23 July 2026
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Human Medicines Division

Assessment report for paediatric studies submitted according to Article 46 of the Regulation (EC) No 1901/2006

Lupkynis

Voclosporin

Procedure no: EMA/PAM/0000348692

Procedure no: EMA/PAM/0000348696

Note

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

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
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Status of this report and steps taken for the assessment			
Current step[1]	**Description**	**Planned date**	**Actual Date**
☐	Start date	25 May 2026	2 June 2026
☐	CHMP Rapporteur AR	29 June 2026	29 June 2026
☐	CHMP comments	13 July 2026	n/a
☐	Updated CHMP Rapporteur AR	16 July 2026	n/a
☒	CHMP outcome	23 July 2026	23 July 2026

[1] Tick the box corresponding to the applicable step – do not delete any of the steps. If not applicable, add n/a instead of the date.

[2] Criteria for CHMP plenary discussion: substantial disagreement between the Rapporteur and other CHMP members and/or at the request of the Rapporteur or the Chair

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1. Introduction

On 12 May 2026, the MAH submitted completed paediatric studies for Lupkynis, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

A short critical expert overview has also been provided.

2. Scientific discussion

2.1. Information on the development program

The MAH stated that the studies VOCAL (AUR-VCS-2020-03) and VOCAL-EXT (AUR-VCS-2020-04) are part of a clinical development program. These trials are part of the EU Paediatric Investigation Plan EMEA-002264-PIP01-17 that was initially agreed upon with the European Medicines Agency (EMA) on 17 Apr 2019 and subsequently modified with procedure EMA/PE/0000228081 on 19 Mar 2025.

A line listing of all the concerned studies is annexed.

2.2. Information on the pharmaceutical formulation used in the studies

The formula used in the studies was 7.9 mg of voclosporin per softgel capsule.

2.3. Clinical aspects

Introduction

The MAH submitted a final report for:

- **AUR-VCS-2020-03 (VOCAL)** – A Double-blind, Placebo-controlled, Dose Escalation Study to Assess the Efficacy, Safety, and Pharmacokinetics of Voclosporin in Adolescents with Lupus Nephritis
- **AUR-VCS-2020-04 (VOCAL-EXT)** – An Open-label Extension Study to Assess the Long-term Safety and Efficacy of Voclosporin in Adolescent Subjects with Lupus Nephritis

The VOCAL and VOCAL-EXT trials were terminated early due to challenges related to patient recruitment. Following review of unblinded data, the Data and Safety Monitoring Board (DSMB) recommended permanently halting enrolments of VOCAL and VOCAL-EXT based on (a) a disproportionate number of trial withdrawals in one treatment arm and preliminary evidence of clinical benefit in the other treatment arm and (b) the placebo arm no longer meeting the threshold for standard of care treatment, as represented by the 2024 ACR guideline for LN and the Kidney Disease: Improving Global Outcomes (KDIGO) guidelines.

Clinical studies

Description

The VOCAL study was a prospective, multi-centre, 24-week, dose escalation trial, designed to evaluate the efficacy, safety, and pharmacokinetics (PK) of voclosporin in addition to background standard of care with mycophenolate mofetil (MMF) and oral steroids in paediatric patients with LN.

The VOCAL-EXT study was an open-label extension trial to assess the long-term safety and efficacy of voclosporin in adolescents with LN.

Methods

Study participants

The VOCAL study enrolled participants aged 12 to <18 years with LN. The study excluded participants with an estimated glomerular filtration rate (eGFR) as calculated by Schwartz Pediatric Bedside method of <60 mL/min/1.73 m^2 at screening confirmed before randomization. The study included participants with a previous diagnosis of systemic lupus erythematosus (SLE) according to the 2019 EULAR/ACR classification criteria, as well as a kidney biopsy result within 6 months prior to screening, or during the screening period prior to randomization, with evidence of active LN, defined as follows:

- Class III, IV-S, or Class IV-G alone or in combination with Class V: urine protein:creatinine ratio (UPCR) of ≥ 1.0 mg/mg at screening.
- Class V (alone): UPCR of ≥ 2.0 mg/mg at screening.

OR

- a kidney biopsy result within 1 year prior to screening indicating active LN with a UPCR ≥ 3.0 mg/mg at screening or with a doubling or greater increase of UPCR within the last 6 months to a minimum of ≥ 1.0 mg/mg for Class III/IV alone or in combination with Class V or to a minimum of ≥ 2.0 mg/mg for Class V at screening.

Biopsy results over 6 months prior to screening had to be reviewed with a Medical Monitor to confirm eligibility.

Treatments

The VOCAL trial was planned to consist of 3 periods of 24 weeks of treatment each (Figure 1):

- Period 1 (Groups 1 and 2): Randomized, double-blind, placebo-controlled period to assess PK, efficacy, and safety of voclosporin 15.8 mg (2 capsules) twice daily (BID) compared to placebo.
- Period 2 (Group 3): Additional open-label group with increased dose of voclosporin to 23.7 mg (3 capsules) BID.
- Period 3 (Group 4): Final open-label group with potential further increase of voclosporin dose to 31.6 mg (4 capsules) BID.

All participants were to initiate treatment at 7.9 mg BID, to be escalated over 4 weeks to the final dose, contingent upon safety and exposure data. Background therapy comprised MMF at 2 g/day and intravenous methylprednisolone totalling 1.5 g over 1 to 3 days (max 1 g/day), followed by oral corticosteroids (≤ 1 mg/kg/day, max 30 mg/day), tapered to 5 mg/day over 16 weeks, consistent with European League Against Rheumatism (EULAR)/European Renal Association-European Dialysis and Transplant Association (ERA-EDTA) guidelines.

Enrolment into Group 3 was to commence after review of PK, safety, and efficacy data from approximately the first 16 participants who had completed the double-blind treatment in Period 1 (Groups 1 and 2). Recruitment into Group 4 was to commence after DSMB review of PK, safety, and efficacy data from the first 8 participants who had completed treatment in Group 3. Escalation to 4 capsules BID in Group 4 was to be permitted only if the predicted exposure was not higher than that seen at the indicated dose in adults (23.7 mg BID, as used in Group 3) and the safety profile remained favorable. If the decision was made not to escalate to 4 capsules BID, Group 4 was to receive 3 capsules BID.

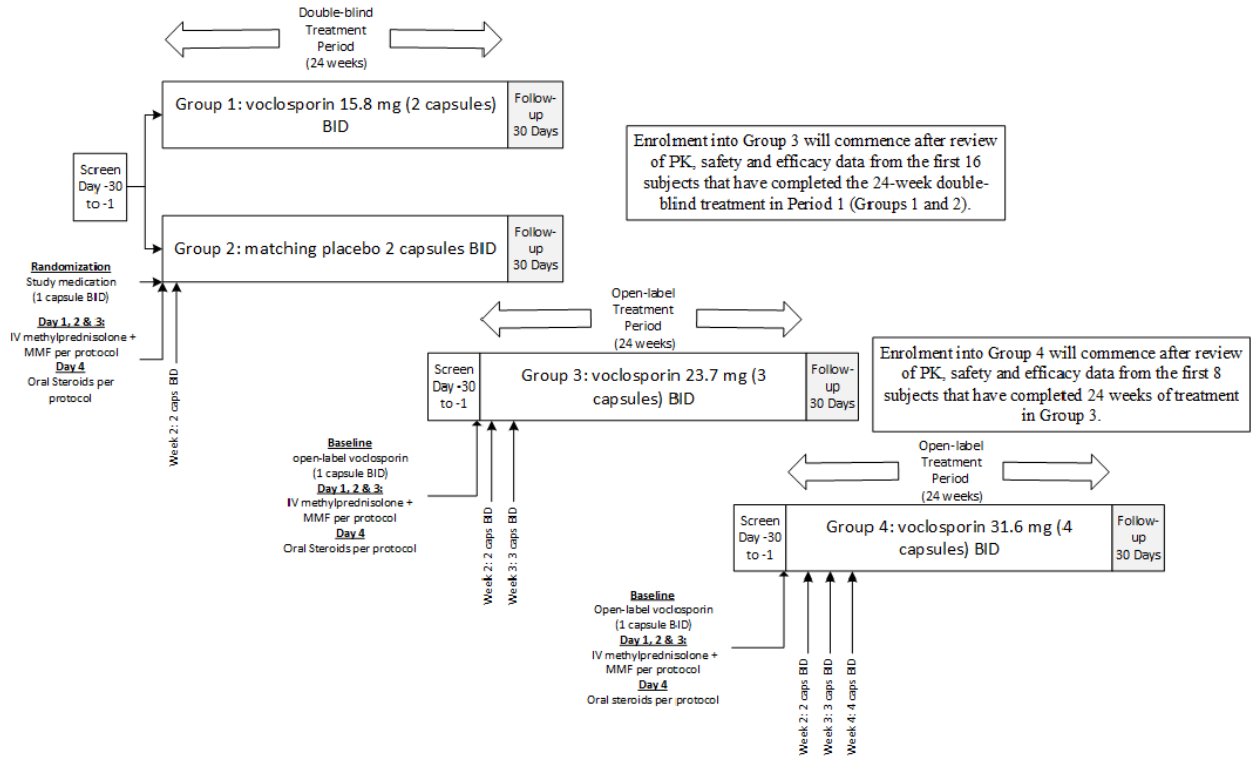
At the time of trial termination, participants were only randomized into Period 1 (Groups 1 and 2).

Participants who completed participation and trial treatment through 24 weeks had the opportunity to receive a further 12 months of treatment with voclosporin in the VOCAL-EXT trial (Figure 2), initially at the same dose/number of capsules they had received at the end of VOCAL, End of Study (EoS) Visit/Visit 13 (Week 24). When entering VOCAL-EXT, the trial treatment for Groups 1 and 2 in the VOCAL trial was still blinded.

Dose adjustment of voclosporin up or down was done at the Investigator's discretion and after consultation with the Medical Monitor provided the maximum dose studied in VOCAL was not exceeded.

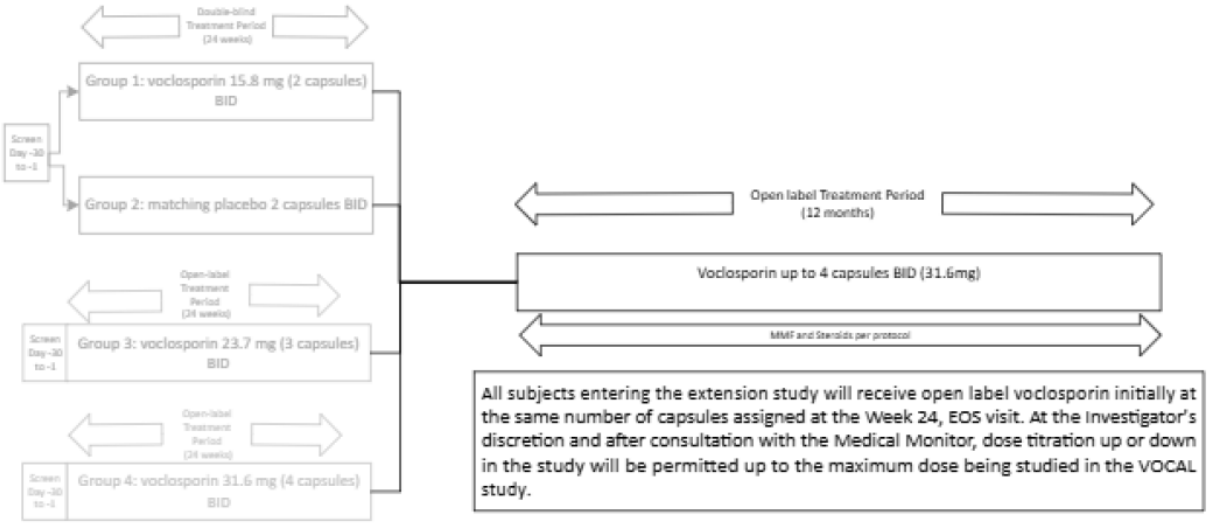
In addition, all participants continued to receive background therapy of MMF and oral corticosteroids.

Figure 1: VOCAL (AUR-VCS-2020-03) trial schema.



Notes: Dosing with 31.6 mg (4 capsules) BID was dependent on the outcome of the review of data from Group 3. The decision may have been made not to escalate to 31.6 mg, in which case the dose in Group 4 was 23.7 mg BID.
BID=twice daily; IV=intravenous; MMF=mycophenolate mofetil; PK=pharmacokinetic.

Figure 2: VOCAL-EXT (AUR-VCS-2020-04) trial schema.



Notes: Dosing with 31.6 mg (4 capsules) BID was dependent on the outcome of the review of data from the VOCAL trial. The decision may have been made not to escalate to 31.6 mg.
The lefthand part of the figure (in gray) refers to the VOCAL trial.
BID=twice daily; EoS=End of Study; MMF=mycophenolate mofetil.

CHMP comment:

The initial agreed PIP (P/0152/2019) proposed a double-blind, placebo-controlled study in paediatric subjects aged ≥12 years (Protocol AURORA PEDS 01, referred to as the VOCAL study) to be followed by a prospective, open-label, efficacy and safety study in children ages 5 to ≤17 years (AURORA PEDS 02) and an extrapolation, modelling and simulation study to confirm whether observed paediatric data are consistent with extrapolated efficacy predictions from adults. It was anticipated that the Vocal study would include 40 patients, and the AURORA peds 02 would include 75 patients.

The Vocal study was not able to begin enrolling subjects until March 2023 and during this period of delay, both Lupkynis and Benlysta received approval for the treatment of LN in adults and Benlysta was also approved for the treatment of LN in paediatrics. Thus, the VOCAL study experienced persistently slow enrolment and a modification of the PIP was submitted and accepted (EMA/PE/0000228081, 2025). The main topics of this modification was maintaining the commitments to provide data on exposure for 12 months and to include children aged 5 to <12 years. Children aged 5 to <12 years (reduced numbers from 10 to 5) were to be included in the final treatment group of VOCAL and the AURORA PEDS 02 was removed from the PIP, replacing it with the ongoing VOCAL-EXT study to provide long term safety and efficacy data.

The study schedule above for the Vocal study are thus showing the initially planned study and are not reflecting the amendments made. However, since the study was prematurely ended and only a few patients were included in the first part of the study this was not further pursued.

Objective(s)

The primary objective for the VOCAL trial was to assess the efficacy of voclosporin compared to placebo in achieving renal response following 24 weeks of therapy in adolescents with active LN.

The primary objective of the VOCAL-EXT trial was to assess the long-term safety and tolerability of voclosporin for up to an additional 12 months following completion of treatment in the AUR-VCS-2020-03 trial (VOCAL) in adolescent participants with LN.

Outcomes/endpoints

The primary endpoint was renal response at Week 24, defined as:

- UPCR of ≤0.5 mg/mg, and
- eGFR ≥60 mL/min/1.73 m2 or no confirmed decrease from Baseline in eGFR of >20%, and
- Received no rescue medication for LN and
- Did not receive >10 mg/day prednisone for ≥3 consecutive days or for ≥7 days in total between Week 16 and Week 24 (VOCAL).

There were several secondary efficacy endpoints, including but not limited to: time to UPCR of ≤0.5 mg/mg, UPCR of ≤0.7 mg/mg, time to UPCR of ≤0.7 mg/mg, partial renal response as defined by ≥50% reduction from baseline in UPCR, time to 50% reduction in UPCR from baseline, etc. Due to early termination of the trial, analyses relating to endpoints adjudicated by the Clinical Endpoints Committee (renal response, renal flare, and extra-renal flare) were not undertaken as the committee did not sit.

Safety endpoints included number of TEAEs, ECG abnormalities, and routine biochemical and haematological assessments. Pharmacokinetic endpoints were $C_{max,ss}$ and $AUC_{0\text{-}12h,ss}$.

Sample size

A total of 40 participants, 10 participants per treatment group, were planned to be enrolled.

Randomisation and blinding (masking)

The first 20 eligible study participants were to be randomized at a ratio of 1:1 to receive either voclosporin 15.8 mg BID or matching placebo (Groups 1 and 2). Participants in Groups 3 and 4 were to receive voclosporin open-label. Due to early termination of the trial, no participants were enrolled in Groups 3 and 4.

Statistical Methods

No formal statistical hypothesis was formulated; all comparisons between placebo and voclosporin were to be considered descriptive in nature.

Results

Participant flow

<u>VOCAL</u>

Twenty patients were screened for the VOCAL trial, of whom 14 were screen failures: 13 failed to meet the eligibility criteria and 1 withdrew consent during screening. Three patients were re-screened, bringing the total number of participants in the screened population to 23. The leading cause for failing screening was lack of a biopsy within 6 months of screening with evidence of active LN (9 screened patients, 64.3% of the screened population;

Overall, 9 participants were enrolled in the VOCAL trial (intent-to-treat [ITT] population), of whom 5 were randomized to receive voclosporin 15.8 mg BID and 4 to receive placebo.

Most of the participants (4 participants [80%]) in the voclosporin arm completed the trial and the remaining participant could not complete the VOCAL trial due to the termination of the trial by the Sponsor. In the placebo arm, only 1 participant completed the trial. Two participants withdrew due to lack of efficacy and 1 due to requiring prohibited medication.

VOCAL-EXT

Of the 5 completers of the VOCAL trial, 4 participants, all from the voclosporin arm, continued to VOCAL-EXT. Three of them completed the trial and a single participant remained in the trial until its termination by the Sponsor. One placebo participant (who was a responder) completed VOCAL and could not roll over due to trial termination by the Sponsor.

Recruitment

VOCAL: First patient screened 15 Sep 2023; first patient randomized/enrolled 10 Oct 2023. Last patient last visit (30-day safety follow-up call) 03 Jul 2025

VOCAL-EXT: First patient enrolled 28 Mar 2024. Last patient last visit (30-day safety follow-up call) 04 Jul 2025.

Baseline data

The mean (standard deviation [SD]) age of participants was 14.3 (1.6) years, with a median age of 14 years (range: 12–17). The majority were female (8/9 [88.9%]), and most identified as Hispanic or Latino (7/9 [77.8%]). All participants had a prior diagnosis of SLE and biopsy-confirmed active LN, with the most common biopsy class being Class IV (5/9 [55.6%]).

At Baseline, the mean (SD) time since LN diagnosis was 11.2 (15.7) months, and the mean (SD) time since onset of the current flare was 3.3 (1.6) months. All participants were receiving MMF at screening, with a mean (SD) dose of 1.8 (0.4) g/day

Table 1: Summary of Demography – VOCAL (ITT)

Parameter	Placebo (N=4)	Voclosporin 15.8 mg BID (N=5)	Overall (N=9)
Age (years)			
n	4	5	9
Mean (SD)	14.0 (1.15)	14.6 (1.95)	14.3 (1.58)
Median	14.0	14.0	14.0
Min, Max	13, 15	12, 17	12, 17
IQR	13.0, 15.0	14.0, 16.0	13.0, 15.0
Sex [n (%)]			
Female	3 (75.0)	5 (100.0)	8 (88.9)
Male	1 (25.0)	0	1 (11.1)
Child-bearing potential (n [%])			
Child-bearing potential	2 (50.0)	5 (100.0)	7 (77.8)
Not of child-bearing potential	1 (25.0)	0	1 (11.1)
Male	1 (25.0)	0	1 (11.1)
Adequate contraception (n [%])			
Abstinent	4 (100.0)	5 (100.0)	9 (100.0)
Race [n (%)]			
Asian	0	1 (20.0)	1 (11.1)
White	2 (50.0)	1 (20.0)	3 (33.3)
American Indian or Alaska Native	1 (25.0)	1 (20.0)	2 (22.2)
Other	1 (25.0)	2 (0.0)	3 (33.3)
Ethnicity [n (%)]			
Hispanic or Latino	3 (75.0)	4 (80.0)	7 (77.8)
Not Hispanic or Latino	1 (25.0)	1 (20.0)	2 (22.2)
Country [n (%)]			
Colombia	1 (25.0)	2 (40.0)	3 (33.3)
Mexico	2 (50.0)	2 (40.0)	4 (44.4)
Thailand	0	1 (20.0)	1 (11.1)
United States of America	1 (25.0)	0	1 (11.1)

Source: Table T15DM.2.10.1.
BID=twice daily; IQR=inter-quartile range; ITT=intent-to-treat; max=maximum; min=minimum; SD=standard deviation.

Table 2: Summary of Baseline Characteristics – VOCAL (ITT)

Parameter	Placebo (N=4)	Voclosporin 15.8 mg BID (N=5)	Overall (N=9)
Months since SLE diagnosis			
n	4	5	9
Mean (SD)	14.4 (20.02)	22.9 (35.78)	19.1 (28.46)
Median	5.3	5.1	5.1
Min, Max	3, 44	2, 85	2, 85
IQR	2.9, 25.9	1.9, 20.5	2.8, 20.5
Months since significant proteinuria			
n	4	5	9
Mean (SD)	15.6 (12.87)	21.9 (16.41)	19.1 (14.41)
Median	11.7	14.4	12.1
Min, Max	5, 34	9, 49	5, 49
IQR	8.0, 23.1	11.8, 24.4	11.3, 24.4
Months since LN diagnosis			
n	4	5	9
Mean (SD)	7.5 (10.23)	14.2 (19.70)	11.2 (15.69)
Median	3.0	5.1	3.3
Min, Max	1, 23	2, 48	1, 48
IQR	1.9, 13.0	1.9, 14.4	1.9, 14.4
Months since onset of current flare			
n	4	5	9
Mean (SD)	2.9 (1.31)	3.7 (1.81)	3.3 (1.57)
Median	3.1	4.5	3.3
Min, Max	1, 4	2, 5	1, 5
IQR	2.0, 3.7	1.9, 5.1	1.9, 4.5
Any previous dialysis? (n [%])			
Yes	0	0	0
No	4 (100.0)	5 (100.0)	9 (100.0)
Missing	0	0	0
Prior treatment for LN? (n [%])			
Yes	3 (75.0)	4 (80.0)	7 (77.8)
N	1 (25.0)	1 (20.0)	2 (22.2)
Missing	0	0	0
MMF at Screening? (n [%])			
Yes	4 (100.0)	5 (100.0)	9 (100.0)
No	0	0	0
Missing	0	0	0
MMF dose at Screening (g/day)			
n	4	5	9
Mean (SD)	1.75 (0.500)	1.90 (0.224)	1.83 (0.354)

Table 3: Summary of Kidney Biopsy – VOCAL (ITT)

Parameter	Placebo (N=4)	Voclosporin 15.8 mg BID (N=5)	Overall (N=9)
Biopsy Class (n [%])			
Class I	0	0	0
Class II	0	0	0
Class III	0	0	0
Class IV	3 (75.0)	2 (40.0)	5 (55.6)
Class V	0	0	0
Class VI	0	0	0
Class III/V	1 (25.0)	2 (40.0)	3 (33.3)
Class IV/V	0	1 (20.0)	1 (11.1)
Missing	0	0	0
Age of Biopsy (months)			
n	4	5	9
Mean (SD)	0.3 (0.50)	1.4 (1.95)	0.9 (1.54)
Median	0.0	0.0	0.0
Min, Max	0, 1	0, 4	0, 4
IQR	0.0, 0.5	0.0, 3.0	0.0, 1.0

Source: Table T20BC.2.10.4.
BID=twice daily; IQR=interquartile range; ITT=intent-to-treat; max=maximum; min=minimum; SD=standard deviation.

Number analysed

All participants in the VOCAL trial were included in both the ITT and safety populations (N=9), and all participants who continued to VOCAL-EXT were included in both the VOCAL-EXT ITT and safety populations (N=4)

Efficacy results

VOCAL

Table 4: Renal Response Rate

	Voclosporin (N=5)	Placebo (N=4)
Week 24 Renal Response Rate (UPCR ≤ 0.5 mg/mg)		
n (%)	3 (60.0)	1 (25.0)
Odds ratio (95% CI)	3.27 (0.20-52.70)	
Week 24 Partial Renal Response Rate (≥50% reduction in UPCR)		
n (%)	4 (80.0)	1 (25.0)
Odds ratio (95% CI)	7.00 (0.37-133)	

CI=confidence interval.; UPCR=Urine protein:creatinine ratio

Overall, 3 participants (60%) in the voclosporin arm and 1 participant (25%) in the placebo arm achieved UPCR of ≤0.5 mg/mg at Week 24 and were considered "responders"

Of the 2 non-responders in the voclosporin arm:

- One withdrew at Week 16 due to trial termination by Sponsor with a UPCR of 0.5 mg/mg
- One participant responded with an 87% reduction in UPCR from 7.54 at Baseline to 1.01 at Week 24 but did not meet the threshold of ≤0.5 mg/mg for the trial endpoint.

The median time to achieve UPCR ≤ 0.5 mg/mg in the voclosporin arm was 86 days. Partial renal response, defined as a ≥ 50% reduction in UPCR from baseline, was observed in 4/5 (80%) voclosporin-treated participants and 1/4 (25%) placebo participants at Week 24. The median time to partial renal response was 23 days in the voclosporin arm.

The reduction in proteinuria was more rapid and sustained in the voclosporin arm, as reflected in the least square (LS)-means (standard error [SE]) change in UPCR from baseline to Week 12: -4.19 (0.76) mg/mg for voclosporin versus 1.35 (0.85) mg/mg for placebo. At Week 24, the LS-means (SE) change was 6.39 (0.25) mg/mg for voclosporin and 6.87 (0.56) mg/mg for placebo; however, only 1 placebo participant, a responder, remained at this time point.

Prednisone dosing equivalent ≤ 7.5 mg/day at Week 24 was achieved by 3/5 (60%) in the voclosporin arm and 1/4 (25%) in the placebo arm.

At Week 12, the improvement in disease activity, as measured by the Safety of Estrogens in Lupus Erythematosus National Assessment - Systemic Lupus Erythematosus Disease Activity Index (SELENA-SLEDAI) score, was notably greater in the voclosporin arm compared to placebo. The LS-means (SE) change from baseline to Week 12 in total SELENA-SLEDAI was -11.3 (1.8) for voclosporin and -3.4 (2.0) for placebo.

When examining the renal subscore, the LS-means (SE) change from baseline to Week 12 was -7.1 (1.0) for voclosporin, compared to 0.9 (1.1) for placebo. For the non renal subscore, the LS-means (SE) change was -4.7 (1.2) for voclosporin and 3.6 (1.3) for placebo.

Safety results

Eight out of the 9 participants in the Safety population experienced at least 1 TEAE, with an overall similar incidence across treatment arms (5 participants [100%] in the voclosporin arm reported a total of 19 TEAEs and 3 participants [75%] reported a total of 27 TEAEs in the placebo arm). Only 1 TEAE (hypertransaminasemia), reported in the placebo arm, was according to the MAH considered to be treatment-related.

Serious TEAEs were reported in 1 participant (20%) in the voclosporin arm and 3 participants (75%) in the placebo arm. Severe TEAEs were reported in 1 participant in the voclosporin arm (20%) and 2 participants (50%) in the placebo arm. TEAEs leading to study drug discontinuation were reported in 2 participants (50%) in the placebo arm and were not considered treatment-related by the Investigator. No TEAEs leading to death were reported in the trial.

Table 5: Overall Summary of Treatment-emergent Adverse Events – VOCAL (Safety)

	Placebo (N=4)			Voclosporin 15.8 mg BID (N=5)		
Event Category	**n**	**(%)**	**E**	**n**	**(%)**	**E**
Any TEAE	3	(75.0)	27	5	(100.0)	19
Any treatment-related TEAE	1	(25.0)	1	0		0
Any serious TEAE	3	(75.0)	5	1	(20.0)	1
Any treatment-related serious TEAE	0		0	0		0
Any severe TEAE	2	(50.0)	3	1	(20.0)	1
Any TEAE leading to dose modification	1	(25.0)	1	0		0
Any treatment-related TEAE leading to dose modification	0		0	0		0
Any TEAE leading to study drug discontinuation	2	(50.0)	2	0		0
Any treatment-related TEAE leading to study drug discontinuation	0		0	0		0
Any TEAE leading to death	0		0	0		0

Source: Table T40AE.1.10.1.
BID=twice daily; E=number of events; TEAE=treatment-emergent adverse event.
Treatment emergence defined as starting on or after first dose of VOCAL trial medication, up to the earlier of: 30 days following last dose of VOCAL trial medication or first day of VOCAL-EXT trial medication.
Coding Dictionary: MedDRA v26.1 - Sep 2023

Most Common TEAEs

In the voclosporin arm, 19 events were reported by 5 participants (100%) and in the placebo arm, 27 events were reported by 3 participants (75%). Most TEAEs were each reported by a single participant, with no specific TEAE arising as a safety signal for voclosporin in this population. The highest number of TEAEs occurred in the Infections and Infestations, Investigations, Vascular Disorders, Blood and Lymphatic System Disorders, and Skin and Subcutaneous Tissue Disorders System Organ Class.

The most common TEAEs in the voclosporin arm were anemia (2 participants [40%] in the voclosporin arm and 2 participants [50%] in the placebo arm) and hypertension (2 participants [40%] in the voclosporin arm and 1 participant [25%] in the placebo arm).

Table 6: Summary of Treatment Emergent Adverse Events by Decreasing Frequency of Preferred Term

	Placebo (N=4)			Voclosporin 15.8 mg BID (N=5)		
Preferred Term	n	(%)	E	n	(%)	E
Any TEAE	3	(75.0)	27	5	(100.0)	19
Anaemia	2	(50.0)	2	2	(40.0)	2
Hypertension	1	(25.0)	1	2	(40.0)	2
Hyperphosphataemia	1	(25.0)	1	1	(20.0)	1
Butterfly rash	2	(50.0)	2	0		0
Proteinuria	2	(50.0)	2	0		0
Tachycardia	0		0	1	(20.0)	2
Blood alkaline phosphatase increased	0		0	1	(20.0)	1
Cushing's syndrome	0		0	1	(20.0)	1
Deep vein thrombosis	0		0	1	(20.0)	1
Neutrophil count decreased	0		0	1	(20.0)	1
Oedema peripheral	0		0	1	(20.0)	1
Paraesthesia	0		0	1	(20.0)	1
Pneumonia	0		0	1	(20.0)	1
Pulmonary valve incompetence	0		0	1	(20.0)	1
Rash	0		0	1	(20.0)	1
Respiratory tract infection	0		0	1	(20.0)	1
Tricuspid valve incompetence	0		0	1	(20.0)	1
Weight decreased	0		0	1	(20.0)	1
Acne	1	(25.0)	1	0		0
Arthritis	1	(25.0)	1	0		0

VOCAL-EXT

During VOCAL-EXT, 6 events were reported by 3 participants (75%), all of whom had previously received voclosporin treatment (no placebo participants rolled over into VOCAL-EXT). Each TEAE was reported by a single participant.

Table 7: Summary of Treatment-emergent Adverse Events by Decreasing Frequency of Preferred Term – VOCAL-EXT

	Voclosporin 15.8 mg BID (N=4)		
Preferred Term	**n**	**(%)**	**E**
Any TEAE	3	(75.0)	6
Contusion	1	(25.0)	1
Eosinophilia	1	(25.0)	1
Hepatic enzyme increased	1	(25.0)	1
Neuropsychiatric lupus	1	(25.0)	1
Osteonecrosis	1	(25.0)	1
Urine protein:creatinine ratio increased	1	(25.0)	1

Source: Table T40AE.5.10.2.1.
BID=twice daily; E=number of events; TEAE=treatment-emergent adverse event.
Treatment emergence defined as starting on or after first dose of VOCAL trial medication, up to the earlier of: 30 days following last dose of VOCAL trial medication or first day of VOCAL-EXT trial medication.
Coding Dictionary: MedDRA v26.1 - Sep 2023.

Voclosporin was generally well tolerated up to 18 months of exposure. No new safety signals were identified. Importantly, no treatment-related serious adverse events (SAEs) were reported, and no participants in the voclosporin arm discontinued treatment due to AEs. All participants in the voclosporin arm completed treatment. Notably, there were no dose reductions required for eGFR decreases or increased blood pressure. In the VOCAL-EXT trial, all reported TEAEs were mild, non serious, and not considered related to treatment.

In the VOCAL trial, voclosporin was generally well tolerated in the adolescent population. All voclosporin treated participants (5/5 [100%]) and 3/4 (75%) placebo participants experienced at least 1 TEAE (19 and 27 TEAEs, respectively). Serious TEAEs occurred in 1/5 (20%) voclosporin participants and 3/4 (75%) placebo participants. Severe TEAEs were reported in 1/5 (20%) voclosporin and 2/4 (50%) placebo participants. TEAEs leading to discontinuation occurred only in the placebo group (2/4 [50%]). No deaths were reported. The most common TEAEs in the voclosporin group were anemia (2/5 participants [40%]) and hypertension (2/5 participants [40%]). Only 1 TEAE (hypertransaminasemia, 1/5 participants [20%] in placebo arm) was considered treatment-related. Laboratory parameters, vital signs, and electrocardiograms (ECGs) showed no consistent trends or clinically meaningful differences between groups.

Serious events

Six serious TEAEs were reported in 4 participants in VOCAL (1 [20%] participant with a single event in the voclosporin arm and 3 [75%] participants with 5 events in the placebo arm).

A single serious TEAE of pneumonia was reported in the voclosporin arm, classified as moderate in severity and was not considered treatment or disease-related. Serious TEAEs of cellulitis, proteinuria, and viral upper respiratory tract infection were reported in 1 participant in the placebo arm, with single serious TEAEs reported in 2 other participants (nephrotic syndrome and SLE [verbatim: SLE flare], each in 1 participant). Of these, the viral upper respiratory tract infection, SLE, and proteinuria were classified as severe, and the others as moderate. None of the serious TEAEs reported in the placebo arm were evaluated as treatment-related, and all were considered disease-related.

Table 8: Summary of Serious Treatment-emergent Adverse Events by System Organ Class and Preferred Term

	Placebo (N=4)			Voclosporin 15.8 mg BID (N=5)		
System Organ Class Preferred Term	**n**	**(%)**	**E**	**n**	**(%)**	**E**
Any TEAE	3	(75.0)	5	1	(20.0)	1
Infections and infestations	1	(25.0)	2	1	(20.0)	1
Pneumonia	0		0	1	(20.0)	1
Cellulitis	1	(25.0)	1	0		0
Viral upper respiratory tract infection	1	(25.0)	1	0		0
Renal and urinary disorders	2	(50.0)	2	0		0
Nephrotic syndrome	1	(25.0)	1	0		0
Proteinuria	1	(25.0)	1	0		0
Musculoskeletal and connective tissue disorders	1	(25.0)	1	0		0
Systemic lupus erythematosus	1	(25.0)	1	0		0

Source: Table T40AE.1.10.3.1.
BID=twice daily; E=number of events; TEAE=treatment-emergent adverse event.
Treatment emergence defined as starting on or after first dose of VOCAL trial medication, up to the earlier of: 30 days following last dose of VOCAL trial medication or first day of VOCAL-EXT trial medication.

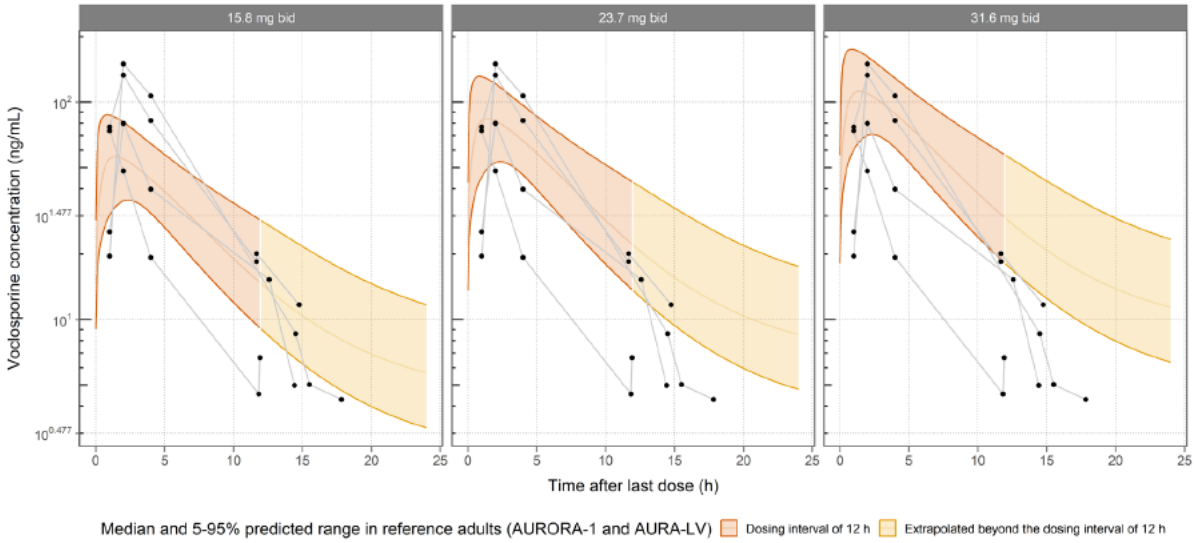
None of the TEAEs reported during VOCAL-EXT were serious.

Pharmacokinetic results

Whole blood samples for assessment of voclosporin concentrations were collected at Weeks 8 and 24. In total, 35 samples from 4 study participants assigned to active treatment were collected and analysed for voclosporin.

Voclosporin concentrations from adolescents were integrated into a 2-compartment population PK model of voclosporin developed from previous clinical studies in adults with LN (Population PK Report 19 041). A Bayesian feedback analysis was used to estimate PK parameters in the adolescent population. *Figure 3* shows voclosporin concentrations (observations) in adolescent patients receiving 15.8 mg BID overlaid with the 5-95% predicted range of concentrations when modelled at BID doses of 15.8 mg, 23.7 mg and 31.6 mg in adults. Given the small number of adolescents in VOCAL, the ability to make any conclusive statements about this data is limited. Visually, the most comparable overlay of concentrations from 15.8 mg in adolescents is with those from 15.8 mg BID in adults.

Figure 3: Overlay of voclosporin concentrations in adolescents with the 5 to 95% predicted range of concentrations when modelled at BID doses of 15.8 mg, 23.7 mg, and 31.6 mg in adults.



A summary of the estimated steady-state PK parameters for voclosporin 15.8 mg BID in adolescents and the reported steady-state PK parameters for voclosporin 23.7 mg BID in adults is presented in Table 9. In Study AUR-VCS-2018-01, voclosporin PK parameters were determined in 24 adults with SLE receiving voclosporin 23.7 mg BID after 10 days of dosing with mycophenolate 1 gram BID. Estimated voclosporin PK exposure parameters with 15.8 mg BID in adolescents, such as $AUC_{0\text{-}12h,ss}$, $C_{trough,ss}$, and $C_{avg,ss}$, are comparable to, though generally less than, those observed with 23.7 mg BID in adults. For example, the estimated ranges for voclosporin $AUC_{0\text{-}12h,ss}$, $C_{trough,ss}$, and $C_{avg,ss}$ in adolescents fall within the corresponding adult ranges. The estimated $C_{max,ss}$ in adolescents dosed at 15.8 mg BID is approximately half of the $C_{max,ss}$ reported in adults dosed at 23.7 mg BID.

Table 9: Summary of voclosporin estimated steady-state exposures from 15.8 mg BID in adolescents and actual steady-state exposures from 23.7 mg BID in adults.

	$C_{trough,ss}$ (ng/mL)	$C_{max,ss}$ (ng/mL)	$AUC_{0\text{-}12h,ss}$ (ng*h/mL)	$C_{avg,ss}$ (ng/mL)	CL (L/h)
15.8 mg BID simulated exposures in adolescents					
N	4	4	4	4	4
Median	12.1	50.6	360	30.0	43.9
Min-Max	7.90-18.9	45.1-76.7	272-535	22.6-44.5	29.6-58.1
23.7 mg BID exposures in adults					
N	24	24	24	24	24
Median	12.6	108	392	32.7	60.5
Min-Max	5.10-31.8	68.7-216	204-927	17.0-77.3	25.6-116

Source: LAPP Leiden Advanced PK-PD Interim Report; AUR-VCS-2018-01 (Appendix 16.1.10).
$AUC_{0\text{-}12h,ss}$=area under the curve from time zero to 12 hours at steady state; BID=twice daily dosing; $C_{avg,ss}$=average concentration at steady state; $C_{max,ss}$=maximum concentration at steady state; $C_{trough,ss}$=trough concentration at steady state; CL=total drug clearance; min=minimum; max=maximum

Discussion on clinical aspects

Voclosporin was approved in 2022 for the treatment of LN in adults with the posology of 23.7 mg Q2D. The initial agreed PIP (P/0152/2019) proposed a double-blind, placebo-controlled, 3 part study in paediatric subjects with LN aged ≥12 years (Protocol AURORA PEDS 01, referred to as the VOCAL study) to be followed by a prospective, open-label, efficacy and safety study in children ages 5 to ≤17 years (AURORA PEDS 02) and an extrapolation, modelling and simulation study to confirm whether observed paediatric data are consistent with extrapolated efficacy predictions from adults. It was anticipated that the Vocal study would include 40 patients and the AURORA peds 02 would include 75 patients. However, due to enrollment difficulties and changes in the therapeutic landscape, the PIP was modified in 2025 (EMA/PE/0000228081) and the AURORA peds 02 study was deleted. Instead, the VOCAL study was anticipated to include also at least 5 patient 5-12 years with OL treatment in part 3 of the study and an extension of the VOCAL study (VOCAL-EXT) was included to provide long term safety and efficacy data.

The first patient was enrolled in Oct 2023. However, the VOCAL and VOCAL-EXT trials were terminated early due to challenges related to patient recruitment and following review of unblinded data, the DSMB recommended permanently halting enrolments to the study based on (a) a disproportionate number of trial withdrawals in one treatment arm and preliminary evidence of clinical benefit in the other treatment arm and (b) the placebo arm no longer meeting the threshold for standard of care treatment.

Overall, 9 participants were enrolled in the VOCAL trial, of whom 5 were randomized to receive voclosporin 15.8 mg BID and 4 to receive placebo. Most of the participants (4/5 participants) in the voclosporin arm completed the trial and the remaining participant could not complete the VOCAL trial due to the termination of the trial by the Sponsor. In the placebo arm, only 1/4 participant completed the trial; two participants withdrew due to lack of efficacy and 1 due to requiring prohibited medication. Of the 5 completers of the VOCAL trial, 4 participants, all from the voclosporin arm, continued to VOCAL-EXT. Three of them completed the trial and a single participant remained in the trial until its termination by the Sponsor.

Since the VOCAL and VOCAL-EXT trials were terminated early, there is only limited information available on efficacy, safety, and PK of voclosporin in adolescent patients with LN.

Regarding efficacy, 3 participants (60%) in the voclosporin arm and 1 participant (25%) in the placebo arm achieved UPCR of ≤0.5 mg/mg at Week 24 and were considered "responders". Of the 2 non-responders in the voclosporin arm one withdrew at Week 16 due to trial termination by Sponsor with a UPCR of 0.5 mg/mg and one participant responded with an 87% reduction in UPCR from 7.54 at Baseline to 1.01 at Week 24 but did not meet the threshold of ≤0.5 mg/mg for the trial endpoint. Prednisone dosing equivalent ≤ 7.5 mg/day at Week 24 was achieved by 3/5 (60%) in the voclosporin arm and 1/4 (25%) in the placebo arm.

Regarding safety, 8/9 participants in the Safety population experienced at least 1 TEAE, with an overall similar incidence across treatment arms. Most TEAEs were reported by a single participant, with no specific TEAE arising as a safety signal for voclosporin in this population. The most common TEAEs in the voclosporin arm were anaemia (2 participants [40%] in the voclosporin arm and 2 participants [50%] in the placebo arm) and hypertension (2 participants [40%] in the voclosporin arm and 1 participant [25%] in the placebo arm). A single serious TEAE of pneumonia was reported in the voclosporin arm, classified as moderate in severity and was not considered treatment or disease-related.

The PK data were analysed using a population PK model, previously developed on data from adult patients with LN. Due to the sparse nature of the PK data in adolescents, the population parameters were fixed to the estimates received in adults and only individual parameters were estimated for the adolescent patients. This strategy was agreed. However, it was noted that the individually estimated $C_{max,ss}$ in adolescent patients were 45.1 to 76.7 ng/mL, whereas the corresponding observed $C_{max,ss}$ appeared to be approximately 45 to 130 ng/mL, and the individually estimated clearance (CL) in adolescent patients was lower than the corresponding CL in adults, although the observed concentrations appear to drop faster in adolescents than in adults. The limited data prevents any conclusions to be drawn based on these observations. Further analyses are required before a potential paediatric indication can be sought in a future Type II variation.

To conclude, only 5 voclosporin- and 4 placebo-treated patients were evaluated in these prematurely terminated studies and there are thus limited data regarding efficacy, safety, and PK in paediatric LN. No update to the SmPC text is currently needed. However, the efficacy data, although limited, points toward an effect and there were no apparent safety findings in the paediatric population that are not already known.

3. CHMP overall conclusion and recommendation

☒ **Fulfilled:**

No regulatory action required.

Annex. Line listing of all the studies included in the development program

The studies should be listed by chronological date of completion:

Clinical studies

Product Name: Lupkynis Active substance: Voclosporin

Study title	Study number	Date of completion	Date of submission of final study report
A Double-blind, Placebo-controlled, Dose Escalation Study to Assess the Efficacy, Safety, and Pharmacokinetics of Voclosporin in Adolescents with Lupus Nephritis (VOCAL)	AUR-VCS-2020-03	Decision to close study: 13 Nov 2025 LPLV: 03 Jul 2025	May 2026
An Open-label Extension Study to Assess the Long-term Safety and Efficacy of Voclosporin in Adolescent Subjects with Lupus Nephritis (VOCAL-EXT)	AUR-VCS-2020-04	Decision to close study: 13 Nov 2025 LPLV: 04 Jul 2025	May 2026