Table 2: Components of Complete Renal Response Endpoint at Week 52 (AURORA-1; ITT Population)

Components in the primary endpoint	Placebo	Voclosporin 23.7 mg	Odds Ratio (95%)	p-value
UPCR ≤ 0.5 mg/mg	41 (23.0)	81 (45.3)	3.1 (1.9, 5.0)	<.001
eGFR success	135 (75.8)	147 (82.1)	1.5 (0.8, 2.5)	0.1

Source: Voclosporin Unireview, accessed January 19, 2021

Table 3: Intercurrent Events (AURORA-1; ITT Population)

Intercurrent events	Placebo	Voclosporin 23.7 mg	Odds Ratio (95%)	p-value
Received no rescue medication for lupus nephritis	154 (86.5)	163 (91.1)	1.6 (0.8, 3.2)	0.2
Did not receive more than 10 mg prednisone	152 (85.4)	156 (87.2)	1.3 (0.6, 2.3)	0.5

Source: Voclosporin Unireview; last accessed January 19, 2021

By Week 24 of the AURORA-1 study, 70.4% of subjects in the voclosporin arm had a partial renal response. At Week 52, 69.8% of voclosporin treated subjects had a partial renal response. Labeling will reflect this by directing prescribers to discontinue voclosporin use after 24 weeks if no response.

Table 4 shows the results from the Week 24 Complete Renal Response Analysis. While there was a significantly greater percentage of subjects in the voclosporin 23.7 mg BID (Twice daily) arm that had a complete response versus placebo (32.6% vs. 19.3%), the difference in complete responses between the two voclosporin treatment arms was not significant (32.6% vs. 27.3%).

Table 4: Proportion of Subjects Achieving Complete Response at Week 24 (AURA-LV; FAS)

Treatment Arm	*Response n/N (%)*	*Odds Ratio vs Placebo*	*95% CI*	*p-value*
Placebo (N=88)	17 (19.3)	-	-	-
Voclosporin 23.7mg BID (N=89)	29 (32.6)	2.0	(1.1, 4.1)	0.045
Voclosporin 39.5mg BID (N=88)	24 (27.3)	1.6	(0.8, 3.3)	0.204

N=number of subjects in the analysis set, n= number of responders CI=confidence interval
Complete remission was defined as a confirmed decrease in proteinuria (UPCR <0.5 mg/mg) and no confirmed eGFR <60 mL/min/1.73m^2 or no confirmed decrease from baseline in eGFR of ≥20% at Week 24 (in the absence of recuse medication) and did not receive >10 mg prednisone for ≥3 consecutive days or ≥7 days in total during Weeks 16 through 24/26.
Source: Voclosporin Unireview, last accessed January 19, 2021

The clinical reviewer concluded that the voclosporin data from the phase 3 study demonstrated statistically and clinically significant benefits of voclosporin.

5 Risk Assessment & Safe-Use Conditions

Voclosporin is a member of the calcineurin inhibitor class of drugs, and being structurally similar to cyclosporin, has many of the same well-known toxicities of the drug class. Upon review of the data, the clinical reviewer concludes that the safety profiles are similar, (b) (4) [7] Therefore, the safety review focuses on known calcineurin inhibitor adverse events, such as hypertension, and nephrotoxicity, for which all renal adverse events (acute renal toxicity, eGFR decrease) will be grouped together. Labeling will closely align with other drugs in the class.

Safety data is based on the pooled lupus nephritis group of 533 subjects from the placebo and voclosporin 23.7 mg dosing arms from AURORA-1 and AURA-LV. Data from the 39.5 mg dose arm of the AURA-LV study was not included in the integrated safety analysis as the dose was used in only 1 study; however, reference to relevant safety data will be included. The current long-term data population includes 356 subjects in the AURORA-1 study.[7]

Twenty-three percent of subjects taking voclosporin reported adverse events, versus 19% of those taking placebo. The most commonly reported adverse events were infections/infestations. Other than renal and urinary system disorder, hypertension, gastroenteritis, and anemia were the only other serious adverse events reported with greater frequency in the voclosporin treated subjects.

Dose adjustments are necessary in patients with moderate hepatic impairment after volunteers with mild and moderate hepatic impairment experienced an approximately 1.67 and 2-fold increase in AUC.

Due to potential safety issues at 2-fold increases, labeling will include instructions to reduce the dose to 15.8 mg twice daily in patients with moderate hepatic impairment, and not to use in patients with severe hepatic impairment. Food study IAS04-02 demonstrated a high-fat meal decreased voclosporin's AUC and C_{max} by 25% and 53%, respectively. Voclosporin will be labeled to be taken without food. Voclosporin is a CYP3A4 substrate, and study exposure to a moderate CYP3A4 inhibitor increased AUC and C_{max} by 2.71 and 2.08-fold, respectively. Labeling will include instructions to reduce dosage with moderate CYP3A4 inhibitors, and due to uncertainty of CYP3A4 induction and deduction, as well as the nonlinear pharmacokinetics of voclosporin, labeling will recommend against co-administering with moderate or strong CYP3A4 inducers.

5.1 DEATHS

The AURA-LV study contained small, but as the clinical reviewer notes, potentially meaningful baseline differences between treatment arms. Both voclosporin treatment arms were of lower median and mean age compared to those in the placebo arm. There was also a disproportionate number of subjects who had higher proteinuria, lower serum albumin, and lower mean eGFR at baseline randomized to the voclosporin 23.7 mg BID treatment arm than the higher dose or placebo arms. This imbalance becomes apparent in the number of deaths in the 23.7 mg voclosporin treatment arm. The clinical reviewer notes in his ongoing review that disproportionate randomization of those patients who appear to have greater disease activity may have contributed to the higher mortality rate of the 23.7mg treatment arm.

In the AURORA-1 study, 5 deaths occurred in the placebo group. They were attributed to pneumonia, lupus nephritis, pulmonary embolism, pneumonia/sepsis, and acute respiratory failure. One 21-year-old female subject in the voclosporin 23.7 mg arm died of pneumonia. On study Day 244, she developed nausea and vomiting, and was unable to take the study medication from Day 248 to Day 257. From study Days 251 to 356, she was hospitalized multiple times for gastritis, a lupus flare, lupus encephalitis and acute renal failure, seizure, decreased consciousness, pneumonia, and subsequent nosocomial pneumonia requiring mechanical ventilation and hemodialysis. Her subsequent death occurred on Day 356. In the ongoing clinical review, the clinical reviewer states that the death does not suggest a direct causal relationship to voclosporin.

The deaths in the AURA-LV study are summarized in the table below. The clinical reviewer noted that voclosporin may have contributed to the deaths of the following subjects: (b) (6) . The clinical reviewer states that while not from a direct causal relationship with voclosporin, the deaths of these subjects were likely exacerbated by being immunosuppressed while taking voclosporin, MMF, corticosteroids, or the combination thereof.

Table 5. Summary of Deaths in AURA-LV

Subject Number	Age (Gender)	Country	Adverse Event	Infection (Y/N)	Event Start (Study Day)	Death (Study Day)
Placebo						
(b) (6)	38 (F)	Russia	CVA	N	6	6
Voclosporin 23.7 mg BID						
(b) (6)	38 (F)	Sri Lanka	Multi-organ failure	Y	43	43
	19 (F)	Sri Lanka	Cardiac Tamponade	N	237	237
	50 (M)	Russia	ARDS	Y	165	168
	23 (F)	Philippines	TB Pericarditis	Y	40	47
	48 (F)	Philippines	ARDS	Y	119	120
	30 (F)	Bangladesh	Pneumonia	Y	21	41
	21 (M)	Bangladesh	Pulmonary embolism	N	28	29
	38 (F)	Bangladesh	Pneumonia	Y	57	59
	20 (F)	Bangladesh	Pulmonary hemorrhage	N	169	170
	20 (F)	Bangladesh	Pulmonary embolism	N	22	22
Voclosporin 39.5 mg BID						
(b) (6)	24 (F)	Bangladesh	Sepsis	Y	16	32
	18 (F)	Bangladesh	Pulmonary embolism	N	26	26

Adapted from Applicant's AURA-LV Mortality Analysis Version 3.0 Table 3.

Source: Voclosporin Unireview; Accessed January 19, 2021

5.2 INCREASED RISK OF SERIOUS INFECTIONS

In the pooled lupus nephritis population, there were 27 adverse events of infections/infestations in both the voclosporin treated group and the placebo group. However, in an early trial, 3 subjects experienced 9 adverse events from pneumonia (n=2), and acute tonsillitis (n=1). Again, this is expected with this drug class, and voclosporin will receive the same boxed warning of increased risk of developing malignancies and serious infections.

5.3 RENAL TOXICITY

Serious renal and urinary system disorder incidence was 5% or less in all treatment arms. In the voclosporin group, there were eight events of acute kidney injury, while the placebo group had 2 events reported. Four adverse events of lupus nephritis were reported in the placebo group and only a single event was reported in the voclosporin group. In the voclosporin treated group, the most common adverse event leading to study discontinuation was decreased eGFR (4% in voclosporin treated versus 2% in placebo treated). The majority of subjects who experienced a renal adverse event had a decrease in eGFR (26% in voclosporin treated subjects versus 9% in placebo subjects). The clinical reviewer concluded that the decreases in eGFR appeared reversible and were associated with the hemodynamic effects seen in other calcineurin inhibitors. The potential nephrotoxicity will be listed as a warning and precaution in voclosporin's label, as well as having dosing per eGFR outlined extensively in the dosing and administration section as follows:

- Voclosporin is not recommended for use in patients with eGFR $\leq$45 ml/min/1.73m^2 unless benefit exceeds the risk
- Every 2 weeks for the first month of therapy, then every four weeks after, eGFR should be assessed.
- If eGFR is <60 ml/min/1.73m^2 and reduced from baseline by >20% and <30%, voclosporin dose should be reduced by 7.9 mg twice daily. If eGFR is still reduced by >20% from baseline in two weeks, reduce dose again by 7.9 mg twice daily.
- If eGFR is <60 ml/min/1.73m^2 and reduced from baseline by $\geq$30%, voclosporin should be discontinued. If eGFR has improved to $\geq$80% of baseline two weeks after discontinuation, consider restarting voclosporin at a lower dose (7.9 mg twice daily).
- If patient has had a dose decrease due to eGFR decrease, consider increasing the dose by 7.9 mg twice daily for each eGFR measurement that is $\geq$80% of baseline (not to exceed the starting dose).

5.4 HYPERTENSION

In the pooled lupus nephritis population, there were six adverse events of hypertension leading to dose modification. This is not unexpected for calcineurin inhibitors and will be managed in labeling with a warning and precaution as well as instructions in dosing and administration not to initiate voclosporin if the patient's blood pressure is >165/105 mmHg, assess blood pressure (b) (4) every 2 weeks for the first month, (b) (4)

6 Expected Postmarket Use

Voclosporin is expected to be prescribed by rheumatologists and nephrologists. These prescribers should be familiar with the risks associated with calcineurin inhibitors. As voclosporin's labeling will closely align with other drugs in this class, the risk messaging is not novel for voclosporin.

7 Risk Management Activities Proposed by the Applicant

The Applicant did not propose any risk management activities for voclosporin beyond routine pharmacovigilance and labeling.

8 Discussion of Need for a REMS

Voclosporin demonstrated efficacy in adult patients with active lupus nephritis in combination with a background immunosuppressive therapy regimen. The background trial therapy is considered the current standard of care of active proliferative and/or membranous lupus nephritis. The clinical reviewer recommends approval based on the efficacy data in a disease that only received the first approved US therapy in December 2020.

DRM and DRTM considered the benefit of voclosporin treatment with the risks including nephrotoxicity, hypertension, and increased risk of serious infections. The review team discussed these risks and if a REMS was necessary to mitigate them. Many of these risks are class-wide for calcineurin inhibitors and are conveyed via class-wide labeling. Many other products are metabolized by CYP3A4 hand have drug-drug interactions and communicate them via dosing and administration instructions as well as in the drug interactions sections of labeling. Changes in dosing for hepatic function will also be managed in the dosing and administration section of the label. The increased risk of developing serious infections will be communicated via a boxed warning, as it is with other members of this drug class. The risks of nephrotoxicity and hypertension will be communicated as warnings and precautions in voclosporin labeling, as they are also a class-wide concern. Blood pressure monitoring instructions will be included in the dosing and administration section, as well as doing based on eGFR. Safety messages will be conveyed to patients via a Medication Guide. We expect these patients will be seen on a regular basis by prescribers familiar with both lupus nephritis and class-wide risks of calcineurin inhibitors. Therefore, risk mitigation measures beyond labeling, such as a REMS, are not necessary for voclosporin to ensure the benefits outweigh the risks.

9 Conclusion & Recommendations

Based on available data, a REMS is not necessary to ensure the benefits of voclosporin outweigh the risks including nephrotoxicity, hypertension, and increased risk of infections. The risks will be communicated via labeling with a boxed warning, warnings and precautions, and in dosing and administration. A Medication Guide for patients is also included in voclosporin labeling.

At the time of this review, labeling is still under negotiations and the clinical review is ongoing. Should DRTM have any concerns or if new safety information becomes available, please send a consult to DRM.

10 Appendices

10.1 References

1. Aurinia Pharmaceuticals Summary of Clinical Efficacy of Voclosporin
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7. Aurinia Pharmaceuticals Summary of Clinical Safety of Voclosporin.

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