discovery, Use in Foreign Countries, and Other Information

Lupus nephritis (LN) is one of the major manifestations of systemic lupus erythematosus (SLE). It occurs when immune complexes formed by excessively produced autoantibodies, such as anti-DNA antibodies, deposit in renal tissues and trigger inflammation, leading to glomerular damage, proteinuria, and decreased renal function. LN is classified into Classes I to VI according to the histological classification of the International Society of Nephrology/Renal Pathology Society (ISN/RPS). The treatment of LN is primarily determined based on this classification. Class I (minimal mesangial LN) and Class II (mesangial proliferative LN) are often manageable with corticosteroids and generally do not require immunosuppressive therapy, such as mycophenolate mofetil (MMF), cyclophosphamide (CY), azathioprine, mizoribine, tacrolimus hydrate, or cyclosporine. However, Class III (focal LN) and Class IV (diffuse LN) require aggressive treatment with corticosteroids (including pulse therapy) and immunosuppressants. Class V (membranous LN) is treated with corticosteroids and MMF. However, if Class V LN is associated with nephrotic-level proteinuria or has Class III/IV features as well, it is treated as in Class III/IV. For Class VI (advanced sclerotic LN), renal transplantation becomes a therapeutic option.

Voclosporin, the active ingredient of Lupkynis, is a calcineurin inhibitor (CNI) discovered by Aurinia Pharmaceuticals. By inhibiting T-cell activation and suppressing cytokine production, it mitigates renal disorder in LN and is anticipated to serve as a therapeutic agent for Class III to V LN.

The applicant has submitted the application for marketing approval of voclosporin, asserting its efficacy and safety based on the results of a global study involving patients with LN.

As of June 2024, voclosporin has been approved for the indication of LN in 33 countries/regions, including the US and Europe.

2. Quality and Outline of the Review Conducted by PMDA

2.1 Drug substance

The drug substance, voclosporin, is registered by Lonza AG, Switzerland, under the master file (MF) registration number 305MF10058. In this MF, the manufacturing process from the starting material to the intermediate product, cyclosporin, references an MF registered under a separate MF registration number [redacted] by [redacted]. The intermediate product, cyclosporin, is listed in the Japanese Pharmacopoeia.

2.1.1 Characterization

The drug substance is white to off-white powder or a solid-containing powder, and its description, solubility, melting point, partition coefficient, optical rotation, and hygroscopicity have been determined. The drug substance has been found to exist in at least 2 crystalline forms ([redacted] and [redacted]), but [redacted] is produced through the manufacturing process on a commercial scale. The resulting drug substance has been confirmed to remain stable under its storage conditions.

The chemical structure of the drug substance has been confirmed by infrared absorption spectroscopy (IR), nuclear magnetic resonance spectroscopy (^{1}H-NMR, ^{13}C-NMR), mass spectrometry, differential

scanning calorimetry, and thermogravimetry. The drug substance contains 12 chiral carbon atoms. In the manufacturing process on a commercial scale, the trans isomer (voclosporin) is synthesized as the main product, with the cis isomer existing as a geometric isomer. The content of the trans isomer is controlled through the specifications (purity test) for the drug substance.

2.1.2 Manufacturing process

See supplement.

2.1.3 Control of drug substance

The proposed specifications for the drug substance include content, description, identification (IR, high performance liquid chromatography [HPLC]), optical rotation, purity (related substances [HPLC], trans-isomer [HPLC], residual solvents [gas chromatography]), water content (coulometric titration), residue on ignition, microbial limit test, and assay (HPLC).

2.1.4 Stability of drug substance

The main stability study conducted on the drug substance is shown in Table 1, and the results demonstrated stability. The results of the photostability testing indicated that the drug substance is photostable.

Table 1. Stability studies of the drug substance

Study	Primary batches	Temperature	Humidity	Storage form	Storage period
Long-term	3 commercial-scale batches	−20 ± 5°C	-	Low-density polyethylene bag (double-layered) + 3-layer aluminum bag with desiccant	36 months

Based on the above, a retest period of [redacted] months has been proposed for the drug substance when stored at −25°C to −15°C in double-layered low-density polyethylene bags, further sealed with a 3-layer aluminum bag (polyethylene terephthalate/aluminum/polyethylene) containing a desiccant. Long-term stability testing will be continued up to [redacted] months.

2.2 Drug product

2.2.1 Description and composition of drug product and formulation development

The drug product is an immediate-release soft capsule containing 7.9 mg of the drug substance per capsule. The drug product contains the following excipients: anhydrous ethanol, d-α-tocopherol polyethylene glycol succinate, polysorbate 40, medium-chain fatty acid triglycerides, gelatin, a mixture of D-sorbitol, sorbitan solution, and glycerin, yellow ferric oxide, red ferric oxide, and titanium oxide

2.2.2 Manufacturing process

The manufacturing process of the drug product comprises [redacted], [redacted], [redacted], [redacted], [redacted], and packaging. [redacted], [redacted], and [redacted] are identified as the critical steps, with in-process control parameters and action limits have been established for each.

The following critical quality attributes (CQAs) were identified, and process parameters affecting the CQAs were evaluated to develop quality control strategy (Table 2).

Table 2. Summary of control strategy for drug product

CQA	Control method
Content (assay)	Manufacturing process, specifications
Description (appearance)	Manufacturing process, specifications
Identification	Specifications
Degradation products	Manufacturing process, specifications
Ethanol content	Manufacturing process, specifications
Water content	Manufacturing process, specifications
Uniformity of dosage unit	Manufacturing process, specifications
Solubility	Manufacturing process, specifications

2.2.3 Control of drug product

The proposed specifications for the drug product include strength, description, identification (HPLC, ultraviolet-visible spectroscopy), purity (related substances [HPLC]), ethanol content (gas chromatography), water content (volumetric titration), uniformity of dosage unit (content uniformity [HPLC]), dissolution (HPLC), and assay (HPLC).

2.2.4 Stability of drug product

The main stability studies conducted on the drug product are summarized in Table 3, and the results demonstrated stability. The results of the photostability testing indicated that the drug product is photostable.

Table 3. Stability studies of drug product

Study	Primary batches	Temperature	Humidity	Storage form	Storage period
Long-term	3 pilot batches	25°C	60% RH	Aluminum blister packaging	48 months
Accelerated	3 pilot batches	40°C	75% RH		6 months

Based on the above, the shelf life of 36 months has been proposed for the drug product when stored at room temperature in aluminum blister packaging (polyvinyl chloride/aluminum/polyamide and aluminum foil).

2.R Outline of the review conducted by PMDA

Based on the submitted data and the following evaluations, PMDA concluded that the quality of the drug substance and drug product is appropriately controlled.

2.R.1 Novel excipient

The drug product contains polysorbate 40, a new excipient, in an amount exceeding that contained in any existing oral formulation.

2.R.1.1 Specifications and stability

The new excipient, polysorbate 40, conforms to the specification of the Japanese Pharmaceutical Excipients, and PMDA determined that there are no problems regarding its specifications or stability.

2.R.1.2 Safety

Based on the submitted data, PMDA concluded that polysorbate 40, at the concentration used in the drug product, poses a low risk of safety concerns when administered orally.

3. Non-clinical Pharmacology and Outline of the Review Conducted by PMDA

As primary pharmacodynamic studies, investigations were conducted on voclosporin's calcineurin inhibitory activity, various effects on T cells, and immunosuppressive effects in autoimmune disease model animals and transplantation model animals. Safety pharmacology studies were conducted to evaluate its effects on the cardiovascular, central nervous, respiratory, renal, and urinary systems. Voclosporin is in the trans-isomeric form. The proposed process used for manufacturing of voclosporin also produces a cis-isomer, with the trans-isomer comprising 90% to 95% of voclosporin. However, in early-stage non-clinical studies, voclosporin used as the test substance had a different cis-to-trans isomer ratio. Unless otherwise specified, vehicle used in *in vivo* studies was a mixture of d-α-Tocopherol polyethylene glycol succinate (vitamin E TPGS), medium chain triglyceride oil (MCT oil), polyoxyethylene sorbitan monopalmitate (Tween 40), and 95% ethanol ([redacted]).

3.1 Primary pharmacodynamics

3.1.1 *In vitro* studies

3.1.1.1 Calcineurin inhibitory activity (CTD 4.2.1.1-01)

The calcineurin inhibitory activity of voclosporin was evaluated. The half maximal inhibitory concentration (IC_{50}) values for voclosporin (containing 82% trans-isomer) and voclosporin (containing approximately 20% trans-isomer) against calcineurin activity in human blood were 560 and 650 ng/mL, respectively. The results demonstrated that voclosporin exhibited calcineurin inhibitory activity, regardless of the trans-isomer content.

3.1.1.2 Various effects on T Cells (CTD 4.2.1.1-03, *J Heart Lung Transplant.* 2003;22:1343-52, *Transpl Int.* 2005;17:767-71 [Reference data])

In whole blood from monkeys, voclosporin (containing 45%-50% trans-isomer) suppressed lymphocyte proliferation, T-cell cytokine production, and T-cell activation surface antigen expression, with the half maximal effective concentration (EC_{50}) values ranging from 135 to 267 ng/mL.

3.1.1.3 Lymphocyte proliferation inhibition effect by voclosporin metabolites (CTD 4.2.1.1-04 [Reference data])

The lymphocyte proliferation inhibitory effects of major metabolites of voclosporin, including IM1c (cyclized metabolite), IM1-diol-1 (dihydrodiol metabolite), IM4 (hydroxylated metabolite), IM4n (N-demethylated metabolite), and IM9 (hydroxylated metabolite), were evaluated. The IC_{50} value for lymphocyte proliferation inhibitory activity of voclosporin was 17.5 ng/mL. In contrast, the lymphocyte proliferation inhibitory activities of all metabolites were less than one-ninth of that of voclosporin.

3.1.2 *In vivo* studies

3.1.2.1 Immunosuppressive effects of voclosporin in animal models of autoimmune diseases (CTD 4.2.1.1-09)

A collagen-induced arthritis model was generated in male mice (n = 20-26/group) by subcutaneous injection of 100 μg of chicken type II collagen at the base of the tail. Starting 28 days after the collagen injection, voclosporin (containing 45%-50% trans-isomer) was administered intraperitoneally once daily at doses of 0 (vehicle control[1)]), 125, 250, and 500 μg for 10 days to evaluate its immunosuppressive effects. In groups receiving ≥125 μg, improvements were observed compared with the vehicle group in visual limb symptom scores, paw swelling, synovial histological scores, and articular cartilage damage scores. Furthermore, in the 500 μg group, fewer occurrences of proximal interphalangeal joint erosion were noted compared with the vehicle group.

Rabbits (n = 4/sex/group) were injected intramuscularly and subcutaneously at multiple sites in the neck with 10 mg of ovalbumin emulsified with complete Freund's adjuvant and, starting 14 days after ovalbumin injection, 5 mg of ovalbumin and 65 ng of transforming growth factor-β2 (TGF-β2) were administered intraarticularly twice daily for 14 days to generate an antigen-induced arthritis model of rabbits. Beginning 28 days after the initial ovalbumin injection, voclosporin (containing 45%-50% trans-isomer) was administered intraperitoneally once daily for 14 days at doses of 0 (vehicle control[1)]), 2.5, 5, and 10 mg/kg to evaluate its immunosuppressive effects. In groups receiving ≥2.5 mg/kg, improvements in synovial histological scores were observed compared with the vehicle group.

3.1.2.2 Immunosuppressive effects of voclosporin in transplantation model animals (CTD 4.2.1.1-07)

Heart xenotransplantation was performed on male rats (n = 6/group), and the graft survival was evaluated following intraperitoneal administration twice daily for 30 days of either vehicle,[2)] voclosporin (trans-isomer content approximately 80%) at 0.875 mg/kg, voclosporin (trans-isomer content 45%-50%) at 0.875 mg/kg, or voclosporin (trans-isomer content approximately 20%) at 0.875 mg/kg. The mean graft survival durations in each group were 9 days, 44 days, 82 days, and 32 days, respectively. The proportion of grafts that remained viable at 30 days post-transplantation was 0%, 100%, 100%, and 33%, respectively.

3.2 Safety pharmacology

Table 4 shows the outline of the results of safety pharmacology studies.

1) The vehicle was a mixture of Cremophor EL and ethanol (78:22) diluted 50-fold with physiological saline.
2) The solvent used was physiological saline.

Table 4. Outline of safety pharmacology study results

Organ system	Test system	Endpoints and methods	Dose	Administration method	Findings	Attached document CTD
Cardiovascular system	CHO cells (3 specimens/group)	hERG current	Voclosporin[a)] 0.1, 1, 10 µmol/L	*In vitro*	IC_{20} (estimate): 11 µmol/L	Non-GLP 4.2.1.3-01
	Rabbit heart Purkinje fibers (6 specimens/group)	Action potential	Voclosporin 0.01, 0.1, 1, 10 µmol/L	*In vitro*	10 µmol/L: Decreased maximum upslope velocity in phase 0	Non-GLP 4.2.1.3-02
	Monkey (6 females/group)	Clinical signs, body temperature, blood pressure, heart rate, electrocardiogram	Voclosporin 20, 60, 200 mg/kg	Single nasogastric tube administration	200 mg/kg: Decrease in body temperature, increase in blood pressure, QT prolongation	4.2.1.3-03
	Monkey (3/sex/group)	Body temperature, blood pressure, heart rate, electrocardiogram	Voclosporin[a)] 200 mg/kg	Single nasogastric tube administration	200 mg/kg: Decrease in body temperature, QT prolongation	4.2.1.3-04
Central nervous system	Rat (10 males/group)	Irwin method	Voclosporin[a)] 2.5, 10, 25 mg/kg	Single dose oral administration	25 mg/kg: Decrease in body temperature	4.2.1.3-05
Respiratory system	Rat (8 males/group)	Respiratory rate, tidal volume	Voclosporin[a)] 2.5, 10, 25 mg/kg	Single dose oral administration	25 mg/kg: Decrease in respiratory rate	4.2.1.3-06
Renal/urinary system	Rat (10 males/group)	Urinary volume, urinary pH, urinary electrolytes (Na^+, K^+, Cl^-), urine specific gravity, urine protein, blood urea nitrogen, blood creatinine, and blood protein	Voclosporin[a)] 2.5, 10, 25 mg/kg	Single dose oral administration	No effect	4.2.1.3-07

a) Contains 90% to 95% trans isomer

3.R Outline of the review conducted by PMDA

Based on the submitted data and the following review, PMDA has concluded that voclosporin is expected to demonstrate efficacy in the clinical management of LN, despite the need for caution regarding cardiovascular risks.

3.R.1 Pharmacological effects

The applicant's explanation about the pharmacological action of voclosporin:

LN is an organ disorder that occurs frequently in SLE, an autoimmune disease (*Clin J Am Soc Nephrol.* 2017;12:825-35).

As a CNI, voclosporin is considered to exert the following immunosuppressive effects:

- Voclosporin reversibly inhibits cytokine production in immune responsive lymphocytes at the G0 or G1 phase of the cell cycle, particularly in T lymphocytes.
- Voclosporin suppresses the proliferation of T lymphocytes by binding to intracellular protein cyclophilin.
- The complex of voclosporin and cyclophilin inhibits calcineurin, which subsequently suppresses the activation of transcription factors that induce cytokine genes (such as interleukin [IL]-2, IL-4,

interferon-γ, and granulocyte-macrophage colony-stimulating factor), thereby inhibiting T cell activation.

In primary pharmacodynamic studies, voclosporin demonstrated immunosuppressive effects in transplantation model and autoimmune disease model animals. Thus, voclosporin is expected to exert its effects on LN through its immunosuppressive actions.

PMDA's view:
Based on the submitted primary pharmacodynamic study results and the applicant's explanations, voclosporin possesses pharmacological actions that are expected to be effective against LN.

3.R.2 Safety pharmacology

The applicant's explanations about findings observed in the safety pharmacology studies:
For effects on the cardiovascular system, voclosporin was associated with decrease in Phase 0 maximal upstroke velocity, decreased body temperature, increased blood pressure, and QT prolongation. Regarding the decrease in Phase 0 maximal upstroke velocity, although the precise mechanism is unclear, the no-observed effect level (NOEL) (1 μmol/L) identified in the safety pharmacology study using rabbit cardiac Purkinje fibers is approximately 10 times the C_{max} (0.093 μmol/L) observed in humans at a near clinical dose of voclosporin 0.4 mg/kg administered twice daily. Moreover, no arrhythmias were reported in clinical studies. Based on these results, the potential for the decrease in Phase 0 maximal upstroke velocity to pose a safety concern in the clinical use of voclosporin is considered low. Increased blood pressure is thought to be related to inhibition of calcineurin substrate dephosphorylation, increased expression of angiotensin-1 receptors leading to vasoconstriction, sympathetic nervous system activation, and endothelial dysfunction (*Heart.* 2014;46:312-7). The NOEL (60 mg/kg) in safety pharmacology studies using monkeys resulted in a C_{max} (274.8 ng/mL) approximately 2 times the C_{max} (113 ng/mL) observed in humans at a clinical dose of voclosporin 0.4 mg/kg administered twice daily. While the extent of blood pressure increase was up to 10 mmHg, taking into account that the risk of blood pressure increase is expected from the mechanism of action of voclosporin and the observed adverse drug reaction of hypertension was observed in clinical studies, blood pressure increase will be highlighted in the package insert of voclosporin to raise caution. Decreased body temperature was observed at 200 mg/kg in cardiovascular studies using monkeys and at 25 mg/kg in central nervous system studies using rats. This phenomenon is known to be associated with calcineurin inhibition (*Transplantation.* 1998;65:18-26). It is also known that QT intervals (QTs) are influenced by changes in body temperature (e.g., *Br J Pharmacol.* 2008;154:1474-81, *J Pharmacol Toxicol Methods.* 2014;69:61-101). Since decreased body temperature and QT prolongation occurred simultaneously, QT prolongation is considered a secondary effect of decreased body temperature. Administration at the NOEL in monkeys and rats (60 mg/kg and 10 mg/kg, respectively) resulted in C_{max} values (274.8 ng/mL and 1243.7 ng/mL, respectively) approximately 2-fold and 11-fold higher than the C_{max} (113 ng/mL) observed in humans at a clinical dose of voclosporin 0.4 mg/kg administered twice daily. Furthermore, decreased body temperature and QT prolongation were not observed in clinical studies involving patients with LN. Based on these findings, the potential for decreased body temperature and QT prolongation to pose safety concerns in the clinical use of voclosporin is considered low.

Regarding effects on the central nervous system, no impacts from voclosporin other than the aforementioned decreased body temperature were observed.

For effects on the respiratory system, voclosporin was associated with a decrease in the respiratory rate. Since the respiratory rate is known to be influenced by changes in body temperature (*J Therm Biol.* 2000;25:273-9) and both decreased body temperature and decrease in respiratory rate were observed simultaneously, the decrease in the respiratory rate is considered a consequence of decreased body temperature. The NOEL (10 mg/kg) in safety pharmacology studies using rats resulted in a C_{max} (1243.7 ng/mL) approximately 11 times the C_{max} (113 ng/mL) observed in humans at a clinical dose of voclosporin 0.4 mg/kg administered twice daily. Moreover, no decrease in the respiratory rate was reported in clinical studies. Based on these findings, the potential for decrease in respiratory rate to pose a safety concern in the clinical use of voclosporin is considered low.

For effects on the renal and urinary systems, no impact from voclosporin was observed.

In summary, while increased blood pressure requires a precautionary statement in the package insert, the likelihood of other observations posing a safety concern during the clinical use of voclosporin is considered low.

PMDA's view:
Based on the submitted safety pharmacology study results and the applicant's explanations, PMDA considers it appropriate to include a precautionary statement regarding increased blood pressure in the package insert. QT prolongation observed in QT/corrected QT interval (QTc) evaluation studies [see Section 6.2.15] will be further discussed in Section 6.R.6. Based on the submitted safety pharmacology study results, apart from increased blood pressure and QT prolongation, the likelihood of voclosporin posing a safety concern to the cardiovascular, central nervous, respiratory, or renal and urinary systems during the clinical use is considered low.

4. Non-clinical Pharmacokinetics and Outline of the Review Conducted by PMDA

The pharmacokinetics of voclosporin and ^{14}C-labeled voclosporin was evaluated in rats and monkeys. For the measurement of voclosporin concentrations in whole blood, liquid chromatography-mass spectrometry (LC-MS) and liquid chromatography-tandem mass spectrometry (LC-MS/MS) methods were employed, with lower limit of quantification (LLOQ) of 0.1, 1, or 2 ng/mL. For the measurement of radioactivity using ^{14}C-labeled voclosporin, liquid scintillation counting or microplate scintillation/luminescence counting method was utilized.

4.1 Absorption

4.1.1 Single-dose studies

4.1.1.1 Single-dose study of voclosporin in rats (CTD 4.2.2.2-01)

Table 5 shows the pharmacokinetic parameter values of voclosporin following a single intravenous or oral administration in male and female rats.

Table 5. Pharmacokinetic parameters of voclosporin in whole blood following a single dose administration in rats

Dose of voclosporin	Route of administration	Sex	C_{max} [a] (ng/mL)	t_{max} (h)	AUC_{inf} (ng▪h/mL)	$t_{1/2}$ (h)	Bioavailability [b] (%)
5 mg/kg	i.v.	Female	3,923 ± 60.2	0.25	15,189	4.8	-
		Male	5,844 ± 493	0.25	31,251	8.3	-
	p.o.	Female	272 ± 76.3	2.00	1,155	4.8	7.6
		Male	307 ± 44.2	3.00	2,441	6.2	7.8

Calculated from the mean value at each measurement point (3 animals/time point); -, Not applicable

a) Mean ± standard deviation (SD)

b) (AUC_{inf} of voclosporin after oral administration/oral dose) / (AUC_{inf} of voclosporin after intravenous administration/intravenous dose) × 100

4.1.1.2 Single-dose study of voclosporin in monkeys (CTD 4.2.2.2-04)

Table 6 shows the pharmacokinetic parameter values of voclosporin following a single dose oral administration in male and female monkeys.

Table 6. Pharmacokinetic parameters of voclosporin in whole blood following a single-dose administration in monkeys

Dose of voclosporin	Sex	C_{max} (ng/mL)	t_{max} (h)	AUC_{inf} (ng▪h/mL)	$t_{1/2}$ (h)
5 mg/kg	Female	181, 150	2.0, 3.0	1,410, 1,210	8.5, 5.5
	Male	235, 174	3.0, 3.0	2,380, 1,320	8.9, 8.7

Individual values of 2 animals

4.1.2 Repeated-dose studies

4.1.2.1 Repeated-dose study of voclosporin in rats (CTD 4.2.2.2-07)

The toxicokinetics of voclosporin was evaluated following once-daily repeated oral administration for 10 days in male and female rats. Table 7 shows the pharmacokinetic parameter values of voclosporin in whole blood. C_{max} and $AUC_{0–24h}$ of voclosporin tended to be higher in males compared to females. The applicant attributed this finding to potential sex-specific differences in metabolic enzymes unique to rats. Both C_{max} and $AUC_{0–24h}$ increased more than proportionally to the administered dose within the examined dose range. The applicant explained that this was likely due to saturation of the P-glycoprotein (P-gp)-mediated efflux of voclosporin in the gastrointestinal tract with increasing doses. There was no observed trend toward increased exposure with repeated administration of voclosporin.

Table 7. Pharmacokinetic parameters of voclosporin in whole blood following repeated administration in rats

Dose of voclosporin	Sex	Day of measurement	C_{max} (ng/mL)	t_{max} (h)	AUC_{0-24h} (ng▪h/mL)	$t_{1/2}$ (h)
2.5 mg/kg	Female	Day 1	90.4	2.0	335	3.5
		Day 10	71.1	2.0	291	4.6
	Male	Day 1	84.8	2.0	489	6.8
		Day 10	93.3	2.0	642	10.7
25 mg/kg	Female	Day 1	1,920	2.0	10,476	5.4
		Day 10	1,472	2.0	8,253	4.3
	Male	Day 1	2,473	2.0	21,704	7.1
		Day 10	2,596	2.0	25,344	7.9

Calculated from the mean value at each measurement time point (3 animals/time point).

4.1.2.2 Repeated-dose study of voclosporin in monkeys (CTD 4.2.2.2-10)

The toxicokinetics of voclosporin was evaluated following once-daily repeated oral administration for 10 days in male and female monkeys. Table 8 shows the pharmacokinetic parameter values of voclosporin in whole blood. Despite notable inter-individual variability, C_{max} and $AUC_{0–24h}$ of

voclosporin generally increased in proportion to the administered dose. No clear sex differences in pharmacokinetics were observed. There was no trend toward increased exposure with repeated administration.

Table 8. Pharmacokinetic parameters of voclosporin in whole blood following repeated administration in monkeys

Dose of voclosporin	Sex	Day of measurement	C_{max} (ng/mL)	t_{max} (h)	$AUC_{0\text{-}24h}$ (ng▪h/mL)	$t_{1/2}$ (h)
40 mg/kg	Female	Day 1	113, 82.3	4.0, 4.0	1,598, 934	7.5, 4.2
		Day 10	83.4,128	3.0, 8.0	673, 1,778	7.5, 4.9
	Male	Day 1	100, 155	4.0, 4.0	1,341, 2,111	7.1, 8.6
		Day 10	120, 75.5	3.0, 4.0	1,291, 745	9.3, 7.6
150 mg/kg	Female	Day 1	619, 727	8.0, 3.0	7,834, 6,984	18.3, 6.4
		Day 10	337, 720	2.0, 4.0	2,768, 6,161	6.4, 4.5
	Male	Day 1	727, 397	3.0, 2.0	6,984, 2,489	6.4, 5.2
		Day 10	375, 293	3.0, 2.0	3,288, 1,603	5.5, 8.3

Individual values of 2 animals

4.2 Distribution

4.2.1 Tissue distribution in rats (CTD 4.2.2.2-02)

A single oral dose of ^{14}C-labeled voclosporin 5 mg/kg was administered to male and female albino rats. The radioactivity concentrations in various tissues[3)] were analyzed at 1, 2, 4, 8, 12, 24, and 72 hours post-dose. Radioactivity concentrations peaked in most tissues by 8 hours post-dose and subsequently decreased over time. In male rats, non-gastrointestinal tissues with radioactivity concentrations exceeding 4 times that in the blood at 8 hours post-dose included mesenteric lymph nodes, liver, pancreas, thyroid gland, kidneys, salivary glands, spleen, adrenal glands, brown adipose tissue, and submandibular lymph nodes. These tissues exhibited concentrations that were 10.0, 9.7, 9.0, 8.9, 7.7, 7.2, 6.0, 4.8, 4.7, and 4.4 times that of whole blood, respectively. In female rats, non-gastrointestinal tissues with radioactivity concentrations exceeding 4 times that in the blood at 8 hours post-dose included the vagina, uterus, pancreas, thyroid gland, liver, spleen, mesenteric lymph nodes, salivary glands, ovaries, kidneys, extraorbital lacrimal glands, intraorbital lacrimal glands, submandibular lymph nodes, bone marrow, adrenal glands, abdominal fat, mammary glands, brown adipose tissue, Harderian glands, and the pituitary gland. These tissues exhibited concentrations that were 31.0, 20.0, 18.0, 17.0, 14.0, 13.0, 13.0, 13.0, 13.0, 11.0, 11.0, 9.8, 6.5, 6.4, 6.3, 5.9, 5.7, 5.6, 4.8, and 4.0 times that of whole blood, respectively. Additionally, a single oral dose of ^{14}C-labeled voclosporin 5 mg/kg was administered to male and female pigmented rats. The radioactivity concentrations in various tissues[4)] were analyzed at 1, 2, 4, 8, 24, 72, 240, 336, and 504 hours post-dose. In all tissues, radioactivity concentrations decreased over time after 8 hours post-dose, and no trend toward accumulation was observed in pigmented tissues (e.g., eyeballs or pigmented skin).

4.2.2 Protein binding (CTD 4.2.2.3-02)

The protein binding of ^{14}C-labeled voclosporin (20-2,000 ng/mL) was evaluated using plasma from mice, rats, rabbits, dogs, and monkeys. The protein binding was 97.9% to 98.5%, 98.0% to 98.7%,

3) Whole blood, aorta, vena cava, brain, spinal cord, eyes, cardiac muscle, kidneys, liver, lungs, spleen, adrenal glands, extraorbital lacrimal glands, Harderian glands, intraorbital lacrimal glands, submandibular lymph nodes, mesenteric lymph nodes, pancreas, pituitary gland, salivary glands, thymus, thyroid gland, epididymis (male), prostate gland (male), seminal vesicles (male), testes (male), mammary glands (female), ovaries (female), uterus (female), vagina (female), bone, bone marrow, brown adipose tissue, abdominal fat, muscles, skin, trachea, stomach, small intestine, large intestine, esophagus, and bladder.

4) Whole blood, eye, kidney, liver, skin (non-pigmented and pigmented)

97.0% to 97.6%, 97.7% to 97.8%, and 97.1% to 97.9%, respectively. No concentration-dependent effects on protein binding were observed across the tested concentration range.

4.2.3 Placental transfer in rats (CTD 4.2.2.3-04)

Pregnant rats received a single oral dose of ^{14}C-labeled voclosporin 2.5 mg/kg on Gestational Day 19. Radioactivity concentrations in maternal and fetal tissues,[5)] as well as maternal whole blood, were assessed up to 24 hours post-dose. The fetal tissue-to-maternal whole blood concentration ratios reached a maximum of 1.53 within 24 hours post-dose. The detection of radioactivity in fetal tissues indicated that voclosporin crosses the placenta and transfers to the fetus in rats.

4.3 Metabolism

4.3.1 *In vitro* metabolite analysis (CTD 4.2.2.4-01 to 4.2.2.4-05)

The metabolism of voclosporin (9.9-16.5 µmol/L) was investigated using liver microsomes from mice, rats, rabbits, dogs, and monkeys. The primary metabolites identified were as follows: IM9 (hydroxylated metabolite) and IM4n (N-demethylated metabolite) in mice; IM9, IM1c (cyclized metabolite), IM4 (hydroxylated metabolite), IM4n, and IM1-diol-1 (hydroxylated metabolite) in rats; IM9, IM4n, and IM1-diol-1 in rabbits; IM4n and IM9 in dogs; IM4n and IM9 in monkeys.

4.3.2 Proportions of unchanged voclosporin and metabolites in whole blood, urine, feces, and bile (CTD 4.2.2.2-02)

The proportions of unchanged voclosporin and its metabolites[6)] in whole blood, urine, feces, and bile were evaluated following a single oral administration of ^{14}C-labeled voclosporin (5 mg/kg) in male and female rats. The proportion of unchanged voclosporin relative to the total radioactivity in whole blood at various time points between 1 and 24 hours post-dose ranged from 51.8% to 80.4% in males and 52.8% to 73.3% in females. IM9 was identified as the major metabolite in whole blood. The proportion of IM9 relative to the total radioactivity in whole blood was 11.4% to 24.6% in males and 20.3% to 27.4% in females. In urine collected up to 168 hours post-dose, 1.75% and 1.25% of the total radioactivity was detected in males and females, respectively. In urine collected up to 24 hours post-dose, the primary metabolites in males were IM9 (14.5% of urinary total radioactivity), M1 (12.9% of urinary total radioactivity), M3 (11.5% of urinary total radioactivity), and M5 (10.7% of urinary total radioactivity). In females, the primary metabolites were M1 (14.7% of urinary total radioactivity), IM9 (12.2% of urinary total radioactivity), and M3 (10.8% of urinary total radioactivity). In feces collected up to 168 hours post-dose, 94.6% and 97.1% of the total radioactivity was detected in males and females, respectively. In bile collected up to 48 hours post-dose, 2.50% and 5.14% of the total radioactivity was detected in males and females, respectively. In males, the primary metabolites in bile were IM9 (20.9% of biliary total radioactivity), IM1-diol-1 (16.0% of biliary total radioactivity), M9 (8.8% of biliary total radioactivity), M6 (8.9% of biliary total radioactivity), and IM4n (8.8% of biliary total radioactivity). In females, the primary metabolites in bile were IM1-diol-1 (20.0% of biliary total radioactivity), IM9 (16.2% of biliary total radioactivity), M6 (12.2% of biliary total radioactivity), and M5 (8.2% of biliary total radioactivity).

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5) In the maternal body: Amniotic fluid, brain, kidney, liver, placenta, spleen, and uterus
In the fetus: Kidney, liver, spleen, carcass, and whole blood

6) Total radioactivity derived from ^{14}C-labeled voclosporin and its cis-isomer was determined.

4.4 Excretion

4.4.1 Excretion in bile, urine, and feces in rats (CTD 4.2.2.2-02)

When a single oral dose of ^{14}C-labeled voclosporin (5 mg/kg) was administered to male and female rats, the cumulative excretion rates of radioactivity in urine and feces up to 168 hours post-dose were 1.75% and 94.6% of the administered dose in males and 1.25% and 97.1% in females, respectively.

In bile duct cannulated male and female rats, following a single oral administration of ^{14}C-labeled voclosporin (5 mg/kg), the cumulative excretion rates of radioactivity in bile, urine, and feces up to 48 hours post-dose were 2.50%, 0.46%, and 92.6% of the administered dose in males and 5.14%, 0.54%, and 91.2% in females, respectively.

4.4.2 Excretion in urine and feces in monkeys (CTD 4.2.2.2-04)

When a single oral dose of ^{14}C-labeled voclosporin (40 mg/kg) was administered to male and female monkeys, the cumulative excretion rates of radioactivity in urine and feces up to 168 hours post-dose were 0.76% and 79.2% of the administered dose in males and 1.87% and 77.0% in females, respectively.

4.4.3 Excretion into milk in rats (CTD 4.2.2.3-04)

In rats on Postpartum Day 10 or 11, the concentration of radioactivity in milk was assessed up to 24 hours after a single oral administration of ^{14}C-labeled voclosporin (2.5 mg/kg). The maximum concentration of radioactivity in milk (239 ng eq./g) was observed at 4 hours post-dose. At this time point, the milk-to-whole blood concentration ratio of radioactivity was approximately 0.99. These findings indicate that voclosporin is transferred into milk following oral administration in rats.

4.R Outline of the review conducted by PMDA

Based on the submitted non-clinical pharmacokinetic study results and the applicant's explanations, PMDA concluded that the non-clinical pharmacokinetics of voclosporin were appropriately evaluated. From the perspective of non-clinical pharmacokinetics, while caution is warranted regarding placental transfer and secretion into milk, there are no significant concerns that would impede the clinical use of voclosporin.

5. Toxicology and Outline of the Review Conducted by PMDA

In order to evaluate the toxicity of voclosporin, various studies were conducted using voclosporin and voclosporin (containing 45%-50% of trans isomer), including single-dose toxicity studies, repeated-dose toxicity studies, genotoxicity studies, carcinogenicity studies, reproductive and developmental toxicity studies, and other studies such as phototoxicity studies using voclosporin and genotoxicity studies using impurities. Unless otherwise specified, the vehicle used was a mixture of vitamin E TPGS, MCT oil, Tween 40, and 95% ethanol ([redacted]). The primary results are summarized below.

5.1 Single-dose toxicity

The acute toxicity of voclosporin was assessed based on the results following the initial dose in repeated-dose toxicity studies in rats and dogs [see Section 5.2]. No signs of acute toxicity were

observed. The approximate lethal doses of voclosporin after oral administration were determined to be >80 mg/kg in rats and >300 mg/kg in monkeys.

5.2 Repeated-dose toxicity

Repeated-dose toxicity studies were conducted in rats for up to 26 weeks and in monkeys for up to 39 weeks. Additionally, a 13-week repeated-dose study in rats was performed to compare the toxicity profiles of voclosporin formulations with differing cis-trans isomer ratios (Table 9).

In rats, toxicological findings were observed primarily in the eyes, kidneys, and nervous system, similar to those reported for cyclosporine A (CsA). In monkeys, gingival findings and lymphomas were attributed to the immunosuppressive effects of voclosporin.

Table 9. Summary of results of repeated-dose toxicity studies

Test system	Route of administration	Administration period	Dose (mg/kg/day)	Main findings	NOAEL (mg/kg/day)	Attached document CTD
Male and female rats (SD)	p.o.	4 weeks (once daily) + 2-week withdrawal	Voclosporin[a)] 0, 4.6, 24.2, 80	≥24.2: Decreased WBC, Hb, and MCH; increased blood BUN; increased blood cholesterol; increased urine glucose; decreased urine chloride; increased liver and ovary weight; lens degeneration; thymic medulla atrophy; disappearance of germinal centers in the spleen and lymph nodes; mineral deposition in the renal cortex and medulla; and basophilic tubules 80: Reduced body weight gain; cataracts; anterior and subcapsular lens opacities; anisocytosis; microcytosis; polychromatic erythrocytes; increased blood creatinine; increased blood phosphorus and triglycerides; increased total bilirubin; and increased weight of the adrenal glands, brain, heart, lungs, and kidneys Reversible[b)]	24.2	4.2.3.2-06
Male and female rats (SD)	p.o.	13 weeks (once daily) + 4-week withdrawal	Voclosporin[a)] 0,[c)] 0,[d)] 2.5, 10, 25	≥2.5: Vacuolization of neural networks in the brain. ≥10: Piloerection; decreased activity; decreased locomotor activity; increase in body temperature; decreased WBC; increased total bilirubin level in the blood; thymic medulla atrophy; lympholysis; disappearance of germinal centers in the spleen and lymph nodes; gliosis in the brain; inflammatory cell infiltration around blood vessels in the brain, spinal cord, and sciatic nerve; and vacuolization in the spinal cord 25: Dehydration; hunchback position; emaciation; decreased body weight and body weight gain; cataracts; decreased MCH, MCV, and platelet levels; anisocytosis; microcytosis; polychromatic erythrocytes; increased blood BUN; increased urine glucose; increased weight of the adrenal glands, spleen, kidneys, and liver; mineral deposition in the renal cortex and medulla; basophilic tubules; spinal cord gliosis; and lens degeneration Reversible[b)]	<2.5	4.2.3.2-07
Male and female rats (SD)	p.o.	26 weeks (once daily) + 4-week withdrawal	Voclosporin[a)] 0,[d)] 1.25, 2.5, 10	≥2.5: Tubular degeneration and regeneration; tubular mineral deposition; and subacute spinal inflammation, nerve fiber degeneration, gliosis, and vasculitis 10: Decreased body weight and body weight gain; increased blood BUN, ALP, AST, and ALT levels; low blood magnesium levels; increased urinary glucose levels; cataract; increased weights of adrenal gland, kidney, and thymus; decreased weights of prostate and testis; subacute brain inflammation, nerve fiber degeneration, gliosis, and vasculitis; peripheral nerve fiber degeneration, gliosis, and lymphocytic infiltration; subacute pulmonary inflammation, and alveolar macrophage aggregation Reversible[b)]	1.25	4.2.3.2-08

Test system	Route of administration	Administration period	Dose (mg/kg/day)	Main findings	NOAEL (mg/kg/day)	Attached document CTD
Male and female rats (SD)	p.o.	13 weeks (once daily) + 4-week withdrawal	Voclosporin 0, 2.5, 10, 25	≥10: Increased blood creatinine levels; decreased blood magnesium levels; mandibular lymph node germinal center atrophy; tubular degeneration and regeneration; perivascular inflammation in the brain 25: Emaciation; decreased body weight; corneal opacity; decreased lymphocyte count; increased blood BUN levels; increased total bilirubin levels; increased AST, ALT, and ALP levels; increased blood sodium, potassium, calcium, chloride, and phosphorus levels; increased urinary RBC and glucose levels; decreased urinary pH; duodenal thickening; cecal dilation; renal pelvis dilation; small thymic; decreased weights of prostate and thymus; renal cortex-medulla mineral deposition; thymic atrophy; and lens degeneration Reversible	2.5	4.2.3.2-09
Male and female cynomolgus monkeys	p.o.	13 weeks (once daily) + 4-week withdrawal	Voclosporin[a)] 0,[c)] 0,[d)] 25, 75, 150/300[e)]	≥25: Gingival inflammation, disappearance of germinal centers in mesenteric lymph nodes, reduction in the number and size of follicular germinal centers in the spleen, and thymic atrophy ≥75: Gingival hypertrophy 300: Emaciation, tremor, and gingival swelling Reversible	<25	4.2.3.2-14
Male and female cynomolgus monkeys	p.o.	39 weeks (once daily) + 4-week withdrawal	Voclosporin[a)] 0,[c)] 0,[d)] 25, 75, 150	Death: 150 (1 of 5 females)[f)] ≥75: Gingival hypertrophy, decreased blood $CD2^+$ cell count and $CD2^+/CD4^+$ cell ratio, increased $CD20^+$ cell counts, and splenic lymphoid tissue hyperplasia 150: Lymphosarcoma Reversible[g)]	25	4.2.3.2-15

a) Containing 45% to 50% of the trans-isomer
b) Excluding findings of cataracts and kidneys
c) Physiological saline
d) Vehicle
e) Dose increased to 300 mg/kg/day from Day 50
f) Death due to lymphosarcoma
g) Excluding lymphosarcoma

5.3 Genotoxicity

An *in vitro* bacterial reverse mutation assay, an *in vitro* chromosomal aberration assay using mammalian cells, and an *in vivo* micronucleus assay in rats were conducted (Table 10). All tests yielded negative results, indicating that voclosporin is unlikely to exhibit genotoxicity *in vivo*.

Table 10. Summary of genotoxicity studies

Study		Test system	Metabolic activation (duration)	Concentration or dose	Results	Attached document CTD
In vitro	Bacterial reverse mutation assay	*Salmonella typhimurium*: TA98, TA100, TA1535, TA1537 *Escherichia coli*: WP2uvrA	S9- S9+	Voclosporin 0,[a] 1.5, 5.0, 15, 50, 150, 500, 1,500, 5,000 µg/plate	Negative	4.2.3.3.1-02 4.2.3.3.1-3
	Chromosomal aberration assay using cultured mammalian cells	Chinese hamster ovary-derived cells	S9− (4 hours)	Voclosporin Batch 102: 0,[b] 100, 500, 1000 µg/mL Batch 106: 0,[b] 100, 500, 2500 µg/mL	Negative	4.2.3.3.1-05
			S9+ (4 hours)	Voclosporin Batch 102: 0,[b] 100, 500, 1000 µg/mL Batch 106: 0,[b] 50, 100, 500 µg/mL		
			S9− (20 hours)	Voclosporin Batch 102: 0,[b] 5, 15, 250 µg/mL Batch 106: 0,[b] 5, 15, 50 µg/mL		
In vivo	Micronucleus assay in rodents	Male and female rats (SD) Bone marrow		Voclosporin [b] 0,[c] 500, 1,000, 2,000 mg/kg/day (single oral administration)	Negative	4.2.3.3.2-01

a) Dimethylsulfoxide (DMSO)
b) Contains 45% to 50% trans isomer
c) Corn oil

5.4 Carcinogenicity

Carcinogenicity studies conducted in mice and rats revealed no evidence of carcinogenicity associated with voclosporin (Table 11).

Table 11. Summary of carcinogenicity tests

<table>
<tr><td rowspan="2">Test system</td><td rowspan="2">Route of administration</td><td rowspan="2">Treatment duration</td><td rowspan="2">Main lesions</td><td>Sex</td><td colspan="5">Dose (mg/kg/day)</td><td rowspan="2">Non-carcinogenic dose (mg/kg/day)</td><td rowspan="2">Attached document CTD</td></tr>
<tr><td>No. of animals</td><td>0[a)]
65 each</td><td>0[b)]
65 each</td><td>3
65 each</td><td>10
65 each</td><td>30
65 each</td></tr>
<tr><td rowspan="2">Male and female mice (CD-1)</td><td rowspan="2">p.o.</td><td rowspan="2">60-89 weeks[c)] (once daily)</td><td>Neoplastic lesion</td><td colspan="6">None</td><td rowspan="2">30</td><td rowspan="2">4.2.3.4.1-03</td></tr>
<tr><td>Non-neoplastic lesion</td><td colspan="6">None</td></tr>
<tr><td rowspan="5">Male and female rats (SD)</td><td rowspan="5">p.o.</td><td rowspan="5">96 weeks[d)] (once daily)</td><td rowspan="3">Main lesions</td><td rowspan="2">Sex</td><td colspan="5">Dose (mg/kg/day)</td><td rowspan="5">1.25 (male)
2.5 (female)</td><td rowspan="5">4.2.3.4.1-04</td></tr>
<tr><td>0[a)]</td><td>0[b)]</td><td>Male 0.05
Female 0.1</td><td>Male 0.25
Female 0.5</td><td>Male 1.25
Female 2.5</td></tr>
<tr><td>No. of animals</td><td>65/sex</td><td>65/sex</td><td>65/sex</td><td>65/sex</td><td>65/sex</td></tr>
<tr><td>Neoplastic lesion</td><td colspan="6">None</td></tr>
<tr><td>Non-neoplastic lesion</td><td colspan="6">None</td></tr>
</table>

a) Physiological saline
b) Vehicle
c) Although administration was initially planned for 104 weeks, it was terminated due to a decrease in the number of surviving animals, and necropsy was performed at the following time points. The entire study was terminated during Week 88 to 89 because of the decrease in the survival rate in the vehicle control group.
   • Male mice in the 3 mg/kg/day group: Administration was terminated and necropsy was performed at Week 82.
   • Female mice in the 30 mg/kg/day group: Administration was terminated at Week 60 and necropsy was performed at Week 88.
   • Male mice in the 30 mg/kg/day group: Administration was terminated at Week 60, and necropsy was performed at Week 80.
d) Due to a decrease in the survival rate in the vehicle control group, the entire study was terminated during Week 95 to 97.

5.5 Reproductive and developmental toxicity

The following studies were conducted: A study of fertility and early embryonic development to implantation in rats, studies for embryo-fetal development in rats and rabbits, and study for pre- and post-natal development, including maternal function, in rats (Table 12).

In the studies for embryo-fetal development studies conducted in rats and rabbits, reduced body weight and delayed ossification were observed in fetuses.

Table 12. Summary of reproductive and developmental toxicity studies

Study	Test system	Route of administration	Administration period	Dose (mg/kg/day)	Main findings	NOAEL (mg/kg/day)	Attached document CTD
Fertility and early embryonic development to implantation	Male and female rats (SD)	p.o.	Male: 49 days before mating to 1 day before necropsy (once daily)	Voclosporin[a] 0,[b] 0,[c] 2.5, 10, 25	Death: 10 (1 of 25 animals), 25 (1 of 25 animals)[d] 25: Low body weight, reduced body weight gain, and low food intake; and decreased weights of the left cauda epididymis, epididymis, seminal vesicles, and prostate	General toxicity: 10 Reproductive function: 25 Early embryonal development: 25	4.2.3.5.1-01
			Female: 15 days before mating to Gestation Day 7 (once daily)		Death: 25 (1 of 25 animals)[d]	General toxicity: 10 Reproductive function: 25 Early embryonal development: 25	
Embryo-fetal development	Female rats (SD)	p.o.	Gestation Day 6 to 17 (once daily)	Voclosporin[a] 0, 2.5, 10, 25	Maternal animals: 25: Red discoloration around the mouth; low body weight, reduced body weight gain, and low food intake; decreased weight of the uterine and ovarian, and increased weights of the adrenal and brain Fetuses: 25: Low body weight, increased resorbed embryos, decreased number of viable fetuses, and delayed ossification of metatarsal bones	Maternal animals (general toxicity): 10 Embryo-fetal development: 10	4.2.3.5.2-03
	Female rabbits (NZW)	p.o.	Gestation Day 6 to 18 (once daily)	Voclosporin 0,[b] 0,[c] 1, 5, 20	Maternal animals: Death: 20 (1 of 22 animals)[e] ≥5: Mammary gland swelling 20: Low food intake Fetuses: ≥5: Low body weight 20: Unossified sternum, and unossified hyoid body and hyoid arch	Maternal animals (general toxicity): 1 Embryo-fetal development: 1	4.2.3.5.2-06
Pre- and post-natal development, including maternal function	Female rats (SD)	p.o.	Maternal animals: Gestation Day 7 to Lactation Day 22 (once daily)	Voclosporin[a] 0,[b] 0,[c] 2.5, 10, 25	Maternal animals: Death: 2.5 (1 of 24 animals), 25 (12 of 23 animals)[f] 25: Red or brown discoloration of the vagina and paravaginal area, pale mucous membranes, loose stools and watery diarrhea, dehydration, emaciation, reduced body weight gain, and low food intake, and uterine adhesion. F1 offspring: 25: Decreased number of live births and live pups F2 fetuses: None.	Maternal animals (general toxicity): 10 Development of F1 offspring: 10 F2 fetuses: 25	4.2.3.5.3-01

a) Contains 45% to 50% of the trans isomer.
b) Physiological saline
c) Vehicle
d) Deaths unrelated to voclosporin
e) Deaths due to administration error
f) One animal in the 2.5 mg/kg/day group died due to an administration error. Twelve animals in the 25 mg/kg/day group were moribund sacrificed due to incomplete delivery.

5.6 Study in juvenile animals

A repeated oral dose toxicity study was conducted in juvenile rats (Table 13). No novel toxicological findings were observed in juvenile rats compared to those identified in adult rats following oral administration.

Table 13. Summary of repeated-dose toxicity study results in juvenile animals

Test system	Route of administration	Administration period	Dose (mg/kg/day)	Main findings	NOAEL (mg/kg/day)	Attached document CTD
Male and female rats (SD)	p.o.	10 weeks (started on 28 days of age) (once daily) + 5-week recovery	Voclosporin Male: 0,[a] 0,[b] 1.25, 2.5, 5 Female: 0,[a] 0,[b] 2.5, 5, 10	≥2.5: Vacuolation of the thymic cortex 10: Mineral deposition in the renal cortex and medulla, vacuolation in the brain's neural network, and multifocal lymphocyte infiltration in the sciatic nerve Reversible[c]	Male: 1.25 Female: 2.5	4.2.3.5.4-01

a) Water for injection
b) Vehicle
c) Except for mineral deposition in the kidneys. Changes in the brain and sciatic nerve could not be evaluated for reversibility due to their low frequency of occurrence.

5.7 Other studies

5.7.1 Toxicity study with co-administration of prednisone (CTD 4.2.3.7.7-01)

A 13-week repeated-dose toxicity study of voclosporin in combination with prednisone was conducted in rats. No new toxicities or exacerbations of known toxicities were observed with the co-administration.

5.R Outline of the review conducted by PMDA

Based on the submitted data and subsequent evaluations, PMDA concluded that no significant issues were identified in the toxicity studies that would impede the clinical use of voclosporin. However, further assessment of neurotoxicity is deemed necessary and is discussed in Section 7.R.2.4.4.

5.R.1 Neurotoxicity in rats

The applicant's explanation about neurotoxicity (gliosis in the brain and spinal cord and perivascular cell infiltration) observed in repeated-dose toxicity studies in rats [see Section 5.2]:

Neurotoxicity has been reported with other CNIs, and while the detailed mechanism of neurotoxicity induced by CNIs remains unclear, an association with hypomagnesemia has been documented (*Mol Interv.* 2004;4:97-107). Considering the similarity in neurotoxic findings observed in rats administered either voclosporin or CsA, along with the hypomagnesemia associated with voclosporin administration, the findings are likely attributable to a class effect of CNIs. In the pooled safety analysis population from patients with LN in the clinical study of voclosporin,[7] central nervous system adverse events with a ≥2% higher incidence in the voclosporin group that the placebo group were tremor (0.8% [2 of 266 subjects] in the placebo group, 3.4% [9 of 267 subjects] in the voclosporin group) and headache (8.3% [22 of 266 subjects] in the placebo group, 15.0% [40 of 267 subjects] in the voclosporin group). However, the incidence of tremor was lower than that reported in clinical studies of tacrolimus,

7) Integrated analysis population from the foreign phase II dose-finding study (Study AURA-LV, excluding the 39.5 mg voclosporin group) and the global phase III study (AURORA 1 study).

another CNI (*Ann Rheum Dis.* 2016;75:30-6) (0% [0 of 76 subjects] in the control [MMF] group, 20.3% [15 of 74 subjects] in the tacrolimus group). Regarding headache, in the case of CsA, the vasodilatory properties or endothelial dysfunction might be contributing factors (*J Neurol.* 1999;246:339–346, *Headache.* 2005;45:211–214). Thus, it is considered unlikely that the neurotoxicity observed in rats is related to headaches associated with voclosporin. Based on the above, the neurotoxicity observed in rats is considered unlikely to pose a safety concern when voclosporin is used in patients with LN according to the proposed dosing regimen. Nevertheless, considering that neurotoxicity has been reported with other CNIs and was also observed in clinical studies of voclosporin, it is deemed appropriate to include precautionary statement in the package insert.

The PMDA's view:
While the neurotoxicity observed in rats is likely a common risk associated with CNIs, based on the applicant's explanation, there is insufficient evidence to determine that voclosporin is safer than other drugs in the same class. Given that related findings were observed even in the low-dose group of voclosporin, further examination of the human safety profile concerning neurotoxicity is considered necessary and will be discussed in Section 7.R.2.4.4.

6. Summary of Biopharmaceutic Studies and Associated Analytical Methods, Clinical Pharmacology, and Outline of the Review Conducted by PMDA

6.1 Summary of biopharmaceutic studies and associated analytical methods

Table 14 shows the formulations used in the main clinical studies submitted for the present application.

Table 14. Formulations used in clinical studies

Clinical studies	Formulation
Studies ISA03-11, ISA03-12, and LX211-05	Formulation A: Liquid formulation containing 50 mg of voclosporin per capsule
Studies ISA05-03, ISA07-07, ISA07-08, ISA07-09, LX211-06, LX211-07, LX211-08, and LX211-09	Formulation B: Each capsule containing 10 mg of voclosporin
Studies 348-102-00010, AUR-VCS-2015-J01, AUR-VCS-2018-01, AUR-VCS-2021-02, AUR-VCS-2012-01, AUR-VCS-2016-01, AUR-VCS-2016-02, and AUR-VCS-2014-01	Formulation C (proposed formulation): Each capsule containing 7.9 mg of voclosporin

The concentrations of unchanged voclosporin and its metabolites, IM4n and IM9, in whole blood and urine were measured using LC-MS or LC-MS/MS methods. The concentrations of unchanged voclosporin in breast milk were determined using the LC-MS/MS method. The LLOQ for unchanged voclosporin was 0.1 to 2 ng/mL in whole blood, 1 ng/mL in urine, and 0.5 ng/mL in breast milk. For its metabolites IM4n and IM9, the LLOQ was 2 to 5 ng/mL in whole blood and 1 ng/mL in urine.

6.1.1 Studies using human biological samples

6.1.1.1 Plasma protein binding and distribution in blood cells (CTD 4.2.2.3-01 to 4.2.2.3-03)

When ^{14}C-labeled voclosporin (50-800 ng/mL) was added to human plasma, the plasma protein binding was 96.7% to 97.3%.

When IM9 (0.1-10 μmol/L) was added to human plasma, human serum albumin solution, and α1-acid glycoprotein solution, the protein binding was 61.3% to 72.4%, 23.7% to 34.4%, and 50.7% to 64.3%, respectively.

Distribution of voclosporin (10-600 ng/mL) in blood cells was investigated using human blood samples. The ratio of concentration (blood/plasma) ranged from 0.9 to 1.4 at 4°C and from 1.5 to 6.3 at 22°C.

6.1.1.2 Investigation of metabolites *in vitro* (CTD 4.2.2.4-06)

The metabolism of voclosporin, voclosporin (containing 45%-50% trans isomer), and the cis isomer of voclosporin (9.9 μmol/L) was evaluated using human liver microsomes. IM4n and IM9 were detected as the main metabolites in all cases, with no significant differences in their formation rates or quantities due to the cis-trans isomer ratio. The primary metabolic pathway of voclosporin in humans was oxidative metabolism.

6.1.1.3 Investigation of enzymes involved in the metabolism of voclosporin (CTD 4.2.2.4-08)

Using human liver microsomes, the correlation between the formation rate of metabolites of voclosporin (containing 45%-50% trans isomer; 1,000 ng/mL) and the metabolic activity of various cytochrome P450 (CYP) isoforms (CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, CYP3A4/5, and CYP4A9/11) toward their substrates[8)] was investigated. A positive correlation was observed between the metabolic activity of CYP3A4 and CYP3A5 and the formation rate of metabolites of voclosporin (containing 45%-50% trans isomer), with correlation coefficients ranging from 0.90 to 0.98. Positive correlations were found between the metabolic activity of CYP2B6 and CYP2C8 and the formation rate of metabolites of voclosporin (containing 45%-50% trans isomer),[9)] with correlation coefficients of 0.51 to 0.59 for CYP2B6 and 0.52 to 0.57 for CYP2C8.

When voclosporin (containing 45%-50% trans isomer, 4,000 ng/mL) and inhibitors[10)] of CYP isoforms (CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A4) were added to human liver microsomes, ketoconazole (0.5 μmol/L), a CYP3A4 inhibitor, reduced the mean concentration of voclosporin metabolites by approximately 85%.

The applicant's explanation:
Based on the results of *in vitro* studies using human liver microsomes, no significant differences were observed in the formation rates or quantities of the main metabolites (IM4n and IM9) between voclosporin and voclosporin (containing 45%-50% trans isomer) [see Section 6.1.1.2]. This suggests that CYP3A4 and CYP3A5 are primarily responsible for the metabolism of voclosporin. Since the metabolic activities of CYP2B6 and CYP2C8 correlated with those of CYP3A4 and CYP3A5

8) The following were used:
7-ethoxyresorufin for CYP1A2, coumarin for CYP2A6, (S)-mephenytoin for CYP2B6, paclitaxel for CYP2C8, diclofenac for CYP2C9, (S)-mephenytoin for CYP2C19, dextromethorphan for CYP2D6, chlorzoxazone for CYP2E1, testosterone for CYP3A4/5, and lauric acid for CYP4A9/11.
9) Metabolites AM4n-2, AM9, and AM1-diol-2.
10) The following were used: Furafylline for CYP1A2, sulfaphenazole for CYP2C9, omeprazole and tranylcypromine for CYP2C19, quinidine for CYP2D6, and ketoconazole for CYP3A4.

(correlation coefficients CYP2B6, 0.58; CYP2C8, 0.57), the observed correlation with CYP2B6 and CYP2C8 activity in Study ISA01-06 reflects the significant contribution of CYP3A4 and CYP3A5 to the metabolism of voclosporin. Thus, no definitive involvement of CYP2B6 or CYP2C8 in the metabolism of voclosporin was suggested.

6.1.1.4 Inhibitory effects of voclosporin and its metabolites on human hepatic drug-metabolizing enzymes (CTD 4.2.2.4-13 and 4.2.2.4-14)

The inhibitory effects of voclosporin (0.4-9.9 µmol/L) on CYP isoforms (CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A4/5) were evaluated using human liver microsomes. Voclosporin exhibited strong inhibitory effect against CYP3A4/5 ($IC_{50,}$ 1.2 µmol/L) but did not inhibit other CYP isoforms within the tested concentration range. Voclosporin did not exhibit any notable time-dependent inhibitory effects on any CYP isoforms.

The inhibitory effects of IM9 (a metabolite of voclosporin, 0.003-3 µmol/L) on CYP isoforms (CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A) were also evaluated using human liver microsomes. IM9 did not exhibit any significant inhibitory effects on any of the CYP isoforms within the tested concentration range.

6.1.1.5 Inductive effects of voclosporin on human hepatic drug-metabolizing enzymes (CTD 4.2.2.4-17)

Voclosporin (0.03-7 µmol/L) was incubated with human hepatocytes and its inductive effects on each CYP isoform (CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, and CYP3A4/5) were investigated. Voclosporin did not exhibit clear inductive effects on the messenger ribonucleic acid (mRNA) expression levels of CYP1A2, CYP2B6, CYP2C8, CYP2C9, and CYP3A4, nor on the enzymatic activity of CYP2C19, within the concentration range tested.

6.1.1.6 Studies on transport mediated by transporters (CTD 4.2.2.6-01 and 4.2.2.6-02)

The P-gp-mediated transport of ^{14}C-labeled voclosporin (0.4-4 µmol/L) was investigated using human colon cancer-derived cell (Caco-2 cell) monolayers. Voclosporin was suggested to be a substrate of P-gp.

Breast cancer resistance protein (BCRP)-mediated transport of voclosporin (0.3-10 µmol/L) was investigated using BCRP-expressing Mardin-Darby canine kidney cells (MDCKII cells). Voclosporin was shown not to be a substrate of BCRP.

Organic anion transporting polypeptide (OATP)1B1- and OATP1B3-mediated transport of voclosporin (0.03-1 µmol/L) was investigated using human embryonic kidney cell line 293 (HEK293) cells expressing OATP1B1 and OATP1B3. Voclosporin was shown not to be a substrate of either OATP1B1 or OATP1B3.

6.1.1.7 Investigation of transporter inhibitory effects (CTD 4.2.2.6-01 to 4.2.2.6-04)

The inhibitory effects of ^{14}C-labeled voclosporin (0.04-4 µmol/L) on P-gp were investigated using Caco-2 cell monolayers. Voclosporin was suggested to have inhibitory effects on P-gp.

The inhibitory effects of voclosporin (0.01-10 μmol/L) on the transport of BCRP substrates were investigated using membrane vesicles expressing BCRP. Voclosporin showed inhibitory effects on BCRP, with an IC_{50} value exceeding 10 μmol/L.

The inhibitory effects of voclosporin (0.01-10 μmol/L) on the transport of OATP1B1 and OATP1B3 substrates were investigated using Chinese hamster ovary (CHO) cells expressing OATP1B1 and OATP1B3. Voclosporin showed inhibitory effects on OATP1B1 and OATP1B3, with IC_{50} values of 0.49 and 0.24 μmol/L, respectively.

The inhibitory effects of voclosporin (0.2-2 μmol/L) on the transport of substrates for organic anion transporter (OAT)1, OAT3, organic cation transporter (OCT)2, multidrug and toxin extrusion (MATE)1, and MATE2-K were investigated using HEK293 cells expressing these transporters. Voclosporin did not exhibit clear inhibitory effects on OAT1, OAT3, OCT2, MATE1, or MATE2-K.

6.2 Clinical pharmacology

6.2.1 Phase I single and multiple dose study in healthy Japanese adults (CTD 5.3.3.3-01 [Reference data], Study AUR-VCS-2015-J01 [October to December 2016])

A placebo-controlled, randomized, double-blind study was conducted at a single study site in foreign country to evaluate the pharmacokinetics and safety of single and multiple oral doses of voclosporin in healthy Japanese adults (target sample size, 40 subjects [10 per group, including 2 in the placebo group and 8 in the voclosporin group]).

A single oral dose of placebo or voclosporin 0.25, 0.5, 1.0, or 1.5 mg/kg was administered on Day 1 under fasted conditions, followed by multiple oral administrations[11)] twice daily under fasted conditions from Day 3 to Day 13.

All 40 subjects who received the study drug were included in the safety analysis population, of which, 32 subjects who received voclosporin were included in the pharmacokinetic analysis population.

Table 15 shows the whole-blood pharmacokinetic parameters of voclosporin after single and multiple oral administrations. Within the examined dose range, the C_{max} and $AUC_{0–24h}$ of voclosporin increased more than proportionally to the dose.

11) On Day 13, only the morning dose was administered.

Table 15. Whole-blood pharmacokinetic parameters of voclosporin following single and multiple oral administration in healthy Japanese adults

Voclosporin	Measuring time point	N	C_{max} (ng/mL)	t_{max}[a)] (h)	$AUC_{0\text{-}24h}$ (ng•h/mL)	$t_{1/2}$ (h)
0.25 mg/kg	Day 1	8	46.6 ± 10.9	1.85 (1.12, 2.55)	199 ± 33.8[b)]	NC
	Day 13	8	70.3 ± 19.6	1.57 (1.08, 2.13)	372 ± 104	27.1 ± 4.27
0.5 mg/kg	Day 1	8	130 ± 36.4	1.55 (1.10, 2.55)	492 ± 201	NC
	Day 13	8	160 ± 56.7	1.56 (1.08, 4.07)	921 ± 399	29.6 ± 4.58[c)]
1.0 mg/kg	Day 1	8	314 ± 70.0	1.57 (1.53, 2.57)	1,260 ± 245	NC
	Day 13	8	416 ± 46.7	2.12 (1.57, 2.55)	2,510 ± 317	29.9 ± 4.00
1.5 mg/kg	Day 1	8	441 ± 131	2.09 (1.53, 2.57)	1,780 ± 498	NC
	Day 13	8	619 ± 82.5	2.00 (1.50, 3.00)	4,390 ± 945	30.6 ± 3.81[c)]

Mean ± SD; NC, Non-calculable
a) Median (min., max.); b) N = 6; c) N = 7

Adverse events were observed in 37.5% (3 of 8) of subjects in the placebo group, 62.5% (5 of 8) of subjects in the voclosporin 0.25 mg/kg group, 37.5% (3 of 8) of subjects in the 0.5 mg/kg group, 25.0% (2 of 8) of subjects in the 1.0 mg/kg group, and 100% (8 of 8) of subjects in the 1.5 mg/kg group. Adverse drug reactions were reported in 12.5% (1 of 8) of subjects in the placebo group, 12.5% (1 of 8) of subjects in the 0.5 mg/kg group, 25.0% (2 of 8) of subjects in the 1.0 mg/kg group, and 100% (8 of 8) of subjects in the 1.5 mg/kg group. No deaths, serious adverse events, nor adverse events leading to treatment discontinuation were observed.

6.2.2 Phase I study (effect of food) (CTD 5.3.1.1-02, Study 348-102-00010 [[redacted] to [redacted] 20[redacted]])

A randomized, open-label, two-treatment, two-period crossover study was conducted at a single study site in Japan to evaluate the effect of food on the pharmacokinetics of voclosporin after a single oral administration in healthy Japanese adults (target sample size, 16 subjects).

A single oral dose of voclosporin 23.7 mg was administered under fasted conditions or within 10 minutes after completing a high-fat meal[12)] consumed within 20 minutes. A 9-day washout period was specified between each dosing period.

All 16 subjects who received voclosporin were included in both the safety and pharmacokinetic analysis populations.

Table 16 shows the whole-blood pharmacokinetic parameters of voclosporin following single oral administration under fasted or fed conditions. The geometric mean ratios [90% confidence interval (CI)] of administration under fed condition to administration under fasted condition for C_{max} and AUC_{inf} were 0.91 [0.77, 1.09] and 1.14 [1.02, 1.28], respectively, indicating no significant effect of food on the pharmacokinetics of voclosporin.

[12)] Approximately 50% of the total 900 to 1,000 kcal calories comprised lipids.

Table 16. Whole-blood pharmacokinetic parameters of voclosporin following a single oral administration under fasted or fed conditions in healthy Japanese adults

Condition of administration	N	C_{max} (ng/mL)	t_{max}[a)] (h)	AUC_{inf} (ng▪h/mL)	$t_{1/2}$ (h)
Fasted	16	115 ± 19.9	1.50 (1.00, 2.50)	455 ± 110[b)]	13.1 ± 4.6[b)]
Fed	16	110 ± 33.4	2.00 (1.50, 4.00)	522 ± 179	14.2 ± 6.8

Mean ± SD
a) Median (min., max.); b) N = 15

Adverse events were observed in 12.5% (2 of 16) of subjects during the administration under fasted condition and 6.3% (1 of 16) of subjects during the administration under fed condition. Adverse drug reactions were reported in 6.3% (1 of 16) of subjects during both the administrations under fasted and fed conditions. No deaths, serious adverse events, nor adverse events leading to treatment discontinuation were observed.

6.2.3 Phase I study (mass balance study) (CTD 5.3.3.1-03, Study LX211-05 [[redacted]])

An open-label study was conducted at a single study site in foreign country to evaluate the mass balance and related parameters of ^{14}C-labeled voclosporin after a single oral administration in healthy non-Japanese adults (target sample size, 6 subjects).

A single oral dose of approximately 70 mg of ^{14}C-labeled voclosporin was administered under fasted conditions.

All 6 subjects who received the study drug were included in the pharmacokinetic analysis population.

Table 17 shows the whole-blood pharmacokinetic parameters of voclosporin. The ratios of the AUCs for unchanged voclosporin, the cis-isomer of unchanged voclosporin, and their metabolites to total radioactivity in whole blood were 38.5%, 2.54%, and 59.1%, respectively.

Table 17. Whole-blood pharmacokinetic parameters of ^{14}C-labeled voclosporin following a single oral administration

Voclosporin dose	N	Analyte	C_{max} (ng/mL)	t_{max}[a)] (h)	AUC_{inf} (ng▪h/mL)	$t_{1/2}$ (h)
70 mg	6	Cis-isomer of unchanged voclosporin	18.3 ± 2.49	1.01 (1.00, 2.00)	82.1 ± 22.5	20.0 ± 7.55
		Unchanged voclosporin	224 ± 34.5	1.25 (1.00, 1.50)	1,245 ± 274	58.9 ± 11.9
		Unchanged voclosporin and cis-isomer of unchanged voclosporin	242 ± 35.7	1.25 (1.00, 1.50)	1,324 ± 294	58.2 ± 11.8
		Unchanged voclosporin, cis-isomer of unchanged voclosporin, and their metabolites	492 ± 69.0[b)]	1.50 (1.50, 2.00)	3,237 ± 401[c)]	11.0 ± 0.419

Mean ± SD
a) Median (min., max.); b) The unit is ng eq/mL; c) The unit is ng eq▪h /ml.

In whole blood up to 24 hours post-dose of ^{14}C-labeled voclosporin, the main components detected were unchanged voclosporin, IM9, IM1-diol-1, IM4n9, IM4n, and IM1w, with their respective proportions to total blood radioactivity being 37.1%, 16.7%, 9.47%, 4.03%, 4.00%, and 3.40%, respectively.

By 168 hours post-dose, 2.11% of the administered radioactivity was excreted in urine and 92.7% in feces. Up to 48 hours post-dose, unchanged voclosporin was the primary component detected in both urine and feces, comprising 0.25% and 5.00% of the administered radioactivity, respectively.

6.2.4 Phase I study (study on distribution in milk) (CTD 5.3.3.1-04, Study AUR-VCS-20[redacted]-04 [[redacted] 20[redacted] to [redacted] 20[redacted]])

An open-label study was conducted at a single study site in foreign country to evaluate the voclosporin excretion in milk in lactating healthy non-Japanese adult women (target sample size, 12 subjects).

A single oral dose of 23.7 mg of voclosporin was administered.

All 12 subjects who received voclosporin and provided milk samples up to 48 hours post-dose were included in the pharmacokinetic analysis population.

Regarding the pharmacokinetic parameters of voclosporin in whole blood and milk, the milk-to-whole blood concentration ratio of voclosporin 48 hours after administration was 0.66, indicating that voclosporin is excreted into milk. The median (minimum, maximum) t_{max} of voclosporin concentration in milk was 3.99 (1.99, 9.99) hours.

6.2.5 Global phase III study (CTD 5.3.5.1-02, Study AUR-VCS-2016-01 [May 2017 to October 2019])

The pharmacokinetics of voclosporin following multiple oral administration was evaluated in non-Japanese and Japanese patients with LN [For an overview of the study, and efficacy and safety results, see Section 7.2.1.].

Placebo or voclosporin 23.7 mg was administered twice daily under fasted conditions for 52 weeks.

Table 18 shows the whole blood concentrations of voclosporin following multiple oral administration in patients with LN.

Table 18. Whole blood concentrations of voclosporin following multiple oral administration in patients with LN

Dosage regimen	Measuring time point	C_{trough} (ng/mL)	C_{2h} (ng/mL)
23.7 mg twice daily	Week 24	20.1 ± 29.9 (136)	94.6 ± 62.4 (124)
	Week 52	17.8 ± 20.8 (136)	93.0 ± 61.9 (126)

Mean ± SD (number of subjects)

6.2.6 Phase I study (effect of renal impairment) (CTD 5.3.3.3-02, Study ISA07-08 [[redacted] 20[redacted] to [redacted] 20[redacted]])

An open-label study was conducted at 4 foreign study sites to evaluate the effect of renal impairment on the pharmacokinetics of voclosporin in non-Japanese subjects with normal renal function (CL_{cr}: ≥90 mL/min), mild (≥60 to <90 mL/min), moderate (≥30 to <60 mL/min), and severe (<30 mL/min) renal impairment (target sample size; 32 subjects, 8 per group).

For non-Japanese subjects with normal renal function, mild renal impairment, and moderate renal impairment, voclosporin was administered as a single oral dose of 0.4 mg/kg on Day 1, followed by multiple oral doses of 0.4 mg/kg twice daily from Day 3 to Day 10.[13)] For subjects with severe renal impairment, a single oral dose of 0.4 mg/kg was administered.

A total of 32 subjects who were enrolled in the study and received the study drug (7 with normal renal function, 5 with mild renal impairment, 12 with moderate renal impairment, and 8 with severe renal impairment) were included in the pharmacokinetic analysis population.

The geometric mean ratios [90% CI] of whole blood pharmacokinetic parameters of voclosporin on Day 10 for subjects with mild renal impairment compared to those with normal renal function were 1.02 [0.69, 1.51] for C_{max} and 0.95 [0.66, 1.36] for $AUC_{0\text{-}12h}$. The geometric mean ratios of whole blood pharmacokinetic parameters of voclosporin on Day 10 for subjects with moderate renal impairment compared to those with normal renal function were 1.11 [0.80, 1.53] for C_{max} and 1.06 [0.78, 1.44] for $AUC_{0\text{-}12h}$. The geometric mean ratios of whole blood pharmacokinetic parameters of voclosporin for subjects with severe renal impairment compared to those with normal renal function were 1.46 [1.05, 2.03] for C_{max} and 1.74 [1.20, 2.51] for $AUC_{0\text{-}48h}$.

6.2.7 Phase I study (effect of hepatic impairment) (CTD 5.3.3.3-03, Study ISA07-09 [[redacted] 20[redacted] to [redacted] 20[redacted]])

An open-label clinical study was conducted at 3 foreign study sites to evaluate the effect of hepatic impairment on the pharmacokinetics of voclosporin in non-Japanese subjects with normal hepatic function, mild (Child-Pugh class A), and moderate (Child-Pugh class B) liver impairment (target sample size; 18 subjects, 6 per group).

For subjects with normal hepatic function and those with mild hepatic impairment, voclosporin was administered as a single oral dose of 0.4 mg/kg on Day 1, followed by multiple oral doses of 0.4 mg/kg twice daily from Day 3 to Day 10.[13)] For subjects with moderate hepatic impairment, a single oral dose of 0.4 mg/kg was administered.

A total of 18 subjects who were enrolled in the study and received the study drug (6 per group) were included in the pharmacokinetic analysis population.

The geometric mean ratios [90% CI] of whole blood pharmacokinetic parameters of voclosporin on Day 10 for subjects with mild hepatic impairment compared to those with normal hepatic liver function were 1.48 [0.91, 2.40] for C_{max} and 1.79 [1.07, 2.98] for $AUC_{0\text{-}12h}$. The geometric mean ratios of whole blood pharmacokinetic parameters of voclosporin on Day 1 for subjects with moderate hepatic impairment compared to those with normal liver function, were 1.45 [0.97, 2.17] for C_{max} and 1.96 [1.25, 3.07] for $AUC_{0\text{-}48h}$.

13) On Day 10, only a morning dose was administered.

6.2.8 Phase I study (drug-drug interaction with ketoconazole) (CTD 5.3.3.4-03, Study LX211-06 [[redacted] to [redacted] 20[redacted]])

In vitro studies indicated that the metabolism of voclosporin is primarily mediated by CYP3A4 [see Section 6.1.1.3] and that voclosporin is a substrate of P-gp [see Section 6.1.1.6]. Therefore, an open-label study was conducted in non-Japanese healthy adults (target sample size, 24 subjects) to investigate the effects of ketoconazole, a CYP3A4 and P-gp inhibitor, on the pharmacokinetics of voclosporin.

Table 19 shows the geometric mean ratios of C_{max} and $AUC_{0\text{-}12h}$ of voclosporin co-administered with ketoconazole to those of voclosporin alone.

Table 19. Geometric mean ratios of whole blood pharmacokinetic parameters of voclosporin co-administered with ketoconazole to those of voclosporin alone

Voclosporin	Concomitant drug (p.o.)	N	C_{max}	$AUC_{0\text{-}12h}$
0.4 mg/kg	Ketoconazole[a)]	11	6.45 [5.02, 8.29]	18.5 [15.9, 21.6]

Geometric mean ratio [90% CI]

a) From Day 1 to Day 19, voclosporin was administered at 0.4 mg/kg twice daily, and from Day 11 to Day 19, ketoconazole was administered at 400 mg once daily.
Geometric mean ratio = C_{max} or $AUC_{0\text{-}12h}$ of voclosporin co-administered with ketoconazole / C_{max} or $AUC_{0\text{-}12h}$ of voclosporin alone

6.2.9 Phase I study (drug-drug interaction study with rifampicin) (CTD 5.3.3.4-06, Study LX211-09 [[redacted] 20[redacted] to [redacted] 20[redacted]])

In vitro studies indicated that the metabolism of voclosporin is primarily mediated by CYP3A4 [see Section 6.1.1.3] and that voclosporin is a substrate of P-gp [see Section 6.1.1.6]. An open-label study was conducted in non-Japanese healthy adults (target sample size, 24 subjects) to investigate the effects of rifampicin, a CYP3A4 and P-gp inducer, on the pharmacokinetics of voclosporin.

Table 20 shows the geometric mean ratios of C_{max} and AUC_{inf} of voclosporin co-administered with rifampicin to those of voclosporin alone.

Table 20. Geometric mean ratio of whole blood pharmacokinetic parameters of voclosporin co-administered with rifampicin to those of voclosporin alone

Voclosporin	Concomitant drug (p.o.)	N	C_{max}	AUC_{inf}
0.4 mg/kg	Rifampicin[a)]	22	0.32 [0.28, 0.37]	0.13 [0.11, 0.15][b)]

Geometric mean ratio [90% CI]

a) On Day 1, a single dose of voclosporin 0.4 mg/kg was administered once daily. From Day 6 to Day 16, rifampicin 600 mg was administered once daily, followed by a single dose of voclosporin 0.4 mg/kg on Day 16. Geometric mean ratio = C_{max} or AUC_{inf} of voclosporin co-administered with rifampin / C_{max} or AUC_{inf} of voclosporin alone

b) N = 20

6.2.10 Phase I study (drug-drug interaction study with verapamil) (CTD 5.3.3.4-04, Study LX211-07 [[redacted] to [redacted] 20[redacted]])

In vitro studies indicated that the metabolism of voclosporin is primarily mediated by CYP3A4 [see Section 6.1.1.3] and that voclosporin is a substrate of P-gp [see Section 6.1.1.6]. An open-label study was conducted in non-Japanese healthy adults (target sample size, 24) to investigate the effects of verapamil, a strong P-gp and moderate CYP3A4 inhibitor, on the pharmacokinetics of voclosporin.

Table 21 shows the geometric mean ratios of C_{max} and $AUC_{0\text{-}12h}$ of voclosporin co-administered with verapamil to those of voclosporin alone.

Table 21. Geometric mean ratios of whole blood pharmacokinetic parameters of voclosporin co-administered with verapamil to those of voclosporin alone

Voclosporin	Concomitant drug (p.o.)	N	C_{max}	$AUC_{0\text{-}12h}$
0.4 mg/kg	Verapamil[a)]	20	2.08 [1.89, 2.28]	2.71 [2.56, 2.87]

Geometric mean ratio [90% CI]

a) From Day 1 to Day 20, voclosporin 0.4 mg/kg was administered twice daily. From Day 11 to Day 20, verapamil 80 mg was administered 3 times daily. Geometric mean ratio = C_{max} or $AUC_{0\text{-}12h}$ of voclosporin co-administered with verapamil / C_{max} or $AUC_{0\text{-}12h}$ of voclosporin alone

6.2.11 Phase I study (drug-drug interaction study with midazolam) (CTD 5.3.3.4-02, Study ISA07-07 [[redacted] 20[redacted]])

In vitro studies indicated that voclosporin inhibits CYP3A4 [see Section 6.1.1.4]. An open-label study was conducted in non-Japanese healthy adults (target sample size, 24 subjects) to investigate the effects of voclosporin on the pharmacokinetics of midazolam, a substrate of CYP3A4.

Table 22 shows the geometric mean ratios of C_{max} and AUC_{inf} of midazolam co-administered with voclosporin to those of midazolam alone.

Table 22. Geometric mean ratios of plasma pharmacokinetic parameters of midazolam co-administered with voclosporin to those of midazolam alone

Voclosporin	Concomitant drug (p.o.)	N	C_{max}	AUC_{inf}
0.4 mg/kg	Midazolam[a)]	22	0.89 [0.80, 0.99]	1.02 [0.93, 1.12]

Geometric mean ratio [90% CI]

a) On Day 1, a single dose of midazolam 7.5 mg was administered once daily. From Day 2 to Day 12, voclosporin 0.4 mg/kg was administered twice daily, followed by a single dose of midazolam 7.5 mg on Day 12. Geometric mean ratio = C_{max} or AUC_{inf} of midazolam co-administered with voclosporin / C_{max} or AUC_{inf} of midazolam alone

6.2.12 Phase I study (drug-drug interaction study with digoxin) (CTD 5.3.3.4-05, Study LX211-08 [[redacted] to [redacted] 20[redacted]])

In vitro studies indicated that voclosporin inhibits P-gp [see Section 6.1.1.7]. An open-label study was conducted in non-Japanese healthy adults (target sample size, 24 subjects) to investigate the effects of voclosporin on the pharmacokinetics of digoxin, a substrate of P-gp.

Table 23 shows the geometric mean ratios of C_{max} and $AUC_{0\text{-}24h}$ of digoxin co-administered with voclosporin to those of digoxin alone.

Table 23. Geometric mean ratios of plasma pharmacokinetic parameters of digoxin co-administered with voclosporin to those of digoxin alone

Voclosporin	Concomitant drug (p.o.)	N	C_{max}	$AUC_{0\text{-}24h}$
0.4 mg/kg	Digoxin[a)]	23	1.51 [1.40, 1.63]	1.25 [1.19, 1.31]

Geometric mean ratio [90% CI]

a) On Day 1, a single dose of digoxin 0.5 mg was administered. From Day 2 to Day 18, digoxin 0.25 mg was administered once daily, followed by twice daily dose of voclosporin 0.4 mg/kg from Day 8 to Day 18. Geometric mean ratio = C_{max} or $AUC_{0\text{-}24h}$ of digoxin co-administered with voclosporin / C_{max} or $AUC_{0\text{-}24h}$ of digoxin alone

6.2.13 Phase I study (drug-drug interaction study with MMF) (CTD 5.3.3.4-01, Study AUR-VCS-2018-01 [[redacted] 20[redacted] to [redacted] 20[redacted]])

Voclosporin is used in combination with MMF, and cyclosporine A, a CNI, is known to inhibit the enterohepatic circulation of MMF (the package insert of "Neoral Oral Solution 10%, etc."). An

open-label study was conducted in non-Japanese patients with SLE (target sample size, 24 subjects) to investigate the effects of voclosporin on the pharmacokinetics of MMF.

Table 24 shows the geometric mean ratios of C_{max} and $AUC_{0\text{-}12h}$ of mycophenolic acid and mycophenolic acid glucuronide (the active metabolite and inactive metabolite of MMF, respectively) following co-administration of MMF with voclosporin to those of the metabolites after administration of MMF alone.

Table 24. Geometric mean ratios of whole blood pharmacokinetic parameters of mycophenolic acid and mycophenolic acid glucuronide following co-administration of MMF with voclosporin to those of the metabolites after administration of MMF alone

Voclosporin	Concomitant drug (p.o.)	Analyte	N	C_{max}	$AUC_{0\text{-}12h}$
0.4 mg/kg	MMF[a)]	Mycophenolic acid	24	0.94 [0.77, 1.16]	1.09 [0.94, 1.26]
		Mycophenolic acid glucuronide	24	1.12 [0.98, 1.28]	1.27 [1.07, 1.49]

Geometric mean ratio [90% CI]

a) From ≥28 days before screening and during the study period, MMF 1.0 g was administered twice daily. From the evening of Day 1 to the morning of Day 7, voclosporin 23.7 mg was administered twice daily. Geometric mean ratio = C_{max} or $AUC_{0\text{-}12h}$ of mycophenolic acid and mycophenolic acid glucuronide following co-administration of MMF with voclosporin / C_{max} or $AUC_{0\text{-}12h}$ of mycophenolic acid and mycophenolic acid glucuronide after administration of MMF alone

6.2.14 Phase I study (drug-drug interaction study with simvastatin) (CTD 5.3.3.4-07, Study AUR-VCS-2021-02 [December 2021 to April 2022])

In vitro studies indicated that voclosporin inhibits BCRP, OATP1B1, and OATP1B3 [see Section 6.1.1.7]. An open-label study was conducted in non-Japanese healthy adults (target sample size, 24 subjects) to investigate the effects of voclosporin on the pharmacokinetics of simvastatin, a substrate of BCRP, and its active metabolite, simvastatin acid, which is a substrate of OATP1B1 and OATP1B3.

Table 25 shows the geometric mean ratios of C_{max} and AUC_{inf} of simvastatin and simvastatin acid following co-administration of simvastatin with voclosporin to those of simvastatin and simvastatin acid after administration of simvastatin alone.

Table 25. Geometric mean ratios of plasma pharmacokinetic parameters of simvastatin and simvastatin acid following co-administration of simvastatin with voclosporin to those of simvastatin and simvastatin acid after administration of simvastatin alone

Voclosporin	Concomitant drug (p.o.)	Analyte	N	C_{max}	AUC_{inf}
23.7 mg twice daily	Simvastatin[a)]	Simvastatin	24	1.60 [1.38, 1.84]	0.94 [0.82, 1.07]
		Simvastatin acid	24	3.10 [2.58, 3.73]	1.84 [1.53, 2.20]

Geometric mean ratio [90% CI]

a) On Day 1 and Day 8, a single dose of simvastatin 40 mg was administered once daily. From Day 2 to Day 8, voclosporin 23.7 mg was administered twice daily. Geometric mean ratio = C_{max} or AUC_{inf} of simvastatin and simvastatin acid following co-administration of simvastatin with voclosporin / C_{max} or AUC_{inf} of simvastatin and simvastatin acid after administration of simvastatin alone

6.2.15 Phase I study (QT/QTc evaluation study) (CTD 5.3.4.1-01, Study ISA03-11 [[redacted] to [redacted] 20[redacted]])

A placebo- and active drug-controlled, randomized, double-blind study was conducted in healthy non-Japanese adults (target sample size, 240 subjects) to evaluate the effect of a single oral administration of voclosporin on QT/QTc.

Placebo, voclosporin 0.5, 1.5, 3.0, and 4.5 mg/kg, or the positive control moxifloxacin 400 mg was administered orally under fasted conditions as a single dose.

All 240 subjects who received the study drug were included in the QTc analysis population, safety analysis population, and pharmacokinetic analysis population.

For QTc, the largest difference of change from baseline in Fridericia-corrected QT interval (QTcF) (ΔΔQTcF [upper limit of 95% one-sided CI]) for voclosporin 0.5, 1.5, 3.0, and 4.5 mg/kg compared to placebo was 6.4 (11.6) ms, 14.9 (20.1) ms, 25.7 (30.9) ms, and 34.6 (39.8) ms, respectively. In all voclosporin groups, the upper limit of the 95% confidence interval for ΔΔQTcF exceeded 10 ms. For moxifloxacin, the maximum ΔΔQTcF value (lower limit of the 95% one-sided CI) was 17.9 (12.7) ms, with the lower limit of the 95% confidence interval exceeding 5 ms, indicating that the study had sufficient analytical sensitivity. The above results suggest that voclosporin may have a potential risk of prolonging QT/QTc intervals.

Table 26 shows the pharmacokinetic parameters of voclosporin in whole blood after a single oral administration of 0.5, 1.5, 3.0, or 4.5 mg/kg.

Table 26. Pharmacokinetic parameters of voclosporin in whole blood after a single oral administration of voclosporin

Voclosporin	Analyte	N	C_{max} (ng/mL)	t_{max}[a)] (h)	AUC_{inf} (ng▪h/mL)	$t_{1/2}$ (h)
0.5 mg/kg	Cis isomer	40	3.0 ± 0.9	1.0 (0.5, 2.5)	17.0 ± 42.5	5.2 ± 18.4
	Trans isomer	40	112 ± 28.2	1.5 (1.0, 2.5)	483 ± 125	7.4 ± 0.9
1.5 mg/kg	Cis isomer	40	13.0 ± 3.7	1.5 (1.0, 3.0)	42.4 ± 15.6	2.2 ± 1.0
	Trans isomer	40	558 ± 148	1.5 (1.0, 3.0)	2,465 ± 763	7.8 ± 0.9
3.0 mg/kg	Cis isomer	40	24.0 ± 7.4	1.5 (1.0, 4.0)	103 ± 32.6	3.4 ± 0.9
	Trans isomer	40	1,026 ± 269	1.5 (1.0, 4.0)	5,516 ± 1,447	7.6 ± 1.0
4.5 mg/kg	Cis isomer	40	31.5 ± 10.5	2.0 (1.0, 4.0)	167 ± 82.2	4.4 ± 3.0
	Trans isomer	40	1,122 ± 284	1.5 (1.0, 4.0)	7,223 ± 2,894	7.7 ± 0.9

Mean ± SD
a) Median (min., max.)

Adverse events were observed in 12.5% (5 of 40) of subjects in the placebo group, 25.0% (10 of 40) of subjects in the voclosporin 0.5 mg/kg group, 25.0% (10 of 40) of subjects in the 1.5 mg/kg group, 42.5% (17 of 40) of subjects in the 3.0 mg/kg group, 57.5% (23 of 40) of subjects in the 4.5 mg/kg group, and 20.0% (8 of 40) of subjects in the moxifloxacin group. Adverse drug reactions were observed in 7.5% (3 of 40) of subjects in the placebo group, 12.5% (5 of 40) of subjects in the voclosporin 0.5 mg/kg group, 20.0% (8 of 40) of subjects in the 1.5 mg/kg group, 37.5% (15 of 40) of subjects in the 3.0 mg/kg group, 55.0% (22 of 40) of subjects in the 4.5 mg/kg group, and 15.0% (6 of 40) of subjects in the moxifloxacin group. No deaths, serious adverse events, nor adverse events leading to treatment discontinuation were reported.

6.2.16 Phase I study (QT/QTc evaluation study) (CTD 5.3.4.1-02, Study ISA05-03 [[redacted] 20[redacted] to [redacted] 20[redacted]])

A placebo- and active drug-controlled, randomized, double-blind,[14] 4-treatment, 5-period crossover study was conducted to evaluate the effects of multiple oral administration of voclosporin on QT/QTc in healthy non-Japanese adults (target sample size, 60 subjects).

Placebo, voclosporin 0.3, 0.5, or 1.5 mg/kg was administered twice daily (morning doses were administered under fasted conditions) for 6 consecutive days. The positive control moxifloxacin 400 mg was administered as a single oral dose. A ≥10-day washout period was specified between each dosing periods.

All 60 subjects who received the study drug[15] were included in the QTc analysis population and safety analysis population. Pharmacokinetic analyses included 38 subjects during the placebo period, 37 subjects during the 0.3 and 1.5 mg/kg periods, and 36 subjects during the 0.5 mg/kg period.

For QT/QTc, the largest difference of change from baseline in QTcF between placebo and treatment (ΔΔQTcF) (upper limit of 95% one-sided CI) during steady state (Day 7) was 0.8 ms (4.7 ms) for the 0.3 mg/kg dose, 2.4 ms (6.2 ms) for the 0.5 mg/kg dose, and 2.8 ms (6.9 ms) for the 1.5 mg/kg dose. In all cases, the upper limit of the 95% confidence interval remained below 10 ms. For the moxifloxacin group, the maximum ΔΔQTcF (lower limit of 95% one-sided CI) was 22.7 ms (17.5) ms, with the lower limit of the 95% CI exceeding 5 ms, indicating that the study had sufficient analytical sensitivity. Thus, voclosporin did not show a tendency to prolong QT/QTc.

Table 27 shows the pharmacokinetic parameters of voclosporin in whole blood after multiple oral administration at doses of 0.3, 0.5, or 1.5 mg/kg.

Table 27. Pharmacokinetic parameters of voclosporin in whole blood following multiple oral administration

Voclosporin	N	C_{max} (ng/mL)	t_{max}[a] (h)	$AUC_{0\text{-}12h}$ (ng▪h/mL)
0.3 mg/kg	37	87.8 ± 28.7	1.5 (1.0, 3.0)	364 ± 169
0.5 mg/kg	36	215 ± 114	1.5 (1.0, 4.0)	840 ± 402
1.5 mg/kg	37	801 ± 171	2.5 (1.5, 4.0)	3,813 ± 1,283

Mean ± SD
a) Median (min., max.)

Adverse events were observed in 71.1% (32 of 45) of subjects during the placebo period, 79.1% (34 of 43) of subjects during the voclosporin 0.3 mg/kg period, 60.5% (26 of 43) of subjects during the 0.5 mg/kg period, 97.6% (41 of 42) of subjects during the 1.5 mg/kg period, and 51.6% (16 of 31) of subjects during the moxifloxacin period. Adverse drug reactions were observed in 55.6% (25 of 45) of subjects during the placebo period, 65.1% (28 of 43) of subjects during the voclosporin 0.3 mg/kg period, 53.5% (23 of 43) of subjects during the 0.5 mg/kg period, 95.2% (40 of 42) of subjects during the 1.5 mg/kg period, and 38.7% (12 of 31) of subjects during the moxifloxacin period. No deaths occurred. Serious adverse events were observed in 1 subject (active tuberculosis infection) during the

[14] Moxifloxacin administration was open-label.
[15] Of the 60 subjects, 20 subjects discontinued the study due to cohort-wide risk associated with tuberculosis detected in 1 subject.

0.3 mg/kg period and in 1 subject (human immunodeficiency virus [HIV] positivity) during the 1.5 mg/kg period. The active tuberculosis infection in 1 subject during the 0.3 mg/kg period was considered to be an adverse drug reaction. Adverse events leading to treatment discontinuation occurred in 1 subject (increased blood creatine phosphokinase) during the placebo period and in 2 subjects (rash maculo-papular and HIV positivity in 1 subject each) during the 1.5 mg/kg period. The increased blood creatine phosphokinase in 1 subject during the placebo period and the rash maculo-papular in 1 subject during the 1.5 mg/kg period were assessed as adverse drug reactions, but both resolved completely.

6.2.17 Population pharmacokinetic analysis (CTD 5.3.3.5-01)

Population pharmacokinetic analysis was conducted using pharmacokinetic data (312 subjects receiving voclosporin and 1,526 sampling points) from clinical studies of voclosporin in non-Japanese and Japanese patients with LN (AURA-LV and AURORA 1 studies) (software, NONMEM Version 7.4).

The pharmacokinetics of voclosporin in patients with LN were described using a two-compartment model with first-order absorption and elimination processes. Based on the covariate analysis,[16)] ethnicity (Asian or non-Asian) was selected as a determinant for the bioavailability of voclosporin. The population pharmacokinetic parameters estimated from the final model were CL/F of 41.2 L/h, Vc/F of 34.4 L, and ka of 0.19 h^{-1}.

An evaluation of dose-dependent exposure at daily doses of 23.7 to 39.5 mg (administered twice daily) revealed no significant differences in dose-adjusted median whole-blood voclosporin concentrations across the dose range tested.

6.R Outline of the review conducted by PMDA

Based on the submitted data and review results in Sections 6.R.1 to 6.R.6, PMDA concluded that the pharmacokinetics of voclosporin were appropriately evaluated. From the perspective of pharmacokinetics and clinical pharmacology, cautionary advice in the following situations should be included in the package insert: Administration to patients with LN with severe renal impairment or hepatic impairment; co-administration of voclosporin with drugs that inhibit or induce CYP3A or P-gp; and potential QT/QTc prolongation risks associated with voclosporin.

6.R.1 Differences in the pharmacokinetics of voclosporin between Japanese and non-Japanese subjects

The applicant's explanation about the differences in the pharmacokinetics of voclosporin between Japanese and non-Japanese subjects:

In the population pharmacokinetic analysis of patients with LN [see Section 6.2.17], the bioavailability of voclosporin in Asian patients was estimated to be 26% higher than that in non-Asian patients. Consequently, the $AUC_{0\text{-}12h}$ of Asian patients was estimated to be 22% higher than that of non-Asian patients. As the tolerability of voclosporin at 39.5 mg twice daily was confirmed in the AURA-LV

[16)] The following parameters were evaluated as possible covariates: Body weight, alanine aminotransferase (ALT), age, albumin, bilirubin, estimated glomerular filtration rate (eGFR), sex, ethnicity (Caucasian, Asian, Indian, and Black), and cholesterol for CL/F of voclosporin; age, sex, and ethnicity (Caucasian, Asian, Indian, and Black) for bioavailability; and body weight for V_C.

study, the difference in exposure at the clinical dose (23.7 mg twice daily) is unlikely to pose any clinical concern.

Table 28 shows trough and post-dose (2-hour) whole-blood concentrations following multiple oral administration of voclosporin in Japanese and non-Japanese patients (both Asian and non-Asian) in the global phase III study in patients with LN [see Section 6.2.5]. Although the Japanese subgroup included only 4 patients, no significant differences were observed between Japanese and non-Japanese patients in trough or 2-hour post-dose concentrations.

Table 28. Whole-blood voclosporin concentrations in Japanese and non-Japanese patients with LN

Ethnicity	Measuring time point	C_{trough} (ng/mL)	C_{2h} (ng/mL)
Japanese	Week 24	17.4 ± 9.61 (4)	99.2 ± 27.8 (4)
	Week 52	19.5 ± 16.4 (4)	133 ± 83.6 (4)
Non-Japanese (Asian)	Week 24	22.8 ± 42.5 (34)	105 ± 64.1 (31)
	Week 52	14.8 ± 8.57 (34)	89.9 ± 53.3 (33)
Non-Japanese (Non-Asian)	Week 24	19.3 ± 24.9 (98)	90.8 ± 63.0 (89)
	Week 52	18.8 ± 23.8 (98)	92.4 ± 64.0 (89)

Mean ± SD

The above findings suggest no significant differences in exposure between Japanese and non-Japanese patients with LN.

PMDA's view:
Due to limited data on voclosporin pharmacokinetics in Japanese patients, precise comparisons are challenging. Although the efficacy and safety profiles of Japanese patients in the global phase III study in patients with LN did not exhibit trends distinct from those of the overall population [see Sections 7.R.1.2 and 7.R.2.1], the possibility of pharmacokinetic differences between Japanese and non-Japanese patients with LN cannot be entirely excluded. Given the applicant's explanation of the relationship between dose and tolerability, however, there are no clinically significant safety concerns arising from the differences in the pharmacokinetics of voclosporin between Japanese and non-Japanese patients with LN.

6.R.2 Effects of renal impairment on the pharmacokinetics of voclosporin

The applicant's explanation about the impact of renal impairment on the pharmacokinetics of voclosporin:
In Study ISA07-08, the pharmacokinetics of voclosporin was evaluated in subjects with mild, moderate, and severe renal impairment.[17)] The results showed that the exposure to voclosporin in subjects with mild or moderate renal impairment was comparable to that in subjects with normal renal function [see Section 6.2.6]. Dose adjustment is therefore deemed unnecessary for patients with LN with mild or moderate renal impairment. However, as the AURORA 1 study excluded patients with LN with an estimated glomerular filtration rate (eGFR) of ≤45 mL/min/1.73 m², the efficacy and safety of voclosporin in patients with LN with moderate renal impairment have not been investigated in clinical studies. It is appropriate to caution that voclosporin should be used only when the expected therapeutic benefits are judged to outweigh the possible risks.

17) End-stage renal failure patients with an eGFR of <15 mL/min/1.73 m² were not included.

In subjects with severe renal impairment, the exposure to voclosporin was approximately 1.5 to 1.7 times higher than in subjects with normal renal function. While avoiding treatment with voclosporin in such patients is preferable, if the use of voclosporin is necessary, the dosage should be reduced to 15.8 mg twice daily to achieve comparable C_{max} and $AUC_{0\text{-}48h}$ values to those observed after administration of 23.7 mg in patients with LN with normal renal function.

Since the exposure to voclosporin in subjects with mild, moderate, or severe renal impairment based on classification by eGFR was similar to that observed with classification by creatinine clearance,[18)] the cautionary statements in the package insert will adopt the more commonly used eGFR-based classification.

PMDA's view:
The applicant's explanation about the administration of voclosporin to patients with LN with mild or moderate renal impairment is appropriate.

In the study on the effect of renal impairment (Study ISA07-08), subjects with severe renal impairment exhibited higher exposure to voclosporin compared to subjects with normal renal function. While rapid renal disorder could occur following voclosporin administration, patients with LN with severe renal impairment were not enrolled in the global phase III study [see Section 6.2.5]. As a result, the extent of risk for further deterioration of renal disorder in patients with LN with severe renal impairment remains unclear. Given these considerations, avoiding the administration of voclosporin in such patients is deemed appropriate. If the use of voclosporin is necessary despite the potential risks, the dose should be reduced to 15.8 mg twice daily, and the patient must be carefully monitored for renal function and other conditions. This caution should be explicitly stated in the package insert. Furthermore, since the safety and pharmacokinetics of voclosporin in patients with LN with renal impairment are insufficiently characterized, the applicant should continue gathering data on the impact of renal impairment on the safety of voclosporin.

6.R.3 Effects of hepatic impairment on the pharmacokinetics of voclosporin

The applicant's explanation about the impact of hepatic impairment on the pharmacokinetics of voclosporin:
In Study ISA07-09, the pharmacokinetics of voclosporin was evaluated in subjects with mild and moderate hepatic impairment. Compared with subjects with normal hepatic function, the C_{max} and $AUC_{0\text{-}12h}$ of voclosporin in subjects with mild hepatic impairment were 1.5-fold and 1.7-fold higher, respectively, while in subjects with moderate hepatic impairment, the C_{max} and $AUC_{0\text{-}48h}$ were 1.5-fold and 2.0-fold higher, respectively [see Section 6.2.7]. Based on these findings, reducing the dose to 15.8 mg (two-thirds of the clinical dose) in patients with LN with mild or moderate hepatic

18) In Study ISA07-08, the geometric mean ratios [90% CI] of C_{max} and $AUC_{0\text{-}12h}$ at 10 days post-dose in subjects with mild (eGFR ≥60 to ≤90 mL/min/1.73 m²) or moderate (eGFR ≥30 to <60 mL/min/1.73 m²) renal impairment relative to those in subjects with normal renal function were 0.92 [0.67, 1.28] and 0.99 [0.73, 1.33] for C_{max} and $AUC_{0\text{-}12h}$, respectively or 1.03 [0.66, 1.61] and 1.05 [0.70, 1.58] for C_{max} and $AUC_{0\text{-}12h}$, respectively.
The geometric mean ratios [90% CI] of C_{max} and $AUC_{0\text{-}48h}$ at 1 day post-dose in subjects with severe renal impairment (eGFR <30 mL/min/1.73 m²) relative to those in subjects with normal renal function were 1.33 [0.95, 1.84] for C_{max} and 1.61 [1.12, 2.29] for $AUC_{0\text{-}48h}$.

impairment is expected to achieve exposure levels (C_{max} and AUC_{0-48h}) comparable to those observed in patients with LN with normal hepatic function receiving 23.7 mg of voclosporin.

Clinical studies in subjects with severe hepatic impairment have not been conducted. Furthermore, AURA-LV and AURORA 1 studies excluded patients with LN with aspartate aminotransferase (AST), alanine aminotransferase (ALT), or bilirubin levels ≥ 2.5 times the upper limit of normal. The impact of severe hepatic impairment on the pharmacokinetics of voclosporin remains unclear. However, given the potential for increased exposure, as observed in mild and moderate hepatic impairment, it is preferable to avoid administering voclosporin to patients with LN with severe hepatic impairment. This cautionary statement should be clearly stated in the package insert. As there is currently no information available on the safety or pharmacokinetics of voclosporin in patients with LN with severe hepatic impairment, continued collection of such data is warranted to evaluate the impact of severe hepatic impairment on the safety of voclosporin.

Based on the above findings, the recommended dosage for patients with LN with mild or moderate hepatic impairment is 15.8 mg twice daily, which is expected to yield exposure levels comparable to those in patients with LN with normal hepatic function. For patients with LN with severe hepatic impairment, it is advisable to avoid voclosporin administration, and this caution should be emphasized in the package insert.

PMDA's view:
The applicant's explanation about the administration of voclosporin to patients with LN with mild or moderate hepatic impairment is considered appropriate.

For patients with LN with severe hepatic impairment, the pharmacokinetics of voclosporin is unknown. Considering the potential for greater exposure compared to patients with LN with mild or moderate hepatic impairment, the package insert includes the cautionary statement that voclosporin should not be used in such patients whenever possible. Should data on the administration of voclosporin in patients with LN with severe hepatic impairment become available, a reassessment of the impact of severe hepatic impairment on the safety of voclosporin would be warranted.

6.R.4 Interactions mediated by CYP3A and P-gp

The applicant's explanation about the effects of drugs that inhibit or induce CYP3A4 or P-gp on the pharmacokinetics of voclosporin, based on the role of CYP3A4 as the primary enzyme responsible for the metabolism of voclosporin [see Section 6.1.1.3] and the fact that voclosporin is a substrate of P-gp [see Section 6.1.1.6]:
For co-administration with potent CYP3A4 inhibitors, in a foreign phase I study (Study LX211-06), co-administration of voclosporin (0.4 mg/kg) with ketoconazole, a potent CYP3A4 inhibitor, resulted in a 6.45-fold increase in C_{max} and an 18.5-fold increase in AUC_{0-12h} compared to voclosporin monotherapy [see Section 6.2.8]. Thus, co-administration with potent CYP3A4 inhibitors is considered contraindicated.

For co-administration with moderate CYP3A4 inhibitors, in another foreign phase I study (Study LX211-07), co-administration of voclosporin (0.4 mg/kg) with verapamil, a moderate CYP3A4 inhibitor, resulted in a 2.08-fold increase in C_{max} and a 2.71-fold increase in $AUC_{0\text{-}12h}$ compared to monotherapy [see Section 6.2.10]. Additionally, physiologically based pharmacokinetic (PBPK) model analysis[19)] was performed to evaluate the pharmacokinetics of voclosporin (0.4 mg/kg, administered orally twice daily for 10 days) following co-administration[20)] of voclosporin with fluconazole, a moderate CYP3A4 inhibitor. The analysis showed that the geometric mean ratios of C_{max} and $AUC_{0\text{-}12h}$ of voclosporin co-administered with fluconazole to those of voclosporin alone were 2.12 and 3.05, respectively. Based on the above, a total daily dose of voclosporin of 23.7 mg (15.8 mg in the morning and 7.9 mg in the evening) is expected to achieve exposure comparable to that to voclosporin alone. Therefore, the recommended daily dose of voclosporin when co-administered with moderate CYP3A4 inhibitors is 23.7 mg (morning, 15.8 mg; evening, 7.9 mg).

For co-administration with weak CYP3A4 inhibitors, PBPK model analysis also evaluated the pharmacokinetics of voclosporin (0.4 mg/kg, administered orally twice daily for 10 days) when co-administered with fluvoxamine and cimetidine, both weak CYP3A4 inhibitors.[21)] The geometric mean ratios of C_{max} and $AUC_{0\text{-}12h}$ of voclosporin co-administered with fluvoxamine to those of voclosporin alone were 1.20 and 1.23, respectively, while those with cimetidine were both 1.18. These findings suggest that co-administration with weak CYP3A4 inhibitors does not significantly affect the exposure to voclosporin. Therefore, pharmacokinetic interactions with weak CYP3A4 inhibitors are unlikely to be clinically relevant.

For co-administration with potent CYP3A4 inducers, in a foreign phase I study (Study LX211-09), co-administration of voclosporin (0.4 mg/kg) with rifampin (multiple administration), a potent CYP3A4 inducer, resulted in a 0.32-fold reduction in C_{max} and a 0.13-fold reduction in AUC_{inf} compared to monotherapy [see Section 6.2.9]. PBPK model analysis also evaluated the pharmacokinetics of voclosporin (0.4 mg/kg, administered orally twice daily for 10 days) following co-administration of voclosporin with efavirenz, a moderate CYP3A4 inducer.[22)] The geometric mean ratios of C_{max} and $AUC_{0\text{-}12h}$ of voclosporin co-administered with efavirenz to those of voclosporin alone were 0.39 and 0.30, respectively. An integrated intention-to-treat (ITT) analysis[7)] of patients with LN in clinical studies of voclosporin showed that at Week 52, the proportion of subjects achieving renal response who received moderate or potent[23)] CYP3A4 inducers was compared with that of those not receiving such drugs (see Table 29). Although the limited number of subjects with co-administration precludes the stringent interpretation of the results, the achievement rate of renal response at Week 52 was lower in subjects receiving CYP3A4-inducing drugs compared to those without such co-administration. This finding suggests that the efficacy of voclosporin may be attenuated when co-administered with CYP3A4 inducers.

19) Simcyp version 17 was used for the PBPK model analysis
20) A single dose of 400 mg was administered on Day 1, followed by 200 mg once daily for 10 consecutive days.
21) Fluvoxamine was administered at 100 mg twice daily for 10 days, while cimetidine was administered at 400 mg twice daily for 10 days.
22) A dose of 600 mg was administered once daily for 10 consecutive days.
23) As moderate or strong CYP3A4 inducers or inhibitors were considered to exhibit clinically significant drug interactions with voclosporin, these drugs were analyzed.

Table 29. Renal response at Week 52 with and without co-administration of CYP3A4-inducing drugs[a)] (integrated ITT analysis population)

	Voclosporin	
	Without drug with CYP3A4-inducing effect (n = 250)	With drug with CYP3A4-inducing effect (n = 18)
Proportion of subjects with renal response in % (number of subjects with response)	44.8% (112)	27.8% (5)
Odds ratio to placebo [95% CI]	3.02 [2.03, 4.48]	0.13 [<0.01, 3.25]

a) As drugs with CYP3A4-inducing effects, asunaprevir, veclabuvir, daclatasvir, and others were evaluated.

Based on the above, co-administration of voclosporin with moderate or potent CYP3A4 inducers may reduce the efficacy of voclosporin. It is deemed appropriate to classify such combinations as requiring caution.

Furthermore, an analysis using a PBPK model to evaluate the contributions of CYP3A4 and P-gp demonstrated that the metabolism of voclosporin is primarily inhibited via CYP3A4, with minimal effects observed from P-gp inhibition. Accordingly, co-administration of voclosporin with P-gp inhibitors is not expected to result in clinically significant drug interactions. Dose adjustment of voclosporin is considered unnecessary when co-administered with P-gp inhibitors.

PMDA's view:
Co-administration of voclosporin with potent CYP3A4 inhibitors is expected to significantly increase its exposure. The use of potent CYP3A4 inhibitors was prohibited in the foreign phase II study (AURA-LV study) and the global phase III study (AURORA 1 study). As a result, the safety of voclosporin in combination with potent CYP3A4 inhibitors has not been confirmed in patients with LN. Based on the above, the co-administration of voclosporin with potent CYP3A4 inhibitors should be contraindicated.

For co-administration of voclosporin with moderate CYP3A4 and P-gp inhibitors, the constructed PBPK model showed a discrepancy of up to approximately 2-fold between the observed and predicted blood concentrations of voclosporin. This indicates that the model is not sufficiently accurate to predict drug interactions involving voclosporin and there are limitations to the prediction of drug-drug interactions based on the PBPK model. However, considering the findings from Study LX211-07, where co-administration with verapamil (a moderate CYP3A4 inhibitor) increased voclosporin exposure by approximately 2.1 to 2.7 times, a reduced daily dose of voclosporin of 23.7 mg (15.8 mg in the morning and 7.9 mg in the evening) is unlikely to cause the exposure that significantly impacts the safety and efficacy. Therefore, the package insert should provide moderate CYP3A4 inhibitors in the Precautions for Concomitant Use section and include the cautionary statement that when co-administering voclosporin with moderate CYP3A4 inhibitors, the daily dose of voclosporin should be reduced to 23.7 mg (15.8 mg in the morning and 7.9 mg in the evening).

For co-administration with weak CYP3A4 inhibitors, although an increase in exposure to voclosporin is possible, the results of drug interaction studies suggest that such an increase is unlikely to affect its safety. Thus, the dose adjustment is unnecessary.

Regarding co-administration with moderate or potent CYP3A4 inducers, while the limited number of subjects with co-administration precludes the stringent interpretation of the results, the efficacy of voclosporin may be reduced as suggested by the applicant. Based on this, it is appropriate to classify moderate or potent CYP3A4 inducers as requiring caution when co-administered.

Although the PBPK model analysis indicated minimal effects of P-gp inhibition on the pharmacokinetics of voclosporin, there are limitations to the prediction of drug-drug interactions based on the PBPK model constructed, as discussed above. Considering that *in vitro* studies demonstrated that voclosporin is a substrate of P-gp [see Section 6.1.1.6] and CYP3A4 inhibitors or inducers identified in drug interaction studies also possess P-gp inhibitory or inducing effects, P-gp likely contributes to the pharmacokinetics of voclosporin. Thus, it cannot be excluded that drugs with P-gp inhibitory or inducing effects may influence voclosporin's pharmacokinetics. Information should be provided indicating that voclosporin is a substrate of P-gp.

6.R.5 Interaction mediated by BCRP

The applicant's explanation about the interaction between voclosporin and drugs that are substrates of BCRP, based on the finding that voclosporin inhibits BCRP [see Section 6.1.1.7]:

A study in non-Japanese healthy adults investigated the effect of voclosporin on the pharmacokinetics of simvastatin, a BCRP substrate. Co-administration of simvastatin with voclosporin 23.7 mg resulted in a 1.60-fold increase in the C_{max} of simvastatin, while the AUC_{inf} remained comparable at 0.94-fold [see Section 6.2.14].

Table 30 shows the incidence of adverse events in the integrated safety analysis population stratified by use of concomitant BCRP substrates. There were no significant differences in the incidence of adverse events between subgroups with and without concomitant BCRP substrates.

Table 30. Incidence of adverse events stratified by use of concomitant BCRP substrates[a)] (integrated safety analysis population)

	Voclosporin	
	Without concomitant BCRP substrates (n = 190)	With concomitant BCRP substrates (n = 77)
All adverse events	90.0 (171)	94.8 (73)
All adverse drug reactions	43.7 (83)	54.5 (42)
Serious adverse events	20.5 (39)	28.6 (22)
Serious adverse drug reactions	4.2 (8)	5.2 (4)
Adverse events leading to treatment discontinuation	12.1 (23)	16.9 (13)

Incidence in % (number of subjects with events)

a) The following compounds were evaluated as substrates for BCRP: Atorvastatin, glecaprevir/pibrentasvir, simvastatin, tenofovir /disoproxil, pazopanib, berotralstat, riociguat, rosuvastatin, imatinib, and sulfasalazine.

It is thus considered unlikely that drug interactions mediated by BCRP inhibition with voclosporin would impact patient safety. No specific precautions regarding such co-administration are deemed necessary.

PMDA's view:

Although the C_{max} of simvastatin increased 1.60-fold following its co-administration with voclosporin, the AUC_{inf} remained comparable at 0.94-fold, and no significant differences in the incidence of

adverse event were observed between subgroups with and without concomitant BCRP substrates. Hence, the applicant's explanation is considered reasonable, and no specific precautions are necessary for the co-administration of voclosporin with BCRP substrates.

6.R.6 Risk of QT/QTc prolongation

The applicant's explanation about the risk of QT/QTc prolongation associated with voclosporin:
In a QT/QTc evaluation study (Study ISA03-11) conducted in healthy adults with a single-dose administration of voclosporin at 0.5 to 4.5 mg/kg, the upper limit of the 95% confidence interval for ΔΔQTcF exceeded 10 ms in all voclosporin groups, suggesting that voclosporin may have a risk of QT/QTc prolongation [see Section 6.2.15]. Conversely, in a QT/QTc evaluation study (Study ISA05-03) conducted in healthy adults with multiple-dose administration of voclosporin at 0.3 to 1.5 mg/kg twice daily, the upper limit of the 95% confidence interval for ΔΔQTcF remained below 10 ms at steady state for all doses, and no evident QTcF prolongation was observed [see Section 6.2.16]. Regarding the maximum change in mean QTcF from baseline, the AURA-LV study showed larger changes in the voclosporin 23.7 mg and 39.5 mg groups compared to the placebo group. However, in the AURORA 1 study, changes were comparable between the voclosporin and placebo groups. Regarding subjects with QTcF ≥450 msec and an increase from baseline by >60 msec or with QTcF >500 msec, none were observed in any group in the AURA-LV study. However, such cases were observed in the AURORA 1 study, where the incidence was higher in the voclosporin group than in the placebo group. Based on the above findings, the AURA-LV and AURORA 1 studies did not demonstrate a consistent trend regarding the effects of voclosporin on electrocardiograms.

The results of single-dose and multiple-dose administration studies on QT prolongation differed. However, in Studies ISA03-11 and ISA05-03, compared to the exposure level during multiple-dose administration of voclosporin 1.5 mg/kg, which showed no effect on QT/QTc, the exposure level during a single-dose administration of voclosporin 1.5 mg/kg, which showed a positive effect on QT/QTc, was lower. Thus, the differences in the effects of voclosporin on QT/QTc observed in the single-dose and multiple-dose administration cannot be explained by differences in exposure. In a safety pharmacology study using CHO cells, the concentration of voclosporin required to inhibit human ether-a-go-go related gene (hERG) channels was higher than the C_{max} (0.9 μmol/L [1122.2 ng/mL]) observed with a single oral administration of 4.5 mg/kg in Study ISA03-11 in which the highest voclosporin exposure was shown, suggesting that QT/QTc prolongation with voclosporin is not attributable to hERG inhibition. The precise mechanism remains unclear.

Based on these findings, the risk of QT/QTc prolongation associated with voclosporin is considered low. Nevertheless, for patients with a risk or history of QT/QTc prolongation, or patients using QT/QTc-prolonging drugs, the risk of QT/QTc prolongation due to voclosporin administration or co-administration cannot be excluded. A precaution regarding the risk of QT/QTc prolongation associated with voclosporin should be included in the package insert.

PMDA's view:
Clinical studies suggest that voclosporin may influence QT/QTc intervals. Although significant QT prolongation was not observed following voclosporin administration in Study ISA05-03, Study

ISA03-11 showed that the upper limit of the 95% confidence interval for ΔΔQTcF exceeded 10 ms in all voclosporin groups, which should not be overlooked. The extent to which hERG channel inhibition contributes to QT/QTc prolongation with voclosporin is unclear, and the precise mechanism remains unknown. However, the possibility that voclosporin poses a risk of QT/QTc prolongation cannot be excluded. Therefore, it is reasonable to include in the package insert a precaution about the potential for clinically significant QT prolongation when voclosporin is administered to patients with a risk or history of QT/QTc prolongation or in combination with QT/QTc-prolonging drugs, as explained by the applicant.

7. Clinical Efficacy and Safety and Outline of the Review Conducted by PMDA

The applicant submitted the results of 4 Japanese and foreign clinical studies listed in Table 31 as the efficacy and safety evaluation data.

Table 31. Outline of the efficacy and safety evaluation data

Region	Phase	Study ID	Study design	Number of subjects in each group	Primary endpoints
Foreign	II	AUR-VCS-2012-01 (AURA-LV)	Double-blind, placebo-controlled	Placebo: 88 Voclosporin 23.7 mg: 89 Voclosporin 39.5 mg: 88	Renal response at Week 24
Foreign	II	AUR-VCS-2014-01 (AURION)	Open-label, uncontrolled	Voclosporin (23.7 mg): 10	Decrease or normalization of biomarker levels at Week 8
Global	III	AUR-VCS-2016-01 (AURORA 1)	Double-blind, placebo-controlled	Placebo: 178 Voclosporin (23.7 mg): 179	Renal response at Week 52
Global	III	AUR-VCS-2016-02 (AURORA 2)	Double-blind, placebo-controlled (continuation from the AURORA 1 study)	Placebo: 100 Voclosporin (23.7 mg): 116	Safety and efficacy during 24 months after the AURORA 1 study

Table 32 shows the histological classification of LN used in the submitted clinical studies (ISN/RPS 2003 classification, *J Am Soc Nephrol.* 2004:15:241–50), and Table 33 shows the definition of "renal response" used as an efficacy endpoint.

Table 32. Histological classification of LN (ISN/RPS 2003 classification)

Class I: Minimal mesangial lupus nephritis Class II: Mesangial proliferative lupus nephritis Class III: Focal lupus nephritis Class IV: Diffuse lupus nephritis (IV-S, Segmental; IV-G, Global) Class V: Membranous lupus nephritis Class VI: Advanced sclerosing lupus nephritis

Table 33. Definition of renal response

Renal response was defined as meeting all of the following criteria: • UPCR ≤0.5 mg/mg • eGFR ≥60 mL/min/1.73 m², or no reduction of ≥20% from baseline The following conditions were not considered as responses: • Use of rescue medications • The dose of prednisone exceeding 10 mg/day for ≥3 consecutive days or for a total of ≥7 days during 8 weeks prior to evaluation (in the AURA-LV study, >3 consecutive days or a total of >7 days) • Discontinuation of the study before the final evaluation

7.1 Phase II study

7.1.1 Foreign phase II dose-finding study (AURA-LV) (CTD 5.3.5.1-01, Study AUR-VCS-2012-01 [June 2014 to January 2017])

A multicenter, placebo-controlled, randomized, double-blind, parallel-group study was conducted at 79 study sites in 20 countries to evaluate the efficacy and safety of voclosporin in patients with active LN (Table 34) (target sample size, 258 subjects[24]).

Table 34. Main inclusion/exclusion criteria

Main inclusion criteria • Aged ≥18 and ≤75 years • Diagnosed with SLE based on the American College of Rheumatology criteria (1997) • Renal biopsy within 6 months confirming LN histological classification (ISN/RPS 2003 classification): Class III, IV-S, IV-G, or Class V (alone or in combination with Class III/IV) • For Class III or IV, UPCR ≥1.5 mg/mg; for Class V, UPCR ≥2.0 mg/mg Main exclusion criteria • eGFR (CKD-EPI) ≤45 mL/min/1.73 m² • Serum potassium >5.5 mmol/L • Requires dialysis (hemodialysis or peritoneal dialysis) or is expected to require it during the study • History of renal transplantation or planned transplantation during the study

Placebo, voclosporin 23.7 mg, or voclosporin 39.5 mg[25] was administered orally twice daily under fasted conditions for 48 weeks. All subjects received concomitant corticosteroids (Table 35) and MMF (Table 36).

Table 35. Standard corticosteroid administration schedule

	Day 1-2	Day 3-14	Week 3	Week 4	Week 6	Week 8	Week 12	Week 16
Drug	Methylprednisolone (i.v.)	Prednisone (p.o.)						
Body weight <45 kg	0.25 g/day	20 mg/day	15 mg/day	10 mg/day	10 mg/day	5 mg/day	5 mg/day	2.5 mg/day
Body weight ≥45 kg	0.5 g/day	25 mg/ day	20 mg/day	15 mg/day	10 mg/day	5 mg/day	5 mg/day	2.5 mg/day
• Methylprednisolone IV administration could be initiated before randomization if deemed optimal for the subject (total dose by Day 2 not to exceed 0.5 g for body weight <45 kg or 1 g for ≥45 kg). • Oral corticosteroid tapering and discontinuation was allowed based on clinical judgment.								

Table 36. Standard MMF administration schedule

• Continuation of MMF was allowed if started prior to randomization. • For those not on MMF before randomization (or switched from other immunosuppressants to MMF), 500 mg was administered twice daily from Day 1 to 7, followed by 1000 mg twice daily from Day 8 onward. • Dose reduction or discontinuation was permitted in cases of safety concerns, such as neutropenia.

A total of 265 randomized subjects (88 in the placebo group, 89 in the voclosporin 23.7 mg group, 88 in the voclosporin 39.5 mg group) were included in the full analysis set (FAS), which served as the population for efficacy and safety analyses. Discontinuation occurred in 42 subjects (18 subjects, 16 subjects, 8 subjects) for reasons including “death” in 13 subjects (1 subject, 10 subjects, 2 subjects), “consent withdrawal” in 10 subjects (5 subjects, 3 subjects, 2 subjects), “investigator’s decision” in 8

[24] The study did not adjust for multiplicity in hypothesis testing. With a two-sided significance level of 0.05, assuming a 20% renal response rate in the placebo group, a sample size of 258 subjects (86 per group) was calculated to provide 81% power to detect a renal response rate of 41% in the treatment groups (odds ratio, 2.78).

[25] Subjects initially received voclosporin 23.7 mg twice daily, which was increased to 39.5 mg twice daily after 2 weeks. Dose escalation could be postponed for gastrointestinal intolerance; if escalation was not feasible, the dose was maintained at 23.7 mg twice daily or reduced as needed.

subjects (5 subjects, 1 subject, 2 subjects), “lost to follow-up” in 5 subjects (3 subjects, 1 subject, 1 subject), and “other reasons” in 6 subjects (4 subjects, 1 subject, 1 subject).

As for efficacy, Table 37 shows the renal response rate at Week 24, the primary endpoint. The odds ratios [95% CI] compared to placebo were 2.03 [1.01, 4.05] for the 23.7 mg group and 1.59 [0.78, 3.27] for the 39.5 mg group.

Table 37. Renal response at Week 24 (FAS)

	Placebo	Voclosporin 23.7 mg	Voclosporin 39.5 mg
Proportion of subjects achieving renal response (%) (No. of subjects achieving response/No. of subjects evaluated)	19.3 (17/88)	32.6 (29/89)	27.3 (24/88)
Odds ratio to placebo [95% CI][a)]	-	2.03 [1.01, 4.05]	1.59 [0.78, 3.27]

a) Calculated using logistic regression analysis with treatment groups, histological classifications (Class V and others), and the administration of MMF at screening as explanatory variables.

Adverse events were observed in 85.2% (75 of 88) of subjects in the placebo group, 92.1% (82 of 89) of subjects in the voclosporin 23.7 mg group, and 96.6% (85 of 88) of subjects in the voclosporin 39.5 mg group. Adverse drug reactions were observed in 17.0% (15 of 88) of subjects in the placebo group, 50.6% (45 of 89) of subjects in the voclosporin 23.7 mg group, and 62.5% (55 of 88) of subjects in the voclosporin 39.5 mg group. Tables 38 and 39 show the incidences of adverse events and adverse drug reactions observed in ≥5% of subjects in any group, respectively.

Table 38. Adverse events observed in ≥5% of subjects in any group (safety analysis population)

	Placebo (n = 88)	Voclosporin 23.7 mg (n = 89)	Voclosporin 39.5 mg (n = 88)
All adverse events	85.2 (75)	92.1 (82)	96.6 (85)
Glomerular filtration rate decreased	13.6 (12)	30.3 (27)	30.7 (27)
Upper respiratory tract infection	15.9 (14)	13.5 (12)	20.5 (18)
Hypertension	9.1 (8)	16.9 (15)	18.2 (16)
Headache	12.5 (11)	11.2 (10)	17.0 (15)
Diarrhoea	15.9 (14)	18.0 (16)	15.9 (14)
Anaemia	8.0 (7)	14.6 (13)	15.9 (14)
Hypokalaemia	10.2 (9)	13.5 (12)	13.6 (12)
Nausea	8.0 (7)	18.0 (16)	12.5 (11)
Pyrexia	1.1 (1)	6.7 (6)	11.4 (10)
Vomiting	11.4 (10)	16.9 (15)	10.2 (9)
Renal failure acute	0	5.6 (5)	9.1 (8)
Oedema peripheral	9.1 (8)	10.1 (9)	8.0 (7)
Arthralgia	8.0 (7)	10.1 (9)	8.0 (7)
Pneumonia	2.3 (2)	7.9 (7)	8.0 (7)
Dyslipidaemia	6.8 (6)	6.7 (6)	8.0 (7)
Herpes zoster	5.7 (5)	5.6 (5)	8.0 (7)
Abdominal pain upper	5.7 (5)	5.6 (5)	8.0 (7)
Hypertrichosis	0	3.4 (3)	8.0 (7)
Urinary tract infection	5.7 (5)	9.0 (8)	6.8 (6)
Dyspepsia	4.5 (4)	6.7 (6)	6.8 (6)
Gingival hypertrophy	0	3.4 (3)	6.8 (6)
Bronchitis	3.4 (3)	2.2 (2)	6.8 (6)
Cough	3.4 (3)	18.0 (16)	5.7 (5)
Back pain	3.4 (3)	9.0 (8)	5.7 (5)
Decreased appetite	2.3 (2)	7.9 (7)	5.7 (5)
Insomnia	4.5 (4)	4.5 (4)	5.7 (5)
Blood pressure increased	1.1 (1)	3.4 (3)	5.7 (5)
Tachycardia	1.1 (1)	2.2 (2)	5.7 (5)
Oedema	1.1 (1)	2.2 (2)	5.7 (5)
Oral candidiasis	0	2.2 (2)	5.7 (5)
Alopecia	2.3 (2)	7.9 (7)	4.5 (4)
Gastroenteritis	2.3 (2)	6.7 (6)	4.5 (4)
Nasopharyngitis	3.4 (3)	5.6 (5)	4.5 (4)
Gastritis	5.7 (5)	2.2 (2)	4.5 (4)
Leukopenia	6.8 (6)	1.1 (1)	3.4 (3)
Muscle spasms	3.4 (3)	5.6 (5)	2.3 (2)
Dizziness	1.1 (1)	5.6 (5)	2.3 (2)
Iron deficiency anaemia	0	5.6 (5)	0

Medical Dictionary for Regulatory Activities Japanese version (MedDRA/J) ver.17.0
Incidence in % (number of patients with adverse events)

Table 39. Adverse drug reactions observed in ≥5% of subjects in any group (safety analysis population)

	Placebo (n = 88)	Voclosporin 23.7 mg (n = 89)	Voclosporin 39.5 mg (n = 88)
All adverse drug reactions	17.0 (15)	50.6 (45)	62.5 (55)
Glomerular filtration rate decreased	2.3 (2)	21.3 (19)	26.1 (23)
Hypertension	1.1 (1)	7.9 (7)	9.1 (8)
Nausea	0	5.6 (5)	3.4 (3)
Vomiting	3.4 (3)	5.6 (5)	0

MedDRA/J ver.17.0, Incidence in % (number of patients with adverse drug reactions)

Death occurred in 1.1% (1 of 88 subjects; cerebrovascular accident in 1 subject) in the placebo group, 11.2% (10 of 89 subjects; pneumonia in 2 subjects, pulmonary embolism in 2 subjects, acute respiratory distress syndrome in 2 subjects; and multi-organ failure, cardiac tamponade, pericarditis tuberculous, and pulmonary alveolar haemorrhage in 1 subject each) in the voclosporin 23.7 mg group, and 2.3% (2 of 88 subjects; sepsis and pulmonary embolism in 1 subject each) in the voclosporin 39.5 mg group. None of these deaths were determined to be adverse drug reactions. Serious adverse

events were observed in 15.9% (14 of 88) of subjects in the placebo group, 28.1% (25 of 89) of subjects in the voclosporin 23.7 mg group, and 25.0% (22 of 88) of subjects in the voclosporin 39.5 mg group (Table 40).

Table 40. Incidence of serious adverse events (safety analysis population)

Group	Serious adverse events
Placebo 15.9% (14 of 88 subjects)	Pneumonia and systemic lupus erythematosus in 2 subjects each, Gastroenteritis, cellulitis, herpes zoster, bronchiolitis,[a)] Escherichia urinary tract infection, gastroenteritis viral, cerebrovascular accident, acute coronary syndrome, congestive cardiomyopathy,[a)] gastritis, gastrooesophageal reflux disease, strangury, diabetes mellitus inadequate control, anaemia, hypochromic anaemia, and dysfunctional uterine bleeding in 1 subject each (some subjects had multiple events)
Voclosporin 23.7 mg 28.1% (25 of 89 subjects)	Pneumonia[b)] in 5 subjects, Renal failure acute[b)] in 4 subjects, Urinary tract infection, posterior reversible encephalopathy syndrome, hypertension,[b)] pulmonary embolism, and acute respiratory distress syndrome in 2 subjects each Gastroenteritis, sepsis,[b)] cellulitis, Dengue fever, pericarditis tuberculous, pneumonia bacterial, skin infection, cerebral haemorrhage, convulsion,[b)] systemic lupus erythematosus, cardiac failure, cardiac tamponade, gastrointestinal haemorrhage, peptic ulcer, renal dysfunction, pulmonary alveolar haemorrhage, multi-organ failure, iron deficiency anaemia, uterine prolapse, and diabetes mellitus in 1 subject each (some subjects had multiple events)
Voclosporin 39.5 mg 25.0% (22 of 88 subjects)	Pneumonia in 3 subjects Gastroenteritis, sepsis,[c)] reversible posterior leukoencephalopathy syndrome, systemic lupus erythematosus, and hypertension[c)] in 2 subjects each Body tinea,[c)] urinary tract infection, cellulitis,[c)] herpes zoster, bacterial pyelonephritis,[c)] bacterial sepsis,[c)] bronchitis,[c)] subcutaneous abscess, tuberculosis of genitourinary system,[c)] viral upper respiratory tract infection, intracranial pressure increased, migraine, costochondritis, pericardial effusion, pericarditis, diarrhoea, gastritis erosive, renal failure acute, pulmonary embolism, pyrexia, hypothyroidism, drug-induced liver injury, hypersensitivity,[c)] and procedural pain in 1 subject each (some subjects had multiple events)

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a) Serious adverse drug reactions in the placebo group: Bronchiolitis and congestive cardiomyopathy in 1 subject each
b) Serious adverse drug reactions in the voclosporin 23.7 mg group: Pneumonia, sepsis, convulsion, hypertension, and renal failure acute in 1 subject each
c) Serious adverse drug reactions in the voclosporin 39.5 mg group: Hypertension in 2 subjects and hypersensitivity, bronchitis, body tinea, bacterial sepsis, cellulitis, bacterial pyelonephritis, and tuberculosis of genitourinary system in 1 subject each

Table 41 shows the incidence of adverse events leading to treatment discontinuation.

Table 41. Incidence of adverse events leading to treatment discontinuation (safety analysis population)

Group	Adverse events leading to treatment discontinuation
Placebo 10.2% (9 of 88 subjects)	Glomerular filtration rate decreased, proteinuria increased, bronchiolitis,[a)] constipation, diarrhoea, systemic lupus erythematosus, back pain, cerebrovascular disorder, lupus nephritis, proteinuria,[a)] strangury, leukopenia, and rash generalized in 1 subject each (some subjects had multiple events)
Voclosporin 23.7 mg 18.0% (16 of 89 subjects)	Glomerular filtration rate decreased[b)] in 7 subjects Pneumonia in 2 subjects Pulmonary tuberculosis,[b)] back pain,[b)] convulsion,[b)] headache,[b)] posterior reversible encephalopathy syndrome, hypoaesthesia,[b)] renal failure acute,[b)] renal dysfunction, WPW syndrome,[b)] fatigue,[b)] and acute respiratory distress syndrome in 1 subject each (some subjects had multiple events)
Voclosporin 39.5 mg 15.9% (14 of 88 subjects)	Glomerular filtration rate decreased in 5 subjects[c)] Bacterial pyelonephritis,[c)] herpes zoster, sepsis, tuberculosis of genitourinary system,[c)] urinary tract infection, gastritis erosive,[c)] gingival hypertrophy,[c)] systemic lupus erythematosus, hypersensitivity,[c)] and hypertension[c)] in 1 subject each (some subjects had multiple events)

MedDRA/J ver.17.0

a) Adverse drug reactions leading to treatment discontinuation in the placebo group: Bronchiolitis and proteinuria in 1 subject each
b) Adverse drug reactions leading to treatment discontinuation in the voclosporin 23.7 mg group: Glomerular filtration rate decreased in 5 subjects, pulmonary tuberculosis, back pain, convulsion, headache, hypoaesthesia, renal failure acute, WPW syndrome, and fatigue in 1 subject each
c) Adverse drug reactions leading to treatment discontinuation in the voclosporin 39.5 mg group: Glomerular filtration rate decreased in 3 subjects, bacterial pyelonephritis, tuberculosis of genitourinary system, gastritis erosive, gingival hypertrophy, hypersensitivity, and hypertension in 1 subject each

7.1.2 Foreign phase II exploratory study (AURION) (CTD 5.3.5.2-01, Study AUR-VCS-2014-01 [June 2015 to February 2017])

An open-label, single-arm study was conducted at 2 study sites in Malaysia to evaluate the efficacy and safety of voclosporin in patients with active LN (Table 42) (target sample size, 10 subjects[26)]).

Table 42. Main inclusion/exclusion criteria

Main inclusion criteria • Aged ≥18 and ≤75 years • Diagnosed with SLE according to the American College of Rheumatology diagnostic criteria (1997) • Renal biopsy within 24 months prior to screening showing LN histological classification (ISN/RPS 2003) as Class III, IV-S, IV-G, or Class V (alone or combined with Class III/IV) • For Class III or IV, UPCR ≥1.0 mg/mg. For Class V, UPCR ≥1.5 mg/mg Main exclusion criteria • eGFR (CKD-EPI) ≤45 mL/min/1.73 m² • Requiring dialysis (hemodialysis or peritoneal dialysis) or expected to require dialysis during the study • History of kidney transplantation or planned kidney transplantation during the study

Voclosporin 23.7 mg was administered orally twice daily under fasted conditions for 48 weeks. All subjects received concomitant corticosteroid (Table 35) and MMF (Table 36).

All 10 enrolled subjects received the study drug and were included in both the FAS and safety analysis population. The FAS was used as the efficacy analysis set. One subject discontinued the study due to glomerular filtration rate decreased.

As for efficacy, Table 43 shows the proportion of subjects achieving "reduction or normalization of biomarkers at Week 8."

Table 43. Reduction or normalization of biomarkers at Week 8 (FAS)

	UPCR	Anti-dsDNA	C3	C4
Achievement rate (%) (No. of subjects achieving the endpoint/ No. of subjects evaluated)	70.0 (7/10)	40.0 (4/10)	20.0 (2/10)	20.0 (2/10)
Criteria for reduction or normalization of each biomarker • UPCR: A reduction of ≥25% compared to baseline • Anti-dsDNA: ○ If the baseline level is >200 IU/mL, a decrease to ≤60 IU/mL. ○ If the baseline level is >30 IU/mL and ≤200 IU/mL, a decrease to ≤30 IU/mL. • C3: If the baseline level is <0.9 g/L, an increase to ≥0.9 g/L. • C4: If the baseline level is <0.16 g/L, an increase to ≥0.16 g/L.				

Adverse events were observed in 100% (10 of 10) of subjects, and adverse drug reactions were observed in 80.0% (8 of 10) of subjects. Adverse events observed in ≥2 subjects included pyrexia and upper respiratory tract infection (5 subjects each), diarrhoea, glomerular filtration rate decreased, and hypertension (4 subjects each), cough (3 subjects), and vision blurred, dyspepsia, chest pain, local swelling, oedema, nasopharyngitis, arthralgia, and dizziness (2 subjects each). Adverse drug reactions observed in ≥2 subjects were glomerular filtration rate decreased (4 subjects) and upper respiratory tract infection (2 subjects).

[26)] Target sample size was based on feasibility.

No deaths were reported, and serious adverse events were observed in 30.0% of subjects (3 subjects; acute tonsillitis/systemic lupus erythematosus, pneumonia/anemia/pleural effusion, and pyrexia). None were judged to be adverse drug reactions, and all resolved with recovery. Adverse events leading to treatment discontinuation were observed in 10.0% of subjects (1 subject; glomerular filtration rate decreased), which was judged as an adverse drug reaction.

7.2 Phase III studies

7.2.1 Global phase III study (AURORA 1) (CTD 5.3.5.1-02, Study AUR-VCS-2016-01 [May 2017 to October 2019])

A multicenter, placebo-controlled, randomized, double-blind, parallel-group study was conducted at 142 study sites in 27 countries (including 10 Japanese sites) to evaluate the efficacy and safety of voclosporin in subjects with active LN (Table 44) (target sample size, 324 subjects[27)]).

Table 44. Main inclusion and exclusion criteria

Main inclusion criteria • Aged ≥18 and ≤75 years. • Diagnosed with SLE according to the criteria of the American College of Rheumatology (1997). • Histological classification of LN (ISN/RPS 2003 classification) confirmed by renal biopsy within 2 years prior to screening as Class III, IV-S, IV-G, or Class V (alone or in combination with Class III/IV). • For Class III/IV, UPCR ≥1.5 mg/mg. For Class V, UPCR ≥2.0 mg/mg. • If renal biopsy was performed ≥6 months before screening, documentation of a ≥2-fold increase in UPCR within the 6 months prior to screening.
Main exclusion criteria • eGFR (CKD-EPI) ≤45 mL/min/1.73 m². • Requirement for dialysis (hemodialysis or peritoneal dialysis) or anticipated need for dialysis during the study period. • History of kidney transplantation or planned kidney transplantation during the study period.

Placebo or voclosporin 23.7 mg was administered orally twice daily under fasted conditions for 52 weeks. All subjects received concomitant treatment with corticosteroid (Table 35) and MMF (Table 36).

A total of 357 randomized subjects (178 in the placebo group [including 5 Japanese subjects], 179 in the voclosporin group [including 8 Japanese subjects]) were included the ITT population, which was used for the efficacy analysis. The safety analysis population included 356 subjects, the remaining 1 subject was excluded from the ITT population because the subject did not receive the study drug. A total of 47 subjects (31 in the placebo group, 16 in the voclosporin group) discontinued the study, with the following reasons: “Consent withdrawal” in 21 subjects (14 in the placebo group, 7 in the voclosporin group), “death” in 6 subjects (5 in the placebo group, 1 in the voclosporin group), “investigator’s decision” in 5 subjects (3 in the placebo group, 2 in the voclosporin group), “lost to follow-up” in 4 subjects (3 in the placebo group, 1 in the voclosporin group), “adverse events” in 2 subjects (voclosporin group), “noncompliance” in 2 subjects (1 in the placebo group, 1 in the voclosporin group), “use of prohibited concomitant medications” in 1 subject (voclosporin group), “pregnancy” in 1 subject (voclosporin group), “lack of efficacy” in 1 subject (placebo group), and

[27)] For the proportion achieving the primary endpoint, the power to detect an odds ratio of 2.1 (placebo group, 20.0%; voclosporin group, 34.4%) at a two-sided significance level of 0.05 using a continuity-corrected chi-square test was calculated as 80% with 162 subjects per group (total 324 subjects).

"other reasons" in 4 subjects (placebo group). Among Japanese subjects, 3 discontinued the study (consent withdrawal in 2 subjects and lost to follow-up in 1 subject in the voclosporin group).

Regarding efficacy, Table 45 shows the proportion of subjects achieving renal response (Table 33) at Week 52, the primary endpoint. The response rate in the voclosporin group was significantly higher than in the placebo group ($P < 0.001$, logistic regression analysis, two-sided significance level of 5%).

Table 45. Renal response at Week 52 (ITT population)

	Placebo (n = 178)	Voclosporin (n = 179)
Proportion of subjects achieving renal response in % (No. of subjects with response)	22.5 (40)	40.8 (73)
Odds ratio [95% CI] compared to the placebo[a)]	2.65 [1.64, 4.27]	
P value[a)b)]	$P < 0.001$	

a) Calculated using logistic regression analysis with treatment groups, baseline urine protein creatinine ratio (UPCR), histological classifications (Class V and others), the use of MMF at baseline, and region as explanatory variables.
One subject in the voclosporin group was excluded from the analysis due to missing baseline UPCR data.
b) Two-sided significance level of 5%.

Adverse events were observed in 88.8% (158 of 178) of subjects in the placebo group and 91.0% (162 of 178) of subjects in the voclosporin group. Adverse drug reactions were reported in 25.3% (45 of 178) of subjects in the placebo group and 44.9% (80 of 178) of subjects in the voclosporin group. Table 46 shows the incidence of adverse events observed in ≥5% of subjects in either group. Table 47 shows the incidence of adverse drug reactions observed in ≥2% of subjects in either group.

Table 46. Incidence of adverse events observed in ≥5% of subjects in either group (safety analysis population)

	Placebo (n = 178)	Voclosporin (n = 178)
All adverse events	88.8 (158)	91.0 (162)
Glomerular filtration rate decreased	8.4 (15)	24.2 (43)
Hypertension	8.4 (15)	20.2 (36)
Diarrhoea	12.4 (22)	19.1 (34)
Upper respiratory tract infection	14.6 (26)	17.4 (31)
Headache	6.2 (11)	16.9 (30)
Anaemia	5.6 (10)	11.8 (21)
Viral upper respiratory tract infection	10.1 (18)	11.2 (20)
Urinary tract infection	7.3 (13)	10.7 (19)
Herpes zoster	5.1 (9)	7.9 (14)
Abdominal pain upper	0.6 (1)	7.3 (13)
Cough	1.7 (3)	7.3 (13)
Renal dysfunction	3.4 (6)	7.3 (13)
Influenza	5.6 (10)	6.7 (12)
Oedema peripheral	6.2 (11)	6.2 (11)
Abdominal pain	1.1 (2)	5.6 (10)
Nausea	9.6 (17)	5.6 (10)
Dyspepsia	1.7 (3)	5.6 (10)
Alopecia	2.8 (5)	5.6 (10)
Gastroenteritis	5.6 (10)	5.1 (9)
Pneumonia	6.2 (11)	5.1 (9)
Systemic lupus erythematosus	5.6 (10)	4.5 (8)
Arthralgia	9.6 (17)	4.5 (8)
Leukopenia	5.6 (10)	3.9 (7)
Vomiting	6.7 (12)	2.8 (5)
Hypokalaemia	5.6 (10)	1.7 (3)
Bronchitis	5.6 (10)	1.7 (3)
Pharyngitis	5.1 (9)	1.7 (3)
Lupus nephritis	6.7 (12)	1.1 (2)

MedDRA/J ver.20.0, Incidence in % (number of subjects with events)

Table 47. Incidence of adverse drug reactions observed in ≥2% of subjects in either group (safety analysis population)

	Placebo (n = 178)	Voclosporin (n = 178)
All adverse drug reactions	25.3 (45)	44.9 (80)
Glomerular filtration rate decreased	2.8 (5)	18.0 (32)
Hypertension	1.7 (3)	7.3 (13)
Herpes zoster	1.7 (3)	3.9 (7)
Headache	1.1 (2)	3.4 (6)
Renal dysfunction	1.1 (2)	3.4 (6)
Upper respiratory tract infection	2.8 (5)	2.8 (5)
Nausea	1.1 (2)	2.2 (4)
Urinary tract infection	1.1 (2)	2.2 (4)
Viral upper respiratory tract infection	2.2 (4)	1.7 (3)

MedDRA/J ver.20.0, Incidence in % (number of subjects with events)

Deaths were reported in 1.7% (3 of 178 subjects; pneumonia, pneumonia with septic shock, and lupus nephritis in 1 subject each) in the placebo group. Serious adverse events occurred in 21.3% (38 of 178) of subjects in the placebo group and 20.8% (37 of 178) of subjects in the voclosporin group. Serious adverse drug reactions were observed in 4.5% (8 of 178) of subjects in both the placebo and voclosporin groups (Table 48). Among the serious adverse drug reactions observed in the voclosporin group, renal dysfunction in 1 subject remained unresolved, while all others recovered.

Table 48. Incidence of serious adverse events (safety analysis population)

Group	Serious adverse events and number of subjects with events
Placebo 21.3% (38 of 178 subjects)	Pneumonia[a)] in 8 subjects Lupus nephritis in 4 subjects Bronchitis[a)] and systemic lupus erythematosus in 3 subjects each Acute kidney injury and hypertensive crisis in 2 subjects each Urinary tract infection, pyelonephritis acute, upper respiratory tract infection,[a)] diarrhoea infectious, Escherichia sepsis, herpes zoster disseminated,[a)] intervertebral discitis, paravertebral abscess, pyelonephritis,[a)] salmonellosis, salpingitis, sepsis, septic shock, renal dysfunction,[a)] renal failure, haemorrhagic stroke, hypertension, musculoskeletal pain, acute myocardial infarction, glomerular filtration rate decreased, diarrhoea, gastrooesophageal reflux disease, upper gastrointestinal haemorrhage, pleural effusion, lupus pleurisy, pulmonary embolism, generalised oedema, Schwannoma,[a)] hypokalaemia, metabolic acidosis, cholecystitis chronic, abortion spontaneous, and uterine haemorrhage in 1 subject each (some subjects had multiple events)
Voclosporin 20.8% (37 of 178 subjects)	Pneumonia[b)] in 7 subjects Acute kidney injury[b)] in 4 subjects Hypertension,[b)] gastroenteritis, anaemia,[b)] and systemic lupus erythematosus in 3 subjects each Urinary tract infection and renal dysfunction[b)] in 2 subjects each Pyelonephritis acute,[b)] upper respiratory tract infection,[b)] acute sinusitis,[b)] bacterial diarrhoea, cystitis, herpes zoster, lung abscess,[b)] pneumonia cytomegaloviral, pulmonary tuberculosis, lupus nephritis, renal failure, cerebral infarction, headache, lupus encephalitis, migraine, neuropsychiatric lupus, neutropenia, hypertensive crisis, acute coronary syndrome, cardiac failure, cardiac failure acute, cardiac failure congestive, glomerular filtration rate decreased, blood lactate dehydrogenase increased, gastritis, pleural effusion, generalised oedema, cervix carcinoma stage 0, developmental hip dysplasia, intentional overdose, and abortion induced in 1 subjects each (some subjects had multiple events)

MedDRA/J ver. 20.0

a) Serious adverse drug reactions in the placebo group: Pneumonia in 2 subjects, upper respiratory tract infection, bronchitis, herpes zoster disseminated, pyelonephritis, renal dysfunction, and Schwannoma in 1 subject each

b) Serious adverse drug reactions in the voclosporin group: Hypertension in 2 subjects, acute kidney injury, renal dysfunction, pneumonia, upper respiratory tract infection, acute sinusitis, pyelonephritis acute, lung abscess, and anaemia in 1 subject each (some subjects had multiple events)

Table 49 shows the incidence of adverse events leading to treatment discontinuation.

Table 49. Incidence of adverse events leading to treatment discontinuation (safety analysis population)

Group	Adverse events leading to treatment discontinuation
Placebo 14.6% (26 of 178 subjects)	Lupus nephritis in 5 subjects Renal dysfunction,[a] proteinuria, and glomerular filtration rate decreased[a] in 4 subjects each Pneumonia[a] and systemic lupus erythematosus in 2 subjects each Cutaneous tuberculosis,[a] urinary tract infection,[a] renal failure, chronic kidney disease, abortion spontaneous, and pulmonary mass in 1 subject each (some subjects had multiple events)
Voclosporin 11.2% (20 of 178 subjects)	Renal dysfunction[b] in 4 subjects Lupus nephritis[b] and hypertension[b] in 2 subjects each Renal failure, glomerulonephritis, glomerular filtration rate decreased,[b] electrocardiogram QT prolonged,[b] pneumonia, lung abscess,[b] pulmonary tuberculosis, cervix carcinoma stage 0, uterine leiomyoma, systemic lupus erythematosus, anaemia,[b] cardiac failure acute, hyperkalaemia, neuropsychiatric lupus, and photosensitivity reaction[a] in 1 subject each (some subjects had multiple events)

MedDRA/J ver. 20.0

a) Events regarded as adverse drug reactions in the placebo group: Renal dysfunction, glomerular filtration rate decreased, pneumonia, cutaneous tuberculosis, and urinary tract infection in 1 subject each

b) Events regarded as adverse drug reactions in the voclosporin group: Hypertension in 2 subjects, renal dysfunction, lupus nephritis, glomerular filtration rate decreased, electrocardiogram QT prolonged, lung abscess, anaemia, and photosensitivity reaction in 1 subject each

As for safety in the Japanese population, adverse events were observed in 100% (5 of 5) of subjects in the placebo group and 100% (8 of 8) of subjects in the voclosporin group. Adverse drug reactions were reported in 40.0% (2 of 5) of subjects in the placebo group and 75.0% (6 of 8) of subjects in the voclosporin group. Table 50 shows adverse events observed in ≥2 subjects in either group. The adverse drug reaction observed in this context was herpes zoster (none in the placebo group, 3 subjects in the voclosporin group).

Table 50. Incidence of adverse events observed in ≥2 subjects in either group in the Japanese population (safety analysis population)

	Placebo (n = 5)	Voclosporin (n = 8)
All adverse events	100.0 (5)	100.0 (8)
Viral upper respiratory tract infection	60.0 (3)	37.5 (3)
Herpes zoster	0	37.5 (3)
Diarrhoea	20.0 (1)	25.0 (2)
Muscle spasms	20.0 (1)	25.0 (2)
Hypertension	20.0 (1)	25.0 (2)
Oral candidiasis	0	25.0 (2)
Renal dysfunction	0	25.0 (2)
Oedema peripheral	0	25.0 (2)
Neutropenia	40.0 (2)	12.5 (1)
Dyslipidaemia	40.0 (2)	12.5 (1)

MedDRA/J ver. 20.0; Incidence in % (number of subjects with events)

No deaths were reported. Serious adverse events were observed in 2 subjects only in the voclosporin group (neuropsychiatric lupus and lung abscess/cerebral infarction in 1 subject each). Among these, the lung abscess was classified as an adverse drug reaction, and the outcome was recovery. Adverse events leading to treatment discontinuation were observed in 2 subjects only in the voclosporin group (neuropsychiatric lupus and lung abscess in 1 subject each). Among these, the lung abscess was classified as an adverse drug reaction, and the outcome was recovery.

7.2.2 Global phase III study (extension study) (AURORA 2) (CTD 5.3.5.1-03, Study AUR-VCS-2016-02 [September 2019 to October 2021])

A multicenter, placebo-controlled, double-blind, parallel-group study was conducted to evaluate the long-term safety and efficacy of voclosporin in patients with LN who completed 52 weeks of the study drug treatment in the AURORA 1 study (including subjects who resumed treatment during the

AURORA 1 study after a treatment interruption) at 100 study sites across 24 countries, including 5 sites in Japan.

The same dosage regimen as those at the end of the AURORA 1 study was used, with the study drug administered orally at the same dose twice daily under fasted conditions. MMF was continued at the same dose as at the end of the AURORA 1 study, while corticosteroids could be tapered (including discontinuation after tapering) or increased as needed.

Of the 357 subjects in the AURORA 1 study, 216 subjects (100 of 178 subjects in the placebo group [3 Japanese subjects], 116 of 179 subjects in the voclosporin group [3 Japanese subjects]) were enrolled in this study and received the study drug. These subjects were included in the ITT population and the safety analysis population, and the ITT population was used as the efficacy analysis population. A total of 30 subjects discontinued the study (15 in the placebo group, 15 in the voclosporin group), with the following reasons for discontinuation: "Consent withdrawal" in 9 subjects (5 in the placebo group, 4 in the voclosporin group), "lost to follow-up" in 4 subjects (1 in the placebo group, 3 in the voclosporin group), "investigator's decision" in 4 subjects (2 in the placebo group, 2 in the voclosporin group), "pregnancy" in 4 subjects (1 in the placebo group, 3 in the voclosporin group), "death" in 3 subjects (3 in the placebo group, 0 in the voclosporin group), "adverse events": 2 subjects (2 in the placebo group, 0 in the voclosporin group), "lack of efficacy" in 2 subjects (0 in the placebo group, 2 in the voclosporin group), and "noncompliance" in 2 subjects (1 in the placebo group, 1 in the voclosporin group). No discontinuations were reported among Japanese subjects.

Regarding efficacy, Table 51 presents the proportion of subjects achieving renal response at each time point. A higher tendency was observed in the voclosporin group compared to the placebo group.

Table 51. Proportion of subjects achieving renal response (ITT population)

Evaluation time point	Placebo (n = 100)	Voclosporin 23.7 mg (n = 116)	Odds ratio relative to placebo [95% CI][a)]
Month 12 (at the end of the AURORA 1 study)	34.0 (34)	52.6 (61)	2.30 [1.30, 4.05]
Month 18	46.0 (46)	63.8 (74)	2.19 [1.25, 3.83]
Month 24	43.0 (43)	56.0 (65)	1.81 [1.04, 3.16]
Month 30	42.0 (42)	59.5 (69)	2.24 [1.28, 3.92]
Month 36	39.0 (39)	50.9 (59)	1.74 [1.00, 3.03]

Proportion of subjects achieving renal response in % (number of subjects with renal response)

a) Calculated by logistic regression analysis with the administration group, baseline UPCR, histological classification (Class V, others), the use of MMF at baseline, and region as explanatory variables.

Adverse events were reported in 80.0% (80 of 100) of subjects in the placebo group and 86.2% (100 of 116) of subjects in the voclosporin group. Adverse drug reactions were observed in 21.0% (21 of 100) of subjects in the placebo group and 24.1% (28 of 116) of subjects in the voclosporin group. Table 52 shows the incidence of adverse events occurring in ≥5% of subjects in either group, and Table 53 shows the incidence of adverse drug reactions occurring in ≥2% of subjects in either group.

Table 52. Incidence of adverse events observed in ≥5% of subjects in either group (safety analysis population)

	Placebo (n = 100)	Voclosporin (n = 116)
All adverse events	80.0 (80)	86.2 (100)
Urinary tract infection	8.0 (8)	12.9 (15)
Glomerular filtration rate decreased	5.0 (5)	10.3 (12)
Hypertension	7.0 (7)	8.6 (10)
Diarrhoea	5.0 (5)	8.6 (10)
Lupus nephritis	4.0 (4)	8.6 (10)
Viral upper respiratory tract infection	4.0 (4)	8.6 (10)
Upper respiratory tract infection	3.0 (3)	8.6 (10)
Headache	5.0 (5)	6.9 (8)
Coronavirus infection	12.0 (12)	6.0 (7)
Arthralgia	4.0 (4)	6.0 (7)
Anaemia	0 (0)	6.0 (7)
Systemic lupus erythematosus	9.0 (9)	5.2 (6)
Neutropenia	5.0 (5)	5.2 (6)
Gastroenteritis	3.0 (3)	5.2 (6)
Oedema peripheral	8.0 (8)	3.4 (4)
Herpes zoster	7.0 (7)	3.4 (4)
Nausea	5.0 (5)	2.6 (3)

MedDRA/J ver.20.0; Incidence in % (number of subjects with events)

Table 53. Incidence of adverse drug reactions observed in ≥2% of subjects in either group (safety analysis population)

	Placebo (n = 100)	Voclosporin (n = 116)
All adverse drug reactions	21.0 (21)	24.1 (28)
Glomerular filtration rate decreased	3.0 (3)	6.9 (8)
Renal dysfunction	1.0 (1)	2.6 (3)
Herpes zoster	3.0 (3)	1.7 (2)
Urinary tract infection	3.0 (3)	0.9 (1)
Bronchitis	2.0 (2)	0.9 (1)
Hypertension	3.0 (3)	0 (0)

MedDRA/J ver.20.0; Incidence in % (number of subjects with events)

Death occurred in 3.0% (3 of 100 subjects; coronavirus infection in 2 subjects and pulmonary embolism in 1 subject) in the placebo group, but was not observed in the voclosporin group.

Serious adverse events were observed in 23.0% (23 of 100) of subjects in the placebo group and 18.1% (21 of 116) of subjects in the voclosporin group. Serious adverse drug reactions occurred in 1 subject in each group (Table 54). The serious adverse drug reaction observed in the voclosporin group was an upper respiratory tract infection, which resolved after interruption of voclosporin.

Table 54. Incidence of serious adverse events (safety analysis population)

Group	Serious adverse events
Placebo 23.0% (23 of 100 subjects)	Coronavirus infection in 5 subjects Lupus nephritis and systemic lupus erythematosus in 3 subjects each Pneumonia viral and osteonecrosis in 2 subjects Gastroenteritis, pneumonia, disseminated tuberculosis, radius fracture, nephropathy toxic, nephrotic syndrome, arthralgia, flank pain, osteoarthritis, cataract, malignant glaucoma, cholecystitis, hypertension,[a] venous thrombosis limb, thrombocytopenia, gastritis, uterine leiomyoma, syncope, and pulmonary embolism in 1 subject each (some subjects had multiple events)
Voclosporin 18.1% (21 of 116 subjects)	Coronavirus infection, urinary tract infection, and lupus nephritis in 2 subjects each Gastroenteritis, pneumonia, appendicitis, upper respiratory tract infection,[b] fibula fracture, post procedural haematoma, post procedural haemorrhage, systemic lupus erythematosus, cataract, hepatitis toxic, lupus pericarditis, chest pain, glomerular filtration rate decreased, endometriosis, and abortion induced in 1 subject each (some subjects had multiple events)

MedDRA/J ver.20.0

a) Serious adverse drug reaction in the placebo group: Hypertension in 1 subject

b) Serious adverse drug reaction in the voclosporin group: Upper respiratory tract infection in 1 subject

Table 55 shows the incidence of adverse events leading to treatment discontinuation.

Table 55. Incidence of adverse events leading to treatment discontinuation (safety analysis population)

Group	Adverse events leading to treatment discontinuation
Placebo 17.0% (17 of 100 subjects)	Lupus nephritis and glomerular filtration rate decreased[a] in 3 subjects each Systemic lupus erythematosus, nephrotic syndrome and coronavirus infection in 2 subjects each Electrocardiogram QT prolonged,[a] hypertension, renal dysfunction,[a] pulmonary tuberculosis, disseminated tuberculosis,[a] and sinobronchitis[a] in 1 subject each (some subjects had multiple events)
Voclosporin 9.5% (11 of 116 subjects)	Lupus nephritis in 5 subjects Renal dysfunction[b] in 2 subjects Lymph node tuberculosis,[b] glomerular filtration rate decreased,[b] hypertension, and systemic lupus erythematosus in 1 subject each (some subjects had multiple events)

MedDRA/J ver.20.0

a) Adverse drug reactions leading to treatment discontinuation in the placebo group: Glomerular filtration rate decreased in 2 subjects, renal dysfunction, disseminated tuberculosis, electrocardiogram QT prolonged, and sinobronchitis in 1 subject each

b) Adverse drug reactions leading to treatment discontinuation in the voclosporin group: Renal dysfunction, lymph node tuberculosis, and glomerular filtration rate decreased in 1 subject each

Regarding safety in the Japanese population, adverse events were observed in 100.0% (3 of 3) of subjects in both the placebo and voclosporin groups. Adverse events observed in ≥2 subjects were oral herpes in 2 subjects in the voclosporin group. Adverse drug reactions were reported in 1 subject in the voclosporin group (nephropathy) and 1 subject in the placebo group (sinobronchitis). No deaths nor serious adverse events were reported. Adverse events leading to treatment discontinuation were observed in 1 subject in the placebo group (sinobronchitis).

7.R Outline of the review conducted by PMDA

7.R.1 Efficacy

PMDA's view:

The submitted data and the discussions in Sections 7.R.1.1 to 7.R.1.3 demonstrate the clinically significant efficacy of voclosporin for LN. However, the risk-benefit profile of voclosporin in patients who have impaired renal function before the start of treatment should be carefully assessed to identify their eligibility for treatment with voclosporin.

7.R.1.1 Study design of the global phase III study (AURORA 1 study)

The applicant's explanation about the design of the AURORA 1 study, the confirmatory study in this development program:

Eligible patients were those diagnosed with SLE according to the 1997 diagnostic criteria of the American College of Rheumatology and classified into the histological categories requiring immunosuppressive therapy (Table 32) as Class III, IV, or Class V LN. Patients in Class I and II were excluded because they generally do not require immunosuppressive therapy, and patients in Class VI was excluded because treatment options such as dialysis or renal transplantation are more appropriate, making voclosporin unsuitable. For active LN requiring treatment with glucocorticoid (GC) and immunosuppressants among Classes III, IV, or V, the urine protein creatinine ratio (UPCR) thresholds were ≥1.5 mg/mg for Classes III and IV and ≥2.0 mg/mg for Class V to ensure appropriate patient selection.

Regarding the control group, based on findings from the foreign phase II dose-ranging study (AURA-LV study), which confirmed that adding voclosporin to the basic therapy (placebo group) consisting of corticosteroid (Table 35) and MMF (Table 36) (the widely used therapies for active Class III, IV, or Class V LN) could yield higher efficacy, the study was designed to evaluate the superiority of voclosporin over the basic therapy as the control.

As for the primary endpoint, given that many clinical studies in patients with LN use a composite criterion combining proteinuria and renal function as the primary endpoint (Guideline for the Management of Systemic Lupus Erythematosus 2019, edited by the Japan College of Rheumatology, Research on Autoimmune Disease, Research on Policy Planning and Evaluation for Rare and Intractable Diseases, a research project funded by the Ministry of Health, Labour Sciences Research Grants), renal response, defined using UPCR and eGFR (Table 33), was adopted as the primary endpoint, as a certain level of clinically significant improvement. Concerning the evaluation time point for the primary endpoint, while the AURA-LV study suggested the superiority of voclosporin over placebo even at Week 24 (Table 37), the renal response rate at Week 48 was 23.9% (21 of 88 subjects) in the placebo group and 49.4% (44 of 89 subjects) in the 23.7 mg voclosporin group, demonstrating a higher renal response rate in the voclosporin group and a clearer difference from the placebo group at Week 48 compared to Week 24. Reports indicating a correlation between reductions in proteinuria at Month 12 and favorable renal outcomes (*Ann Rheum Dis.* 2016;75:526-31) were also taken into account. The primary evaluation time point for the AURORA 1 study was specified as Week 52.

Regarding the inclusion of Japanese patients with LN in the AURORA 1 study, while a phase II study of voclosporin in Japanese patients with LN was not conducted, the following points supported their participation: The diagnostic criteria and treatment algorithm for SLE in Japan (Guideline for the Management of Systemic Lupus Erythematosus 2019, edited by the Japan College of Rheumatology, Research on Autoimmune Disease, Research on Policy Planning and Evaluation for Rare and Intractable Diseases, a research project funded by the Ministry of Health, Labour Sciences Research Grants) are consistent with those in the US and Europe. Moreover, results from the Japanese phase I study (Study AUR-VCS-2015-J01) and the foreign phase I study (Study ISA03-12) indicated that although Japanese subjects tended to have lower drug exposure compared to non-Japanese subjects,

the exposure difference for the doses of voclosporin ≤0.5 mg/kg was not substantial enough to necessitate dose modification. The same dosage regimen (voclosporin 23.7 mg twice daily) was considered applicable for Japanese patients with LN. Based on the above, the AURORA 1 study was conducted as a global study including Japan.

PMDA's view:
The applicant's explanation of the patient population, control group, and primary endpoint settings in the AURORA 1 study, the confirmatory study, is appropriate. While the pre-study investigation of the appropriateness of conducting the study as a global study including Japanese subjects (e.g., the significance of the difference in the exposure level between Japanese and non-Japanese subjects) was insufficient, it is feasible to evaluate the efficacy of voclosporin based on the results of the AURORA 1 study, should the study results indicate that the inclusion of Japanese patients was justifiable.

7.R.1.2 Results of the AURORA 1 study

The applicant's explanation about the main efficacy results of the AURORA 1 study:
In the AURORA 1 study, the proportion of subjects achieving renal response at Week 52, the primary endpoint, was 22.5% (40 of 178 subjects) in the placebo group and 40.8% (73 of 179 subjects) in the voclosporin group (Table 45). The proportion was statistically significantly higher in the voclosporin group than in the placebo group ($P < 0.001$, logistic regression analysis, two-sided significance level of 5%). For the Japanese population, although the number of subjects was limited, the proportion achieving renal response at Week 52 was 20.0% (1 of 5 subjects) in the placebo group and 37.5% (3 of 8 subjects) in the voclosporin group, showing a trend similar to that of the entire population.

Table 56 shows the achievement rates for each component, the primary endpoint (renal response), and the proportion of subjects achieving renal response at Week 24, the secondary endpoint. In the entire population, these results consistently demonstrated higher trends in the voclosporin group compared to the placebo group. In the Japanese population, while a lower achievement rate for some components of the renal response was observed in the voclosporin group compared to the placebo group, this was likely influenced by the fact that discontinuation in 3 subjects (consent withdrawal in 2 subjects and loss to follow-up in 1 subject) occurred only in the voclosporin group. One subject in the voclosporin group had a final dose of prednisone 12.5 mg, which may have also affected the results. Given that the composite renal response rate was consistent with the trend observed in the entire population, the results do not negate the efficacy of voclosporin in Japanese patients with LN. Figure 1 shows the Kaplan-Meier curve for the time to achieve UPCR ≤0.5 mg/mg in the entire population. A difference between the voclosporin and placebo groups was observed within the first month after the start of voclosporin treatment and was sustained thereafter.

Table 56. Results of the primary and main secondary endpoints (AURORA 1 study, ITT population)

	Entire population			Japanese population		
	Placebo (n = 178)	Voclosporin (n = 179)	Odds ratio [95% CI]	Placebo (n = 5)	Voclosporin (n = 8)	Odds ratio [95% CI]
Renal response at Week 52 (primary endpoint)	22.5 (40)	40.8 (73)	2.65 [1.64, 4.27]	20.0 (1)	37.5 (3)	2.37 [0.17, >9.99]
UPCR ≤0.5 mg/mg	23.0 (41)	45.3 (81)	3.11 [1.93, 5.00]	20.0 (1)	37.5 (3)	2.37 [0.17, >9.99]
Stable eGFR[a)]	75.8 (135)	82.1 (147)	1.50 [0.89, 2.52]	80.0 (4)	62.5 (5)	0.42 [0.03, 5.97]
No rescue treatment	86.5 (154)	91.1 (163)	1.62 [0.82, 3.20]	80.0 (4)	100 (8)	- [c)]
Prednisone dose below prescribed level[b)]	85.4 (152)	87.2 (156)	1.26 [0.68, 2.34]	100 (5)	87.5 (7)	- [c)]
Not discontinued at Week 52	86.0 (153)	92.2 (165)	1.98 [0.98, 3.97]	100 (5)	62.5 (5)	- [c)]
Renal response at Week 24 (secondary endpoint)	19.7 (35)	32.4 (58)	2.19 [1.32, 3.63]	20.0 (1)	25.0 (2)	1.01 [0.05, >9.99]

Proportion of subjects achieving the endpoint in % (number of subjects achieving the endpoint)
a) eGFR ≥60 mL/min/1.73 m^2 or no decrease of ≥20% from baseline
b) The dose of prednisone <10 mg/day during the period before renal response assessment (Week 44 to 52)
c) Analysis impossible due to lack of convergence

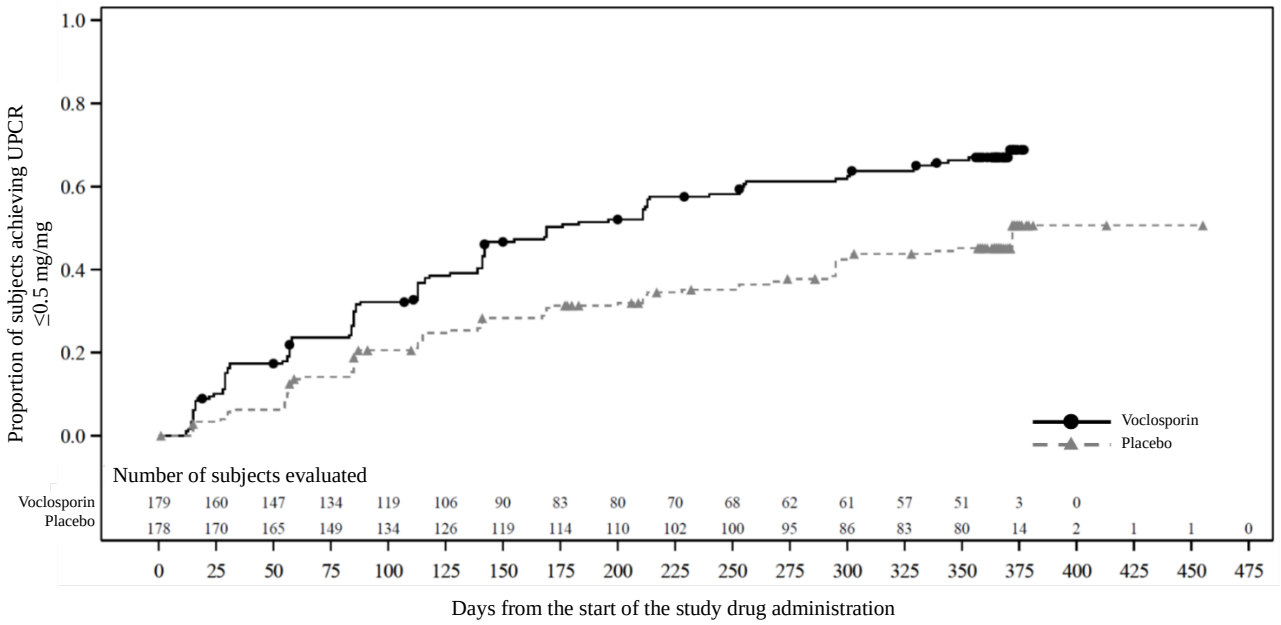

Figure 1. Kaplan-Meier curve for the time to achieve UPCR ≤0.5 mg/mg (AURORA 1 study, ITT population)

PMDA's view:

For the primary endpoint, the proportion of subjects achieving renal response at Week 52 was statistically significantly higher in the voclosporin group than in the placebo group. The results for each component of the renal response and the secondary endpoint showed trends consistent with the primary endpoint, demonstrating the clinically meaningful efficacy of voclosporin. Regarding the results for the Japanese population, although the small sample size limited the evaluation, the trends were generally consistent with those observed in the overall population. The clinical significance of pre-study concerns, (such as differences in exposure levels between Japanese and non-Japanese populations) was estimated to be minimal overall. In conclusion, the results of the AURORA 1 study for the entire population were consistent with those for the Japanese population, supporting the evaluation of the efficacy of voclosporin in Japanese patients from the results of the AURORA 1 study. Voclosporin can thus be expected to provide efficacy in Japanese patients with LN.

7.R.1.3 Efficacy by patient characteristics

The applicant's explanation about the efficacy based on patient characteristics:

Table 57 shows the proportion of subjects achieving renal response at Week 52, stratified by patient characteristics in the AURORA 1 study. Across all subgroups, a trend of higher renal response rates was observed in the voclosporin group compared to the placebo group. In some subgroups, the lower limit of the 95% confidence interval for the odds ratio fell below 1. This was considered to be due to the small sample sizes in these subgroups. In the subgroups of "no prior MMF treatment" and "no prior MMF or intermittent intravenous cyclophosphamide therapy (IVCY) treatment," the odds ratios were smaller. This was attributed to the higher response rate in the placebo group.

Table 57. Proportion of subjects achieving renal response at Week 52 by patient characteristics (AURORA 1 study, ITT population)

		Placebo (n = 178)	Voclosporin (n = 179)	Odds ratio [95% CI]
Age	≤30	18.1 (15/83)	40.4 (36/89)	3.03 [1.47, 6.24]
	>30	26.3 (25/95)	41.1 (37/90)	2.40 [1.25, 4.60]
Sex	Female	23.0 (35/152)	40.4 (65/161)	2.48 [1.49, 4.12]
	Male	19.2 (5/26)	44.4 (8/18)	4.18 [1.04, 16.71]
Body weight	Below median (63.3 kg)	24.4 (20/82)	44.2 (38/86)	2.45 [1.27, 4.75]
	At or above median (63.3 kg)	20.8 (20/96)	37.6 (35/93)	2.29 [1.20, 4.38]
Tissue classification	non-Class V	22.6 (24/106)	42.3 (47/111)	2.51 [1.39, 4.53]
	Class V mixed	21.3 (10/47)	34.9 (15/43)	1.98 [0.78, 5.07]
	pure Class V	24.0 (6/25)	44.0 (11/25)	2.49 [0.74,8.35]
Prior treatment with MMF	Yes	13.5 (13/96)	44.0 (44/100)	5.76 [2.78, 11.93]
	No	32.9 (27/82)	36.7 (29/79)	1.25 [0.64, 2.45]
Prior treatment with MMF and IVCY	Yes	16.3 (21/129)	39.7 (54/136)	3.83 [2.09, 7.01]
	No	38.8 (19/49)	44.2 (19/43)	1.23 [0.52, 2.89]
Hydroxychloroquine co-administration	Yes	18.6 (19/102)	37.6 (38/101)	2.63 [1.39, 5.00]
	No	27.6 (21/76)	44.9 (35/78)	2.13 [1.09, 4.18]
Baseline eGFR (mL/min/1.73 m^2)	<60	17.6 (6/34)	21.9 (7/32)	1.31 [0.39, 4.41]
	≥60 to <90	14.9 (7/47)	37.7 (20/53)	3.46 [1.30, 9.19]
	≥90	27.8 (27/97)	49.5 (46/93)	2.54 [1.39, 4.63]
Baseline UPCR (mg/mg)	<2	36.4 (12/33)	56.8 (21/37)	2.30 [0.88, 6.01]
	≥2	19.3 (28/145)	36.9 (52/141)	2.44 [1.43, 4.17]

Proportion of subjects achieving renal response in % (number of subjects with renal response/number of subjects evaluated)

PMDA's view:

Regarding efficacy by patient characteristics, the proportions of subjects achieving renal response tended to be higher in the voclosporin group than in the placebo group across all subgroups. In the "no prior MMF treatment" and "no prior MMF or IVCY treatment" subgroups as well, the efficacy of voclosporin can still be expected albeit at a relatively small odds ratio, given that combination therapy with corticosteroid and MMF was implemented in the placebo group from the start of the study and a certain level of efficacy of voclosporin was demonstrated. Therefore, there is no need to restrict the use of voclosporin based on the factors examined in this study. The relatively small odds ratios observed in these subgroups should be appropriately communicated through relevant informative materials and other resources. In the subgroup with baseline eGFR <60 mL/min/1.73 m^2, the proportion of subjects achieving renal response in the voclosporin group showed a lower trend. Given the safety concerns in this subgroup [see Sections 7.R.2.1, 7.R.2.2, and 7.R.2.4.1], the risk-benefit profile of voclosporin in patients who have impaired renal function should be carefully assessed to identify their eligibility for treatment with voclosporin.

7.R.1.4 Long-term efficacy of voclosporin

The applicant's explanation about the long-term efficacy of voclosporin for treatment exceeding 1 year:

In the extension study (AURORA 2 study) targeting subjects who had completed the AURORA 1 study (52 weeks), the double-blind design was maintained, and the study drug was administered continuously for an additional 24 months (36 months in total). Table 51 shows the proportions of subjects achieving renal response at each time point in the AURORA 2 study. From the start of the study drug administration in the AURORA 1 study to the 36-month time point, the proportion of subjects achieving renal response in the voclosporin group was consistently higher than that in the placebo group. For the Japanese population, 3 of 3 subjects in the placebo group and 2 of 3 subjects in the voclosporin group achieved renal response at the 36-month time point.

Figure 2 shows the changes in UPCR from baseline in the AURORA 1 study in the ITT population of the AURORA 2 study. The changes were maintained at similar levels from the end of the AURORA 1 study (12 months after the start of administration) through the 36-month time point.

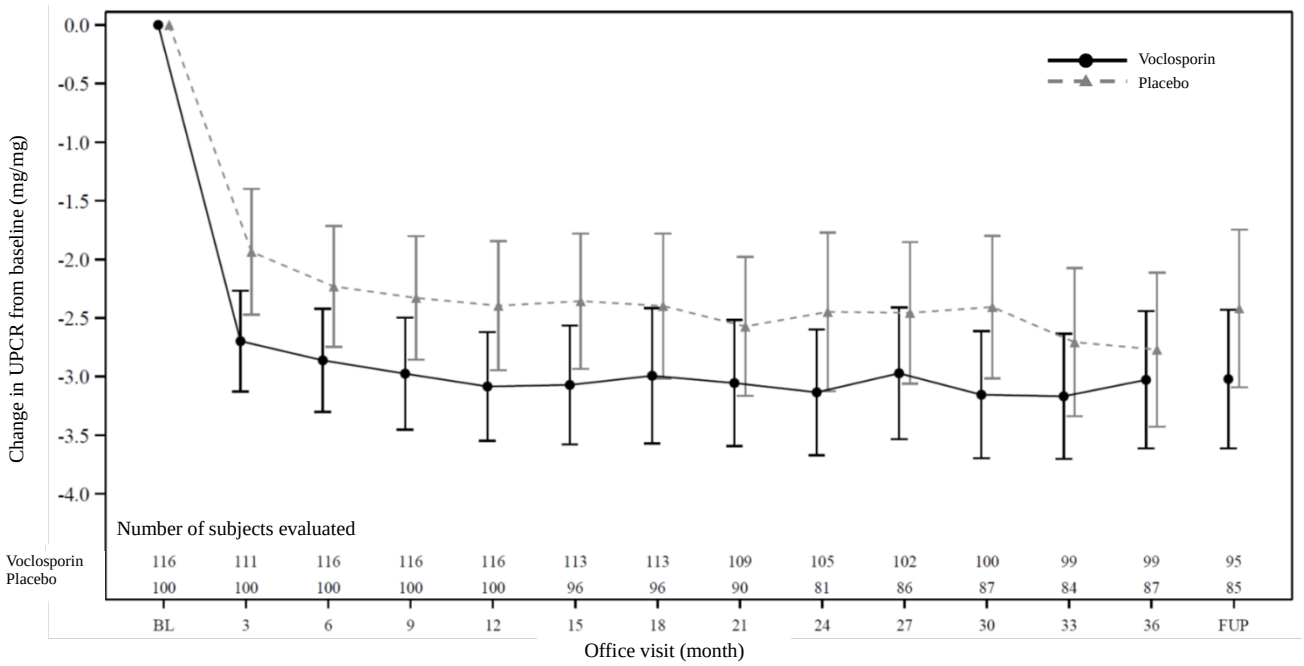

Figure 2. Changes in UPCR (AURORA 2 study, ITT population, mean and 95% CI)

BL, Baseline of the AURORA 1 study
FUP, Follow-up visit

PMDA's view:

Given the proportions of subjects achieving renal response and changes in UPCR observed in the AURORA 2 study, the long-term efficacy of voclosporin is expected to be generally maintained during treatment exceeding 1 year.

7.R.2 Safety

PMDA's view:

Based on the submitted materials and the evaluations in Sections 7.R.2.1 to 7.R.2.6, the safety of voclosporin is manageable if voclosporin is appropriately used under the supervision of physicians

sufficiently experienced in treating LN. Since voclosporin may cause renal function deterioration, special caution is required when administering voclosporin to patients with impaired renal function at the start of treatment.

7.R.2.1 Incidences of adverse events in placebo-controlled studies

The applicant's explanation about the safety profile of voclosporin compared to placebo:

Table 58 presents the overview of adverse event occurrences in the placebo-controlled phase II and phase III studies (AURA-LV, AURORA 1, and AURORA 2 studies). The incidence of adverse events showed no significant differences between the voclosporin and placebo groups in any of the studies. In the AURORA 1 study, the incidence of adverse drug reactions tended to be higher in the voclosporin group than in the placebo group. The incidence of serious adverse events and serious adverse drug reactions, however, was comparable between the 2 groups. For the Japanese population, in the AURORA 1 study, the incidence of adverse drug reactions tended to be higher in the voclosporin group than in the placebo group (40.0% [2 of 5 subjects] in the placebo group, 75.0% [6 of 8 subjects] in the voclosporin group). However, the only adverse drug reaction observed in ≥2 subjects was herpes zoster (3 subjects) in the voclosporin group, all of which were non-serious and moderate in severity. In the Japanese population of the AURORA 1 study, serious adverse events were observed only 2 subjects in the voclosporin group (neuropsychiatric lupus and lung abscess/cerebral infarction in 1 subject each). Among them, the lung abscess was considered an adverse drug reaction, but the outcome was recovery.

The incidence of adverse events leading to dose reduction of the study drug was higher in the voclosporin group than in the placebo group across all studies. Attention to renal function deterioration and increased blood pressure associated with voclosporin is deemed necessary.

Table 58. Incidence of adverse events
(AURA-LV, AURORA 1, and AURORA 2 studies, safety analysis population)

	AURA-LV study			AURORA 1 study		AURORA 2 study	
	Placebo (n = 88)	Voclosporin 23.7 mg (n = 89)	Voclosporin 39.5 mg (n = 88)	Placebo (n = 178)	Voclosporin (n = 178)	Placebo (n = 100)	Voclosporin (n = 116)
All adverse events	85.2 (75)	92.1 (82)	96.6 (85)	89.3 (159)	91.0 (162)	80.0 (80)	86.2 (100)
All adverse drug reactions	17.0 (15)	50.6 (45)	62.5 (55)	25.3 (45)	44.9 (80)	21.0 (21)	24.1 (28)
Death	1.1 (1)	11.2 (10)	2.3 (2)	1.7 (3)	0 (0)	3.0 (3)	0 (0)
Serious adverse events	15.9 (14)	28.1 (25)	25.0 (22)	21.3 (38)	20.8 (37)	23.0 (23)	18.1 (21)
Serious adverse drug reactions	1.1 (1)	4.5 (4)	8.0 (7)	4.5 (8)	4.5 (8)	2.0 (2)	0.9 (1)
Adverse events leading to treatment discontinuation	10.2 (9)	18.0 (16)	15.9 (14)	14.6 (26)	11.2 (20)	17.0 (17)	9.5 (11)
Adverse events leading to dose change	31.8 (28)	53.9 (48)	58.0 (51)	26.4 (47)	44.9 (80)	19.0 (19)	30.2 (35)

Incidence in % (number of subjects with events)

In the AURA-LV study, death was observed more commonly in the voclosporin 23.7 mg group compared to the placebo and voclosporin 39.5 mg groups. An analysis of characteristics factors for the reported deaths in 13 subjects in the study revealed that, except for 1 subject each in the placebo and voclosporin 23.7 mg groups, 11 subjects were from 3 Southeast Asian countries (Bangladesh, Sri Lanka, and the Philippines). The baseline mean UPCR value for the 13 deceased subjects was 7.95 mg/mg, higher than that of non-deceased subjects (4.52 mg/mg). The baseline mean eGFR value

for the deceased subjects was 82.17 mL/min/1.73 m², lower than that of non-deceased subjects (100.6 mL/min/1.73 m²), indicating that deceased subjects had more severe LN. The proportion of subjects from the 3 Southeast Asian countries was 31.8% (28 of 88 subjects) in the placebo group, 47.2% (42 of 89 subjects) in the voclosporin 23.7 mg group, and 37.5% (33 of 88 subjects) in the voclosporin 39.5 mg group, showing a higher trend in the voclosporin 23.7 mg group. The proportion of subjects with low baseline eGFR (≥30 and <60 mL/min/1.73 m²) was 5.7% (5 of 88 subjects) in the placebo group, 12.4% (11 of 89 subjects) in the voclosporin 23.7 mg group, and 6.8% (6 of 88 subjects) in the voclosporin 39.5 mg group, again indicating a higher trend in the voclosporin 23.7 mg group. Furthermore, baseline UPCR was 5.4 mg/mg in the 3 Southeast Asian countries, 4.4 mg/mg in Europe, and 4.0 mg/mg in North and South America. Baseline serum albumin levels were 2.7 g/dL in the 3 Southeast Asian countries, 3.3 g/dL in Europe, and 3.2 g/dL in North and South America, suggesting that subjects with more severe LN were enrolled from the 3 Southeast Asian countries compared to Europe and the Americas. The causes of death included infections and SLE-related complications [see Section 7.1.1]. A causal relationship to the study drug was ruled out for all events. The overall mortality rate in the AURA-LV study was 4.9% (13 of 265 subjects), comparable to the mortality rates reported in other clinical studies in patients with LN (3.7%-4.7%; *Arthritis Rheum.* 2014;66:379-89, *Arthritis Rheum.* 2013;65:2368-79, etc.). The number of deaths in the voclosporin 39.5 mg group was lower than in the voclosporin 23.7 mg group and similar to the placebo group, indicating no correlation between the dose of voclosporin and mortality. The above findings suggest that the higher mortality rate observed in the voclosporin 23.7 mg group was not directly caused by voclosporin but likely influenced by an imbalance in the allocation of subjects with relatively severe LN from the 3 Southeast Asian countries.

In the subsequent AURORA 1 and AURORA 2 studies, no deaths were reported in the voclosporin groups. The incidence of serious adverse events was also comparable between the voclosporin and placebo groups. Based on these results, the safety of voclosporin, including the safety in the Japanese population, is considered acceptable.

PMDA's view:
Regarding the safety of voclosporin compared to placebo, while the incidence of adverse drug reactions tended to be higher in the voclosporin groups than in the placebo group, the incidence of serious adverse events and serious adverse drug reactions was comparable. Considering the demonstrated efficacy [see Section 7.R.1], the safety and tolerability of voclosporin are deemed acceptable if voclosporin is used appropriately by physicians well-versed in LN treatment. However, the AURA-LV study indicated that the higher mortality rate in the voclosporin 23.7 mg group may have been influenced by an imbalance in the inclusion of subjects with impaired renal function at baseline, a factor associated with severe LN. Caution should be exercised when considering administration to patients with impaired renal function at the start of voclosporin therapy, with careful attention to the risk-benefit balance [see Section 7.R.2.2]. Dose reduction criteria were established for safety purposes in the protocols for clinical studies. As adverse events leading to dose reduction occurred more commonly in the voclosporin groups compared to the placebo group, accurate guidelines for dose reduction should be established. Further discussion on dose reduction is provided in Section 7.R.4.

7.R.2.2 Safety by patient characteristics

The applicant's explanation about the safety profile by patient characteristics:

Table 59 shows the incidence of adverse events and serious adverse events by patient characteristics in the integrated safety analysis population.[7)] The incidence of adverse events was comparable between the voclosporin group and the placebo group across all subpopulations. Regarding serious adverse events, a higher tendency of incidence was observed in the voclosporin group compared to the placebo group in the "male" subpopulation and the subpopulation classified as "pure Class V." This was considered to be influenced by the small number of subjects studied and the lower incidence of serious adverse events in the placebo group. Within the voclosporin group, no significant differences in the incidence of serious adverse events were observed between genders or across histological classifications. For subpopulations categorized by baseline eGFR (mL/min/1.73 m²), a higher tendency for the incidence of serious adverse events was noted in the voclosporin group in those with a baseline eGFR <60 mL/min/1.73 m². However, the placebo group also exhibited a similarly high tendency, suggesting that the differences were attributable to baseline renal function. Consequently, no special alerts are deemed necessary.

Table 59. Incidence of adverse events by major patient characteristics (integrated safety analysis population)

		Placebo (n = 266)		Voclosporin (n = 267)	
		Adverse events	Serious adverse events	Adverse events	Serious adverse events
All subjects		87.2 (232/266)	18.8 (50/266)	91.4 (244/267)	22.8 (61/267)
Age	<30	90.8 (99/109)	22.0 (24/109)	89.0 (113/127)	25.2 (32/127)
	≥30	84.7 (133/157)	16.6 (26/157)	93.6 (131/140)	20.7 (29/140)
Sex	Male	85.4 (35/41)	9.8 (4/41)	90.3 (28/31)	29.0 (9/31)
	Female	87.6 (197/225)	20.4 (46/225)	91.5 (216/236)	22.0 (52/236)
Body weight	Below median (63.3 kg)	85.3 (110/129)	14.0 (18/129)	94.9 (129/136)	24.3 (33/136)
	At or above median (63.3 kg)	89.0 (121/136)	23.5 (32/136)	87.7 (114/130)	21.5 (28/130)
Tissue classification	non-Class V	86.7 (143/165)	22.4 (37/165)	91.0 (152/167)	22.2 (37/167)
	Class V mixed	88.9 (56/63)	14.3 (9/63)	92.1 (58/63)	22.2 (14/63)
	pure Class V	86.8 (33/38)	10.5 (4/38)	91.9 (34/37)	27.0 (10/37)
Prior treatment with MMF	Yes	89.8 (114/127)	17.3 (22/127)	95.3 (122/128)	25.0 (32/128)
	No	84.9 (118/139)	20.1 (28/139)	87.8 (122/139)	20.9 (29/139)
Hydroxychloroquine co-administration	Yes	95.1 (137/144)	20.1 (29/144)	94.4 (135/143)	25.9 (37/143)
	No	77.9 (95/122)	17.2 (21/122)	87.9 (109/124)	19.4 (24/124)
Baseline eGFR (mL/min/1.73 m²)	<60	87.8 (36/41)	29.3 (12/41)	97.6 (40/41)	39.0 (16/41)
	≥60 to <90	85.3 (64/75)	24.0 (18/75)	89.2 (74/83)	22.9 (19/83)
	≥90	88.0 (132/150)	13.3 (20/150)	90.9 (130/143)	18.2 (26/143)
Baseline UPCR (g/mg)	<2	88.2 (45/51)	15.7 (8/51)	88.0 (44/50)	24.0 (12/50)
	≥2	87.0 (187/215)	19.5 (42/215)	92.2 (200/217)	22.6 (49/217)

Incidence in % (number of subjects with events/number of subjects evaluated)

PMDA's view:

Regarding safety by patient characteristics, although the number of subjects in the subgroup with a baseline eGFR <60 mL/min/1.73 m² was relatively small, the incidence of serious adverse events was higher in the voclosporin group than in the placebo group within the same subgroup, as well as to other subgroups in the voclosporin group. Renal function may deteriorate after voclosporin administration [see Section 7.R.2.4.1]. Considering the above, particular attention should be given to safety monitoring when administering voclosporin to patients with low eGFR. In clinical studies,

patients with baseline eGFR ≤45 mL/min/1.73 m² were excluded, and dose reduction criteria were established for cases where eGFR declined during the studies [see Section 7.R.4]. Caution should be included in the package insert, advising careful evaluation of the risk-benefit profile when administering voclosporin to patients with impaired renal function. Furthermore, the relationship between renal function and the safety profile of voclosporin in Japanese patients should continue to be monitored and verified in the post-marketing setting. For other patient characteristics and their relationship to safety, no specific alerts are deemed necessary.

7.R.2.3 Long-term safety of voclosporin

The applicant's explanation about the long-term safety of voclosporin:

Regarding the long-term safety of voclosporin, Tables 60 and 61 show the incidence of adverse events by time to event in the integrated safety analysis population and the AURORA 2 study, respectively. In the integrated safety analysis population, the incidence of adverse events by time to event, excluding deaths, was highest during Week 0 to 4 and tended to decrease over Week 26 to 52. Similarly, in the AURORA 2 study, the incidence of all adverse events and all adverse drug reactions was highest during the first year of administration and decreased thereafter. The incidence of serious adverse events, serious adverse drug reactions, and adverse events leading to treatment discontinuation remained similar between Year 1 and 2, and decreased during Year 2 to 3. The incidence of deaths was low throughout the study period.

Since there was no tendency for the incidence of adverse events to increase with longer duration of treatment, the applicant considered that there are no concerns about the long-term safety of voclosporin.

Table 60. Incidence of adverse events by time to event (integrated safety analysis population)

	Week 0 to 4		Week 4 to 12		Week 12 to 26		Week 26 to 52		Entire period	
	Placebo (n = 266)	Voclosporin (n = 267)	Placebo (n = 266)	Voclosporin (n = 267)	Placebo (n = 257)	Voclosporin (n = 247)	Placebo (n = 227)	Voclosporin (n = 233)	Placebo (n = 266)	Voclosporin (n = 267)
All adverse events	51.1 (136)	67.0 (179)	50.0 (133)	61.0 (163)	61.9 (159)	68.4 (169)	50.7 (115)	57.8 (129)	87.2 (232)	91.4 (244)
All adverse drug reactions	7.9 (21)	23.6 (63)	8.3 (22)	21.3 (57)	9.3 (24)	20.2 (50)	7.9 (18)	13.0 (29)	22.6 (60)	46.8 (125)
Death	0.8 (2)	0.7 (2)	0.4 (1)	1.1 (3)	0	1.2 (3)	0.4 (1)	0	1.5 (4)	3.0 (8)
Serious adverse events	3.0 (8)	6.0 (16)	4.9 (13)	8.2 (22)	9.7 (25)	6.5 (16)	4.4 (10)	7.6 (17)	18.8 (50)	22.8 (61)
Serious adverse drug reactions	0	1.5 (4)	0.4 (1)	1.9 (5)	1.9 (5)	1.2 (3)	1.3 (3)	0.4 (1)	3.4 (9)	4.5 (12)
Adverse events leading to treatment discontinuation	1.1 (3)	3.4 (9)	1.5 (4)	3.0 (8)	7.0 (18)	4.9 (12)	4.4 (10)	3.1 (7)	13.2 (35)	13.5 (36)

MedDRA/J ver.20.0; Incidence in % (number of subjects with events)

Table 61. Incidence of adverse events by time to event (AURORA 2 study, safety analysis population)

	Year 0 to 1		Year 1 to 2		Year 2 to 3	
	Placebo (n = 100)	Voclosporin (n = 116)	Placebo (n = 100)	Voclosporin (n = 116)	Placebo (n = 85)	Voclosporin (n = 103)
All adverse events	84.0 (84)	88.8 (103)	66.0 (66)	73.3 (85)	54.1 (46)	65.0 (67)
All adverse drug reactions	20.0 (20)	40.5 (47)	18.0 (18)	18.1 (21)	9.4 (8)	8.7 (9)
Death	0	0	2.0 (2)	0	1.2 (1)	0
Serious adverse events	13.0 (13)	11.2 (13)	18.0 (18)	11.2 (13)	9.4 (8)	7.8 (8)
Serious adverse drug reactions	2.0 (2)	3.4 (4)	2.0 (2)	0.9 (1)	0	0
Adverse events leading to treatment discontinuation	1.0 (1)	1.7 (2)	11.0 (11)	6.0 (7)	7.1 (6)	2.9 (3)

MedDRA/J ver.20.0; Incidence in % (number of subjects with events)

PMDA concluded that, based on the incidence of adverse events by time to event, no trend indicating changes in safety characteristics with the prolonged duration of treatment with voclosporin has been observed. No special safety alerts are deemed necessary currently regarding the long-term treatment of voclosporin.

7.R.2.4 Adverse events of special interest

The applicant described adverse events of special interest related to LN and CNIs, i.e., renal disorder-related events, infections (opportunistic infections), hypertension, other CNI-related events, and malignancies, based on the results of the integrated safety analysis population and the AURORA 2 study, as detailed in Sections 7.R.2.4.1 to 7.R.2.4.5.

7.R.2.4.1 Renal disorder-related events

The applicant's explanation about renal disorder-related events:

Renal disorder-related events were analyzed separately as acute renal failure and chronic kidney disease.

Table 62 shows the incidence of adverse events and serious adverse events related to acute renal failure (events classified as "acute renal failure" according to Medical Dictionary for Regulatory Activities Japanese version [MedDRA/J] SMQ) in the integrated safety analysis population. Glomerular filtration rate decreased was commonly observed in the voclosporin group compared with the placebo group. However, in the clinical studies, the study drug was reduced in dose or interrupted per protocol when eGFR decreased beyond a certain threshold [see Section 7.R.4]. In most cases, the decrease in eGFR was mild or transient. The incidence of serious adverse events related to acute kidney injury was slightly higher in the voclosporin group than in the placebo group.

Table 62. Incidence of acute renal failure (integrated safety analysis population)

	Adverse events		Serious adverse events	
	Placebo (n = 266)	Voclosporin (n = 267)	Placebo (n = 266)	Voclosporin (n = 267)
Acute renal failure	17.7 (47)	33.3 (89)	1.9 (5)	4.9 (13)
Glomerular filtration rate decreased	9.4 (25)	26.2 (70)	0.4 (1)	0.4 (1)
Renal dysfunction	2.6 (7)	5.6 (15)	0.4 (1)	1.1 (3)
Acute kidney injury	0.8 (2)	3.4 (9)	0.8 (2)	3.0 (8)
Blood creatinine increased	0.8 (2)	0.7 (2)	0	0
Azotaemia	0	0.4 (1)	0	0
Renal failure	0.4 (1)	0.4 (1)	0.4 (1)	0.4 (1)
Oliguria	0	0.4 (1)	0	0
Proteinuria	3.8 (10)	0	0	0

MedDRA/J ver.20.0; Incidence in % (number of subjects with events)

In the AURORA 2 study, acute renal failure was observed in 8.0% (8 of 100) of subjects in the placebo group and 16.4% (19 of 116) of subjects in the voclosporin group. The events observed in the voclosporin group (glomerular filtration rate decreased in 12 subjects, and renal dysfunction and proteinuria in 4 subjects each) were similar to those observed during the first year of treatment with the study drug (Table 62). No new safety concerns regarding acute renal failure were identified up to 36 months of voclosporin administration.

Table 63 shows the incidence of adverse events and serious adverse events related to chronic kidney disease (events classified as “chronic kidney disease” according to MedDRA/J SMQ) in the integrated safety analysis population. Apart from the glomerular filtration rate decreased, no specific events occurred significantly more commonly in the voclosporin group. The incidence of serious adverse events was lower in the voclosporin group than in the placebo group.

Table 63. Incidence of chronic kidney disease (integrated safety analysis population)

	Adverse events		Serious adverse events	
	Placebo (n = 266)	Voclosporin (n = 267)	Placebo (n = 266)	Voclosporin (n = 267)
Chronic kidney disease	22.9 (61)	30.0 (80)	2.6 (7)	1.1 (3)
Glomerular filtration rate decreased	9.4 (25)	26.2 (70)	0.4 (1)	0.4 (1)
Hyperkalaemia	0.8 (2)	1.9 (5)	0	0
Lupus nephritis	5.6 (15)	0.7 (2)	1.5 (4)	0.4 (1)
Blood creatinine increased	0.8 (2)	0.7 (2)	0	0
Hypocalcaemia	0.8 (2)	0.4 (1)	0	0
Renal failure	0.4 (1)	0.4 (1)	0.4 (1)	0.4 (1)
Metabolic acidosis	0.4 (1)	0.4 (1)	0.4 (1)	0
Urine protein/creatinine ratio increased	0.4 (1)	0.4 (1)	0	0
Glomerulonephritis	0.4 (1)	0.4 (1)	0	0
Nephrotic syndrome	0.4 (1)	0.4 (1)	0	0
Hyperphosphataemia	0	0.4 (1)	0	0
Hyponatraemia	0	0.4 (1)	0	0
Azotaemia	0	0.4 (1)	0	0
Proteinuria	3.8 (10)	0	0	0
Hypoalbuminaemia	1.5 (4)	0	0	0
Chronic kidney disease	0.4 (1)	0	0	0
Leukocyturia	0.4 (1)	0	0	0
Nephritic syndrome	0.4 (1)	0	0	0

MedDRA/J ver.20.0; Incidence in % (number of subjects with events)

Table 64 shows the incidence of chronic kidney disease-related adverse events and serious adverse events in the AURORA 2 study. Glomerular filtration rate decreased and lupus nephritis were observed relatively commonly. Among the events of glomerular filtration rate decreased in 12 subjects

in the voclosporin group, events in 9 subjects were considered adverse drug reactions, whereas only 1 event of lupus nephritis in the voclosporin group was considered an adverse drug reaction.

Table 64. Incidence of chronic kidney disease (AURORA 2 study, safety analysis population)

	Adverse events		Serious adverse events	
	Placebo (n = 100)	Voclosporin (n = 116)	Placebo (n = 100)	Voclosporin (n = 116)
Chronic kidney disease	16.0 (16)	24.1 (28)	5.0 (5)	2.6 (3)
Glomerular filtration rate decreased	5.0 (5)	10.3 (12)	0	0.9 (1)
Lupus nephritis	4.0 (4)	8.6 (10)	3.0 (3)	1.7 (2)
Proteinuria	1.0 (1)	3.4 (4)	0	0
Nephropathy	0	0.9 (1)	0	0
Blood calcium decreased	0	0.9 (1)	0	0
Focal segmental glomerulosclerosis	0	0.9 (1)	0	0
Hyperkalaemia	0	0.9 (1)	0	0
Hyponatraemia	0	0.9 (1)	0	0
Nephrotic syndrome	2.0 (2)	0	1.0 (1)	0
Blood bicarbonate decreased	1.0 (1)	0	0	0
Hypoalbuminaemia	1.0 (1)	0	0	0
Nephropathy toxic	1.0 (1)	0	1.0 (1)	0
Normochromic normocytic anaemia	1.0 (1)	0	0	0
Urine protein/creatinine ratio increased	1.0 (1)	0	0	0

MedDRA/J ver.20.0; Incidence in % (number of subjects with events)

Since in clinical studies, similar laboratory test abnormalities and symptoms are reported using various adverse events terms, the applicant considered it necessary to objectively evaluate the incidence of renal disorder-related events. For this reason, in addition to the analyses of acute renal failure and chronic kidney disease, the applicant reclassified renal disorder-related events (that had been reported using various MedDRA PT terms, i.e., “glomerular filtration rate decreased,” “acute kidney injury/acute renal failure,” “chronic kidney disease,” “renal failure,” “renal dysfunction,” “renal failure,” and “end-stage renal disease”) into the categories shown in Table 65, and investigated the incidence of real disorder-related adverse events. This reclassification was based on clinical laboratory data and clinical symptoms, referencing multiple clinical guidelines (e.g., KDIGO Clinical Practice Guidelines for glomerulonephritis, https://www.kisupplements.com/issue/s2157-1716(12)X7100-4 [last accessed on July 11, 2024), *Nat Rev Nephrol.* 2017;13:241–57).

Table 65. Incidence of renal disorder-related adverse events

	Integrated safety analysis population		AURORA 2 study (safety analysis population)	
	Placebo (n = 266)	Voclosporin (n = 267)	Placebo (n = 100)	Voclosporin (n = 116)
eGFR decreased[a)]	7.9 (21)	18.4 (50)	5.0 (5)	7.8 (9)
Acute kidney injury[b)]	0	4.1 (11)	0	0
Acute kidney disease[c)]	1.9 (5)	9.4 (25)	0	5.2 (6)
Chronic kidney disease [d)]	3.0 (8)	4.1 (11)	2.0 (2)	0.9 (1)
Renal failure/end stage renal disease[e)]	0.8 (2)	1.1 (3)	0	0
Events not corresponding to any of the above	1.5 (4)	6.0 (16)	0	1.7 (2)

Incidence in % (number of subjects with events)

a) When the corrected eGFR temporarily decreases by 20% to 50% and recovers to baseline (excluding cases where the uncorrected eGFR >90 mL/min/1.73 m²). However, if serum creatinine increases to >1.5 times the baseline value, it is categorized as “acute kidney injury” or “acute kidney disease.”
b) When serum creatinine increases to ≥1.5 times the baseline value within 7 days.
c) When serum creatinine increases to ≥1.5 times the baseline value and persists for 7 days to 3 months.
d) When eGFR decreases to <60 mL/min/1.73 m² and persists for ≥3 months without recovery.
e) When eGFR irreversibly decreases to <15 mL/min/1.73 m².

The most commonly observed event was “eGFR decreased,” which occurred at a higher rate in the voclosporin group compared to the placebo group. In the integrated safety analysis population, the incidence of “acute kidney injury” and “acute renal disease” was higher in the voclosporin group than in the placebo group. For “events not corresponding to any of the renal disorder-related events,” the incidence was also higher in the voclosporin group than in the placebo group. In the AURORA 2 study, the incidence of “acute renal disease” was higher in the voclosporin group than in the placebo group. For other events, the incidence was comparable between the 2 groups.

Based on the above, caution regarding acute nephrotoxicity associated with voclosporin is warranted. Appropriate cautions will be included in the package insert. In contrast, no data suggesting chronic nephrotoxicity associated with voclosporin have been identified. No special cautions related to chronic kidney disease are necessary.

PMDA’s view:
Based on the applicant’s explanation about renal disorder-related adverse events, careful monitoring of decreased eGFR and the occurrence of acute kidney injury/acute renal disease is necessary during voclosporin administration. Renal function should be confirmed before initiating treatment with voclosporin and renal function should be monitored during treatment [see Section 7.R.4 for dose reduction guidelines in cases of decreased eGFR].

7.R.2.4.2 Infections

The applicant’s explanation regarding infections:
As for the incidence of infections (events categorized under “infections and infestations” in MedDRA system organ class [SOC]), Tables 66 and 67 show events observed in ≥2% of subjects in either group within the integrated safety analysis population and the AURORA 2 study, respectively. The incidence of infections was slightly higher in the voclosporin group than in the placebo group in the integrated safety analysis population. There were no significant differences in the incidence of serious infections. Similarly, in the AURORA 2 study, no notable differences in the incidence of infections were observed between the voclosporin and placebo groups.

Table 66. Incidence of infections observed in ≥2% of subjects in either group (integrated safety analysis population)

	Adverse events		Serious adverse events	
	Placebo (n = 266)	Voclosporin (n = 267)	Placebo (n = 266)	Voclosporin (n = 267)
Infections	54.9 (146)	62.2 (166)	10.2 (27)	10.1 (27)
Upper respiratory tract infection	15.0 (40)	15.7 (42)	0.4 (1)	0.4 (1)
Urinary tract infection	6.4 (17)	9.7 (26)	0.4 (1)	1.1 (3)
Viral upper respiratory tract infection	7.5 (20)	9.0 (24)	0	0
Herpes zoster	5.3 (14)	6.7 (18)	0.4 (1)	0.4 (1)
Pneumonia	4.9 (13)	5.6 (15)	3.8 (10)	4.1 (11)
Gastroenteritis	4.5 (12)	5.6 (15)	0.4 (1)	1.5 (4)
Influenza	4.1 (11)	5.2 (14)	0	0
Oral candidiasis	1.1 (3)	2.2 (6)	0	0
Gingivitis	0	2.2 (6)	0	0
Bronchitis	4.9 (13)	1.9 (5)	1.1 (3)	0
Sinusitis	3.0 (8)	1.5 (4)	0	0
Pharyngitis	3.8 (10)	1.1 (3)	0	0

MedDRA/J ver.20.0; Incidence in % (number of subjects with events)

Table 67. Incidence of infections observed in ≥2% of subjects in either group (AURORA 2 study, safety analysis population)

	Adverse events		Serious adverse events	
	Placebo (n = 100)	Voclosporin (n = 116)	Placebo (n = 100)	Voclosporin (n = 116)
Infections	43.0 (43)	49.1 (57)	8.0 (8)	6.9 (8)
Urinary tract infection	8.0 (8)	12.9 (15)	0	1.7 (2)
Viral upper respiratory tract infection	4.0 (4)	8.6 (10)	0	0
Upper respiratory tract infection	3.0 (3)	8.6 (10)	0	0.9 (1)
Coronavirus infection	12.0 (12)	6.0 (7)	5.0 (5)	1.7 (2)
Gastroenteritis	3.0 (3)	5.2 (6)	1.0 (1)	0.9 (1)
Bronchitis	4.0 (4)	4.3 (5)	0	0
Herpes zoster	7.0 (7)	3.4 (4)	0	0
Gingivitis	0	3.4 (4)	0	0
Influenza	1.0 (1)	2.6 (3)	0	0
Oral herpes	0	2.6 (3)	0	0
Sinusitis	2.0 (2)	1.7 (2)	0	0
Pneumonia viral	2.0 (2)	0	2.0 (2)	0
Viral pharyngitis	2.0 (2)	0	0	0

MedDRA/J ver.20.0; Incidence in % (number of subjects with events)

Table 68 shows the incidence of opportunistic infections,[28)] which are concerns for immunosuppressive agents, in the integrated safety analysis population. The incidence was low in both the placebo and voclosporin groups, and only 1 serious opportunistic infection (herpes zoster disseminated) was observed in the placebo group. In the AURORA 2 study, opportunistic infection was observed in 1 subject in the placebo group (disseminated tuberculosis) and 1 subject in the voclosporin group (ophthalmic herpes zoster). Adverse drug reaction was reported in only 1 subject in the placebo group (disseminated tuberculosis).

Table 68. Incidence of opportunistic infections (integrated safety analysis population)

	Placebo (n = 266)	Voclosporin (n = 267)
Opportunistic infection	0.8 (2)	1.1 (3)
CMV chorioretinitis	0 (0)	0.4 (1)
CMV infection	0 (0)	0.4 (1)
Herpes zoster cutaneous disseminated	0 (0)	0.4 (1)
Herpes zoster disseminated	0.4 (1)	0 (0)
Ophthalmic herpes simplex	0.4 (1)	0 (0)

MedDRA/J ver.20.0; Incidence in % (number of subjects with events)

Based on the above, the risk of increased opportunistic infections with voclosporin is not considered significant. However, voclosporin has serious infections during clinical studies and has the potential risk of fatal infections. Voclosporin should be used by physicians who are well-versed in treating LN and have sufficient knowledge of voclosporin in facilities equipped for emergency management. A precaution will be included in the package insert.

PMDA's view:

Although there were no clinically significant differences in the incidence of infections between the voclosporin and placebo groups during clinical studies, both groups had serious infections and

28) Events corresponding to the following in MedDRA ver.20.0 PT
Fungal abscess, Acute haemorrhagic conjunctivitis, Acute pulmonary histoplasmosis, Alcaligenes infection, Anal fungal infection, Filariasis, Fungal arthritis, Aspergilloma, Aspergillus infection, Atypical mycobacterial pneumonia, Atypical pneumonia, Bartonella infection, BK virus infection, Leprosy borderline, Botryomycosis, Bovine tuberculosis, Fungal bronchitis, Bronchopulmonary aspergillosis, Burkholderia cepacia sepsis, Burkholderia gladioli infection, Burkholderia infection, Glanders, Candida osteomyelitis, Candida pneumonia, Candida retinitis, Candida sepsis, Central nervous system fungal infection, Cerebral aspergillosis, Cerebral fungal infection, Cerebral toxoplasmosis, Coccidioides encephalitis, Coccidioidomycosis, Cronobacter infection, Cronobacter necrotising enterocolitis, Cryptococcal fungaemia, Cryptococcosis, Cutaneous coccidioidomycosis, Cytomegalovirus chorioretinitis, Cytomegalovirus infection, Disseminated cryptococcosis, Disseminated cytomegaloviral infection, Disseminated tuberculosis, Fungal encephalitis, Fungal endocarditis, Histoplasma endocarditis, Exserohilum infection, Fungal eye infection, Fungaemia, Fungal abscess central nervous system, Fungal cystitis, Fungal endocarditis, Fungal labyrinthitis, Fungal oesophagitis, Fungal peritonitis, Fungal retinitis, Fungal sepsis, Fungal tracheitis, Gastric fungal infection, Gastrointestinal cryptococcosis, Gastrointestinal candidiasis, Gastrointestinal fungal infection, Genital herpes zoster, Herpes oesophagitis, Herpes sepsis, Herpes simplex colitis, Herpes simplex gastritis, Herpes simplex hepatitis, Herpes simplex meningitis, Herpes simplex meningoencephalitis, Herpes simplex meningomyelitis, Herpes simplex necrotising retinopathy, Herpes simplex oesophagitis, Herpes simplex pharyngitis, Herpes simplex pneumonia, Herpes simplex sepsis, Visceral herpes simplex, Herpes zoster disseminated cutaneous, Herpes zoster disseminated, Herpes zoster meningitis, Herpes zoster meningoencephalitis, Herpes zoster meningomyelitis, Herpes zoster necrotising retinopathy, Herpes zoster pharyngitis, Histoplasmosis, Histoplasmosis disseminated, HIV cardiomyopathy, HIV enteropathy, Human herpesvirus 8 infection, Leprosy, Leprosy atypical, Immunocompromised host infection, JC virus infection, Kaposi's varicelliform eruption, Leprosy, Leprosy lepromatous, Leptotrichia infection, Leuconostoc infection, Meningitis aspergillus, Meningitis candida, Meningitis coccidioides, Meningitis cronobacter, Meningitis cryptococcal, Meningitis exserohilum, Meningitis fungal, Meningitis histoplasma, Meningomyelitis herpetic, Methylobacterium infection, Madura foot fungal, Mycobacterial infection, Mycobacterial peritonitis, Mycobacterium abscessus infection, Mycobacterium avium complex infection, Mycobacterium chelonae infection, Mycotic corneal ulcer, Myocarditis fungal, Necrotising fasciitis fungal, Neurocryptococcosis, Nocardia sepsis, Nocardiosis, Oesophageal candidiasis, Ophthalmic herpes simplex, Ophthalmic herpes zoster, Opportunistic infection, Oropharyngeal aspergillosis, Oropharyngeal candidiasis, Oropharyngitis fungal, Orthopoxvirus infection, Osteomyelitis fungal, Otitis media fungal, Pantoea agglomerans infection, Paracoccidioides infection, Parasitic encephalitis, Pericarditis fungal, Pharyngeal abscess, Pneumocystis jirovecii infection, Pneumocystis jirovecii pneumonia, Pneumonia cryptococcal, Pneumonia fungal, Progressive multifocal leukoencephalopathy, Pseudomonas meningitis, Pulmonary mycosis, Pulmonary trichosporonosis, Pyelonephritis fungal, Raoultella ornithinolytica infection, Respiratory moniliasis, Respiratory tract infection fungal, Retinitis histoplasma, Scedosporium infection, Sinusitis aspergillus, Sinusitis fungal, Sphingomonas paucimobilis infection, Systemic candida, Systemic mycosis, Toxoplasmosis, Tuberculoid leprosy, Upper respiratory tract infection fungal, Urinary tract infection fungal, Varicella zoster gastritis, Varicella zoster oesophagitis, Varicella zoster pneumonia

opportunistic infections. In the AURA-LV study, fatal infections were observed, though causal relationship to voclosporin was ruled out [see Section 7.1.1]. Furthermore, considering the potential administration of voclosporin to patients with diverse characteristics in clinical settings and the mechanism of action of voclosporin, careful attention to infection risks is deemed necessary in its use. PMDA considers the applicant's proposal to include a caution in the package insert appropriate.

7.R.2.4.3 Hypertension

The applicant's explanation on hypertension:

Table 69 shows the incidence of hypertension (events categorized under "hypertension" in MedDRA SMQ) in the integrated safety analysis population. The incidence of adverse events was higher in the voclosporin group than in the placebo group. However, no significant differences were observed between the 2 groups in the incidence of serious adverse events. In the AURORA 2 study, hypertension was observed in 8.0% (8 of 100) of subjects in the placebo group and 8.6% (10 of 116) of subjects in the voclosporin group.

Table 69. Incidence of hypertension (integrated safety analysis population)

	Adverse events		Serious adverse events	
	Placebo (n = 266)	Voclosporin (n = 267)	Placebo (n = 266)	Voclosporin (n = 267)
Hypertension	10.5 (28)	21.0 (56)	1.1 (3)	2.2 (6)
Hypertension	8.6 (23)	19.1 (51)	0.4 (1)	1.9 (5)
Blood pressure increased	1.1 (3)	1.9 (5)	0	0
Blood pressure diastolic increased	0	0.4 (1)	0	0
Hypertensive crisis	1.1 (3)	0.4 (1)	0.8 (2)	0.4 (1)
Essential hypertension	0	0.4 (1)	0	0
Diastolic hypertension	0.4 (1)	0	0	0
Retinopathy hypertensive	0.4 (1)	0	0	0

MedDRA/J ver.20.0; Incidence in % (number of subjects with events)

Hypertension is a predictable event associated with CNI and has also been observed in clinical studies of voclosporin. Therefore, blood pressure should be monitored appropriately during voclosporin treatment, and this precaution will be included in the package insert.

PMDA's view:

Hypertension is a known adverse drug reaction associated with other CNIs. Considering that the incidence of hypertension was higher in the voclosporin group than in the placebo group within the integrated safety analysis population, the following precaution should be included in the package insert: Blood pressure should be monitored periodically during voclosporin treatment. If blood pressure control proves challenging despite appropriate management of hypertension, discontinuation of voclosporin should be considered.

7.R.2.4.4 Adverse events associated with other CNIs

The applicant's explanation regarding adverse events associated with other CNIs:

Table 70 and Table 71 show adverse events associated with CNIs (excluding glomerular filtration rate decreased)[29] observed in ≥1% of subjects in either group in both the integrated safety analysis population and the AURORA 2 study, respectively.

Table 70. Adverse events associated with CNIs observed in ≥1% of subjects in either group (integrated safety analysis population)

	Placebo (n = 266)	Voclosporin (n = 267)
CNI-associated adverse events	22.9 (61)	32.2 (86)
Hypertension	8.6 (23)	19.1 (51)
Tremor	0.8 (2)	3.4 (9)
Hyperlipidaemia	2.3 (6)	2.6 (7)
Weight decreased	0.4 (1)	2.2 (6)
Hypertrichosis	0 (0)	2.2 (6)
Blood pressure increased	1.1 (3)	1.9 (5)
Gingival hypertrophy	0 (0)	1.9 (5)
Hirsutism	0 (0)	1.5 (4)
Hyperglycaemia	1.5 (4)	0.7 (2)
Hypertriglyceridaemia	2.6 (7)	0.4 (1)
Hypertensive crisis	1.1 (3)	0.4 (1)
Proteinuria	3.8 (10)	0

MedDRA/J ver.20.0; Incidence in % (number of subjects with events)

[29] Events corresponding to the following in MedDRA ver.20.0 PT
Diabetic hyperglycaemic coma, Diabetic hyperosmolar coma, Diabetic ketoacidosis, Diabetic ketoacidotic hyperglycaemic coma, Diastolic hypertension, Essential hypertension, Gingival hypertrophy, Glomerular vascular disorder, Glucose tolerance decreased, Glucose tolerance impaired, Glucose tolerance test abnormal, Glucose urine present, Glycosuria, Glycosylated haemoglobin increased, Haematuria, Haemoglobin urine present, Haemoglobinuria, Haemolytic uraemic syndrome, Hair growth abnormal, Hirsutism, Hypercholesterolaemia, Hyperglycaemia, Hyperglycaemic seizure, Hyperglycaemic unconsciousness, Hyperlipidaemia, Hypertension, Hypertensive crisis, Hypertensive emergency, Hypertensive heart disease, Hypertensive nephropathy, Hypertrichosis, Hypertriglyceridaemia, Hypoglycaemia, Hypoinsulinaemia, Impaired fasting glucose, Insulin secretion disorder, Increased appetite, Insulin requirement increased, Impaired glucose tolerance, Insulin autoimmune syndrome, Insulin resistance, Insulin resistant diabetes, Insulin resistance test abnormal, Insulin-requiring type 2 diabetes mellitus, Ischaemic nephropathy, Kidney fibrosis, Labile blood pressure, Labile hypertension, Latent autoimmune diabetes in adults, Malignant hypertension, Malignant renal hypertension, Mean arterial pressure increased, Microalbuminuria, Nephrogenic diabetes insipidus, Nephrotic syndrome, Oedema due to renal disease, Orthostatic proteinuria, Post-transplant distal limb syndrome, Potassium-losing nephropathy, Prehypertension, Protein deficiency, Proteinuria, Protein urine present, Proteinuria, Red blood cells urine positive, Renal arteriosclerosis, Renal arteritis, Renal artery arteriosclerosis, Renal cortical necrosis, Renal hypertension, Renal ischaemia, Renal papillary necrosis, Renal tubular necrosis, Renin abnormal, Renovascular hypertension, Retinopathy hypertensive, Thrombotic microangiopathy, Thrombotic thrombocytopenic purpura, Tremor, Tubulointerstitial nephritis, Type 1 diabetes mellitus, Type 2 diabetes mellitus, Type 3 diabetes mellitus, Underweight, Urine abnormality, Urine albumin/creatinine ratio increased, Urine ketone body present, Urine protein/creatinine ratio abnormal, Urine protein/creatinine ratio increased, Weight decreased, Weight increased, Withdrawal hypertension, Abnormal loss of weight, Abnormal weight gain, Accelerated hypertension, Acquired lipoatrophic diabetes, Albumin globulin ratio increased, Albumin urine present, Albuminuria, Blood cholesterol increased, Blood glucose abnormal, Blood glucose fluctuation, Blood glucose increased, Blood insulin abnormal, Blood insulin decreased, Blood osmolarity increased, Blood pressure abnormal, Blood pressure ambulatory abnormal, Blood pressure ambulatory increased, Diastolic blood pressure abnormal, Diastolic blood pressure increased, Blood pressure fluctuation, Blood pressure inadequately controlled, Blood pressure increased, Blood pressure management, Orthostatic blood pressure abnormal, Orthostatic blood pressure increased, Systolic blood pressure abnormal, Systolic blood pressure increased, Blood triglycerides increased, Body mass index decreased, Body mass index increased, Central obesity, Diabetes mellitus, Diabetes mellitus inadequate control, Diabetes with hyperosmolarity, Diabetic arteritis, Diabetic coma

Table 71. Adverse events associated with CNIs observed in ≥1% of subjects in either group (AURORA 2 study, safety analysis population)

	Placebo (n = 100)	Voclosporin (n = 116)
CNI-associated adverse events	12.0 (12)	20.7 (24)
Hypertension	7.0 (7)	8.6 (10)
Proteinuria	1.0 (1)	3.4 (4)
Hypertriglyceridaemia	1.0 (1)	1.7 (2)
Hypercholesterolaemia	0	1.7 (2)
Weight decreased	0	1.7 (2)
Hyperlipidaemia	1.0 (1)	0.9 (1)
Blood triglycerides increased	1.0 (1)	0.9 (1)
Nephrotic syndrome	2.0 (2)	0
Renovascular hypertension	1.0 (1)	0

MedDRA/J ver.20.0; Incidence in % (number of subjects with events)

The incidence of adverse events associated with CNIs was slightly higher in the voclosporin group than in the placebo group. Specifically, for adverse events other than renal disorder, infections, and hypertension-related events, the voclosporin group showed a higher incidence of tremor and hypertrichosis than the placebo group in the integrated safety analysis population. However, there were no significant differences between the groups in the incidence of adverse events related to dyslipidemia or hyperglycaemia. Serious adverse events associated with CNIs, excluding those related to renal disorder, infections, and hypertension, were limited to diabetes mellitus in 1 subject in the voclosporin group within the integrated safety analysis population. A causal relationship to the study drug was ruled out.

Based on the above findings, the risk of adverse events associated with CNIs, excluding renal disorder, infections, and hypertension, is considered low for voclosporin. However, given the occurrence of neurotoxicity such as tremor in the clinical studies, a cautionary statement will be included in the package insert.

PMDA's view:
The incidence of adverse events associated with CNIs (excluding renal disorder, infections, and hypertension) tended to be slightly higher in the voclosporin group compared to the placebo group. Additionally, there is no direct evidence to conclude that voclosporin is safer than existing CNIs. Therefore, similar precautions should be taken for voclosporin as those for existing CNIs, and this should be reflected in the package insert.

7.R.2.4.5 Malignant tumors

The applicant's explanation regarding the risk of malignant tumors associated with voclosporin:
Table 72 shows the occurrence of malignant tumors (events categorized under "malignant disorders" based on MedDRA/J SMQ) in the integrated safety analysis population. Malignant tumors were observed only in the voclosporin group, but a causal relationship to the study drug was ruled out for all events. Among them, the only serious adverse event was cervix carcinoma stage 0 in 1 subject. In the AURORA 2 study, no malignant tumors were observed.

Table 72. Incidence of malignant tumors (integrated safety analysis population)

	Placebo (n = 266)	Voclosporin (n = 267)
Malignant tumor	0 (0)	1.5 (4)
Cervix carcinoma stage 0	0 (0)	0.4 (1)
Neoplasm skin	0 (0)	0.4 (1)
Pyoderma gangrenosum	0 (0)	0.4 (1)
Breast tumour excision	0 (0)	0.4 (1)

MedDRA/J ver.20.0; Incidence in % (number of subjects with events)

As described above, although clinical study results do not suggest that voclosporin poses a risk of malignant tumors, longer-term data are needed to evaluate the risk. Considering that malignant tumors are a known risk associated with existing immunosuppressants, a caution regarding malignant tumors will be included in the package insert, similar to other immunosuppressive agents.

PMDA's view:
In the integrated safety analysis population, 4 events of malignant tumors were reported exclusively in the voclosporin group, among which only 1 event qualified as cancer (cervix carcinoma stage 0). No malignancies were observed in the AURORA 2 study. While the clinical study results do not indicate a prominent risk of malignant tumors associated with voclosporin, it is difficult to draw definitive conclusions based solely on these findings. The applicant's decision to include a caution regarding malignant tumors, consistent with other immunosuppressants, is considered appropriate. Additionally, the applicant is required to monitor and collect post-marketing data continuously to evaluate the risk of malignant tumors further.

7.R.2.5 Post-marketing safety information

The applicant's explanation about post-marketing safety information for voclosporin in foreign countries:
Voclosporin was approved in the US on January 22, 2021 for the treatment of LN. According to the latest periodic safety update report (covering the period from July 22, 2023, to January 21, 2024), the estimated cumulative post-marketing exposure to voclosporin is 1442.1 person-years. As of the data lock point for the latest periodic safety update report, no significant differences were observed in the trends of adverse events reported in foreign post-marketing safety data compared to those observed in clinical studies. Additionally, no new safety concerns regarding voclosporin have been identified.

PMDA's view:
The applicant's explanation is reasonable, stating that, at present, no events suggestive of new safety concerns distinct from those observed in clinical studies have been identified in the foreign post-marketing safety information for voclosporin.

7.R.2.6 Use in pregnancy and lactation

The applicant's explanation about the use of voclosporin in pregnancy and lactation:
Since SLE predominantly affects young women, the potential effects of voclosporin on pregnancy and lactation were evaluated.

In non-clinical studies, reproductive and developmental toxicity studies indicated that voclosporin did not exhibit teratogenicity. However, maternal effects, including changes in body weight and mammary gland swelling, were observed. Fetal effects, such as reduced body weight and skeletal variations, were also noted [see Section 5.5]. Pharmacokinetic studies demonstrated that voclosporin crosses the placenta [see Section 4.2.3] and transfers to infant via breast milk [see Section 4.4.3].

In all clinical studies of voclosporin, including those for indications other than LN,[30)] pregnancy was reported in 19 cases involving subjects or their partners who received voclosporin (Table 73). Of them, 10 cases involved pregnancies in female subjects, and 9 involved pregnancies in female partners of male subjects. Among the 8 cases that resulted in live births, no congenital abnormalities were observed. One case of intrauterine fetal death was reported, but its causal relationship to voclosporin was ruled out. Two cases of spontaneous abortion were reported, although detailed information regarding these pregnancies was unavailable. In clinical studies for LN, both maternal and fetal risks associated with the underlying disease, SLE, must be considered, as well as the concurrent use of MMF, a known teratogen. Although no adverse effects on mothers or fetuses were identified in clinical studies, the available data are insufficient to determine the risk of congenital abnormalities or miscarriage associated with voclosporin.

Table 73. Pregnancies reported in subjects or their partners who received voclosporin

Disease	Pregnancy of female subjects (n = 10)	Pregnancy of the partners of male subjects (n = 9)
LN	Delivery of normal healthy infant: 2 Induced abortion: 2 Induced abortion due to intrauterine fetal death: 1	Not applicable
Psoriasis vulgaris and uveitis	Delivery of normal healthy infant: 4 Unknown outcome: 1	Delivery of normal healthy infant: 2 Spontaneous abortion: 1 Induced abortion: 1 Unknown outcome: 3
Renal transplant	Not applicable	Spontaneous abortion: 1 Unknown outcome: 1

In a phase I study (Study AUR-VCS-20[redacted]-04) [see Section 6.2.4] involving 12 healthy lactating female subjects who received a single oral dose of 23.7 mg of voclosporin, 4 adverse events were reported in 3 subjects (3 events of headache and 1 event of fatigue). All events were of mild severity and resolved without complications.

Judging from the results of the non-clinical and clinical studies as described above, total prohibition on the administration of voclosporin during pregnancy and lactation is not deemed necessary. However, healthcare providers should be advised to make decisions regarding the use of voclosporin in such situations, based on careful consideration of the benefit-risk profile for individual patients.

PMDA's view:
Given the non-clinical and clinical study findings and the applicant's explanation, there is no evidence of risk that warrants prohibiting voclosporin during pregnancy and lactation. Nonetheless, the potential impact of voclosporin exposure on subsequent generations has not been fully assessed. It is essential to

[30)] Psoriasis (3 phase III studies, 964 subjects), non-infectious uveitis (4 phase II/III studies, 710 subjects), and kidney transplantation (1 late phase II study, 694 subjects).

caution that the decision regarding the administration of voclosporin during pregnancy and lactation, as well as pregnancy and lactation under treatment with voclosporin, should be made considering the benefit-risk balance of the treatment.

7.R.3 Clinical positioning and indication

The applicant's explanation regarding the clinical positioning and indications of voclosporin:
In the Japanese clinical guidelines (Guideline for the Management of Systemic Lupus Erythematosus 2019, edited by the Japan College of Rheumatology, Research on Autoimmune Disease, Research on Rare and Intractable Diseases, a research project funded by the Ministry of Health, Labour Sciences Research Grants), combination therapy with corticosteroids and immunosuppressive agents (MMF or cyclophosphamide [CY]) is recommended as the first-line treatment for LN. However, MMF is widely used as the immunosuppressive agent due to concerns about the toxicity of CY. While CNIs such as tacrolimus (TAC) and CsA are also used, issues with adverse drug reactions, including hyperglycemia and dyslipidemia, mean that some patients cannot receive these treatments. Voclosporin, as a CNI with a lower risk of adverse drug reactions, is expected to not only control active LN when used early in the disease course as a first-line therapy but also to minimize the use of corticosteroids and thereby reduce adverse reactions to corticosteroids.

In the confirmatory AURORA 1 study, voclosporin was added to corticosteroids and MMF from the start of first-line therapy in patients with active LN, regardless of their prior MMF or IVCY treatment. The study demonstrated superior renal response in the voclosporin group compared to the placebo group [see Section 7.R.1.2], indicating that adding voclosporin to corticosteroids and MMF offers superior efficacy to that of the first-line therapy recommended in the guidelines. In addition, subgroup analyses suggested that voclosporin is effective even in patients without prior MMF or IVCY treatment [see Section 7.R.1.3].

Based on the above, although existing CNIs are typically used after first-line therapy with MMF and IVCY, the demonstrated efficacy of voclosporin used concomitantly with corticosteroids and MMF suggests that its use as a first-line treatment is appropriate. In Europe, voclosporin is recommended as one of the early combination therapies for active LN (*Ann Rheum Dis.* 2024;83:15-29).

Regarding indications of voclosporin, the clinical studies in LN patients demonstrated the efficacy of voclosporin [see Section 7.R.1], and no significant safety concerns were identified [see Section 7.R.2]. The proposed indication of "lupus nephritis" is deemed appropriate.

PMDA's view:
In the confirmatory AURORA 1 study, which enrolled patients with active LN, regardless of their prior MMF or IVCY treatment, the add-on effect of voclosporin on the existing standard first-line therapy (corticosteroids and MMF) was demonstrated [see Section 7.R.1.2]. The long-term efficacy of voclosporin was also suggested in the extension study, AURORA 2 [see Section 7.R.1.4]. The clinical studies demonstrated the efficacy of voclosporin even in LN patients without a prior MMF or IVCY treatment, albeit at a smaller odds ratio [see Section 7.R.1.3]. Regarding safety, while no results from clinical studies comparing voclosporin with existing drugs in the same class support the applicant's

assertion that voclosporin has a lower risk of adverse drug reactions compared to such drugs, no significant safety concerns were identified when voclosporin was added to the current standard first-line therapy. Given proper information and caution about reduced renal function, and administration by a physician well-versed in LN treatment, it is considered manageable [see Section 7.R.2]. Based on the above, voclosporin, when combined with corticosteroids and MMF, could serve as a new treatment option for first-line therapy for LN or as a second-line therapy when the combination of corticosteroids and MMF fails to achieve sufficient efficacy. The proposed indication of “lupus nephritis” is thus appropriate.

However, certain considerations must be noted when determining the application of voclosporin for individual patients because (a) the patients with LN included in the clinical trials were histologically classified as Class III, IV, or Class V with UPCR above a certain threshold; (b) for patients with impaired renal function, the benefit-risk balance of voclosporin should be carefully evaluated [see Sections 7.R.1.3, 7.R.2.1, and 7.R.2.2]; (c) patients with eGFR ≤45 mL/min/1.73 m² were excluded from the clinical studies. The above points should be included in the package insert and materials for healthcare professionals to provide adequate cautions and information.

7.R.4 Dosage and administration

The applicant’s explanation about the dosage regimen of voclosporin:

Based on the results of clinical studies of voclosporin in healthy subjects and patients with other conditions (plaque psoriasis, noninfectious uveitis, and renal transplantation), it was shown that body weight did not significantly influence the pharmacokinetics of voclosporin. Therefore, a fixed dose regimen was adopted for clinical studies in patients with LN. In a dose-finding study conducted in patients with plaque psoriasis (ISA04-03), efficacy was observed at doses of voclosporin 0.3 and 0.4 mg/kg, but no significant difference from placebo was observed at 0.2 mg/kg. Based on these findings, the doses of voclosporin for the phase II dose-finding study in patients with LN (AURA-LV study) were 23.7 mg twice daily (equivalent to 0.3-0.4 mg/kg twice daily) and a higher dose of 39.5 mg twice daily (equivalent to 0.5-0.6 mg/kg twice daily). In the AURA-LV study, for the primary endpoint of renal response at Week 24, the lower limit of the 95% confidence interval for the odds ratio in the voclosporin 23.7 mg group exceeded 1 when compared with the placebo group. However, in the 39.5 mg group, the lower limit of the 95% confidence interval for the odds ratio did not exceed 1 [see Section 7.1.1]. Based on these results, the dose of voclosporin for the confirmatory AURORA 1 study was 23.7 mg twice daily.

In the AURORA 1 study which was designed based on the above dose selection, the efficacy of voclosporin 23.7 mg twice daily was demonstrated [see Section 7.R.1.2], and no significant safety concerns were identified [see Section 7.R.2.1].

Since voclosporin carries risks of renal disorder [see Section 7.R.2.4.1] and hypertension [see Section 7.R.2.4.3], patients with eGFR ≤45 mL/min/1.73 m² were excluded from the AURORA 1 study. As shown in Table 74, dose reduction or interruption of the study drug was stipulated based on renal function (eGFR) and blood pressure levels.

Table 74. Dose adjustment criteria for renal function (eGFR) and blood pressure (AURORA 1 study)

When eGFR (CKD-EPI equation) is <60 mL/min/1.73 m^2	
Decrease from baseline	Measures to be taken
Decrease by ≤20%	Monitoring without change in the dosage regimen of voclosporin (23.7 mg twice daily)
Decrease by >20% to <30%	Re-examine within 2 weeks, and if the decrease in eGFR has not improved, take measures such as dose reduction
Decrease by ≥30%	Interrupt voclosporin. If eGFR has recovered, resume voclosporin at a lower dosage level.
Blood pressure	
Blood pressure level	Measures to be taken
Systolic pressure, >130 mmHg and ≤165 mmHg Diastolic pressure, >80 mmHg and ≤105 mmHg	Consider starting antihypertensive treatment.
Systolic pressure >165 mmHg and diastolic pressure >105 mmHg, showing hypertensive symptoms	Discontinue voclosporin and start antihypertensive treatment.

Monitoring: Week 2, Week 4, every 4 weeks from Week 8 to 24, every 6 weeks from Week 30 to 48, Week 52, and Week 56

Table 75 shows the incidence of adverse events leading to dose modifications (dose reduction or treatment interruption) observed in ≥2 subjects in either group in the AURORA 1 study. The incidence was higher in the voclosporin group than in the placebo group.

Table 75. Adverse events leading to dose modifications observed in ≥2 subjects in either group (AURORA 1 study, safety analysis population)

	Placebo (n = 178)	Voclosporin (n = 178)
Adverse events leading to dose modification	26.4 (47)	44.9 (80)
Glomerular filtration rate decreased	6.2 (11)	22.5 (40)
Renal dysfunction	0.6 (1)	3.9 (7)
Gastroenteritis	1.1 (2)	2.8 (5)
Herpes zoster	0.6 (1)	2.8 (5)
Pneumonia	2.8 (5)	2.2 (4)
Upper respiratory tract infection	1.7 (3)	2.2 (4)
Diarrhoea	1.1 (2)	1.7 (3)
Nausea	0.6 (1)	1.7 (3)
Hypertension	0	1.7 (3)
Systemic lupus erythematosus	1.1 (2)	1.1 (2)
Bacterial diarrhoea	0.6 (1)	1.1 (2)
Leukopenia	0.6 (1)	1.1 (2)
Gastritis	0	1.1 (2)
Anaemia	0	1.1 (2)
Neutropenia	0	1.1 (2)
Headache	0	1.1 (2)
Migraine	0	1.1 (2)
Viral upper respiratory tract infection	1.1 (2)	0.6 (1)
Bronchitis	1.7 (3)	0
Influenza	1.1 (2)	0

MedDRA/J ver.20.0; Incidence in % (number of subjects with events)

Data were analyzed to evaluate the efficacy of voclosporin after dose modifications (dose reduction or treatment interruption) as defined by the study protocol. The proportion of subjects who underwent dose modifications in the AURORA 1 study was 40.4% (72 of 178 subjects) in the placebo group and 57.0% (102 of 179 subjects) in the voclosporin group. The proportion of subjects achieving renal response at Week 52 among those with dose modifications was 13.9% (10 of 72 subjects) in the placebo group and 31.4% (32 of 102 subjects) in the voclosporin group. The odds ratio [95% CI][31)] for the voclosporin group compared to the placebo group was 3.11 [1.36, 7.08], showing a trend consistent with that in the overall population.

[31)] Logistic regression analysis was conducted using treatment group, baseline UPCR, histological diagnosis, and use of MMF at baseline as explanatory variables.

Regarding renal function following the discontinuation or interruption of the study drug due to decreased eGFR, the proportion of subjects who discontinued the study drug due to decreased eGFR in the AURORA 1 study was 12.9% (23 of 178 subjects) in the placebo group and 29.2% (52 of 178 subjects) in the voclosporin group. The proportion of subjects whose eGFR recovered to ≥80% of baseline after discontinuation of the study drug was 87.0% (20 of 23 subjects) in the placebo group and 90.4% (47 of 52 subjects) in the voclosporin group, indicating that most subjects recovered to ≥80% of baseline. The above results suggest that the events of decreased eGFR associated with voclosporin are reversible and manageable through dose reduction or treatment interruption

Based on the above, the dosage regimen of voclosporin 23.7 mg twice daily should be selected. The package insert will include a cautionary statement that the dose should be adjusted in accordance with the clinical study protocol when eGFR is <60 mL/min/1.73 m² or when blood pressure increases. For dose reduction of voclosporin when the eGFR decline rate is >20% and <30%, the reduction method used in the AURA-LV study was referenced, setting “the dose reduction by 7.9 mg twice daily (15.8 mg daily dose).” Although voclosporin was administered under fasted conditions during the AURORA 1 study, a study investigating the effects of food on pharmacokinetics (Study 348-102-00010) showed no significant food effect on the pharmacokinetics of voclosporin [see Section 6.2.2]. No dietary restrictions were included in the regimen for voclosporin.

PMDA’s view:
Based on the efficacy [see Section 7.R.1.2] and safety [see Section 7.R.2.1] of voclosporin 23.7 mg twice daily as demonstrated in the AURORA 1 study, and the absence of significant food effects on its pharmacokinetics [see Section 6.2.2], it is reasonable to specify the dosage regimen of voclosporin for LN at 23.7 mg twice daily orally, without dietary restrictions. In clinical studies, dose adjustment criteria (Table 75) were established due to risks of renal function decline and increased blood pressure, with dose modifications (dose reduction or treatment interruption) implemented in approximately 50% of subjects in the voclosporin group. Considering this, dosage regimen of voclosporin should include instructions to reduce the dose as needed based on patient conditions and the package insert should include a cautionary statement that dose adjustments should generally follow the protocol specified in the clinical study.

Furthermore, given that voclosporin was co-administered with corticosteroids (tapered) and MMF during clinical studies, and considering the clinical positioning of voclosporin in the treatment of LN [see Section 7.R.3], the package insert should include a statement that voclosporin should be initiated in combination with corticosteroids and MMF as a general principle.

7.R.5 Post-marketing investigations

The applicant plans to conduct a general use-results survey as outlined in Table 76 after the market launch.

Table 76. General use-results survey (draft)

Objective	To confirm the safety of voclosporin in patients with LN treated with voclosporin in clinical practice, and to collect information on its efficacy.
Survey method	Central registry system
Population	Patients who newly start treatment of lupus nephritis with voclosporin
Planned sample size	400 patients (350 patients for the safety analysis population)
Observation period	3 years
Main survey items	• Patient characteristics: Sex, age, timing of diagnosis of SLE, timing of diagnosis of LN, LN classification, complications, past medical history, etc. • Use of voclosporin: Dose, inpatient/outpatient status, treatment period, objective/reason for change, reason for discontinuation, etc. • Use of concomitant drugs • Change over time in renal function: BUN, serum creatinine, eGFR, total protein, albumin, urine protein, urine creatinine, UPCR, urine occult blood, urine sediment (red blood cells, white blood cells), anti-dsDNA antibody, CH50, C3, C4, etc. • Laboratory tests: Body weight, blood pressure, clinical chemistry (lipid metabolism, serum potassium, serum magnesium, blood glucose, HbA1c), etc. • Adverse events: Event name, date of onset, seriousness, outcome, causal relationship to voclosporin, treatment given, etc.

PMDA' view:

The occurrence of vascular events caused by hypertension [see Section 7.R.2.4.3] and adverse events related to CNI, such as neurotoxicity [see Section 7.R.2.4.4], should continue to be evaluated in the post-marketing setting. The impact of these factors on the risk-benefit balance of voclosporin should be assessed in clinical practice.

7.R.6 Pediatric development of voclosporin

The applicant's explanation:

For the pediatric development of voclosporin, Aurinia Pharmaceuticals is conducting a global study in patients with active LN aged ≥12 to <18 years. Also, the company plans another global study in patients aged ≥5 to <18 years with active LN. The applicant plans to include Japanese participants in the studies, in order to undertake the clinical development in Japan.

PMDA's view:

The pediatric development of voclosporin is necessary and highly significant, given the prevalence of LN in children. In accordance with the guidance titled "Planning of the Pediatric Drug Development Program During the Development of Drugs for Adults" (PSB/PED Notification No. 0112-3, dated January 12, 2024), the pediatric development plan for voclosporin targeting LN presented by the applicant has been reviewed.

8. Results of Compliance Assessment Concerning the New Drug Application Data and Conclusion Reached by PMDA

8.1 PMDA's conclusion concerning the results of document-based GLP/GCP inspections and data integrity assessment

The new drug application data were subjected to a document-based inspection and a data integrity assessment in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices. On the basis of the inspection and assessment, PMDA concluded that there were no obstacles to conducting its review based on the application documents submitted.

8.2 PMDA's conclusion concerning the results of the on-site GCP inspection

The new drug application data (CTD 5.3.5.1-02) were subjected to an on-site GCP inspection, in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices. On the basis of the inspection, PMDA concluded that there were no obstacles to conducting its review based on the application documents submitted.

9. Overall Evaluation during Preparation of the Review Report (1)

On the basis of the data submitted, PMDA has concluded that voclosporin has efficacy in the treatment of lupus nephritis, and that voclosporin has acceptable safety in view of its benefits. Voclosporin is clinically meaningful because it offers a new treatment option for patients with lupus nephritis.

PMDA has concluded that voclosporin may be approved if voclosporin is not considered to have any particular problems based on comments from the Expert Discussion.

Review Report (2)

August 9, 2024

Product Submitted for Approval

Brand Name	Lupkynis Capsules 7.9 mg
Non-proprietary Name	Voclosporin
Applicant	Otsuka Pharmaceutical Co., Ltd.
Date of Application	November 10, 2023

List of Abbreviations
See Appendix.

1. Content of the Review

Comments made during the Expert Discussion and the subsequent review conducted by the Pharmaceuticals and Medical Devices Agency (PMDA) are summarized below. The expert advisors present during the Expert Discussion were nominated based on their declarations, etc. concerning the product submitted for marketing approval, in accordance with the provisions of the Rules for Convening Expert Discussions, etc. by Pharmaceuticals and Medical Devices Agency (PMDA Administrative Rule No. 8/2008 dated December 25, 2008).

1.1 Efficacy and safety

At the Expert Discussion, the expert advisors supported PMDA's conclusion described in Sections "7.R.1 Efficacy" and "7.R.2 Safety" in the Review Report (1).

1.2 Indication

At the Expert Discussion, the expert advisors supported PMDA's conclusion described in Section "7.R.3 Clinical positioning and indication" in the Review Report (1).

PMDA concluded that the indication of voclosporin should be specified as proposed at the time of the application. Additionally, PMDA concluded that the following Precautions Concerning Indication should be established, and the applicant responded appropriately.

Indication
Lupus nephritis

Precautions Concerning Indication

- Renal function may worsen after treatment with voclosporin. Therefore, the necessity of voclosporin treatment in patients with eGFR ≤45 mL/min/1.73 m² should be carefully considered, and the use of voclosporin should be avoided whenever possible in patients with eGFR

<30 mL/min/1.73 m². No clinical studies evaluating the efficacy and safety of voclosporin have been conducted in patients with eGFR ≤45 mL/min/1.73 m².

- Physicians should be well-versed in the findings presented in the "17. Clinical Studies" section to have a full understanding of the subjects included in clinical studies of voclosporin and of efficacy and safety results, thereby using voclosporin only in patients eligible for treatment with voclosporin, with reference to the latest information in clinical guidelines and other sources.

1.3 Dosage and administration

At the Expert Discussion, the expert advisors supported PMDA's conclusion described in Section "7.R.4 Dosage and administration" in the Review Report (1).

PMDA concluded that the "Dosage and Administration" and "Precautions Concerning Dosage and Administration" sections should be described as shown below, and the applicant responded appropriately.

Dosage and Administration

The usual adult dosage is 23.7 mg of voclosporin administered orally twice daily. The dose may be reduced according to the patient's condition.

Precautions Concerning Dosage and Administration

- Treatment with voclosporin should be initiated in combination with adrenalcorticosteroids and mycophenolate mofetil as a general rule.
- The use of voclosporin in patients with severe renal impairment (eGFR <30 mL/min/1.73 m²) should be avoided whenever possible. If the use of voclosporin is unavoidable, the dose should be 15.8 mg twice daily.
- In patients with mild or moderate hepatic impairment (Child-Pugh class A or B), the recommended dose should be 15.8 mg twice daily.
- When co-administering voclosporin with moderate CYP3A4 inhibitors, the daily dose should be adjusted to 23.7 mg (15.8 mg in the morning and 7.9 mg in the evening).
- If renal function deteriorates, voclosporin should be reduced in dose or interrupted based on the following criteria:
  - If eGFR is <60 mL/min/1.73 m² and decreases by >20% from baseline, the dose should be reduced by 7.9 mg twice daily (15.8 mg daily dose). After dose reduction, the eGFR level should be checked within 2 weeks. If the >20% reduction persists, the dose should be reduced by further 7.9 mg twice daily (15.8 mg daily dose).
  - If eGFR is <60 mL/min/1.73 m² and decreases by >30% from baseline, voclosporin should be discontinued.
- If blood pressure rises and cannot be adequately controlled with appropriate antihypertensive treatments, voclosporin should be discontinued.
- The therapeutic effects of voclosporin should be evaluated within 6 months of the treatment to consider whether to continue the treatment.

1.4 Risk management plan (draft)

At the Expert Discussion, the expert advisors supported PMDA's conclusion described in Section "7.R.5 Post-marketing investigations" in the Review Report (1).

In view of the discussion at the Expert Discussion, PMDA has concluded that the risk management plan (draft) for voclosporin currently should include the safety and efficacy specifications presented in Table 77, and that the applicant should conduct additional pharmacovigilance activities and risk minimization activities presented in Tables 78 and 79.

Table 77. Safety and efficacy specifications in the risk management plan (draft)

Safety specification		
Important identified risks	Important potential risks	Important missing information
• Serious infection (including opportunistic infection) • Renal toxicity	• Cardiovascular events • Neurotoxicity • Electrolyte abnormalities (hypomagnesemia, hyperkalemia) • Glucose intolerance • Malignancy associated with long-term use	• Safety during pregnancy and breastfeeding
Efficacy specification		
• None		

Table 78. Summary of additional pharmacovigilance activities and additional risk minimization activities included under the risk management plan (draft)

Additional pharmacovigilance activities	Additional risk minimization activities
• Early post-marketing phase vigilance • General use-results survey	• Disseminate data gathered during early post-marketing phase vigilance

Table 79. General use-results survey (draft)

Objective	To confirm the safety of voclosporin in patients with LN treated with voclosporin in clinical practice, and to collect information on its efficacy.
Survey method	Central registry system
Population	Patients who newly start treatment of lupus nephritis with voclosporin
Planned sample size	400 patients (350 patients for the safety analysis population)
Observation period	3 years
Main survey items	• Patient characteristics: Sex, age, timing of diagnosis of SLE, timing of diagnosis of LN, LN classification, complications, past medical history, etc. • Use of voclosporin: Dose, inpatient/outpatient, treatment duration, objective/reason for change, reason for discontinuation, etc. • Use of concomitant drugs • Presence or absence of pregnancy/lactation during the observation period (if present, conduct follow-up on childbirth, breastfeeding, and the safety of the newborn). • Change over time in renal function: BUN, serum creatinine, eGFR, total protein, albumin, urine protein, urine creatinine, UPCR, urine occult blood, urine sediment (red blood cells, white blood cells), anti-dsDNA antibody, CH50, C3, C4, etc. • Laboratory tests: Body weight, blood pressure, clinical chemistry (lipid metabolism, serum potassium, serum magnesium, blood glucose, HbA1c), renal biopsy (if conducted), etc. • Adverse events: Event name, date of onset, seriousness, outcome, causal relationship with voclosporin, treatment given, etc.

2. Overall Evaluation

As a result of the above review, PMDA has concluded that the product may be approved for the indication and dosage and administration as shown below, with the following condition. Since the product is a drug with a new active ingredient, the re-examination period is 8 years. The product is not classified as a biological product or a specified biological product. The drug product and its drug substance are both classified as powerful drugs.

Indication

Lupus nephritis

Dosage and Administration

The usual adult dosage is 23.7 mg of voclosporin administered orally twice daily. The dose may be reduced according to the patient’s condition.

Approval Conditions

The applicant is required to develop and appropriately implement a risk management plan.

Appendix

List of Abbreviations

ALP	Alkaline Phosphatase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUC	Area under the concentration versus time curve
AUC_{inf}	AUC up to infinity
BCRP	Breast cancer resistance protein
BUN	Blood urea nitrogen
Caco-2 cells	Human colon cancer-derived cells
CD	Cluster of differentiation
CEC	Central evaluation committee
CHO	Chinese hamster ovary
CI	Confidence interval
CKD	Chronic kidney disease
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CL/F	Apparent clearance after administration of the drug
CL_{cr}	Creatinine clearance
C_{max}	Maximum concentration
CNI	Calcineurin inhibitor
CQA	Critical quality attribute
CsA	Cyclosporine A
CTD	Common technical document
C_{trough}	Plasma concentration at the end of dosing interval
CY	Cyclophosphamide
CYP	Cytochrome P450
DMSO	Dimethylsulfoxide
EC_{50}	Half maximal effective concentration
eGFR	Estimated glomerular filtration rate
FAS	Full analysis set
FDA	Food and Drug Administration
GC	Glucocorticoid
Hb	Hemoglobin
HEK293 cells	Human embryonic kidney cell line 293
hERG	Human ether-a-go-go related gene
HIV	Human immunodeficiency virus
HPLC	High performance liquid chromatography
IC_{50}	Half maximal inhibitory concentration
IL	Interleukin
IL-2	Interleukin 2
IL-4	Interleukin 4
IR	Infrared absorption spectroscopy
ISN/RPS	International Society of Nephrology/Renal Pathology Society
ITT	Intention-to-Treat
IVCY	Intermittent intravenous cyclophosphamide therapy
ka	Absorption rate constant
LC-MS	Liquid chromatography-mass spectrometry
LC-MS/MS	Liquid chromatography-tandem mass spectrometry
Lupkynis	Lupkynis Capsules 7.9 mg
MATE	Multidrug and toxin extrusion
MCH	Mean Cell Hemoglobin
MCT oil	Medium Chain Triglyceride oil
MCV	Mean Cell Volume

MDCKII cells	Mardin-Darby canine kidney cells
MedDRA/J	Medical Dictionary for Regulatory Activities Japanese version
MF	Master file
MMF	Mycophenolate mofetil
mRNA	Messenger ribonucleic acid
NMR	Nuclear magnetic resonance spectroscopy
NZW	New Zealand white
OAT	Organic anion transporter
OATP	Organic anion transporting polypeptide
OCT	Organic cation transporter
PBPK	Physiologically based pharmacokinetic
P-gp	P-glycoprotein
PMDA	Pharmaceuticals and Medical Devices Agency
QT	QT interval
QTc	Corrected QT interval
QTcF	Fridericia-corrected QT interval
RBC	Red blood cell
SD	Sprague-Dawley
SLE	Systemic lupus erythematosus
SOC	System organ class
$t_{1/2}$	Elimination half-life
TAC	Tacrolimus
TEAE	Treatment-emergent adverse event
Tg	Transgenic
TGF-β2	Transforming Growth Factor-β2
t_{max}	Time to reach maximum concentration
Tween 40	Polyoxyethylene Sorbitan Monopalmitate
UPCR	Urine protein creatinine ratio
Vc/F	Apparent central volume of distribution
Vitamin E TPGS	d-α-Tocopherol polyethylene glycol succinate
Voclosporin	Voclosporin
WBC	White blood cell