CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

213716Orig1s000

OTHER REVIEW(S)
Division of Pediatric and Maternal Health Review

Date: January 5, 2021  Date consulted: November 3, 2020

From: Christos Mastroyannis, M.D., Medical Officer, Maternal Health, Division of Pediatrics and Maternal Health (DPMH)

Through: Tamara Johnson, MD, MS, Team Leader, Maternal Health, DPMH
Lynne Yao, MD, Director, DPMH

To: Division of Rheumatology and Transplant Medicine (DRTM)

Drug: Lupkynis (voclosporin) capsules for oral use, twice a day

Drug Class: Calcineurin inhibitor (CNI)

NDA: 213716

Applicant: Aurinia Pharmaceuticals Inc

Subject: Pregnancy and Lactation Labeling Rule (PLLR) Recommendations

Indication: Treatment of patients with active lupus nephritis (LN), in combination with a background immunosuppressive therapy regimen.

Limitations of Use: Lupkynis has not been studied in combination with cyclophosphamide. Use of Lupkynis is not recommended in this situation.

Consult Question:
Review of the FPI for PLLR compliance, and any additional labeling recommendations from the Maternal Health Team to ensure the safe use of voclosporin. DRTM would also like DPMH-Maternal Health to provide input on the pregnancy and lactation PMRs which we are considering issuing.

Materials Reviewed:
- May 22, 2020: Original submission for NDA 213716 for New Molecular Entity (NME)
INTRODUCTION AND BACKGROUND
On May 22, 2020, Aurinia Pharmaceuticals Inc. submitted an original NDA 213716 for Lupkynis (voclosporin) capsules for oral use, under the 505 (b)(1) pathway. The Division of Rheumatology and Transplant Medicine (DRTM) consulted the Division of Pediatric and Maternal Health (DPMH) on November 3, 2020, to assist with a quick-turnaround review of the Pregnancy and Lactation subsections of labeling and to determine if pregnancy and lactation Post Marketing Requirements (PMRs) are required.

Drug Characteristics
Lupkynis (voclosporin) is a calcineurin-inhibitor immunosuppressant. It consists of 90-95% trans isomer and 5-10% cis-isomer of voclosporin

Table 1: Voclosporin Drug Characteristics

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Calcineurin inhibitor (CNI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Molecular Weight</td>
<td>1214.6 g/mol g/mol</td>
</tr>
<tr>
<td>Terminal half life</td>
<td>30 hours (range 24.9 to .6.5 hours)</td>
</tr>
<tr>
<td>Bioavailability (oral) in rats</td>
<td>7.6% to 7.8%</td>
</tr>
<tr>
<td>Plasma Protein Binding (in humans and animals)</td>
<td>96.97-98.34%</td>
</tr>
<tr>
<td>Distribution</td>
<td>It is partitioned extensively into red blood cells (RBCs)</td>
</tr>
<tr>
<td>Placenta transfer (animals)</td>
<td>0.019% at 8 hours</td>
</tr>
<tr>
<td>Milk presence and infant relative dose (animals)</td>
<td>Rapid transfer into milk 0.053% of the maternal administered dose</td>
</tr>
<tr>
<td>Mutagenic/Clastogenic/Chromosomal aberration</td>
<td>Negative</td>
</tr>
<tr>
<td>Alcohol Content</td>
<td>21.6 mg of dehydrated ethanol per capsule. A capsule contains 7.9 mg of voclosporin, and recommended maximal dose 23.7 mg voclosporin (3 capsules, twice daily, or daily ethanol intake = 129.6 mg)</td>
</tr>
</tbody>
</table>
| Serious Adverse Events Reported from Clinical Trials | • Serious infection,  
• Nephrotoxicity,  
• Neurotoxicity,  
• Hypertension,  
• Hyperkalemia,  
• QTc prolongation,  
• Pure red cell aplasia, new onset diabetes |

From applicant’s submission of May 22, 2020

Calcineurin inhibitors (CNI) are a family of three drugs (cyclosporine, tacrolimus, and pimecrolimus) that are used to suppress the immune system. CNIs can cause:
- Nephrotoxicity (the most common adverse effect)
- Hypertension.
- Neurotoxicity (tremors, severe headache, visual abnormalities, seizures, encephalopathy, and coma).
- CNIs have also been associated with infections, lymphomas and skin malignancies.

**REVIEW**

**Nonclinical Data**
Reproductive, developmental and peri- and post-natal toxicity studies with mix-ISA247, the drug product used during the development program. In the embryofetal developmental studies the rabbit was more sensitive to voclosporin than the rat (i.e., toxicity at lower doses). The overall reproductive and developmental toxicity NOAEL for mix-ISA247 is 2 mg/kg/day. As with mix-ISA247, embryo-fetal toxicity was only observed at doses that were associated with maternal toxicity. The maternal effects included changes in birthweight (BW) and/or swollen mammary glands. Fetal effects consisted of a slight reduction in BW and related skeletal developmental variations. Neither mix-ISA247 nor voclosporin were teratogenic.

Maternal toxicity was associated with increases in resorbed and dead fetuses and decreases in litter size and placental and fetal weight at doses 5 and 2 times the human therapeutic dose of 23.7 mg BID based on body surface area comparison. Voclosporin was not mutagenic in the Ames test or in a chromosomal aberration study, with and without metabolic activation.

For further details, refer to the full review by Nonclinical reviewer, Lawrence Leshin, DVM, PhD.

**Clinical Data**
An analysis of pregnancy outcomes across the program did not identify any adverse maternal or fetal effects due to voclosporin exposure at the doses used in the clinical studies. Two patients on treatment and one placebo patient discontinue the study. No pregnancy complications were reported for these patients.

In clinical trials with voclosporin, there were 14 reports of pregnancy in subjects treated with voclosporin or their partners. Seven were pregnancies in female study subjects, and 7 were reports of pregnancy in the female partners of male study subjects. There were also two reported pregnancies in female subjects treated with placebo. It is important to note that subjects with LN were also taking MMF as part of the study treatment regimen, which is known to be teratogenic; therefore, any adverse effects on pregnancy outcomes in voclosporin-treated subjects with LN will be confounded by the use of this medication.

Table 2: Outcomes of Pregnancies Reported in Subjects Treated with Voclosporin

<table>
<thead>
<tr>
<th>Pregnancies in a Female Study Subject (n=7)</th>
<th>Pregnancies in a Female Partner of a Male Study Subject (n=7)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4 Pregnancies resulted in delivery of healthy infants</td>
<td>2 Pregnancies resulted in delivery of healthy infants</td>
</tr>
<tr>
<td>1 Pregnancy - Outcome unknown</td>
<td>3 Pregnancies - Outcome unknown</td>
</tr>
<tr>
<td>1 Pregnancy-Induced abortion</td>
<td>1 Pregnancy-Induced abortion</td>
</tr>
<tr>
<td>1 Pregnancy - Ongoing</td>
<td>1 Pregnancy - Spontaneous abortion</td>
</tr>
</tbody>
</table>

From applicant’s submission of May 22, 2020
Of the five cases of pregnancy in female study subjects exposed to voclosporin, four resulted in the delivery of healthy infants, with no reported complications for either the mothers or the infants. In the fifth case, a subject was lost to follow-up after the pregnancy was detected and study treatment was discontinued, but later (date not specified) reported by telephone that the pregnancy had been terminated. No other information was available for this pregnancy. Prior to discontinuing voclosporin (at the time of positive pregnancy test results), these five female subjects had been exposed to voclosporin doses of 0.2 to 0.4 mg/kg BID for 28 days up 320 days. Two pregnancies have been reported in female subjects who received voclosporin 23.7 mg BID in clinical trials. One pregnancy ended by induced abortion. A second pregnancy was ongoing at the time of data cut off. This subject discontinued voclosporin 23.7 mg BID, MMF, and corticosteroids after 553 days of study treatment at the time of discovering the pregnancy (approximately 3 weeks gestation). The most recent information as of 18 weeks gestation indicated she was receiving prenatal care and that the pregnancy was progressing normally. Delivery is planned by cesarean section due to exacerbation of pre-existing arterial hypertension.

Of the seven cases of pregnancy in female partners of male study subjects:

- Two resulted in the delivery of healthy infants and no further follow-up was required.
- One partner pregnancy ended spontaneously at 19 weeks gestation; the male subject had received voclosporin 0.3 mg/kg BID. No further information about this pregnancy is available.
- One pregnancy in the partner of a subject who was receiving voclosporin 0.4 mg/kg for 58 days at the time the study center received notification of the pregnancy, was terminated electively. The partner’s medical history was unremarkable, and she previously had three healthy children. No other information is available.
- Three cases of partner pregnancies in which the outcomes were unknown.
  - The partner of a subject who received approximately 7 months of treatment with voclosporin 0.4 mg/kg, became pregnant on an unknown date. The partner was 1 month pregnant at the time the subject discontinued from study treatment. The study coordinator tried to obtain consent to follow the pregnancy, but outcome of this pregnancy is not known.
  - A subject reported that his partner became pregnant (on an unknown date) during his treatment with voclosporin 0.4 mg/kg. The subject discontinued from the study approximately 7 months after beginning treatment. The subject did consent to follow-up of the pregnancy but was subsequently lost to follow-up; thus the outcome of the pregnancy is unknown.
  - A reported pregnancy in the partner of a subject whose pregnancy occurred >15 days after study treatment stopped (treatment was still blinded at the time of the report), which was outside the window for following up on subjects, and thus no further information was collected, and the outcome is unknown.

Conclusion

From the information available, no adverse maternal or fetal effects were identified due to voclosporin exposure at the doses used in these clinical studies. There are no adequate or well-controlled studies of voclosporin in pregnant women. Available data on use of voclosporin in pregnant women are insufficient to determine whether there is a drug-associated risk for major birth defects or miscarriage, or adverse maternal or infant outcomes. There are risks to the mother and fetus associated with systemic lupus erythematosus (SLE).
DISCUSSION
DPMH had multiple communications with the nonclinical and clinical teams regarding the approach to labeling and about the necessity of Pregnancy and Lactation PMRs to further assess safety for the indicated population. The following describes and captures the essence of these communications.

Nonclinical Reproductive Toxicology Study Findings

1. Swollen mammary glands as part of the maternal toxic picture
   No histopathology findings exist; therefore, no conclusion can be made. This is not a finding in general toxicity studies of adults. Voclosporin is taken up by mammary glands and transferred to suckling neonates. One may contemplate the cause as reduced suckling due to neonate loss or voclosporin-related taste effects. Hormonal actions as a potential effect was not examined or addressed.

2. Resorbed and Dead Fetuses
   A pre-postnatal development study in rats found no reduction in postnatal survival of rat offspring due to infection of disease. Potential immunosuppression was not assessed in the study.

3. Pregnant and lactating animal concerns because of the alcohol presence
   Except for very early nonclinical studies, all studies used the same formulation vehicle that contained ethanol. The vehicle for the drug substance used in the animal studies was Vitamin E-TPGS (d-alpha-tocopherol polyethylene glycol 1000 succinate), Medium Chain triglyceride oil, Tween 40, ethanol. There was not a formulation without alcohol to make a comparison of ethanol’s effects. There were occasional findings in animals that one could attribute to what is known about ethanol’s effects or toxicity. Due to alcohol content in voclosporin and amount consumed per day (“per day” is the usual toxicological assessment unit), there were no specific effects on pregnancy or lactation in the animal studies that could definitely be attributed to ethanol.

Drug Alcohol Type and Content
There are 21.57 mg of dehydrated ethanol per capsule for a daily dose of 129.42 mg/day (3 capsules twice a day). This appears to be a low level of alcohol relative to the quantity in an alcoholic drink (9-14 grams per drink; approximately 200-fold higher than 65 mg (0.065 g)/day). Amount of alcohol consumed for the recommended dose per day (6 capsule/day of voclosporin) is 129.42 mg that is 108-fold less than contained in a single alcoholic drink.

What is the allowable amount of alcohol that safely may be consumed during pregnancy?
According to the Centers for Disease Control (CDC), the Society of Obstetricians and Gynecologists of Canada and American College of Obstetrics and Gynecology and the Surgeon General, pregnant women should not drink any form of alcohol as it has been shown to cause serious and negative effects on the development of the baby (fetus). There is no known safe amount of alcohol to drink during pregnancy.

2 http://www.cdc.gov/ncbddd/fasd/alcohol-use.html
3 http://www.acog.org/About_ACOG/News_Room/News_Releases/2008/Alcohol_and_Pregnancy_Know_the_Facts
Considerations for Labeling

Pregnancy
DPMH internal deliberations concluded that the labeling should include a statement that Lupkynis contains alcohol as one of its inactive ingredients (the mother will receive 129.4 mg/day) and therefore, Lupkynis may cause fetal harm. Based on the assumption that there is no safe level of alcohol exposure in pregnancy, a woman should avoid use of voclosporin in pregnancy. In addition, because Lupkynis may be administered with MMF and corticosteroids, a statement should refer the prescriber to MMF prescribing information for more information on its use during pregnancy. A similar approach to other FDA-approved labeling will be used to address this concern in labeling.

Lactation
Because of high protein binding of voclosporin (almost 98%) and low bioavailability (about 7%), the neonate/infant will be exposed to very low levels of voclosporin during lactation. However, given the serious adverse reactions seen in adult patients treated with Lupkynis, such as increased risk of serious infections, breastfeeding is not recommended during treatment and for at least 7 days after the last dose of Lupkynis (approximately 6 elimination half-lives). There are no concerns about lactation in reference to alcohol because neonates/infants can metabolize alcohol much better than fetuses. Casual use of alcohol (such as 1 glass of wine or beer per day) is unlikely to cause either short- or long-term problems in the nursing infant.6,7 Therefore, no specific language regarding alcohol is needed in the labeling.

Females and Males of Reproductive Potential
There is no recommendation for contraception or pregnancy testing based on mode of action of voclosporin. Voclosporin does not have any effect on fertility in studies with rats. DPMH proposes to include subsection 8.3 Females and Males of Reproductive Potential with information about the combination use with MMF. A similar approach has been used in other FDA-approved product labelings.

Warnings and Precautions
DPMH recommends including a Warnings and Precautions subsection to emphasize potential risk with use of voclosporin in combination with MMF. A similar approach has been used in other FDA-approved product labelings.

5.x Risks Associated with Mycophenolate Mofetil (MMF) Combination Treatment
If LUPKYNIS is administered with mycophenolate mofetil (MMF), the Warnings and Precautions for MMF, including the pregnancy avoidance warning and the association with first trimester pregnancy loss and an increased risk of congenital malformations, apply to this combination regimen. Refer to the MMF prescribing information for a full list of the warnings and precautions for MMF.

The Division does not agree with this Warnings and Precautions statement; however, agrees with maintaining statements about MMF and Lupkynis combination treatment in the

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7 The National Library of Medicine’s LactMed Database
8 Thomas Hale: Medications and Mothers’ Milk
Considerations on Postmarketing Requirement (PMR) Studies
A PMR for pregnancy is not indicated because the drug should not be used during pregnancy due to its alcohol content. In addition, combination use with MMF would lead to significant confounding that would hinder interpretation of findings attributable to voclosporin.

A PMR for a milk only lactation study is in order because the drug is an NME and use of voclosporin is anticipated in females of reproductive potential; therefore, additional data are required. DPMH recommends the following language for the PMR study description in the action letter:

“Perform a lactation study, milk only, in lactating women who have received TRADENAME (Voclosporin) to assess concentrations of voclosporin and its active metabolites in breast milk using a validated assay.”

Any further discussion about the study design and study population will be discussed after approval at the time of the draft study protocol review.

LABELING RECOMMENDATIONS
DPMH revised Highlights, subsection 5.X, subsections 8.1, 8.2 and 8.3, and Section 17 of labeling for compliance with the PLLR (see below). DPMH presented labeling recommendations to the Division on 12/4/2020. DPMH refers to the final NDA action for final labeling.

HIGHLIGHTS OF PRESCRIBING INFORMATION
-------------------------------------WARNINGS AND PRECAUTIONS-------------------------------------
* There are risks associated with mycophenolate mofetil (MMF) combination treatment (5.X)

-------------------------------------USE IN SPECIFIC POPULATIONS-------------------------------------
* Pregnancy: May cause fetal harm (8.1).
* Lactation: Advise not to breastfeed. (8.2)

FULL PRESCRIBING INFORMATION

5. WARNINGS and PRECAUTIONS
5.X Risks Associated with Mycophenolate Mofetil (MMF) Combination Treatment
If LUPKYNIS is administered with mycophenolate mofetil (MMF), the Warnings and Precautions for MMF, including the pregnancy avoidance warning and the association with first trimester pregnancy loss and an increased risk of congenital malformations, apply to this combination regimen. Refer to the MMF prescribing information for a full list of the warnings and precautions for MMF.

8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
Risk Summary
Avoid use of LUPKYNIS in pregnant women due to the alcohol content of the drug formulation. The available data on the use of LUPKYNIS in pregnant patients are insufficient, to determine whether there is a drug-associated risk for major birth defects, miscarriage, or
adverse maternal or fetal outcomes. There are risks to the mother and fetus associated with systemic lupus erythematosus (SLE) (see Clinical Considerations).

LUPKYNIS may be used in combination with a background immunosuppressive therapy regimen that includes mycophenolate mofetil (MMF). MMF used in pregnant women and men whose female partners are pregnant can cause fetal harm (major birth defects and miscarriage). Refer to the MMF prescribing information for more information on its use during pregnancy.

In animal studies with pregnant rats and rabbits, oral administration of voclosporin was embryocidal and fetocidal at doses 15- and 1-times, respectively, the maximum recommended human dose (MRHD) of 23.7 mg BID, based on drug exposure AUC. There were no treatment-related fetal malformations or variations. Additional findings of reduced placental and fetal body weights occurred in rabbits at 0.1 to 0.3-times the MRHD and in rats at higher drug exposures. Voclosporin was transferred across the placenta in pregnant rats. For rats, but not all doses in rabbits, these effects were associated with maternal toxicity consisting of reductions in body weight gain. Dystocia was evident in a pre-and postnatal study in rats, but there were no effects of voclosporin on postnatal growth and development (see Data).

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Clinical Considerations
Disease-Associated Maternal and/or Embryo/Fetal Risk
Pregnant women with SLE are at increased risk of adverse pregnancy outcomes, including worsening of the underlying disease, premature birth, miscarriage, and intrauterine growth restriction. Maternal LN increases the risk of hypertension and preeclampsia/eclampsia. Passage of maternal autoantibodies across the placenta may result in adverse neonatal outcomes, including neonatal lupus and congenital heart block.

Fetal/Neonatal adverse reactions
The formulation for LUPKYNIS contains alcohol (21.6 mg of dehydrated ethanol per capsule for a total daily dose of 129.4 mg/day). Published studies have demonstrated that alcohol is associated with fetal harm including central nervous system abnormalities, behavioral disorders and impaired intellectual development. There is no safe level of alcohol exposure in pregnancy, therefore, avoid use of LUPKYNIS in pregnant women.

Data
Animal Data
Voclosporin (90 to 95% trans-isomer) is the active ingredient in LUPKYNIS. Animal reproductive studies were primarily conducted with an approximate 50:50 mixture of voclosporin and its cis-isomer. Similarity of the toxicity effects of the 50:50 mixture and voclosporin was demonstrated in comparative toxicity studies with adult rats. Interconversion between cis and trans isomers was not detected with in vitro or in vivo studies.
In an embryofetal developmental study, pregnant rats were dosed orally, during the period of organogenesis from gestation days 6-17, with the 50:50 mixture of voclosporin and its cis-isomer, litter size was reduced due to increased fetal resorptions and deaths at drug exposures approximately 15-times the MRHD (on an AUC basis with a maternal oral dose of 25 mg/kg/day). Surviving fetuses had reduced placental weights and slightly reduced fetal weights. There were no treatment-related fetal malformations or variations with doses up to 15-times the MRHD, although reductions in ossification sites were observed in the metatarsal bones. This dose was associated with maternal toxicity based on decreased body weight gain. The no effect dose for both fetal and maternal effects occurred at a drug exposure approximately 7-times the MRHD (on an AUC basis with a maternal oral dose of 10 mg/kg/day).

Two embryofetal developmental studies were conducted in pregnant rabbits that received either the 50:50 mixture of voclosporin and cis-isomer or voclosporin during the period of organogenesis from gestation days 6-18. Litter size was reduced due to increased fetal resorptions at drug exposures approximately 1-times the MRHD (on an AUC basis with maternal oral dose of 20 mg/kg/day); however, litter size was not significantly affected. Decreased placental weights and fetal body weights were observed at doses 0.3-times the MRHD and higher (on an AUC basis with maternal oral doses of 10 mg/kg/day and higher). Decreased fetal body weights were observed with voclosporin at doses 0.1-times the MRHD and higher (on an AUC basis with maternal oral doses of 5 mg/kg/day and higher). There were no treatment-related malformations or variations. Both studies had reductions of ossification sites in the metacarpal bones with 50:50 mixture at doses 2-times the MRHD, and the sternabrae and hyoid body and/or arches with voclosporin at doses 0.1-times the MRHD and higher. The high dose of 20 mg/kg/day 50:50 mixture or voclosporin was associated with maternal toxicity based on decreased body weight gains. These rabbit studies indicated that the toxicity of 50:50 mixture of voclosporin and its cis-isomer and voclosporin were qualitatively similar; however, voclosporin was more potent than the 50:50 mixture, consistent with its pharmacological potency. The no effect dose for the fetal effects of voclosporin occurred at a drug exposure approximately-0.01-times the MRHD (on an AUC basis with a maternal oral dose of 1 mg/kg/day).

In a pre-and post-natal developmental study, rats were dosed from gestation day 7 through lactation day 20 with a 50:50 mixture of voclosporin and its cis-isomer. Dystocia (delayed parturition) occurred at a dose 12-times the MRHD (on an AUC basis, 25 mg/kg/day) that resulted in reductions of the mean number of total pups delivered and surviving pups per litter. This dose was associated with maternal toxicity based on decreased body weight gain. No adverse effects on dams or their pups were observed at doses 3-times the MRHD and lower (on an AUC basis with a maternal oral dose of 10 mg/kg/day). There were no effects on behavioral and physical development, or the reproductive performance of male or female pups. The no effect dose for delivery and pup survival was 10 mg/kg/day.

8.2 Lactation
Risk Summary
There are no available data on the presence of voclosporin in human milk, the effects on the breastfed infant, or the effects on milk production. Voclosporin is present in milk of lactating
rats. When a drug is present in animal milk, it is likely that the drug will be present in human milk. Given the serious adverse reactions seen in adult patients treated with LUPKYNIS such as increased risk of serious infections, advise patients that breastfeeding is not recommended during treatment and for 7 days after the last dose of LUPKYNIS (approximately 6 elimination half-lives).

8.3 Females and Males of Reproductive Potential
LUPKYNIS may be used in combination with a background immunosuppressive therapy regimen that includes MMF. If LUPKYNIS is administered with MMF, the information for MMF regarding pregnancy testing, contraception, and infertility also applies to this combination regimen. Refer to MMF prescribing information for additional information.

17 PATIENT COUNSELING INFORMATION
Pregnancy
Inform female patients of the potential risk to a fetus and to avoid use of LUPKYNIS during pregnancy. When LUPKYNIS is administered in combination with MMF, refer patients to the MMF medication guide. Advise females to inform their healthcare provider if they are pregnant or become pregnant [see Use in Specific Populations (8.1, 8.3)].

Lactation
Advise women not to breastfeed during treatment with LUPKYNIS and for 7 days after the last dose of LUPKYNIS [see Use in Specific Populations (8.2)].
This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

CHRISTOS MASTROYANNIS
01/05/2021 04:52:53 PM

TAMARA N JOHNSON
01/06/2021 10:57:28 AM

LYNNE P YAO
01/07/2021 10:54:25 AM
Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy

PATIENT LABELING REVIEW

Date: January 5, 2021

To: Sadaf Nabavian
Regulatory Project Manager
Division of Rheumatology and Transplant Medicine (DRTM)

Through: LaShawn Griffiths, MSHS-PH, BSN, RN
Associate Director for Patient Labeling
Division of Medical Policy Programs (DMPP)

Marcia Williams, PhD
Team Leader, Patient Labeling
Division of Medical Policy Programs (DMPP)

From: Kelly Jackson, PharmD
Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)

Kyle Snyder, PharmD
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: Review of Patient Labeling: Medication Guide (MG)

Drug Name (established name): LUPKYNIS (voclosporin)

Dosage Form and Route: capsules, for oral use

Application Type/Number: NDA 213716

Applicant: Aurinia Pharmaceuticals, Inc.
1 INTRODUCTION

On May 25, 2020, Aurinia Pharmaceuticals, Inc. submitted for the Agency’s review an original new drug application (NDA) for their product LUPKYNIS (voclosporin) capsules, for oral use with the proposed indication (b) (4). This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Rheumatology and Transplant Medicine on September 22, 2020 and July 14, 2020 respectively, for DMPP and OPDP to review the Applicant’s proposed Medication Guide (MG) for LUPKYNIS (voclosporin) capsules, for oral use.

2 MATERIAL REVIEWED

- Draft LUPKYNIS (voclosporin) MG received on May 25, 2020, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on December 17, 2020.

- Draft LUPKYNIS (voclosporin) Prescribing Information (PI) received on May 25, 2020, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on December 15, 2020.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss.

In our collaborative review of the MG we:

- simplified wording and clarified concepts where possible
- ensured that the MG is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the MG is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG meets the criteria as specified in FDA’s Guidance for Useful Written Consumer Medication Information (published July 2006)
ensured that the MG is consistent with the approved comparator labeling where applicable.

4 CONCLUSIONS
The MG is acceptable with our recommended changes.

5 RECOMMENDATIONS
- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the MG is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG.

Please let us know if you have any questions.
This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

KELLY D JACKSON
01/05/2021 03:09:44 PM

KYLE SNYDER
01/05/2021 03:14:11 PM

MARCIA B WILLIAMS
01/05/2021 03:18:54 PM
Memorandum

Date: December 17, 2020
To: Sadaf Nabavian, Regulatory Project Manager
Division of Rheumatology and Transplant Medicine (DRTM)
From: Kyle Snyder, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)
CC: Kathleen Klemm, Team Leader, OPDP
Subject: OPDP Labeling Comments for LUPKYNIS (voclosporin) capsules, for oral use
NDA: 213716

In response to DRTM’s consult request dated July 14, 2020, OPDP has reviewed the proposed Prescribing Information (PI), Medication Guide (MG), and carton and container labeling for the original NDA submission for LUPKYNIS (voclosporin) capsules, for oral use.

Labeling: OPDP’s comments on the proposed Prescribing Information are based on the draft labeling received by electronic mail from DRTM on December 15, 2020, and are provided below.

OPDP comments on the proposed Medication Guide will be sent under separate cover, either as a combined OPDP and Division of Medical Policy Programs (DMPP) review or a separate OPDP review.

Carton and Container Labeling: OPDP has reviewed the attached proposed carton and container labeling submitted by the Sponsor to the electronic document room on November 19, 2020, and we do not have any comments.

Thank you for your consult. If you have any questions, please contact Kyle Snyder at (240) 402-8792 or kyle.snyder@fda.hhs.gov.
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/s/

KYLE SNYDER
12/17/2020 03:36:52 PM
From: Aliza Thompson, Deputy Director, Division of Cardiology and Nephrology (DCN)
Through: Michael Monteleone, Associate Director for Labeling, DCN
        Mary Ross Southworth, Deputy Director for Safety, DCN
To: Sadaf Nabavian, Regulatory Project Manager, Division of Rheumatology and Transplant Medicine (DRTM)

This memo serves to close out the consult from DRTM dated November 3, 2020.

Background: On May 22, 2020, Aurinia Pharmaceuticals, Inc. submitted NDA 213716 for voclosporin for the treatment of patients with lupus nephritis. On November 3, 2020, DRTM submitted a consult to DCN requesting feedback on the following parts of the voclosporin draft label.

- Section 2 Dosage and Administration particularly the following subsections:
  - 2.2 Prior to Initiating LUPKYNIS Therapy
  - 2.3 Dosing Recommendations
  - 2.4 (b) (4)

- Section 5 Warnings and Precautions particularly the following subsections:
  - 5.3 Nephrotoxicity (Acute and/or Chronic)
  - 5.4 Hypertension

- Section 6.1 Clinical Trials Experience particularly the following subsections:
  - “Nephrotoxicity” and “Hypertension”

- Section 8.6 Renal Impairment

- Section 17 Patient Counseling Information particularly the following subsections:
  - “Nephrotoxicity (Acute and/or Chronic)” and “Hypertension”

DRTM also requested DCN participation at the Late-Cycle Meeting with the Applicant on November 17, 2020.

DCN Consult response: Dr. Thompson provided input on the aforementioned sections of labeling in consultation with DCN’s Associate Director for Labeling (Michael Monteleone) and Deputy Director for Safety (Mary Ross Southworth). Dr Thompson attended the Late-Cycle Meeting with the Applicant.
This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

ALIZA M THOMPSON
12/04/2020 01:57:49 PM

MICHAEL V MONTELEONE
12/04/2020 01:59:22 PM

MARY R SOUTHWORTH
12/04/2020 02:30:53 PM
Clinical Inspection Summary

<table>
<thead>
<tr>
<th>Date</th>
<th>November 12, 2020</th>
</tr>
</thead>
<tbody>
<tr>
<td>From</td>
<td>Tina Chang, M.D., Reviewer</td>
</tr>
<tr>
<td></td>
<td>Min Lu, M.D., M.P.H., Team Leader</td>
</tr>
<tr>
<td></td>
<td>Kassa Ayalew, M.D., M.P.H, Branch Chief</td>
</tr>
<tr>
<td></td>
<td>Good Clinical Practice Assessment Branch (GCPAB)</td>
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<td></td>
<td>Division of Clinical Compliance Evaluation (DCCE)</td>
</tr>
<tr>
<td></td>
<td>Office of Scientific Investigations (OSI)</td>
</tr>
<tr>
<td>To</td>
<td>Keith M. Hull, M.D., Ph.D., Clinical Reviewer</td>
</tr>
<tr>
<td></td>
<td>Anil Rajpal, M.D., Clinical Team Leader</td>
</tr>
<tr>
<td></td>
<td>Nikolay Nikolov, M.D., Acting Division Director</td>
</tr>
<tr>
<td></td>
<td>Sadaf Nabavian, PharmD, Regulatory Project Manager</td>
</tr>
<tr>
<td>NDA #</td>
<td>213716</td>
</tr>
<tr>
<td>Applicant</td>
<td>Aurinia Pharmaceuticals, Inc.</td>
</tr>
<tr>
<td>Drug</td>
<td>(voclosporin)</td>
</tr>
<tr>
<td>NME</td>
<td>Yes</td>
</tr>
<tr>
<td>Therapeutic Classification</td>
<td>Calcineurin inhibitor</td>
</tr>
<tr>
<td>Proposed Indication</td>
<td>Treatment of active lupus nephritis</td>
</tr>
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<td>Consultation Request Date</td>
<td>July 27, 2020</td>
</tr>
<tr>
<td>Summary Goal Date</td>
<td>November 20, 2020</td>
</tr>
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<td>Action Goal Date</td>
<td>January 22, 2021</td>
</tr>
<tr>
<td>PDUFA Date</td>
<td>January 22, 2021</td>
</tr>
</tbody>
</table>

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Clinical data from two studies (Protocols AUR-VCS-2012-01 and AUR-VCS-2016-01) were submitted to the Agency in support of a New Drug Application (NDA 213716) for (voclosporin) for the treatment of active lupus nephritis. Two clinical investigators, Dr. James Tumlin and Dr. Ellen Ginzler, were inspected in support of this application. Based on the results of these inspections, the studies (Protocols AUR-VCS-2012-01 and AUR-VCS-2016-01) appear to have been conducted adequately, and the data generated by the clinical investigator sites appear acceptable in support of the respective indication.

II. BACKGROUND

Voclosporin is a calcineurin inhibitor immunosuppressant. The proposed indication of voclosporin is for the treatment of patients with lupus nephritis. There are currently no approved drugs for the treatment of lupus nephritis.
The applicant, Aurinia Pharmaceuticals, Inc., submitted data from two randomized, double-blind, placebo-controlled trials: one Phase 2 study, Protocol AUR-VCS-2012-01 and one Phase 3 study, AUR-VCS-2016-01, for the treatment of lupus nephritis. The following describes briefly the Protocols AUR-VCS-2012-01 and AUR-VCS-2016-01.

**Protocol AUR-VCS-2012-01**

Study Title: A Randomized, Controlled Double-blind Study Comparing the Efficacy and Safety of Voclosporin (23.7 mg BID, or 39.5 mg BID) with Placebo in Achieving Remission in Patients with Active Lupus Nephritis

The primary study objective was to assess the efficacy of 2 doses of voclosporin compared to placebo in achieving complete remission after 24 weeks of therapy in subjects with active lupus nephritis.

The primary efficacy endpoint was complete remission which was defined as:

- Confirmed protein/creatinine ratio of ≤0.5 mg/mg and
- Estimated glomerular filtration rate (eGFR) ≥60 mL/min/1.73 m² or no confirmed decrease from baseline in eGFR of ≥20%.

The study randomized 265 subjects from 79 sites in 20 countries. The first subject was randomized on 26 June 2014 and the last patient completed the study on 6 January 2017.

**Protocol AUR-VCS-2016-01**

Study Title: A Randomized, Controlled Double-blind Study Comparing the Efficacy and Safety of Voclosporin (23.7 mg Twice Daily) with Placebo in Achieving Renal Response in Subjects with Active Lupus Nephritis

The primary study objective was to assess the efficacy of voclosporin compared with placebo in achieving renal response after 52 weeks of therapy in subjects with active lupus nephritis (LN).

The primary efficacy endpoint was the renal response at Week 52 as adjudicated by an independent Clinical Endpoints Committee (CEC) based on the following parameters:

- Urine protein creatinine ratio (UPCR) of ≤0.5 mg/mg, and
- Estimated glomerular filtration rate (eGFR) ≥60 mL/min/1.73 m² or no confirmed decrease from baseline in eGFR of ≥20%, and
- Received no rescue medication for LN, and
- Did not receive more than 10 mg prednisone for ≥3 consecutive days or for ≥7 days in total during Weeks 44–52, just prior to the renal response assessment.

The study randomized 357 subjects from 149 sites in 27 countries. The first subject was randomized on 10 October 2019 and the last patient completed the study on 17 May 2017.

**Rationale for Site Selection**
The clinical investigators, Dr. James Tumlin (Sites 355 and 10348) and Dr. Ellen Ginzler (Sites 354 and 10135) were selected using risk-based approach that also considers numbers of enrolled subjects in both studies and treatment effect.

III. RESULTS:

1. James Tumlin, M.D.

Dr. Tumlin enrolled study subjects for two protocols at different locations.

Protocol AUR-VCS-2012-01
Site #355
Southeast Renal Research Institute (SERRI)
251 N Lyerly Street, Suite 200
Chattanooga, TN 37408
Inspection dates: September 14-16, 2020

At this site for Protocol AUR-VCS-2012-01, nine subjects were screened and three subjects were enrolled. Among the three enrolled subjects, Subject # assigned to placebo group was lost to follow-up. Subject # was discontinued on investigational product due to lack of efficacy but remained in the study through the final follow-up, and Subject # completed the study on investigational product. The inspection reviewed the subject-specific records for all nine subjects.

The inspection evaluated the following documents: paper source worksheets, electronic case report forms (eCRFs), paper dosage diaries, medical histories, adverse event reports, concomitant medications, pharmacy records, investigational product storage area and shipment records, IRB and monitor correspondence, informed consent forms, and training records.

Source documents for the raw data used to assess the primary efficacy endpoint data were verifiable at the study site. There was no evidence of underreporting of adverse events.

Protocol AUR-VCS-2016-01
Site #10348
575 Professional Drive, Suite 250, Georgia Nephrology Research Institute
Lawrenceville, GA 30046
Inspection dates: August 31 – September 2, 2020

At this site for Protocol AUR-VCS-2016-01, nine subjects were screened and three subjects were enrolled at this site. Among the three enrolled subjects, three subjects completed the study. Subject # experienced an adverse event of worsening lupus nephritis but remained in the study despite not receiving the study drug. The inspection reviewed the informed consent forms for all nine subjects screened and data source records for all three completed subjects.
The inspection evaluated the following documents: regulatory files, study protocol, subject medical history and research records, IRB approvals, subject eligibility criteria, informed consent procedures and documentation, source data and case report form evaluation; adverse event report, and drug accountability.

Source documents for the raw data used to assess the primary efficacy endpoint data were verifiable at the study site. There was no evidence of underreporting of adverse events.

Overall, this clinical investigator appeared to be in compliance with Good Clinical Practices. A Form FDA 483 (Inspectional Observations) was not issued. Data submitted by this clinical site appear acceptable in support of this application.

2. Ellen Ginzler M.D.

450 Clarkson Avenue
Brooklyn, NY 11203

Inspection dates: October 5-8, 2020

For Protocol AUR-VCS-2012-01, two subjects were screened and enrolled at this site. Both enrolled subjects discontinued the study treatment early with Subject # (b)(6) due to lack of efficacy and Subject # (b)(6) due to an adverse event of decreased glomerular filtration rate. The inspection reviewed the subject-specific records for all two subjects.

For Protocol AUR-VCS-2016-01, five subjects were screened and three subjects were enrolled at this site. Subject # (b)(6) assigned to placebo group discontinued the study treatment due to lack of efficacy and dosing noncompliance and two subjects completed the study. The inspection reviewed the subject-specific records for all five subjects.

The inspection evaluated the following documents: subject records, informed consent, eligibility, protocol adherence, adverse event reporting, delegation of authority, financial disclosure, institutional review board approvals, investigational product accountability.

Source documents for the raw data used to assess the primary efficacy endpoint data were verifiable at the study site. There was no evidence of underreporting of adverse events.

This clinical investigator appeared to be in compliance with Good Clinical Practices. A Form FDA 483 (Inspectional Observations) was not issued. Data submitted by this clinical site appear acceptable in support of this application.
Suyoung Tina Chang, M.D.
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

Min Lu, M.D., M.P.H.
Team Leader,
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

Kassa Ayalew, M.D., M.P.H.
Branch Chief
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

Central Doc. Rm.
Review Division/Division Director/
Review Division/Medical Team Leader/
Review Division/Project Manager/
Review Division/MO/
OSI/Office Director/
OSI/DCCE/ Division Director/
OSI/DCCE/Branch Chief/
OSI/DCCE/Team Leader/
OSI/DCCE/GCP Reviewer/
OSI/GCP Program Analysts/
OSI/Database PM/Dana Walters
This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

SUYYOUNG T CHANG
11/12/2020 12:56:51 PM

MIN LU
11/12/2020 12:58:35 PM

KASSA AYALEW
11/16/2020 12:42:55 PM
1 PURPOSE OF MEMORANDUM
The Applicant submitted revised container label and carton labeling received on November 4, 2020 for Lupkynis. The Division of Rheumatology and Transplant Medicine (DRTM) requested that we review the revised container label and carton labeling for Lupkynis (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.¹

2 CONCLUSION
The Applicant implemented all of our recommendations and we have no additional recommendations at this time.

APPENDIX A. IMAGES OF LABEL AND LABELING RECEIVED ON NOVEMBER 4, 2020

Container labels (wallets)

2 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page
This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

TERESA S MCMILLAN
11/10/2020 02:18:20 PM

IDALIA E RYCHLIK
11/10/2020 07:18:19 PM
LABEL LABELING AND PACKAGING REVIEW
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

**Date of This Review:** October 21, 2020  
**Requesting Office or Division:** Division of Rheumatology and Transplant Medicine (DRTM)  
**Application Type and Number:** NDA 213716  
**Product Name, Dosage Form, and Strength:** Lupkynis (voclosporin) Capsules, 7.9 mg  
**Product Type:** Single Ingredient Product  
**Rx or OTC:** Prescription (Rx)  
**Applicant/Sponsor Name:** Aurinia Pharmaceuticals Inc  
**FDA Received Date:** May 22, 2020 and October 8, 2020  
**OSE RCM #:** 2020-1103  
**DMEPA Safety Evaluator:** Teresa McMillan, PharmD  
**DMEPA Team Leader:** Idalia E. Rychlik, PharmD
1 REASON FOR REVIEW
As part of the approval process for Lupkynis (vocolosoprin) Capsules, 7.9 mg, the Division of Rheumatology and Transplant Medicine (DRTM) requested that we review the proposed packaging, label and labeling for areas that may lead to medication errors.

2 MATERIALS REVIEWED
We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

<table>
<thead>
<tr>
<th>Table 1. Materials Considered for this Review</th>
<th>Appendix Section (for Methods and Results)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Material Reviewed</td>
<td></td>
</tr>
<tr>
<td>Product Information/Prescribing Information</td>
<td>A</td>
</tr>
<tr>
<td>Previous DMEPA Reviews</td>
<td>B-N/A</td>
</tr>
<tr>
<td>Human Factors Study</td>
<td>C-N/A</td>
</tr>
<tr>
<td>ISMP Newsletters*</td>
<td>D-N/A</td>
</tr>
<tr>
<td>FDA Adverse Event Reporting System (FAERS)*</td>
<td>E-N/A</td>
</tr>
<tr>
<td>Other</td>
<td>F-N/A</td>
</tr>
<tr>
<td>Labels and Labeling</td>
<td>G</td>
</tr>
</tbody>
</table>

N/A=not applicable for this review
*We do not typically search FAERS or ISMP Newsletters for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 FINDINGS AND RECOMMENDATIONS
Tables 2 and 3 below include the identified medication error issues with the submitted packaging, label and labeling, DMEPA’s rationale for concern, and the proposed recommendation to minimize the risk for medication error.
### Table 2: Identified Issues and Recommendations for Division of Rheumatology and Transplant Medicine (DRTM)

<table>
<thead>
<tr>
<th>IDENTIFIED ISSUE</th>
<th>RATIONALE FOR CONCERN</th>
<th>RECOMMENDATION</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>General Issues</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. Use of the abbreviation (BID) throughout the Dosage and administration sections of the Prescribing Information (Highlights and Full).</td>
<td>Abbreviations are not universally understood and can lead to dosing errors.</td>
<td>Remove all instances of the abbreviation ‘BID’ throughout the Prescribing Information.</td>
</tr>
<tr>
<td>2. Section 16. How Supplied/Storage and Handling states the following: LUPKYNIS is provided in child-proof packaging to avoid unintentional ingestion of medication by children.</td>
<td>This product is supplied in blister packs of 15 capsules—each capsule containing 7.5 mg of voclosporin. We are unsure if the proposed statement in Section 16. How Supplied/Storage and Handling is accurate.</td>
<td>We defer to OPQ on the accuracy of this statement.</td>
</tr>
</tbody>
</table>
### Table 3: Identified Issues and Recommendations for Aurinia (entire table to be conveyed to Applicant)

| All (Container Label-wallet and carton labeling) | 1. The principal display panel does not specifically state that each individual capsule contains 7.9 mg. | Lack of this information may lead to incorrect dosages. It is recommended so that there is no confusion as to how much product is contained in a single unit as compared to the total contents of the entire blister pack. | Revise to the following:
60 capsules
(4 blister packs of 15 capsules)
Each capsule contains 7.9 mg of voclopsorin. |
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>2. The lot number and expiration date formats are missing.</td>
<td>Lack of a defined expiration date and lot number may contribute to expired drug medication errors and verification issues.</td>
<td>Define the expiration date and lot number. To minimize confusion and reduce the risk for expired drug medication errors, identify the format you intend to use. FDA recommends that the human-readable expiration date on the drug package label include a year, month, and non-zero day. FDA recommends that the expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human-readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. FDA recommends that a hyphen or a space be used to separate</td>
<td></td>
</tr>
</tbody>
</table>
3. The terminology used to describe the recommended dosage is not consistently presented.

<table>
<thead>
<tr>
<th>Container Label- wallet/blister pack</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Each individual fixed blister does not state the drug name and strength per capsule.</td>
</tr>
</tbody>
</table>

4 CONCLUSION

Our evaluation of the proposed label and labeling identified areas of vulnerability that may lead to medication errors. Above, we have provided recommendations in Table 2 for the Division and Table 3 for the Applicant. We ask that the Division convey Table 3 in its entirety to Aurinia so that recommendations are implemented prior to approval of this NDA.
Table 2 presents relevant product information for Lupkynis received on October 8, 2020 from Aurinia Pharmaceuticals Inc.

<table>
<thead>
<tr>
<th>Table 2. Relevant Product Information for Lupkynis</th>
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<tr>
<td><strong>Initial Approval Date</strong></td>
</tr>
<tr>
<td><strong>Active Ingredient</strong></td>
</tr>
<tr>
<td><strong>Indication</strong></td>
</tr>
<tr>
<td><strong>Route of Administration</strong></td>
</tr>
<tr>
<td><strong>Dosage Form</strong></td>
</tr>
<tr>
<td><strong>Strength</strong></td>
</tr>
<tr>
<td><strong>Dose and Frequency</strong></td>
</tr>
<tr>
<td><strong>How Supplied</strong></td>
</tr>
<tr>
<td><strong>Storage</strong></td>
</tr>
</tbody>
</table>
APPENDIX B. PREVIOUS DMEPA REVIEWS-N/A
APPENDIX C. HUMAN FACTORS STUDY-N/A
APPENDIX D. ISMP NEWSLETTERS-N/A
APPENDIX E. FDA ADVERSE EVENT REPORTING SYSTEM (FAERS)-N/A
APPENDIX F. N/A
APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,\(^a\) along with postmarket medication error data, we reviewed the following Lupkynis labels and labeling submitted by Aurinia Pharmaceuticals Inc.

- Container label received on October 8, 2020
- Carton labeling received on October 8, 2020
- Prescribing Information (Image not shown) received on October 8, 2020, available from `\\CDSESUB1\evsprod\nda213716\0020\m1\us\114-labeling\draft\labeling\draft-pi.pdf`

G.2 Label and Labeling Images

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

TERESA S MCMILLAN
10/21/2020 01:45:26 PM

IDALIA E RYCHLIK
10/21/2020 02:00:47 PM
Interdisciplinary Review Team for Cardiac Safety Studies

QT Study Review

<table>
<thead>
<tr>
<th>Submission</th>
<th>NDA 213716</th>
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</thead>
<tbody>
<tr>
<td>Submission Number</td>
<td>004 / Labeling</td>
</tr>
<tr>
<td>Submission Date</td>
<td>5/22/2020</td>
</tr>
<tr>
<td>Date Consult Received</td>
<td>7/14/2020</td>
</tr>
<tr>
<td>Drug Name</td>
<td>Voclosporin</td>
</tr>
<tr>
<td>Indication</td>
<td>Treatment of Lupus Nephritis</td>
</tr>
<tr>
<td>Therapeutic dose</td>
<td>23.7 mg twice daily (BID) on an empty stomach</td>
</tr>
<tr>
<td>Clinical Division</td>
<td>DRTM</td>
</tr>
</tbody>
</table>

Note: Any text in the review with a light background should be inferred as copied from the sponsor’s document.

This review responds to your consult dated 7/14/2020 regarding the sponsor’s QT evaluation. We reviewed the following materials:

- Previous IRT review for TQT studies ISA03-11 and ISA05-03 under IND dated 05/08/2007 in DARRTS;
- Clinical study reports for studies ISA03-11 and ISA05-03 (Submission 0004);
- **Clinical Study Report** and **Cardiovascular (QTc) Safety Report** for study AUR-VCS-2012-01 (Submission 0004);
- **Evaluation of Cardiac Repolarization** (Submission 0004);
- Sponsor’s proposed labeling (Submission 0004); and
- **QT Evaluation Report Checklist** with links to Investigator’s Brochure and Highlights of Clinical Pharmacology and Cardiac Safety (Submission 0008).

1 SUMMARY

A dose-dependent, delayed QT prolonging effect was observed after a single dose treatment in 2 QT studies, but the effect appeared to attenuate after repeated dosing for 7 days. Nonclinical cardiac safety studies could not explain the observations in the clinical QT studies.

The effect of voclosporin was evaluated in a single dose, parallel group TQT study ISA03-11 (primary study), a multiple-dose, crossover QT study ISA05-03 (primary study), and a placebo-controlled, parallel-group Phase 2 study AUR-VCS-2012-01 (supportive study). The highest dose evaluated was a single dose of 4.5 mg/kg single dose or 1.5 mg/kg BID, which covers the worst case exposure scenario (strong CYP3A inhibition, section 3.1). The data were analyzed using by-timepoint analysis as the primary analysis, which suggest that voclosporin is associated with dose-dependent QTc prolonging effect after single dose but there is no large mean increase after repeated dosing (refer to section 0) – see Table 1 for overall results. The findings of this analysis
are further supported by data from the concentration-response analysis on the two QT studies (section 4.5) and categorical analysis of all three clinical studies (section 4.4).

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment</th>
<th>Day</th>
<th>Time (hour)</th>
<th>ΔΔQTcF (msec)</th>
<th>90% CI</th>
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</thead>
<tbody>
<tr>
<td>ISA03-11</td>
<td>Voclosporin 0.5 mg/kg (N=40)</td>
<td>1</td>
<td>4</td>
<td>4.9</td>
<td>(1.4, 8.4)</td>
</tr>
<tr>
<td></td>
<td>Voclosporin 1.5 mg/kg (N=40)</td>
<td>1</td>
<td>6</td>
<td>14.2</td>
<td>(10.3, 18.1)</td>
</tr>
<tr>
<td></td>
<td>Voclosporin 3.0 mg/kg (N=40)</td>
<td>1</td>
<td>6</td>
<td>22.5</td>
<td>(18.6, 26.4)</td>
</tr>
<tr>
<td></td>
<td>Voclosporin 4.5 mg/kg (N=40)</td>
<td>1</td>
<td>6</td>
<td>30.6</td>
<td>(26.7, 34.5)</td>
</tr>
<tr>
<td>ISA05-03</td>
<td>Voclosporin 0.3 mg/kg BID (N=40)</td>
<td>7</td>
<td>3</td>
<td>0.9</td>
<td>(-3.1, 4.8)</td>
</tr>
<tr>
<td></td>
<td>Voclosporin 0.5 mg/kg BID (N=40)</td>
<td>7</td>
<td>4</td>
<td>1.1</td>
<td>(-2.6, 4.8)</td>
</tr>
<tr>
<td></td>
<td>Voclosporin 1.5 mg/kg BID (N=41)</td>
<td>7</td>
<td>6</td>
<td>1.8</td>
<td>(-2.7, 6.3)</td>
</tr>
</tbody>
</table>

Systemic exposures at the 0.5 mg/kg treatment groups were similar to that at the proposed therapeutic dose.

1.1 RESPONSES TO QUESTIONS POSED BY SPONSOR
Not applicable.

1.2 COMMENTS TO THE REVIEW DIVISION
We have seen another drug (oliceridine) where the QTc effect attenuates with repeat dosing. Like oliceridine, the QTc increase observed with voclosporin is mediated via an unknown mechanism and appears to attenuate with repeat dosing. However, unlike oliceridine, higher doses of voclosporin were associated with significant QTc prolongation (> 20 msec) and there is a potential for high exposure (i.e. in patients with concomitant strong CYP3A inhibitors). Therefore, we recommend product labeling that includes QT effect in section 12.2 and section 5, Warnings and Precautions.

2 RECOMMENDATIONS

2.1 ADDITIONAL STUDIES
QT prolongation risk can be handled with product labeling and we are not recommending any additional clinical QT studies.

2.2 PROPOSED LABEL
The IRT reviewed the proposed the label submitted to Submission 0004 (link). Because there are major revisions in section 12.2, we are providing IRT’s proposal directly (text in blue) without making modifications on the sponsor’s original language. Our proposals are for suggestions only and we defer final labeling decisions to the Division.

5.X QTc Prolongation

TRADENAME prolongs the QTc interval in a dose-dependent manner [see Clinical Pharmacology (12.2)].

The use of TRADENAME in combination with other drugs that are known to prolong QTc may result in clinically significant QT prolongation.
Certain circumstances may increase the risk of the occurrence of torsade de pointes and/or sudden death in association with the use of drugs that prolong the QTc interval, including (1) bradycardia; (2) hypokalemia or hypomagnesemia; (3) concomitant use of other drugs that prolong the QTc interval; and (4) presence of congenital prolongation of the QT interval.

12.2 Pharmacodynamics

Cardiac Electrophysiology

In a randomized, placebo- and active-controlled (moxifloxacin 400 mg), single dose study with parallel study design, dose-dependent QT prolonging effect was detected with TRADENAME in the dose range of 0.5–4.5 mg/kg (up to 9-fold coverage of the therapeutic exposure). Dose-dependent QT prolongation effect was observed with a time to maximum QTc increase occurring at 4–6-hour postdose across different dose levels. The maximum mean placebo-adjusted changes of QTc from baseline after TRADENAME 0.5 mg/kg, 1.5 mg/kg, 3.0 mg/kg, and 4.5 mg/kg dose were [msec], [msec], [msec], and [msec], respectively.

In a separate, randomized, placebo-controlled, crossover study in 31 healthy subjects, an absence of large mean increases (i.e., > 20 msec) was observed following 7 days of treatment with TRADENAME at 0.3, 0.5 and 1.5 mg/kg BID (approximately 6-fold coverage of the therapeutic exposure).

The mechanism for the QT prolonging effect as observed in the single-dose and multiple-dose studies is unknown.

Reviewer’s comment: The sponsor planned to report results from study ISA05-03 and to claim . We do not agree and we proposes to report results from study ISA03-11 before ISA05-03.

- ISA03-11 suggested a significant, dose-dependent, delayed QT prolonging effect that is not explained by available nonclinical cardiac safety data. It is not known if the effect would occur after the second or third doses.
- ISA05-03 lacks a valid positive control. The study does not provide sufficient exposure margin to waive the need of a separate positive control. The single dose part of data has a small sample size and shows signs for delayed QT prolonging effect which was observed in study ISA03-11. The multiple dose part of data uses an unconventional method for baseline calculation that has not been fully evaluated before.

- As the mechanism, the duration, and the clinical relevance of the observed QT prolonging effect were not known, we recommend including warnings/precautions in the product label, especially considering that some patients may be subject to the high exposure scenarios.
3 SPONSOR’S SUBMISSION

3.1 OVERVIEW

3.1.1 Clinical

Voclosporin (also referred to as ISA247 or [8] (4), MW: 1214.6 g/mol) is a calcineurin-inhibitor immunosuppressant designed with a modification of an amino acid of the cyclosporine molecule. Previously the IRT reviewed two QT studies (ISA03-11 and ISA05-03) for voclosporin (ITR review under IND [4] dated 05/08/2007 in DARRTS). Because of changes in the review practice over the years (e.g. selection of primary endpoint, analysis methods, etc.), the IRT re-analyzed the data in this current review. A summary of study design is provided below:

- Study ISA03-11 was a randomized, moxifloxacin- and placebo-controlled, double-blind, single dose study with parallel study design. Cohort A was open label moxifloxacin 400 mg. Cohorts B-D were double blinded placebo (B), 0.5 mg/kg voclosporin (C) or 4.5 mg/kg voclosporin (D). Two double-blinded treatment cohorts (1.5 and 3.0 mg/kg voclosporin) were added after Cohorts A-D were unblinded. Digital, triplicate ECGs were collected predose and with matching PK data at 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 12, and 24 hours postdose on Day 1 and at matching time points on Day -1). A total of 240 healthy volunteers were enrolled and randomized.

- Study ISA05-03 was a randomized, multiple-dose, double-blinded, 4-way crossover, placebo- and moxifloxacin-controlled, QTc study. The washout period was at least 10 days. 60 healthy volunteers were enrolled and randomized to receive voclosporin 0.3 mg/kg, 0.5 mg/kg, and 1.5 mg/kg, and a placebo capsules twice daily for 6 days and on the morning of Day 7 in Periods 1-4, and a single dose of moxifloxacin 400 mg on Period 5. 40 subjects completed Period 1 and 33 subjects completed Period 4. Triplicate 12-lead Holter ECGs were extracted predose on Day 1 for Periods 1 and 5, and 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, and 12 hours post-morning dose on Day 1 for Periods 1-4 and on Day 7 for Periods 1-4.

Reviewer's comment: Study ISA05-03 has two major design issues. Firstly, the positive control arm was not conducted in a randomized manner with the placebo control and drug treatment; therefore, it cannot be used to establish assay sensitivity. Secondly, predose baseline data was only collected in Period 1; therefore, QTc data on Day 7 at different dose levels were calculated using a common baseline. This is an uncommon practice; the effect of common baseline on study conclusion is not known. It was also noted that the single dose data were only collected in Period 1 of the study (hence a small size sample at each dose level). Day 1 and Day 7 data were not pooled in the by-timepoint analysis and concentration-QTc analysis in the reviewers’ analyses.

The sponsor also provided a QTc analysis report for Phase 2 study AUR-VCS-2012-01 (AURA-LV) and Phase 3 study AUR-VCS-2016-01 (AURORA-1). ECG data from AURORA-1 were not included because the study contained standard 12-lead ECGs at only a few predose timepoints at a single dose level (therapeutic dose). A summary of study AURA-LV is provided below:

- AURA-LV is a randomized, double-blinded study comparing voclosporin (23.7 mg BID or 39.5 mg BID) with their matching Placebo in patients with active Lupus
Nephritis. 265 subjects were randomized (2:2:1:1 randomization) and analyzed. ECGs were performed at screening, baseline, Day 2, Weeks 4, 6, 8, 12, 24, and 48. At Day 2, Weeks 4 and 24 visits, time-matched ECGs were collected at trough and 2 hours post-dose.

**Reviewer’s comment:** While a large number of subjects were enrolled in the study, baseline ECG were only collected in a small number of patients (n=18 at 23.7 mg BID, n=14 at 39.5 mg BID, n=21 with placebo). As delayed effect (or signs of delayed effect) was observed in studies ISA03-11 and ISA05-03, it was desirable to have clinical ECG data after repeated dosing in the patient population to detect potential delayed effect. However, the limited sampling schedule in AURA-LV are not expected to bring additional information to the QT assessment. Given the sub-optimal ECG quality, sparse ECG sample, and small sample size, the reviewers did not conduct by-timepoint analysis or concentration-QTc analysis on AURA-LV. These data were included in the categorical analysis only.

**Highlight of clinical pharmacology:**

- Voclosporin is rapidly absorbed (median Tmax: 1.5 hours) with a terminal elimination half-life of approximately 30 hours. More than dose proportional increase in systemic exposure was reported from 0.25 to 1.5 mg/kg BID. Accumulation of voclosporin is 1.3- to 2.2-fold after 0.25 to 1.5 mg/kg BID dosing. At the 23.7 mg BID, the average (%CV) steady state Cmax is reported to be 120 (32.3%) ng/mL and AUC0-12 is 433 (43.0%) ng.h/mL. Plasma binding is 97%. The drug partitions extensively in to red blood cells. Voclosporin is mainly eliminated by metabolism (primarily by CYP3A4).
- Five metabolites exhibited AUC0-24 >10% of the parent drug. One of them (IM9) accounted for >10% total drug-related exposure (44% of parent drug) in AUC0-24.
- Highest exposure scenario: Ketoconazole (400 mg QD) and verapamil (80 mg TID) increases voclosporin Cmax to 6.5- or 2.1-fold. Mild and moderate hepatic impairment (Child-Pugh A and B) increases Cmax by 45% (increases AUC by 67-96%). The effect of severe hepatic impairment is not available.
- The drug substance consists of two geometric isomers, the trans (E)-isomer and the cis (Z)-isomer. Voclosporin is enriched with the trans-isomer (90 to 95% trans-isomer). No trans- to cis-isomer conversion was observed both in vitro and in vivo. An isomer-specific bioanalytical method was used in early clinical studies including ISA03-11 and ISA05-03; in general, cis-isomer accounted for <5% of the total drug exposure. A non-isomer specific method was used in later clinical development.

### 3.1.2 Nonclinical Safety Pharmacology Assessments

The results of a hERG assay in CHO cells indicated that mix-ISA247, cis-ISA247 and voclosporin inhibit repolarizing currents through hERG K+ channels in vitro at 20% of inhibitory concentration (IC20) values of approximately 6-18 μM (approximately 7,000-22,000 ng/mL) (Study ISA03-14). However, these concentrations are well in excess of the estimated therapeutic whole blood concentrations of approximately 0.1 μM (approximately 120 ng/mL) (Studies [b][c][d]0.06, [b][c][d]0.07 and ISA05-25). Furthermore, in a rabbit Purkinje fiber assay, mix- ISA247 was not associated with the induction of arrhythmias at the concentration range tested (nominally 0.01-10 μM) (Study ISA03-15). In vivo, voclosporin and mix-ISA247 lengthened the electrocardiogram (ECG) interval
measured from the beginning of the QRS complex to the end of the QT and QTc intervals at a dose level of 200 mg/kg, the highest dose tested, in two separate cardiovascular safety pharmacology studies in conscious monkeys but had no effect at lower doses (20 and 60 mg/kg) (Studies ISA02-07 and ISA03-02). In these studies, no effects on heart rate were observed and the ECG waveforms showed no effect on RR, PR and QRS complex duration. Exposure to voclosporin at a dose level of 200 mg/kg in monkeys was approximately 8-fold and 5-fold higher than the estimated therapeutic exposure based on area under the concentration-time curve (AUC) and maximum concentration (Cmax), respectively. Of note, no drug-related ECG abnormalities were observed in any other non-rodent toxicology study including 14-day dog, 13-week dog, 13-week monkey and 39-week monkey studies.

**Reviewer's assessment:** The sponsor evaluated the effects of voclosporin (ISA247), trans-ISA247 and cis-ISA247 on hERG current, a surrogate for IKr that mediate membrane potential repolarization in cardiac myocytes. The hERG study report ([link](#)) describes the potential effects of voclosporin, trans-ISA247 and cis-ISA247 on the hERG current in CHO cells. The hERG current was assessed at room temperature, using a voltage protocol consisting of a depolarizing step from -80 mV to +20 mV (500 ms), followed by a repolarizing step to -40 mV (500 ms), then further hyperpolarized to -120 mV for 200 ms. The voltage waveform was repeated every 10 seconds. The hERG tail currents were assessed at the repolarizing step (-40 mV) for outward tail current and at the hyperpolarized step (-120 mV) for inward current. The sponsor’s voltage protocol to evoke the hERG current is different from the recommended hERG current protocol by the FDA ([link](#)). However, the reviewer does not expect protocol differences to impact hERG current pharmacology since available data have demonstrated that there were good correlations between IC50 values obtained using either a step-pulse or a step-ramp pattern of voltage potential. E-4031 at 10 µM was used for non-hERG currents subtraction. Positive control drugs (such as dofetilide, cisapride and terfenadine) showed IC50 values similar to those reported in literature. Solution samples before applying to the chamber were collected for concentration verification analysis. The actual concentrations of ISA247 at the nominal concentrations of 12.4 µg/ml and 1.21 µg/ml were 10.4 µg/ml and 0.73 µg/ml, respectively. There were deviations (16 ~39% max difference) from the nominal concentrations. Actual concentrations were used to describe drug effects.

Voclosporin, trans-ISA247 and cis-ISA247 caused a concentration-dependent inhibition of hERG current with an IC50 values of 22 µM, 42 µM and 76 µM, respectively. The hERG safety margin of voclosporin is summarized below:

**Table 2: Safety Margin of voclosporin on hERG Current**

<table>
<thead>
<tr>
<th></th>
<th>Cmax (ng/mL)</th>
<th>Protein Binding</th>
<th>Free Cmax (ng/mL)</th>
<th>hERG IC50 (µM)</th>
<th>Mol Weight (g/mol)</th>
<th>Safety Margin (Ratio)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Voclosporin</td>
<td>120</td>
<td>97%</td>
<td>3.6</td>
<td>22</td>
<td>1214.6</td>
<td>7422x</td>
</tr>
</tbody>
</table>

An in vitro Study ISA03-15 ([link](#)) (Non-GLP study) investigated the effects of voclosporin on action potential in isolated rabbit cardiac Purkinje fibers at frequencies of 2, 1 and 0.2 Hz. Voclosporin had no effects on action potential duration at the highest tested
concentration (nominal concentration was 10 µM). However, it slowed the maximum upstroke velocity of the action potential (Vmax) by 25% at the highest tested concentration, indicating that the peak sodium channel may be inhibited by the drug. Solutions from the outflow of the chamber were corrected for concentration verification analysis. This highest test concentration of nominally 10 µM was measured to be 3.3-3.7 µM. There were about 65% drug loss during the experiment. Reference drugs (positive control) such as dofetilide, sparfloxacin and cisapride prolonged the APD90 by 300-1000% at highest tested concentrations of 30 nM, 100 µM and 3 µM, respectively.

Study ISA02-07(link) (GLP compliant) evaluated effects of multiple doses of oral administration of voclosporin on 6 conscious telemetered Cynomolgus female monkeys. Each animal received three dose levels at 20, 60, and 200 mg/kg as well as vehicle treatment in a different order, on day 0, 4, 7, 11, 13, 42, 57, and 60. Pharmacokinetic measurements were performed on day 42. The corresponding voclosporin plasma C_max values were 32.2, 274.8 and 604.8 ng/mL, respectively. The doses tested in this study adequately covered therapeutic exposure level in humans (120 ng/mL; sponsor’s ISA247 at doses of 20, 60 and 200 mg/kg had no effects on heart rate, PR and QRS intervals. ISA247 caused no significant QTc prolongations at dose of 20 and 60 mg/kg. However, ISA247 at dose of 200 mg/kg significantly prolonged QTc interval between 2-6 hours after dosing. No positive control drug was included in this study.

Another in vivo study (link)(GLP compliant) assessed effects of single dose (200 mg/kg) of oral administrations of voclosporin, cis-ISA247 and trans-ISA247 on ECG parameters and cardiovascular hemodynamic in telemetered monkeys. Each animal received the above three test drugs and vehicle control in different order. Measurements were carried out over a period of 2 hours pre-dosing and 24 hours after-dosing. Additional administration of three drugs performed for pharmacokinetic measurements on days 14, 18 or 21, respectively. The corresponding plasma C_max values of voclosporin, cis-ISA247 and trans-ISA247 were 488 ng/ml (183 ng/ml of cis-ISA247 and 305 ng/ml of trans-ISA247), 285 ng/ml and 538 ng/ml. Tmax were between 1.8 to 3.3 hours for the three tested drugs. The dose tested in this study exceeded the therapeutic exposure level in humans (120 ng/ml). All tested drugs at 200 mg/kg had no effects on arterial blood pressure and heart rate. No effects on PR and QRS intervals were observed after administration of either tested drugs. All three drugs induced QTc prolongations. This increase of QT interval was observed from 1-2 hours after administration and reached the peak effects at 6 hours. No positive control drug was included in this study.

In summary, results from experiments that conducted by sponsor suggest that voclosporin does not acutely interact with hERG channels at the therapeutic exposure level. The mechanisms of delayed QTc prolongation after 200 mg/kg dose of voclosporin in monkeys is unclear.

3.2 SPONSOR’S RESULTS

3.2.1 By-Time Analysis

Voclosporin failed to exclude the 10 msec threshold at the 1.5 mg/kg, 3.0 mg/kg and 4.5 mg/kg dose levels for ΔΔQTcF in study ISA03-11. The design of study ISA05-03 lack features of standard TQT study (e.g., moxi was only placed on the last period, thus
limiting the interpretability of study results from ISA05-03). Increase in ΔΔQTcF was observed but the magnitude attenuated from Day 1 to Day 7.

**Reviewer’s comment:** The reviewer’s by-timepoint analysis results are similar to the sponsor’s results.

### 3.2.1.1 Assay Sensitivity

The sponsor claimed assay sensitivity was established by the moxifloxacin arm in study ISA03-11 and study ISA05-03, respectively.

**Reviewer’s comment:** The reviewer’s by-time analysis demonstrates that assay sensitivity was established in study ISA03-11. For study ISA05-03, due to the problematic study design, moxifloxacin treatment in Period 5 was excluded from the reviewer’s by-time point analysis.

#### 3.2.1.1.1 QT Bias Assessment

Not applicable.

### 3.2.2 Categorical Analysis

There were no significant outliers per the sponsor’s analysis for QTcF (i.e., >500 msec or >60 msec increase over baseline).

**Reviewer’s comment:** The sponsor didn’t give much details about categorical analyses. Please see section 4.4 for the reviewer’s analyses.

### 3.2.3 Exposure-Response Analysis

The sponsor did not conduct a formal exposure-response analysis. The sponsor conducted regression analysis of ΔQTcI (study ISA03-11) or ΔQTcF (study ISA05-03) as a function of trans-ISA247, cis-ISA247, total parent drug, individual metabolites, or total drug related concentration. For study AURA-LV, the sponsor conducted regression analysis of the ΔΔQTcF as a function of voclosporin concentration and the analysis did not suggest a positive relationship.

**Reviewer’s comment:** The reviewer conducted linear mixed effect modeling on study ISA03-11 and ISA05-03. For limitations in the study design and presented in the data (i.e. PK/PD hysteresis), the results of linear mixed effect modeling should be interpreted with caution. Refer to section 4.5 for details of the reviewer’s analysis.

### 3.2.4 Safety Analysis

**Reviewer’s comment:** Safety analysis was conducted in previous IRT reviews of the TQT studies.

### 4 REVIEWERS’ ASSESSMENT

#### 4.1 Evaluation of the QT/RR Correction Method

The sponsor used QTcF for the primary analysis, which is acceptable as no large increases or decreases in heart rate (i.e. maximum increase not significantly higher than 10 beats/min) were observed (see section 4.3.2 and 4.5).
4.2 ECG ASSESSMENTS

4.2.1 Overall
Waveforms of study ISA03-11 and ISA05-03 were reviewed. Study 03-11 has much higher QT bias rate than those in TQT studies in the ECG warehouse, only worse than 13% of all studies according to the automated algorithm and the criteria used by the ECG Warehouse. However, due to the positive QT findings for the studies, additional QT Bias analysis is not needed to avoid a false-negative conclusion. On the other hand, acquisition and interpretation in study ISA05-03 appears acceptable.

4.2.2 QT Bias Assessment
Not applicable.

4.3 BY-TIME ANALYSIS
The analysis population used for the by-time analysis included all subjects with a baseline and at least one post-dose ECG. The reviewer conducted by-time analysis for study ISA03-11 and study ISA05-03.

For study ISA03-11, the statistical reviewer used mixed model with repeated measures to analyze the drug effect for each biomarker (e.g., ΔQTcF, ΔHR) independently. The model includes treatment, time (as a categorical variable), and treatment-by-time interaction as fixed effects and baseline as a covariate. The model also includes an unstructured covariance matrix to explain the associated between repeated measures within treatment.

Due to the unbalanced design and the no corresponding Day 7 moxifloxacin in study ISA05-03, moxifloxacin treatment in Period 5 was excluded from the reviewer’s by-time analysis. The reviewer conducted nonparametric analysis for Period 1 Day 1 (in parallel design, with limited number of subjects having ECG collections) data to have some insights about the median ECG values; CIs are unreliable due to small sample size of Period 1 Day 1. For Day 7 data, the reviewer used mixed model with repeated measures appropriate for a crossover design for the analysis. The model includes sequence, period, treatment, time (as a categorical variable), and treatment-by-time interaction as fixed effects and baseline as a covariate. The model also includes an unstructured covariance matrix to explain the association in repeated measures.

4.3.1 QTc
Figure 1 displays the time profile of ΔΔQTcF for different treatment groups in the 2 studies. The maximum ΔΔQTcF values by treatment are shown in Table 3.
Figure 1: Mean and 90% CI of ΔΔQTcF Time Course (unadjusted CIs).

Table 3: The Point Estimates and the 90% CIs Corresponding to the Largest Mean/Median for ΔΔQTcF (msec)

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment</th>
<th>Day</th>
<th>Time (hour)</th>
<th>ΔΔQTcF (msec)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ISA03-11</td>
<td>Voclosporin 0.5 mg/kg (N=40)</td>
<td>1</td>
<td>4</td>
<td>4.9 (1.4, 8.4)</td>
</tr>
<tr>
<td></td>
<td>Voclosporin 1.5 mg/kg (N=40)</td>
<td>1</td>
<td>6</td>
<td>14.2 (10.3, 18.1)</td>
</tr>
<tr>
<td></td>
<td>Voclosporin 3.0 mg/kg (N=40)</td>
<td>1</td>
<td>6</td>
<td>22.5 (18.6, 26.4)</td>
</tr>
<tr>
<td></td>
<td>Voclosporin 4.5 mg/kg (N=40)</td>
<td>1</td>
<td>6</td>
<td>30.6 (26.7, 34.5)</td>
</tr>
<tr>
<td>ISA05-03</td>
<td>Voclosporin 0.3 mg/kg BID (N=13)</td>
<td>1</td>
<td>2</td>
<td>8.0 (-0.8, 16.8)</td>
</tr>
<tr>
<td></td>
<td>Voclosporin 0.5 mg/kg BID (N=14)</td>
<td>1</td>
<td>12</td>
<td>6.3 (1.2, 11.5)</td>
</tr>
<tr>
<td></td>
<td>Voclosporin 1.5 mg/kg BID (N=14)</td>
<td>1</td>
<td>3</td>
<td>16.9 (11.0, 22.8)</td>
</tr>
<tr>
<td></td>
<td>Voclosporin 0.3 mg/kg BID (N=40)</td>
<td>7</td>
<td>3</td>
<td>0.9 (-3.1, 4.8)</td>
</tr>
<tr>
<td></td>
<td>Voclosporin 0.5 mg/kg BID (N=40)</td>
<td>7</td>
<td>4</td>
<td>1.1 (-2.6, 4.8)</td>
</tr>
<tr>
<td></td>
<td>Voclosporin 1.5 mg/kg BID (N=41)</td>
<td>7</td>
<td>6</td>
<td>1.8 (-2.7, 6.3)</td>
</tr>
</tbody>
</table>
4.3.1.1 Assay sensitivity
The same by-time analysis mixed model was used for assay sensitivity analysis in study ISA03-11. The time-course of changes in ΔQTcF is shown in Figure 1 and shows the expected time-profile with a mean effect of >5 msec after Bonferroni adjustment for 4 time points (Table 4).

Table 4: The Point Estimates and the 90% CIs Corresponding to the Largest Lower Bounds for ΔQTcF

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment</th>
<th>Day</th>
<th>Time (hour)</th>
<th>Mean</th>
<th>90% CI</th>
<th>97.5% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>ISA03-11</td>
<td>Moxifloxacin 400 mg (N=40)</td>
<td>1</td>
<td>2</td>
<td>17.6</td>
<td>(14.0, 21.2)</td>
<td>(12.7, 22.5)</td>
</tr>
</tbody>
</table>

4.3.2 HR
Figure 2 displays the time profile of ΔΔHR for different treatment groups in the 2 studies. The maximum ΔΔHR values by treatment are shown in Table 5.

Figure 2: Mean and 90% CI of ΔΔHR Time Course
Table 5: The Point Estimates and the 90% CIs Corresponding to the Largest Mean/Median for ΔΔHR

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment</th>
<th>Day</th>
<th>Time (hour)</th>
<th>Mean/Median</th>
<th>90% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>ISA03-11</td>
<td>Voclosporin 0.5 mg/kg (N=40)</td>
<td>1</td>
<td>1.5</td>
<td>4.9</td>
<td>(2.3, 7.5)</td>
</tr>
<tr>
<td></td>
<td>Voclosporin 1.5 mg/kg (N=40)</td>
<td>1</td>
<td>3</td>
<td>6.9</td>
<td>(4.3, 9.5)</td>
</tr>
<tr>
<td></td>
<td>Voclosporin 3.0 mg/kg (N=40)</td>
<td>1</td>
<td>2.5</td>
<td>10.5</td>
<td>(8.1, 12.8)</td>
</tr>
<tr>
<td></td>
<td>Voclosporin 4.5 mg/kg (N=40)</td>
<td>1</td>
<td>2.5</td>
<td>14.0</td>
<td>(11.7, 16.3)</td>
</tr>
<tr>
<td>ISA05-03</td>
<td>Voclosporin 0.3 mg/kg BID (N=13)</td>
<td>1</td>
<td>3</td>
<td>2.1</td>
<td>(-3.8, 8.0)</td>
</tr>
<tr>
<td></td>
<td>Voclosporin 0.5 mg/kg BID (N=14)</td>
<td>1</td>
<td>3</td>
<td>5.3</td>
<td>(-1.5, 12.0)</td>
</tr>
<tr>
<td></td>
<td>Voclosporin 1.5 mg/kg BID (N=14)</td>
<td>1</td>
<td>3</td>
<td>2.7</td>
<td>(-2.8, 8.2)</td>
</tr>
<tr>
<td></td>
<td>Voclosporin 0.3 mg/kg BID (N=40)</td>
<td>7</td>
<td>2</td>
<td>0.9</td>
<td>(-1.9, 3.8)</td>
</tr>
<tr>
<td></td>
<td>Voclosporin 0.5 mg/kg BID (N=40)</td>
<td>7</td>
<td>2</td>
<td>2.4</td>
<td>(-0.4, 5.2)</td>
</tr>
<tr>
<td></td>
<td>Voclosporin 1.5 mg/kg BID (N=41)</td>
<td>7</td>
<td>2.5</td>
<td>0.5</td>
<td>(-2.3, 3.2)</td>
</tr>
</tbody>
</table>

4.3.3 PR

Figure 3 displays the time profile of ΔΔPR for different treatment groups in the 2 studies. The maximum ΔΔPR values by treatment are shown in Table 6.
Table 6: The Point Estimates and the 90% CIs Corresponding to the Largest Mean/Median for ΔΔPR

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment</th>
<th>Day</th>
<th>Time (hour)</th>
<th>Mean/Median</th>
<th>90% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>ISA03-11</td>
<td>Voclosporin 0.5 mg/kg (N=40)</td>
<td>1</td>
<td>23.5</td>
<td>2.3</td>
<td>(-0.4, 5.0)</td>
</tr>
<tr>
<td></td>
<td>Voclosporin 1.5 mg/kg (N=40)</td>
<td>1</td>
<td>23.5</td>
<td>6.9</td>
<td>(4.2, 9.7)</td>
</tr>
<tr>
<td></td>
<td>Voclosporin 3.0 mg/kg (N=40)</td>
<td>1</td>
<td>23.5</td>
<td>4.7</td>
<td>(2.0, 7.5)</td>
</tr>
<tr>
<td></td>
<td>Voclosporin 4.5 mg/kg (N=40)</td>
<td>1</td>
<td>23.5</td>
<td>5.4</td>
<td>(2.6, 8.2)</td>
</tr>
<tr>
<td>ISA05-03</td>
<td>Voclosporin 0.3 mg/kg BID (N=13)</td>
<td>1</td>
<td>2.5</td>
<td>5.5</td>
<td>(-2.0, 13.0)</td>
</tr>
<tr>
<td></td>
<td>Voclosporin 0.5 mg/kg BID (N=14)</td>
<td>1</td>
<td>6</td>
<td>4.7</td>
<td>(-2.2, 11.5)</td>
</tr>
<tr>
<td></td>
<td>Voclosporin 1.5 mg/kg BID (N=14)</td>
<td>1</td>
<td>4</td>
<td>4.2</td>
<td>(-4.5, 12.8)</td>
</tr>
<tr>
<td></td>
<td>Voclosporin 0.3 mg/kg BID (N=40)</td>
<td>7</td>
<td>4</td>
<td>4.6</td>
<td>(1.8, 7.4)</td>
</tr>
<tr>
<td></td>
<td>Voclosporin 0.5 mg/kg BID (N=40)</td>
<td>7</td>
<td>12</td>
<td>4.7</td>
<td>(1.8, 7.5)</td>
</tr>
<tr>
<td></td>
<td>Voclosporin 1.5 mg/kg BID (N=41)</td>
<td>7</td>
<td>4</td>
<td>2.1</td>
<td>(-0.7, 4.8)</td>
</tr>
</tbody>
</table>
4.3.4 QRS

Figure 4 displays the time profile of ΔΔQRS for different treatment groups in the 2 studies. The maximum ΔΔQRS values by treatment are shown in Table 7.

Table 7: The Point Estimates and the 90% CIs Corresponding to the Largest Mean/Median for ΔΔQRS

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment</th>
<th>Day</th>
<th>Time (hour)</th>
<th>Mean/Median</th>
<th>90% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>ISA03-11</td>
<td>Voclosporin 0.5 mg/kg (N=40)</td>
<td>1</td>
<td>0.5</td>
<td>0.9</td>
<td>(-0.7, 2.6)</td>
</tr>
<tr>
<td></td>
<td>Voclosporin 1.5 mg/kg (N=40)</td>
<td>1</td>
<td>10</td>
<td>1.3</td>
<td>(-0.3, 2.9)</td>
</tr>
<tr>
<td></td>
<td>Voclosporin 3.0 mg/kg (N=40)</td>
<td>1</td>
<td>6</td>
<td>2.1</td>
<td>(0.4, 3.8)</td>
</tr>
<tr>
<td></td>
<td>Voclosporin 4.5 mg/kg (N=40)</td>
<td>1</td>
<td>6</td>
<td>1.8</td>
<td>(0.1, 3.5)</td>
</tr>
<tr>
<td>ISA05-03</td>
<td>Voclosporin 0.3 mg/kg BID (N=13)</td>
<td>1</td>
<td>0.5</td>
<td>2.6</td>
<td>(-1.5, 6.7)</td>
</tr>
<tr>
<td></td>
<td>Voclosporin 0.5 mg/kg BID (N=14)</td>
<td>1</td>
<td>6</td>
<td>0.5</td>
<td>(-2.3, 3.3)</td>
</tr>
<tr>
<td></td>
<td>Voclosporin 1.5 mg/kg BID (N=14)</td>
<td>1</td>
<td>12</td>
<td>4.2</td>
<td>(-0.3, 8.7)</td>
</tr>
</tbody>
</table>
4.4 Categorical analysis

Categorical analysis was performed for different ECG measurements either using absolute values, change from baseline or a combination of both. The analysis was conducted using the safety population and includes both scheduled and unscheduled ECGs. All 3 studies, including data from both Day 1 and Day 7 in study ISA05-03, were included in categorical analyses.

4.4.1 QTc

No subjects experienced QTcF >500 msec in the 3 studies.

No subjects experienced ΔQTcF >60 msec in the 3 studies.

4.4.2 HR

Table 8 lists the categorical analysis results for maximum HR (>100 beats/min and >100 beats/min with >25% increase over baseline) and Table 9 lists the categorical analysis results for minimum HR (>45 beats/min and <45 beats/min).

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment Group</th>
<th>Total N</th>
<th>HR&gt;100 bpm</th>
<th>HR&gt;100 bpm &amp; Increase &gt;25%</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Subj. #</td>
<td>Obs. #</td>
<td>Subj. #</td>
<td>Obs. #</td>
</tr>
<tr>
<td>ISA03-11 Baseline</td>
<td>200 2559</td>
<td>26 (13.0%)</td>
<td>36 (1.4%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Voclosporin 0.5 mg/kg</td>
<td>40 520</td>
<td>5 (12.5%)</td>
<td>10 (1.9%)</td>
<td>4 (10.0%)</td>
</tr>
<tr>
<td>Voclosporin 1.5 mg/kg</td>
<td>40 516</td>
<td>5 (12.5%)</td>
<td>9 (1.7%)</td>
<td>2 (5.0%)</td>
</tr>
<tr>
<td>Voclosporin 3.0 mg/kg</td>
<td>40 513</td>
<td>12 (30.0%)</td>
<td>18 (3.5%)</td>
<td>11 (27.5%)</td>
</tr>
<tr>
<td>Voclosporin 4.5 mg/kg</td>
<td>40 515</td>
<td>16 (40.0%)</td>
<td>46 (8.9%)</td>
<td>15 (37.5%)</td>
</tr>
<tr>
<td>Placebo</td>
<td>40 513</td>
<td>4 (10.0%)</td>
<td>5 (1.0%)</td>
<td>2 (5.0%)</td>
</tr>
<tr>
<td>ISA05-03 Baseline</td>
<td>54 103</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Voclosporin 0.3 mg/kg BID</td>
<td>42 700</td>
<td>5 (11.9%)</td>
<td>7 (1.0%)</td>
<td>5 (11.9%)</td>
</tr>
<tr>
<td>Voclosporin 0.5 mg/kg BID</td>
<td>41 695</td>
<td>8 (19.5%)</td>
<td>15 (2.2%)</td>
<td>7 (17.1%)</td>
</tr>
<tr>
<td>Voclosporin 1.5 mg/kg BID</td>
<td>42 710</td>
<td>4 (9.5%)</td>
<td>11 (1.5%)</td>
<td>4 (9.5%)</td>
</tr>
<tr>
<td>Placebo</td>
<td>43 722</td>
<td>13 (30.2%)</td>
<td>23 (3.2%)</td>
<td>13 (30.2%)</td>
</tr>
<tr>
<td>AUR-VCS-2012-01 Baseline</td>
<td>56 56</td>
<td>6 (10.7%)</td>
<td>6 (10.7%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Voclosporin 23.7 mg BID</td>
<td>90 354</td>
<td>18 (20.0%)</td>
<td>42 (11.9%)</td>
<td>2 (2.2%)</td>
</tr>
<tr>
<td>Voclosporin 39.5 mg BID</td>
<td>74 290</td>
<td>9 (12.2%)</td>
<td>17 (5.9%)</td>
<td>1 (1.4%)</td>
</tr>
<tr>
<td>Voclosporin Other</td>
<td>11 46</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Placebo</td>
<td>88 360</td>
<td>13 (14.8%)</td>
<td>22 (6.1%)</td>
<td>1 (1.1%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment Group</th>
<th>Total N</th>
<th>HR&gt;45 bpm</th>
<th>HR&lt;=45 bpm</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Subj. #</td>
<td>Obs. #</td>
<td>Subj. #</td>
<td>Obs. #</td>
</tr>
<tr>
<td>ISA03-11 Baseline</td>
<td>200 2559</td>
<td>190 (95.0%)</td>
<td>2533 (99.0%)</td>
<td>10 (5.0%)</td>
</tr>
<tr>
<td>Voclosporin 0.5 mg/kg</td>
<td>40 520</td>
<td>40 (100%)</td>
<td>520 (100%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Voclosporin 1.5 mg/kg</td>
<td>40 516</td>
<td>40 (100%)</td>
<td>516 (100%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Study</td>
<td>Treatment Group</td>
<td>Total N</td>
<td>HR&gt;45 bpm</td>
<td>HR&lt;=45 bpm</td>
</tr>
<tr>
<td>-------------</td>
<td>-----------------</td>
<td>---------</td>
<td>-----------</td>
<td>-----------</td>
</tr>
<tr>
<td></td>
<td>Subj. #</td>
<td>Obs. #</td>
<td>Subj. #</td>
<td>Obs. #</td>
</tr>
<tr>
<td>Voclosporin 3.0 mg/kg</td>
<td>40</td>
<td>513</td>
<td>39 (97.5%)</td>
<td>508 (99.0%)</td>
</tr>
<tr>
<td>Voclosporin 4.5 mg/kg</td>
<td>40</td>
<td>515</td>
<td>40 (100%)</td>
<td>515 (100%)</td>
</tr>
<tr>
<td>Placebo</td>
<td>40</td>
<td>513</td>
<td>40 (100%)</td>
<td>513 (100%)</td>
</tr>
<tr>
<td>ISA05-03 Baseline</td>
<td>54</td>
<td>103</td>
<td>52 (96.3%)</td>
<td>101 (98.1%)</td>
</tr>
<tr>
<td>Voclosporin 0.3 mg/kg BID</td>
<td>42</td>
<td>700</td>
<td>39 (92.9%)</td>
<td>696 (99.4%)</td>
</tr>
<tr>
<td>Voclosporin 0.5 mg/kg BID</td>
<td>41</td>
<td>695</td>
<td>39 (95.1%)</td>
<td>690 (99.3%)</td>
</tr>
<tr>
<td>Voclosporin 1.5 mg/kg BID</td>
<td>42</td>
<td>710</td>
<td>39 (92.9%)</td>
<td>696 (98.0%)</td>
</tr>
<tr>
<td>Placebo</td>
<td>43</td>
<td>722</td>
<td>40 (93.0%)</td>
<td>711 (98.5%)</td>
</tr>
</tbody>
</table>

4.4.3 PR
No subjects had PR >220 msec and >25% increase over baseline in the 3 studies.

4.4.4 QRS
No subjects experienced postdose QRS >120 msec and increase >25% over baseline in the 3 studies.

4.5 EXPOSURE-RESPONSE (E-R) ANALYSIS
Exposure-response analysis was conducted using all subjects with baseline and at least one post-baseline ECG with time-matched PK in study ISA03-11 and ISA05-03 separately. Prior to evaluating the relationship between drug-concentration and QTc using a linear model, the three key assumptions of the model were evaluated using exploratory analysis: 1) absence of significant changes in heart rate (more than a 10 beats/min increase or decrease in mean HR); 2) delay between plasma concentration and ΔQTc; and 3) presence of non-linear relationship.

4.5.1 Study ISA03-11
Figure 5 shows the time-course of ΔΔHR, ΔΔQTc, and systemic exposure of voclosporin and its metabolites after a single dose ranging from 0.5–4.5 mg/kg doses.

After oral administration the concentration of trans-voclosporin is approximately 30-fold higher than cis-voclosporin. Cis-voclosporin and the measurable metabolites showed similarity in Tmax and overall PK profile as compared with trans-voclosporin. Trans-voclosporin is used as the only exposure covariate in subsequent analyses.

The Tmax of HR increase coincides with that of maximum trans-voclosporin exposure. Linear mixed effect modeling suggests a significant relationship between trans-voclosporin concentration and ΔHR. The predicted ΔΔHR at the geometric mean Cmax of trans-voclosporin at the 4.5 mg/kg single dose is 12.4 bpm (90% CI: 10.6–14.1 bpm) (data not show). Because the maximum effect at the highest tested dose was slightly above 10 bpm, it was concluded that using QTcF as the primary endpoint is acceptable.
There is a clear, dose-dependent increase in QTcF, however, the time to maximum QTcF increase is approximately 4 hours after Tmax of voclosporin exposure.

**Figure 5: Time course of drug concentration, HR, and QTc in study ISA03-11.**

The White Paper model was applied despite of the apparent delayed effect. The predictions are provided in Table 10. The predictions are considerably lower than the maximum effect as observed at the high dose levels.

**Table 10: Predictions from concentration-QTc model (ISA03-11)**

<table>
<thead>
<tr>
<th>Actual Treatment</th>
<th>Trans Voclosporin (ng/mL)</th>
<th>ΔΔQTcF (msec)</th>
<th>90.0% CI (msec)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Voclosporin 0.5 mg/kg</td>
<td>107.7</td>
<td>6.7</td>
<td>(5.1 to 8.3)</td>
</tr>
<tr>
<td>Voclosporin 1.5 mg/kg</td>
<td>534.2</td>
<td>12.0</td>
<td>(10.3 to 13.7)</td>
</tr>
<tr>
<td>Voclosporin 3.0 mg/kg</td>
<td>711.3</td>
<td>14.2</td>
<td>(12.4 to 16.0)</td>
</tr>
<tr>
<td>Voclosporin 4.5 mg/kg</td>
<td>1,094.6</td>
<td>19.0</td>
<td>(16.7 to 21.2)</td>
</tr>
</tbody>
</table>

**4.5.2 Study ISA05-03**

Due to limitations in the study design, only a small number of subjects provided PK/ECG data on Day 1 (n=10 in each voclosporin treatment group; n=13 in placebo treatment). Figure 6 shows the time-course of ΔΔHR, ΔΔQTc, and systemic exposure of voclosporin after a single dose ranging from 0.3-1.5 mg/kg doses. In this study the exposure to trans-voclosporin were approximately 20-fold that of cis-voclosporin throughout the sampling period. There did not appear to be significant effect on HR at the studied dose levels. There did not appear to be significant delay in the time to maximum exposure and QTc.
changes at the two lower dose levels, but there was an increase in QTc between 3-6 hours postdose in the highest dose group which was suggestive of PK/PD hysteresis as the Tmax of voclosporin concentrations were <2.5 hours in all three dose groups.

**Figure 6: Time course of drug concentration, HR, and QTc in ISA05 03 Day 1.**

The scatter plot of ΔQTcF vs trans-voclosporin concentration supports the use of a linear model (Figure 7 Left). When the linear mixed effect model was applied (ΔQTcF ~ 1 + CONC + treatment + centered baseline + time, random effect on the intercept only), the goodness-of-fit plot is shown in Figure 7 Right and the predictions are show in Table 11. While Day 1 data provided a reasonably large exposure margin (approximately 4-fold of therapeutic Cmax at steady state), due to the observed trend for PK/PD hysteresis, we are reluctant to conclude a lack of clinically relevant effect in the studied exposure range.

**Figure 7. Assessment of linearity (Left) and goodness-of-fit plot (Right) for QTc.**

<table>
<thead>
<tr>
<th>Actual Treatment</th>
<th>Trans Voclosporin (ng/mL)</th>
<th>ΔΔQTcF (msec)</th>
<th>90.0% CI (msec)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Voclosporin 0.3 mg/kg</td>
<td>68.9</td>
<td>4.4</td>
<td>(0.1 to 8.7)</td>
</tr>
<tr>
<td>Voclosporin 0.5 mg/kg</td>
<td>129.4</td>
<td>4.5</td>
<td>(0.2 to 8.8)</td>
</tr>
</tbody>
</table>

Reference ID: 4674120
<table>
<thead>
<tr>
<th>Actual Treatment</th>
<th>Trans Voclosporin (ng/mL)</th>
<th>ΔΔQTcF (msec)</th>
<th>90.0% CI (msec)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Voclosporin 1.5 mg/kg</td>
<td>562.7</td>
<td>5.7</td>
<td>(0.2 to 11.3)</td>
</tr>
</tbody>
</table>

On Day 7, 36-41 subjects provided PK/ECG in the placebo and voclosporin treatments. Predose baseline was collected in Period 1 only. PK profiles and the time course of QTc and HR are shown in Figure 8. There does not appear to be a clear trend for dose dependent change in HR or QTc interval. While the time course of QTc profiles are relatively flat at the two lower dose levels, there appears to be a dip in QTc profile shortly after dosing and an increase at 4-6 hours postdose, in the 1.5 mg/kg BID dose group.

**Figure 8: Time course of drug concentration, HR, and QTc in ISA05 03 Day 7.**

An assessment of linearity generally supports the use of a linear model (Figure 9 Left). When the scientific White paper was applied, the goodness-of-fit plot was shown in Figure 9 (Right). The model does not suggest a positive exposure-response relationship between QTc changes and trans-voclosporin concentration in the studied range. Due to limitations in baseline collection, the E-R analysis results should be interpreted with caution. Geometric mean Cmax at the 1.5 mg/kg BID dose was 739.3 ng/mL.

**Figure 9: Assessment of linearity (Left) and goodness-of-fit plot (Right) for QTc.**
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/s/

NAN ZHENG
09/22/2020 01:30:07 PM

JANELL E CHEN
09/22/2020 01:30:59 PM

DALONG HUANG
09/22/2020 01:52:00 PM

MICHAEL Y LI
09/22/2020 01:53:34 PM

CHRISTINE E GARNETT
09/22/2020 02:03:52 PM