CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

213716Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

IND 114577

MEETING MINUTES

Aurinia Pharmaceuticals Inc.
8689 Ashbury Court
Blaine, WA 98230

Attention: Rashieda Gluck
US Representative

Dear Ms. Gluck:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for voclosporin.

We also refer to the meeting between representatives of your firm and the FDA on February 25, 2020. The purpose of the meeting was to discuss the planned NDA submission for voclosporin for the indication of lupus nephritis.

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me, at (301) 796-1648.

Sincerely,

{See appended electronic signature page}

Phuong Nina Ton, PharmD
Senior Regulatory Project Manager
Division of Pulmonology, Allergy,
and Critical Care
Office of Immunology and Inflammation
Center for Drug Evaluation and Research

Enclosure:
- Meeting Minutes

U.S. FOOD & DRUG ADMINISTRATION

MEMORANDUM OF MEETING MINUTES

Meeting Type: B
Meeting Category: Pre-NDA

Meeting Date and Time: February 25, 2020, 9:30 – 10:30 AM EST
Meeting Location: White Oak Building 22, Conference Room 1419

Application Number: IND 114577
Product Name: Voclosporin
Indication: Lupus nephritis
Sponsor Name: Aurinia Pharmaceuticals Inc.

Meeting Chair: Sally Seymour, MD
Meeting Recorder: Nina Ton, PharmD

FDA ATTENDEES

Sally Seymour, MD, Division Director, Division Director, Division of Pulmonology, Allergy, and Critical Care (DPACC)
Nikolay Nikolov, MD, Acting Division Director, Division of Rheumatology and Transplant Medicine (DRTM)
Rachel Glaser, MD, Clinical Team Leader, DRTM
Keith Hull, MD, PhD, Clinical Reviewer, DRTM
Aliza Thompson, MD, Deputy Director, Division of Cardiology and Nephrology (DCN)
Carol Galvis, PhD, Pharmacology/Toxicology Team Leader, DPACC
Steve Leshin, PhD, Pharmacology/Toxicology Reviewer, DPACC
Rebecca Rothwell, PhD, Team Leader, Division of Biometrics III (DBIII), Office of Biostatistics (OB)
Cesar Torres, PhD, Biostatistics Reviewer, DBIII, OB
Jianmeng Chen, PhD, Acting Team Leader, Division of Clinical Pharmacology II (DCPII), Office of Clinical Pharmacology (OCP)
Ping Ji, PhD, Clinical Pharmacology Reviewer, DCPII, OCP
Priya Brunsdon, PhD, Clinical Pharmacology Reviewer, DCPII, OCP
Xinyuan Zhang, PhD, Reviewer, Division of Pharmacometrics, OCP
Craig Bertha, PhD, CMC Lead, Division of New Drug Products II Branch IV, Office of New Drug Products (ONDP), Office of Pharmaceutical Quality (OPQ)
Saharat Patanavanich, PharmD, BCACP, Safety Regulatory Project Manager, Office of Surveillance and Epidemiology (OSE)
Marriam Nasserjah, Pharmacy Student, Virginia Commonwealth University, School of Pharmacy
Nina Ton, PharmD, Senior Regulatory Project Manager, DPACC

SPONSOR ATTENDEES
Jeremy Hanman, Director, Regulatory Affairs
Laura, Lisk, Head, Clinical Development
Lawrence D. Mandt, SVP, Quality & Regulatory Affairs
Matt Truman, Statistician
Neil Solomons, Chief Medical Officer
Rashieda Gluck, SVP, Clinical Operations
Robert Huizinga, EVP, Corporate Development
Sue Evans, VP, Regulatory Affairs

1. BACKGROUND

Aurinia submitted a Type B meeting request dated November 8, 2019, to discuss the planned NDA submission for voclosporin for the indication of lupus nephritis. The Division provided preliminary comments to the Sponsor's questions in the briefing package via electronic correspondence dated February 20, 2020. Aurinia communicated to the Division via email dated February 24, 2020, that the sponsor requested to discuss Questions 2, 3, 4, 5, 6, 8, and two wrap-up questions. The Sponsor also provided a response document and the responses are incorporated under the corresponding FDA preliminary comment. The Sponsor's questions from the briefing package received January 21, 2020, and the responses are provided below in *italics*, the FDA's responses are in normal font, and the meeting discussion is in **bold**.

2. DISCUSSION

Question 1
Does FDA agree that the efficacy data are sufficient to support the filing for the proposed indication: "Voclosporin is indicated for the treatment of patients with lupus nephritis"?

Response to Question 1
Your overall approach appears to be reasonable to support a submission. However, we will need to review your submitted data and overall package at the time of submission to determine filing status.

Meeting Discussion
This question was not discussed.

Question 2
Does the Division agree that the results of the AURORA 1 trial are consistent with the results of AURA-LV and are clinically meaningful?

Response to Question 2
As presented in your briefing package, the efficacy data appear to demonstrate a benefit to patients with lupus nephritis; however, we note that this is based on limited

information and a final determination cannot be made until after a review of the data has been completed. In your NDA submission, include a scientific justification supporting the use of (b) (4), for your primary endpoint analysis. In addition, we note that you have not included a disposition table to understand the amount of study withdrawals and treatment discontinuations in each study. This will be important for interpreting both the efficacy and safety results in your submission.

Aurinia Response

AURORA 1 and AURA-LV Primary Efficacy Parameter

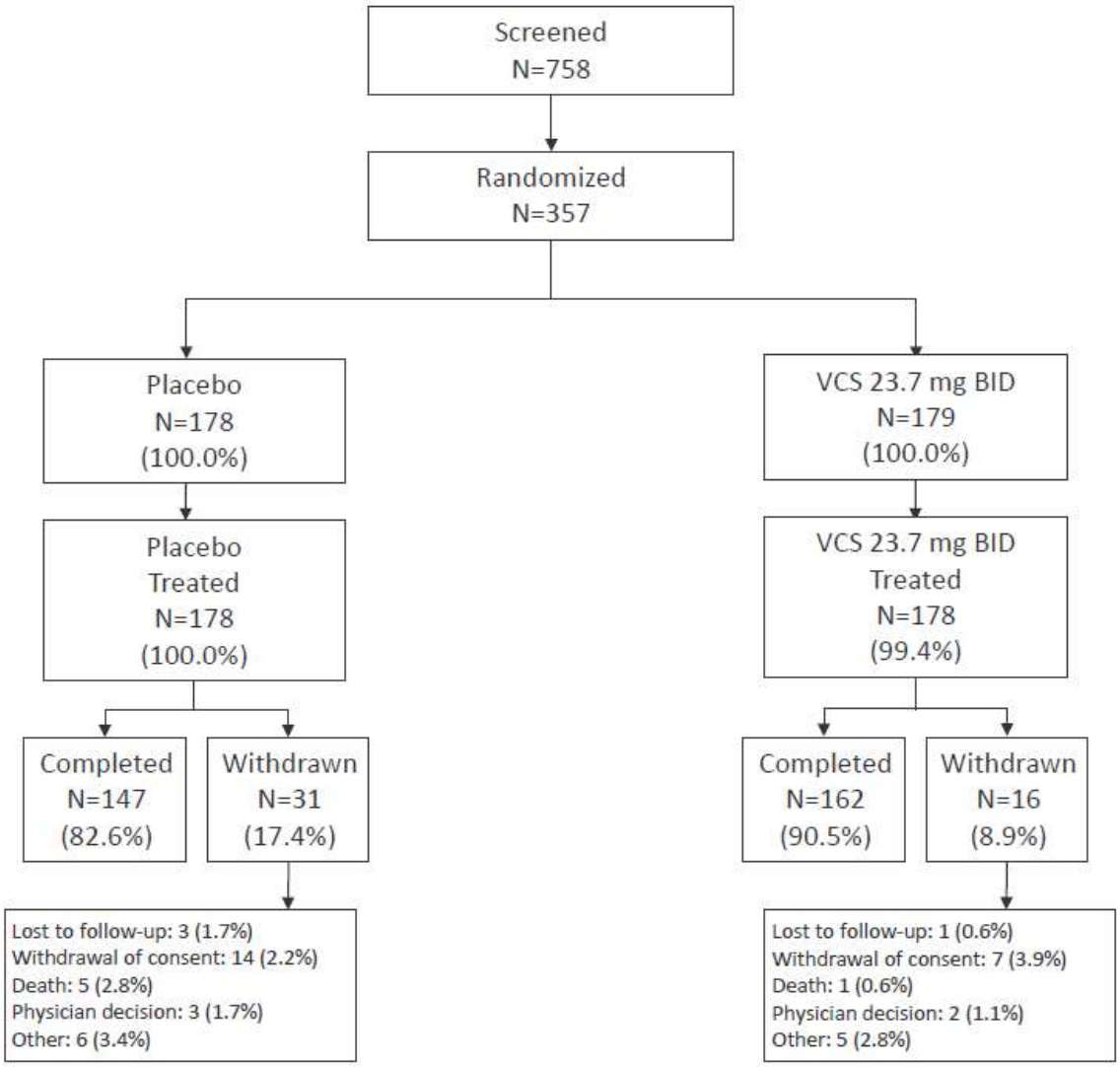
(b) (4)

Scientific Justification

(b) (4)

– (b) (4)

Subject Disposition – AURORA 1



Meeting Discussion

Aurinia discussed the AURORA 1 and AURA-LV primary efficacy endpoint and provided the scientific justification above. Aurinia added that 90.5% AURORA 1 patients treated with voclosporin completed the study, as shown in the disposition figure above. The FDA commented that there is no regulatory precedent for an approval for lupus nephritis and advised the Sponsor to include their scientific justification (b) (4) **in the NDA.**

Question 3
Does FDA agree that the safety database is adequate to support a new drug application for this proposed indication?

Response to Question 3
In general, the proposed safety database appears to be reasonable in the context of the proposed indication; however, additional safety data may be needed in the event a safety signal is identified during the review process. Additionally, since calcineurin-inhibitors are known to have long-term renal toxicity, you will need to provide a scientific justification, relevant analyses, and a plan to address the nephrotoxicity and the benefit-risk of long-term treatment with voclosporin in patients with lupus nephritis, particularly [redacted] (b) (4) as the primary basis to support approval.

Aurinia Response

AURORA 2 Overview:

- *2 year double-blind extension study to assess long-term safety and tolerability of voclosporin compared with placebo*
- *216 subjects (116 voclosporin, 100 placebo) voluntarily rolled over from AURORA 1*
  - *46 subjects completed through 2 years to be included in NDA*
  - *Estimated 135 subjects completed through 2 years to be included in Day 90 update*
- *Subjects attend visits every 3 months with the following assessments:*
  - *UPCR*
  - *eGFR*
  - *AEs & Safety Labs*
  - *SF-36, SELENA-SLEDAI at selected visits*
- *Final data available at end of 2021*

Long-term Assessment of Nephrotoxicity:

- *Continue to monitor eGFR in the AURORA 2 safety extension study. Data from the interim analysis will be presented within the NDA and updated in the subsequent safety update*
- *Including:*
  - *Detailed analyses on renal function will be presented within the NDA for the pooled LN population*

- *Assessment of slope of changes in eGFR (raw and corrected), to differentiate acute (0 to 3 months) and chronic (>3 months from start of treatment) changes over time (Aliza Thompson, FDA Viewpoint, AJKD, 2020)*

- *Adjudication of renal and cardiovascular events by independent and blinded committee to be included within the NDA (as requested at EoP2 meeting)*

- *Ongoing assessment of biomarkers for renal damage*

Meeting Discussion

Aurinia presented the proposal for the safety database as summarized above. The FDA noted that just over 200 patients entered into AURORA 2 and asked about the remaining patients from AURORA 1 who were not included in this continuation study. The Sponsor explained that not all sites were located in countries that approved the continuation of patients into AURORA 2 in time, resulting in the loss of some patients from AURORA 1. Furthermore, some patients did not complete AURORA 1 or did not provide consent and therefore, were not entered into AURORA 2. The FDA noted that this results in a missing data problem for AURORA 2, as a non-randomized subset of subjects will be studied. Thus, while the Agency will consider the totality of the evidence in its evaluation of the safety profile, this evaluation will primarily consider the data from the AURORA 1 and AURA-LV studies. The FDA asked for the rationale for the countries in question not approving AURORA 2. Aurinia replied that AURORA 1 and AURORA 2 are two different studies and some countries have a longer process to approve the protocol causing a delay and the loss of some eligible patients.

The Sponsor outlined their proposed approach to assess for potential nephrotoxicity during longer-term administration. The FDA asked whether kidney biopsies were obtained in any patients during the trials, noting that such biopsies might provide insight into the risk of CNI nephrotoxicity. The Sponsor responded that some patients had kidney biopsies performed as part of an optional kidney biopsy sub-study in AURORA 2 and that some patients also had biopsies performed "for cause." The FDA indicated that it would be important to assess the biopsies obtained in both settings for findings suggestive of CNI nephrotoxicity.

The FDA asked whether renal function was assessed off of treatment at the end of the study. Aurinia confirmed that such an assessment was made in AURA-LV and stated that all AURORA 2 patients will have a follow-up visit after drug discontinuation at the end of the study. Given voclosporin's pharmacodynamic effect on renal function, the FDA noted that such off-treatment data might aid in interpretation of the renal function data and could potentially provide reassurance that voclosporin was not causing chronic progressive renal disease.

With regard to the proposed analyses to assess for possible nephrotoxicity, the FDA observed that it may be challenging to interpret some of the analyses proposed by the Sponsor since only a subset of subjects who were randomized into AURORA 1 were enrolled in AURORA 2.

Post-meeting Note

In your NDA submission, include a plan to obtain additional data to better characterize the risk of CNI nephrotoxicity, and specifically the potential to cause chronic progressive renal disease with long term use.

Question 4

Aurinia intends to present the following safety analyses to compare and contrast the safety profile of voclosporin relative to the known adverse effects of the existing drugs in the CNI class. Does the Division have any comments?

Response to Question 4

Your proposal to include data from the AURORA-1 and AURA-LV studies, individually and combined, as well as new data from the AURORA-2 study appears reasonable. You may include supportive safety data from the voclosporin studies conducted for renal transplant, plaque psoriasis and non-infectious uveitis studies separately from the lupus nephritis data. Labeling statements for voclosporin will be limited to the data that support the safe and effective use of voclosporin. (b) (4) However, including relevant CNI class effects in voclosporin labeling will be warranted, even if they were not observed in the voclosporin clinical program.

Aurinia Response

- *Within the NDA, Aurinia will be submitting non-clinical and clinical evidence* (b) (4)

(b) (4)

(b) (4)

Meeting Discussion
Aurinia discussed the data (b) (4) **The FDA noted that it was premature to comment without reviewing the data; however, the size of the safety database and the duration of exposure is limited** (b) (4)

Question 5
Does the Division agree that the drug-drug interaction studies are adequate to support the new drug application?

Response to Question 5
We acknowledge that you are currently evaluating the potential of voclosporin as a substrate for organic-anion-transporting polypeptide (OATP)1B1 and OATP1B3 in vitro. If voclosporin is a clinically-relevant OATP substrate, you may also need to consider the effect of OATP polymorphisms on the PK of voclosporin and your DDI assessment. Regarding the assessment of voclosporin as an OATP1B1/3 inhibitor, you indicated that 'The predicted ratio of victim drug's AUC in the presence and absence of voclosporin has been estimated to be (b) (4) and (b) (4) for OAT1B1 and OAT1B3, respectively' in your meeting package.

Please clarify if the ratios of (b) (4) and (b) (4) were the R values estimated based on $_{lin,max}$, IC_{50}, and $f_{u,p}$. Additionally, provide details on the calculation.

Further, we note that you did not include the in vitro assessment of voclosporin as a potential BCRP substrate in the background document. Address this in the NDA submission. The adequacy of the data to support the new drug application will be a review issue. Refer to the FDA Guidance for Industry *In Vitro Drug Interaction Studies — Cytochrome P450 Enzyme- and Transporter-Mediated Drug Interactions* at https://www.fda.gov/media/134582/download.

We acknowledge you plan to use PBPK modeling and simulation to evaluate the effects of moderate and weak CYP3A inhibitors, and moderate CYP3A inducers on the PK of voclosporin, and to evaluate the effect of voclosporin on the PK of OATP1B substrates, rosuvastatin and pravastatin. We have additional comments regarding your PBPK analyses for consideration. The adequacy of PBPK analyses for the intended uses will be determined during the new drug application review cycle.

a. Your voclosporin substrate PBPK model should be able to capture all available PK data following single- and multiple- dose administration. For example, the model should capture the greater than dose proportional increase in AUC0-12 and Cmax in the dose range of 0.25-1.0 mg/kg BID with appropriate mechanisms integrated in the model.

b. In order to evaluate the relative impact of CYP3A and P-gp inhibition on the PK of voclosporin, the ketoconazole and verapamil models should be validated using DDI studies with sensitive CYP3A substrate and P-gp substrates.

c. Rosuvastatin and pravastatin as OATP1B1/3 substrate models should be validated with available PK, pharmacogenetic studies, and relevant DDI studies. Pravastatin is also a substrate of OAT3. Clarify, in the PBPK analyses report, if voclosporin may potentially interact with OAT3.

Also refer to FDA guidance *Physiologically Based Pharmacokinetic Analyses — Format and Content* at https://www.fda.gov/media/101469/download.

Additional Clinical Pharmacology Comment

a. If there are significant differences between the clinical trial formulations and the final to-be-marketed formulation, the two formulations must be adequately bridged.

Aurinia Response

1. *Calculations on predicted ratio of victim drug's AUC in the presence and absence of voclosporin were based on lin,max, IC50and fu,pas described in the FDA Guidance (2020) "Clinical Drug Interaction Studies —Cytochrome P450 Enzyme-and Transporter-Mediated Drug Interactions". Details on the calculations will be provided within the NDA.*

2. *In vitro assessment of voclosporin as a potential BCRP substrate will be addressed within the NDA*

3. *PBPK Report to be presented within the NDA:*

   – *The voclosporin substrate PBPK model will capture the single dose (0.25 –4.5 mg/kg) and multiple dose (0.25 to 1.5 mg/kg BID) PK data, including the greater than dose proportional increase in AUC0-12and Cmax*

   – *The validation of the ketoconazole and verapamil models will be discussed*

   – *The validation of the rosuvastatin and pravastatin as OATP1B1/3 substrate models will be discussed*

– *The effect on OAT3 will be assessed*

Meeting Discussion
Aurinia discussed the proposal provided above and the FDA considered this reasonable but also noted the Sponsor could consider submitting a justification for why the OATP1B1/3-mediated DDI potential is not clinically relevant instead of using the PBPK approach. The FDA also referred the Sponsor to the FDA guidance for the format of the PBPK model and requested that the modeling files are submitted with the NDA, if the Sponsor chooses to use the PBPK approach.

Question 6
Does the Division agree with the format and content of the planned datasets used to support the efficacy and safety analyses?

Response to Question 6
Your proposed plan appears to be reasonable. To facilitate the review, we prefer that, for all datasets, the define files be provided in XML format, in place of or in addition to the proposed PDF format.

Aurinia Response
- *Aurinia intends to submit define files in XML format for AURA-LV, AUR-DDI, AURORA 1 and AURORA 2 studies*

- *For legacy studies conducted prior to 2016* (b) (4) *Aurinia intends to submit define files in PDF format*

Meeting Discussion
The FDA found the Sponsor's response reasonable and asked about the missing files for AURA-LV referenced in the meeting package. Aurinia noted that they only have non-executable in-text files for this study and the FDA confirmed that it was reasonable.

Question 7
Does the Division have any comments or guidance on how to most effectively deliver the SAS programs used to generate datasets and analyses from AURORA 1 (non-executable) and the integrated analysis (executable)?

Response to Question 7
Include in your submission the procedures (with full documentation of the approach) for any post-hoc exploratory analyses for which results are included in the submission.

Submit the programs and macros for obtaining the following in individual text files, in addition to or in place of any *.sas* files:

a. Efficacy, disposition, and safety results from prespecified procedures.

b. Results from the aforementioned post-hoc exploratory analyses.

To ensure an efficient review, these files should be provided for both the AURORA 1 study and the AURA-LV study. The documentation should be sufficiently detailed to facilitate replication and validation of the results.

Meeting Discussion
This question was not discussed.

Question 8
Does the Division agree with the proposed Rolling Review schedule for the Aurinia NDA submission?

Response to Question 8
Submit your request for a rolling review to IND 114577 under a separate cover with justification for this request along with timelines proposed in this submission.

Aurinia Response
- *Aurinia has submitted a request for rolling review to the IND 114,577 as S0140 on 20 February 2020*

- *The schedule for rolling review as presented in the pre-NDA Briefing Document was submitted to the IND*

- *Does the Division agree with the proposed rolling review schedule?*

Contents of Rolling Review Submissions

Date of Rolling Review Submission	Contents of Submission
March 2020	**Module 1 Administrative Information:** **Module 2 Summaries:** • 2.4 Nonclinical overview • 2.6 Nonclinical written and tabulated summaries **Module 4 Nonclinical Study Reports:**
April 2020	**Module 3 Quality:**
June 2020	**Module 1 Administrative Information:** **Module 2 Summaries:** • 2.2 Introduction to Summary • 2.3 Quality overall summary • 2.5 Clinical Overview • 2.7 Clinical Summary **Module 3 Quality:** • Sections updated with additional stability data (e.g., 3.2.P.8.1, 3.2.P.8.3, and 3.2.P.5.6) **Module 5 Clinical Study Reports:**

Meeting Discussion

Aurinia discussed the proposed rolling review schedule above and noted that a request for rolling review was submitted to the IND on February 20, 2020. The FDA did not have specific comments on the proposal, but stated that the Division will review the request to make a final determination. The Sponsor informed the FDA that a user fee waiver request was submitted and when both the user free waiver and rolling review are granted, the non-clinical module will be submitted.

Question 9

Does the Division agree that the voclosporin summary data presented support Aurinia's intent to request Priority Review?

Response to Question 9

The decision to grant Priority Review will be made at the time of filing for your application.

Meeting Discussion

This question was not discussed.

Question 10

Assuming Priority Review and Rolling Review are acceptable, does the Division have any comments regarding the timing, format and content of Aurinia's planned Day 120 Safety Update?

Response to Question 10
Provided that your application is granted a Priority Review, the Safety Update is to be submitted at Day 90. We remind you that your application should be complete upon submission, meaning that all efficacy and safety data that you consider necessary for approval should be included with the initial submission. In your Safety Update, provide cumulative and incremental datasets for subjects in AURORA2.

Meeting Discussion
This question was not discussed.

Question 11
Does the Division agree that the safety risks concerning the use of voclosporin have been adequately addressed such that the complete NDA can be submitted without a proposed REMS?

Response to Question 11
A determination on the need for a REMS will be made during the review of your application.

Meeting Discussion
This question was not discussed.

Question 12
Reference is made to IND 114,577 S0023 (dated 21 July 2015) and FDA's response (dated 15 December 2015) conditionally accepting the proprietary name (b) (4) *Aurinia would like to inform the Division of their intention to no longer proceed with* (b) (4) *and will be submitting a request for a new proprietary name* (b) (4) *at the time of the initial NDA rolling submission in March 2020.*

As outlined in FDA Guidance "Contents of a Complete Submission for the Evaluation of Proprietary Names" the PDUFA review timeline is 90 days from the date of a complete submission for a proposed proprietary name. Does the Division agree that the 90-day review timeline for the new proprietary name will begin in March 2020?

Response to Question 12
Yes, we agree that the 90-day review timeline for the proposed proprietary name will begin with a complete submission for a Request for Proprietary Name Review under the NDA. Please note that the conditionally acceptable name, (b) (4) must be withdrawn and a new Request for Proprietary Name Review for the proposed proprietary name (b) (4) must be submitted under the NDA.

If you require information on submitting requests for proprietary name review or PDUFA performance goals associated with proprietary name reviews, we refer you to the following:

- Guidance for Industry Contents of a Complete Submission for the Evaluation of Proprietary Names (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf)

- PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2018 through 2022, (https://www.fda.gov/downloads/forindustry/userfees/prescriptiondruguserfee/ucm511438.pdf

Meeting Discussion
This question was not discussed.

Question 13
Reference is made to the End of Phase 2 Type B Meeting Minutes (dated 06 December 2016) and to the 24 July 2017 Type C Meeting Minutes (dated 02 September 2017), where the Division stated an Advisory Committee could be convened to discuss components of the AURORA trials.

Can the Division comment on any preliminary plans for an Advisory Committee meeting on the voclosporin program for the proposed indication of lupus nephritis?

Response to Question 13
A determination on the need for an Advisory Committee meeting will be made during the review of your application.

Meeting Discussion
This question was not discussed.

Wrap-up Question 1
Should the initial NDA rolling submission be submitted to the Division of Rheumatology & Transplant Medicine (DRTM)?

Meeting Discussion
The FDA noted that the reorganization has not been finalized and Aurinia should follow up with the FDA Project Manager.

Wrap-up Question 2
Does the Division know whether the FDA Review Team for the NDA will remain the same as currently?

Meeting Discussion
The FDA noted that the review team assignment will depend on workload at the time of the NDA submission. Many of the team members are expected to be the

same; however, the Agency noted that the signatory may change due to the ongoing reorganization.

3. ADDITIONAL INFORMATION

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

- The content of a complete application and the Sponsor's proposed rolling review schedule were discussed.

- All applications are expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities included or referenced in the application.

- Major components of the application are expected to be submitted with the original application and are not subject to agreement for late submission. You stated you intend to submit a complete application and therefore, there are no agreements for late submission of application components.

In addition, we note that a chemistry pre-submission meeting was held on October 1, 2019. We refer you to the minutes of that meeting for any additional agreements that may have been reached.

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (iPSP) within 60 days of an End-of-Phase-2 (EOP2) meeting. In the absence of an EOP2 meeting, refer to the draft guidance below. The iPSP must contain an outline of the pediatric study or studies that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. The iPSP should be submitted in PDF and Word format. Failure to include an Agreed iPSP with a marketing application could result in a refuse to file action.

For additional guidance on the timing, content, and submission of the iPSP, including an iPSP Template, please refer to the draft guidance for industry *Pediatric Study Plans:*

Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans.[1] In addition, you may contact the Division of Pediatric and Maternal Health at 301-796-2200 or email Pedsdrugs@fda.hhs.gov. For further guidance on pediatric product development, please refer to FDA.gov.[2]

PRESCRIBING INFORMATION

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57 including the Pregnancy and Lactation Labeling Rule (PLLR) (for applications submitted on or after June 30, 2015). As you develop your proposed PI, we encourage you to review the labeling review resources on the PLR Requirements for Prescribing Information[3] and Pregnancy and Lactation Labeling Final Rule[4] websites, which include:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products.
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information related to pregnancy, lactation, and females and males of reproductive potential.
- Regulations and related guidance documents.
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) – a checklist of important format items from labeling regulations and guidances.
- FDA's established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

Pursuant to the PLLR, you should include the following information with your application to support the changes in the Pregnancy, Lactation, and Females and Males of Reproductive Potential subsections of labeling. The application should include a review and summary of the available published literature regarding the drug's use in pregnant

[1] When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.
[2] https://www.fda.gov/drugs/development-resources/pediatric-and-maternal-health-product-development
[3] https://www.fda.gov/drugs/laws-acts-and-rules/plr-requirements-prescribing-information
[4] https://www.fda.gov/drugs/labeling/pregnancy-and-lactation-labeling-drugs-final-rule

and lactating women and the effects of the drug on male and female fertility (include search parameters and a copy of each reference publication), a cumulative review and summary of relevant cases reported in your pharmacovigilance database (from the time of product development to present), a summary of drug utilization rates amongst females of reproductive potential (e.g., aged 15 to 44 years) calculated cumulatively since initial approval, and an interim report of an ongoing pregnancy registry or a final report on a closed pregnancy registry. If you believe the information is not applicable, provide justification. Otherwise, this information should be located in Module 1. Refer to the draft guidance for industry *Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format*.

Prior to submission of your proposed PI, use the SRPI checklist to ensure conformance with the format items in regulations and guidances.

MANUFACTURING FACILITIES

To facilitate our inspectional process, we request that you clearly identify *in a single location*, either on the Form FDA 356h, or an attachment to the form, all manufacturing facilities associated with your application. Include the full corporate name of the facility and address where the manufacturing function is performed, with the FEI number, and specific manufacturing responsibilities for each facility.

Also provide the name and title of an onsite contact person, including their phone number, fax number, and email address. Provide a brief description of the manufacturing operation conducted at each facility, including the type of testing and DMF number (if applicable). Each facility should be ready for GMP inspection at the time of submission.

Consider using a table similar to the one below as an attachment to Form FDA 356h. Indicate under Establishment Information on page 1 of Form FDA 356h that the information is provided in the attachment titled, “Product name, NDA/BLA 012345, Establishment Information for Form 356h.”

Site Name	Site Address	Federal Establishment Indicator (FEI) or Registration Number (CFN)	Drug Master File Number (if applicable)	Manufacturing Step(s) or Type of Testing [Establishment function]
(1)				
(2)				

Corresponding names and titles of onsite contact:

Site Name	Site Address	Onsite Contact (Person, Title)	Phone and Fax number	Email address
(1)				
(2)				

OFFICE OF SCIENTIFIC INVESTIGATIONS (OSI) REQUESTS

The Office of Scientific Investigations (OSI) requests that the items described in the draft guidance for industry *Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions* (February 2018) and the associated *Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications* be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA ORA investigators who conduct those inspections. This information is requested for all major trials used to support safety and efficacy in the application (i.e., phase 2/3 pivotal trials). Please note that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe location or provide a link to the requested information.

Please refer to the draft guidance for industry *Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions* (February 2018) and the associated *Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications*.[5]

4. ISSUES REQUIRING FURTHER DISCUSSION

There were no issues requiring further discussion.

5. ACTION ITEMS

There were no action items.

6. ATTACHMENTS AND HANDOUTS

A copy of the slides provided by the Sponsor is attached.

[5] https://www.fda.gov/media/85061/download

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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/

PHUONG N TON
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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 114577

MEETING MINUTES

Aurinia Pharmaceuticals Inc.
640 100th Ave SE
Bellevue, WA 98004

Attention: Rashieda Gluck
Vice President, Quality and Regulatory Affairs

Dear Ms. Gluck:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for voclosporin.

We also refer to the meeting between representatives of your firm and the FDA on, October 25, 2016. The purpose of the meeting was to discuss the phase 2 and 3 development plans for voclosporin.

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me, at (240) 402-3720.

Sincerely,

{See appended electronic signature page}

Laura Musse, R.N., M.S., C.R.N.P.
Regulatory Health Project Manager
Division of Pulmonary, Allergy, and Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: B
Meeting Category: End of Phase 2

Meeting Date and Time: Tuesday, October 25, 2016, 3:00 pm-4:00 pm
Meeting Location: White Oak Building 22, Conference Room: 1201

Application Number: 114577
Product Name: voclosporin
Indication: lupus nephritis
Sponsor/Applicant Name: Aurinia Pharmaceuticals Inc.

FDA ATTENDEES

Badrul A. Chowdhury, M.D., Ph.D., Director, Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)
Sarah Yim, M.D., Supervisory Associate Director, DPARP
Gregory Levin, Ph.D., Statistical Team Leader, Division of Biometrics II (DBII)
Robert Abugov Ph.D., Statistical Reviewer, DBII
Anshu Marathe Ph.D., Clinical Pharmacology Team Leader, Division of Clinical Pharmacology II (DCPII)
Jianmeng Chen, Ph.D., Clinical Pharmacology Reviewer, DCPII
Carol Galvis, Ph.D., Acting Nonclinical Team Leader, DPARP
Lawrence Leshin, Ph.D., Nonclinical Reviewer, DPARP
Laura Musse, R.N., M.S. C.R.N.P., Regulatory Health Project Manager, DPARP

SPONSOR ATTENDEES

Sue Evans, Regulatory Manager
Rashieda Gluck, VP Clinical Operations
Robert Huizinga, VP Clinical Affairs
Lawrence Mandt, VP Quality & Regulatory Affairs
Neil Solomons, Chief Medical Officer

1.0 BACKGROUND

On August 3, 2016, Aurinia Pharmaceuticals Inc. requested an End of Phase 2 meeting to discuss the phase II results and the phase III development plans for their drug product, voclosporin. Voclosporin is indicated for the treatment of active lupus nephritis. The meeting was granted on Tuesday, October 25, 2016, and the Preliminary Comments were sent to Aurinia Pharmaceuticals Inc., on October 21, 2016.

2. DISCUSSION

General

Question 1: ***As previously discussed at the Pre-IND stage with the Agency, since the nonclinical safety profile has been adequately elucidated during the voclosporin development process*** (b) (4) ***, no additional nonclinical studies are planned. Does the Division agree with this approach?***

FDA Response to Question 1:
Yes, we agree that additional nonclinical studies are not necessary.

Discussion: No Discussion occurred. Sponsor acknowledged FDA's response.

Question 2: ***Does the Division agree with Aurinia's recommendation of dose selection to proceed into Phase 3?***

FDA Response to Question 2:
Based on preliminary 24-week data from AURA-LV, where 39.5 mg BID did not appear to be associated with additional efficacy, selecting the 23.7 mg BID dose for the proposed phase 3 study is reasonable. We do not agree with your proposed (b) (4). See response to Question 3e below.

Discussion:
Aurinia accepted FDA's recommendation (b) (4)

Question 3: ***With reference to the two Type C meeting requests (S0033: 01 February, 2016 and S0039: 06 May, 2016) and subsequent Division responses, Aurinia seeks to resolve and finalize the remaining outstanding topics within the Phase 3 clinical protocols:***

a. Primary endpoint

FDA Response to Question 3a:
Although we acknowledge the available data (b) (4) the goal of treatment is normalization or preservation of renal function, for which the most direct measure is eGFR. (b) (4)

(b) (4)

Therefore we do not agree that

(b) (4)

Based on the preliminary data from AURA-LV, your previous definition of complete response, which incorporates a criterion based on eGFR, would be feasible. Thus a similar endpoint to the primary endpoint from AURA-LV would be preferable for your Phase 3 study. Irrespective of what primary endpoint you select, if data for eGFR are not consistent with the primary endpoint results, and if improvement in proteinuria and renal parameters are not sustained over time, this would impact the overall risk-benefit assessment and may raise concerns about the clinical meaningfulness of the primary endpoint results.

Discussion:

As described in Sponsor's slide regarding 3a, Aurinia acknowledges FDA's recommendations and proposes a primary endpoint similar to AURA-LV, except that the UPCR criterion will be ≤0.7 mg/mg, but will include the eGFR criterion from AURA-LV, which is that subjects with both confirmed eGFR <60 mL/min/1.73m^2 and confirmed decrease from baseline in eGFR of >20% at Week 24 will not be considered as achieving renal response. Subjects who receive rescue medication for lupus nephritis or >10 mg prednisone for >3 consecutive days or >7 days total from Weeks 16-24 will not be considered as achieving renal response, as originally proposed and consistent with AURA-LV. FDA noted that there is not well established precedent for lupus nephritis studies, and that the exact UPCR cutoff would be at Aurinia's discretion. However, it is likely that public discussion (e.g., at Advisory Committee) would be warranted and Aurinia would have to be able to justify the UPCR criterion they have chosen.

b. Secondary endpoints

FDA Response to Question 3b:

The proposed secondary endpoints themselves are reasonable. See response to Question 3a regarding the importance of results for eGFR. Additionally, we recommend you include normalization of eGFR as a secondary endpoint.

Furthermore, we note that you do not propose to control the type 1 error probability across the analyses of primary and multiple secondary endpoints. We recommend that a plan is specified to control type 1 error probability across analyses of all endpoints to be considered for inclusion on the product label.

Discussion:

Aurinia expressed concerns about normalization of eGFR as a secondary endpoint because voclosporin has hemodynamic effects on the kidney that may make it difficult to demonstrate normalization of eGFR. FDA noted that

a normalization of eGFR endpoint would be in conjunction with the recommendation to obtain off-treatment eGFR measurements at the end of the controlled period, and that this was a recommendation from the Division of Cardio-Renal Products (DCRP) in order to provide clarity on the net renal impact. FDA also noted that additional analyses evaluating the slope of the change in eGFR over time might be helpful, given the sponsor's concerns. Aurinia expressed understanding and stated that they would take these recommendations under consideration.

c. Number of studies

Does the Division agree with the Sponsor's plan to conduct two (b) (4) *studies, and the statistical approach.*

FDA Response to Question 3c:

The Division's preference is for you to conduct a 1-year controlled study. Given that AURA-LV is already designed this way, a second 1-year controlled study for Phase 3, if results are consistent and clinically meaningful, could be adequate to support an NDA for the lupus nephritis indication. (b) (4) the Division believes it would be important to evaluate the duration of proteinuria improvement and the effect on eGFR over a 1-year timeframe, in order to better characterize the risk-benefit of treatment. This longer-term information is considered especially important given the 24-week results you have presented from AURA-LV, in which there was some evidence on an effect on proteinuria but trends for eGFR (and mortality) were in the direction of harm. As discussed in the response to Question 3a, (b) (4) would likely not be considered sufficient to reliably predict improvement in long-term clinical outcomes. (b) (4) We recommend that you conduct a randomized, double-blind, placebo-controlled phase 3 clinical trial of at least 52 weeks in duration in which patients, investigators, and the study team remain blinded to comparative interim results until the end of the double-blind treatment period.

With respect to your proposed statistical approach, we agree with your plan to analyze response endpoints using logistic regression, time-to-event endpoints using the log-rank test, and continuous endpoints using ANOVA. See other responses for specific statistical comments on other aspects of the design and analysis plan.

Discussion:

Aurinia accepted FDA's recommendation to conduct another 1-year controlled study. FDA emphasized that the ability for a single 1-year controlled study in phase 3 to be adequate for an NDA would depend on the 52-week results of AURA-LV (and whether they look more favorable than

the 24-week results), and that the results between the two studies would be expected to be consistent. Also refer to the discussion under Question 3.f. regarding duration of follow-up.

d. Number of subjects: Does the Division agree with the Sponsor's plans for the size of the two studies and the methodology for the treatment of withdrawing subjects?

FDA Response to Question 3d:

See the response to Question 3c. If a 1-year phase 3 study were designed, then the proposed number of subjects in the study may need to be modified to account for differences in assumptions for a 1-year period.

We also refer you to our previous comments on March 4, 2016 recommending that supportive analyses be carried out on each component of the primary endpoint and that a systematic strategy be put in place to avoid missing data. Your full protocol should address these recommendations.

In addition, you should prospectively plan sensitivity analyses that systematically and comprehensively explore the potential effect of missing data on the reliability of results. In particular, we recommend the inclusion of tipping point analyses that systematically vary assumptions about the missing outcomes. The tipping point analyses should be two-dimensional, i.e., should allow assumptions about the missing outcomes on the two arms to vary independently, and should include scenarios where dropouts on treatment have worse outcomes than dropouts on placebo. The goal is to evaluate the plausibility of the assumed expected values for missing outcomes on each treatment arm under which the conclusions change, i.e., under which there is no longer evidence of a treatment effect. In the tipping point analysis, ensure that all observed data is included as non- missing, regardless of adherence to treatment or use of prohibited medications. The analysis datasets should include a column or columns which clearly indicate whether each observation was missing, observed while the patient was on randomized treatment, or observed after the patient discontinued randomized treatment.

Discussion:

Aurinia acknowledged FDA's comments and explained that they expect to have adequate power for a 1-year study with the currently planned patient numbers, particularly because patients withdrawing from the study will be considered as non-responders. Aurinia will conduct tipping point analyses as recommended by FDA. FDA recommended Aurinia consider the impact of missing data also on secondary endpoints which may not be dichotomized, and how those results would be analyzed.

e. Study Design

FDA Response to Question 3e:

- See responses to Questions 3a and 3c above. We do not agree with the proposed primary endpoint [redacted] (b) (4)

- Also, we note that you wish [redacted] (b) (4) (b) (4)

- Regarding the proposed inclusion criteria, we do not agree with the biopsy criterion allowing for a biopsy within 2 years prior to screen [redacted] (b) (4) To help address this concern, we recommend you add an assessment of urinary sediment to provide context on whether the entry flare is nephritic.

Discussion:

Aurinia noted that FDA appeared to accept the 2-year biopsy inclusion criterion in previous written responses from July 2016. FDA responded that different people may be evaluating proposals at any given timepoint and that concerns were raised about the 2-year biopsy timeframe in the discussions for this meeting. The inclusion criteria are ultimately at Aurinia's discretion; however the concern raised currently may portend review concerns in the future. For example, if there are a large proportion of the patients who are enrolled with the 2-year biopsy criterion, then questions may be raised [redacted] (b) (4)

Aurinia acknowledged the concern but stated that in their experience only a small proportion of patients will be enrolled using the 2-year biopsy criterion.

f. Length of follow up

FDA Response to Question 3f:

As previously noted, we believe a minimum 1-year controlled period would provide essential information for the risk-benefit assessment. We also encourage you to continue to follow all patients from AURA-LV long-term to provide longer-term safety and exposure data for the NDA.

Discussion:

As noted in Aurinia's slide on Question 3f, approximately 85% of patients enrolled in AURA-LV have completed the study already, so extended follow-up and treatment of patients from AURA-LV is no longer practical. Aurinia stated that they will consider ways to obtain long-term data from the phase 3 study.

Post-Meeting Comment:

Rather than terminate double-blind placebo-controlled treatment and follow-up for ascertainment of safety and efficacy endpoints at a specific time after randomization (e.g., 52 weeks) in your phase 3 study, we recommend that you continue double-blind, placebo-controlled treatment and follow-up of all randomized patients until the study is complete (e.g., until the last enrolled patient has completed 52 weeks). This approach will allow longer-term treatment and outcome ascertainment on a subset of patients (those enrolled earlier in the trial) and will increase precision in the evaluation of important supportive time-to-event endpoints, such as time to death, time to end-stage renal disease (ESRD), or time to ESRD or death, and time to onset of meaningful decreases in renal function (e.g., doubling of serum creatinine).

g. Patient Reported Outcomes

FDA Response to Question 3g:

The selection of the patient-reported outcomes is at your discretion. FDA will evaluate the supportive data for the instrument(s) you have chosen in the NDA submission. Suitability of the chosen outcomes for labeling will be a review issue.

Discussion: No Discussion occurred. Sponsor acknowledged FDA's response.

Question 4: ***Are there any other parameters or issues the Division believes need to be addressed in the Phase 3 protocols?***

FDA Response to Question 4:

Calcineurin inhibitors have well known toxicities, including hypertension, hyperglycemia, dyslipidemia, tremor, alopecia, hirsutism, gum hypertrophy, long-term risk of cardiovascular events, long-term risk of malignancies, and

nephrotoxicity.[1] In addition to routine surveillance in the study, these events would be considered adverse events of interest and should be carefully captured and characterized in the study. In this regard, you should consider implementing specific renal and cardiovascular event adjudication committees.

Sparse PK samples should be collected in the phase 3 protocols to assess the impact of demographics on the exposure of voclosporin, and to assess the exposure-response relationship for efficacy and safety. Additionally, as voclosporin is planned to be used on background of MMF, and there is known DDI between MMF and cyclosporine, a dedicated DDI study should be conducted to assess the DDI between MMF and voclosporin.

Further comments may be forthcoming once you have submitted the full protocol for review.

Sponsor's slide response sent to FDA before the meeting:

(b) (4)

Discussion:

Aurinia agreed to capture and characterize adverse of interest as described in the FDA response to Question 3f. Aurinia also agrees to include collection of sparse PK samples in the phase 3 protocol.

For the potential DDI between MMF and voclosporin (VCS), FDA acknowledged that the renal transplant study/paper (Busque S, et al) showed similar MMF exposure when administered with VCS or TAC, and the study provided indirect evidence that VCS does not have significant impact on the MMF exposure. Therefore, FDA suggested that the sponsor may consider an alternative approach to assess the DDI between MMF and VCS if they do not

[1] Nieto MF and DR Jayne, "Con: the use of calcineurin inhibitors in the treatment of lupus nephritis." Nephrol Dial Transplant (2016), 0:1-5. Doi: 10.1093/ndt/gfw291.

want to do a dedicated DDI study. The sponsor may evaluate the MMF exposure (AUC) in the phase 3 study, and compare the MMF exposure in the (MMF+Placebo) arm versus (MMF+VCS) arm. If the data demonstrated a lack of interaction between MMF and VCS, then a dedicated DDI study may not be necessary. The sponsor agreed with FDA's suggestion and asked whether a sparse sampling for MMF PK would be adequate. FDA replied that the MMF PK data should be interpretable, and should be adequate to support a lack of DDI between MMF and VCS. Considering the MMF PK profile, intensive PK in a subgroup of patients may be more appropriate.

Question 5: ***Does the Division have any other feedback on the Pediatric Study Plan (S0044: submitted 25 July, 2016) at the End of Phase 2 meeting?***

FDA Response to Question 5:

Refer to FDA's comments on your proposed initial Pediatric Study Plan, conveyed on October 19, 2016.

Discussion:

Aurinia proposed to provide their approach to address the requested revisions in the iPSP for FDA comment via a meeting request, prior to updating the PSP and officially submitting. FDA stated that this is at Aurinia's discretion. As an alternative to a formal meeting, DPARP would be willing to informally evaluate the revisions if e-mailed ahead of the official submission.

Question 6: ***Based on the data from AURA-LV and the proposed synopsis for Phase 3 (Refer to Appendix 1), is the Division supportive of Aurinia moving into Phase 3?***

FDA Response to Question 6:

We recommend changes to the proposed phase 3 protocol as described in the responses above.

Discussion: No Discussion occurred. Sponsor acknowledged FDA's response.

Question 7: ***If granted, how will the Division implement Breakthrough Therapy Designation for voclosporin in the treatment of Active LN (A Breakthrough Designation request was submitted to the Division for review on 23 August 2016)?***

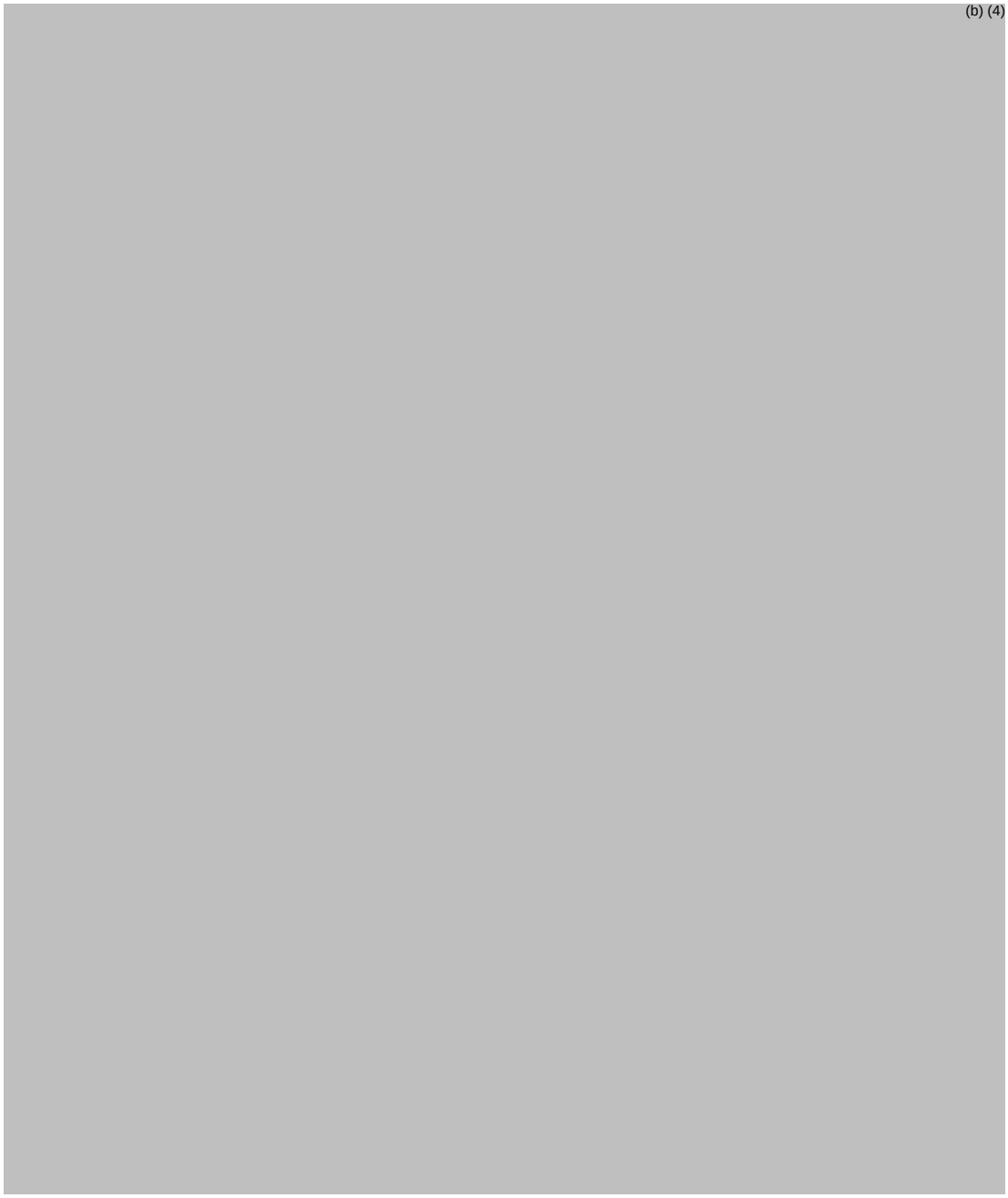
FDA Response to Question 7:

Refer to FDA's response dated October 19, 2016 to your breakthrough therapy designation request.

Discussion:

Aurinia acknowledged the denial of their breakthrough therapy designation request and had several follow up questions.

(b) (4)



Question 8: ***As Aurinia is an SME company, will the waiver still be permitted to allow submissions to the IND in paper format, until e-submissions becomes mandatory in 2018?***

FDA Response to Question 8:
While you will be permitted to continue submissions to the IND in paper format until 2018, we encourage you to begin electronic submissions as soon as possible, as this facilitates simultaneous review of the submissions by the members of the review team.

Discussion: Sponsor acknowledged FDA's response. No Discussion occurred.

3.0 PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (iPSP) within 60 days of an End of Phase (EOP2) meeting. In the absence of an End-of-Phase 2 meeting, refer to the draft guidance below. The PSP must contain an outline of the pediatric study or studies that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. The PSP should be submitted in PDF and Word format. Failure to include an agreed iPSP with a marketing application could result in a refuse to file action.

For additional guidance on the timing, content, and submission of the PSP, including a PSP Template, please refer to the draft guidance for industry, *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans* at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM360507.pdf. In addition, you may contact the Division of Pediatric and Maternal Health at 301-796-2200 or email pdit@fda.hhs.gov. For further guidance on pediatric product development, please refer to: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm.

DATA STANDARDS FOR STUDIES

Under section 745A(a) of the FD&C Act, electronic submissions "shall be submitted in such electronic format as specified by [FDA]." FDA has determined that study data contained in

electronic submissions (i.e., NDAs, BLAs, ANDAs and INDs) must be in a format that the Agency can process, review, and archive. Currently, the Agency can process, review, and archive electronic submissions of clinical and nonclinical study data that use the standards specified in the Data Standards Catalog (Catalog) (See http://www.fda.gov/forindustry/datastandards/studydatastandards/default.htm).

On December 17, 2014, FDA issued final guidance, *Providing Electronic Submissions in Electronic Format--- Standardized Study Data* (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM292334.pdf). This guidance describes the submission types, the standardized study data requirements, and when standardized study data will be required. Further, it describes the availability of implementation support in the form of a technical specifications document, Study Data Technical Conformance Guide (Conformance Guide) (See http://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM384744.pdf), as well as email access to the eData Team (cder-edata@fda.hhs.gov) for specific questions related to study data standards. Standardized study data will be required in marketing application submissions for clinical and nonclinical studies that start on or after December 17, 2016. Standardized study data will be required in commercial IND application submissions for clinical and nonclinical studies that start on or after December 17, 2017. CDER has produced a *Study Data Standards Resources* web page that provides specifications for sponsors regarding implementation and submission of clinical and nonclinical study data in a standardized format. This web page will be updated regularly to reflect CDER's growing experience in order to meet the needs of its reviewers.

Although the submission of study data in conformance to the standards listed in the FDA Data Standards Catalog will not be required in studies that start before December 17, 2016, CDER strongly encourages IND sponsors to use the FDA supported data standards for the submission of IND applications and marketing applications. The implementation of data standards should occur as early as possible in the product development lifecycle, so that data standards are accounted for in the design, conduct, and analysis of clinical and nonclinical studies. For clinical and nonclinical studies, IND sponsors should include a plan (e.g., in the IND) describing the submission of standardized study data to FDA. This study data standardization plan (see the Conformance Guide) will assist FDA in identifying potential data standardization issues early in the development program.

Additional information can be found at http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm.

For general toxicology, supporting nonclinical toxicokinetic, and carcinogenicity studies, CDER encourages sponsors to use Standards for the Exchange of Nonclinical Data (SEND) and submit sample or test data sets before implementation becomes required. CDER will provide feedback to sponsors on the suitability of these test data sets. Information about submitting a test submission can be found here: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm174459.htm

LABORATORY TEST UNITS FOR CLINICAL TRIALS

CDER strongly encourages IND sponsors to identify the laboratory test units that will be reported in clinical trials that support applications for investigational new drugs and product registration. Although Système International (SI) units may be the standard reporting mechanism globally, dual reporting of a reasonable subset of laboratory tests in U.S. conventional units and SI units might be necessary to minimize conversion needs during review. Identification of units to be used for laboratory tests in clinical trials and solicitation of input from the review divisions should occur as early as possible in the development process. For more information, please see the FDA website entitled, Study Data Standards Resources and the CDER/CBER Position on Use of SI Units for Lab Tests website found at http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/ucm372553.htm.

SUBMISSION FORMAT REQUIREMENTS

The Electronic Common Technical Document (eCTD) is CDER and CBER's standard format for electronic regulatory submissions. Beginning **May 5, 2017,** the following submission types: **NDA, ANDA, BLA** and **Master Files** must be submitted in eCTD format. **Commercial IND** submissions must be submitted in eCTD format beginning **May 5, 2018**. Submissions that do not adhere to the requirements stated in the eCTD Guidance will be subject to rejection. For more information please visit: http://www.fda.gov/ectd.

505(b)(2) REGULATORY PATHWAY

The Division recommends that sponsors considering the submission of an application through the 505(b)(2) pathway consult the Agency's regulations at 21 CFR 314.54, and the draft guidance for industry *Applications Covered by Section 505(b)(2)* (October 1999), available at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm. In addition, FDA has explained the background and applicability of section 505(b)(2) in its October 14, 2003, response to a number of citizen petitions that had challenged the Agency's interpretation of this statutory provision (see Docket FDA-2003-P-0274-0015, available at http://www.regulations.gov).

If you intend to submit a 505(b)(2) application that relies for approval, in part, on FDA's finding of safety and/or effectiveness for one or more listed drugs, you must establish that such reliance is scientifically appropriate, and must submit data necessary to support any aspects of the proposed drug product that represent modifications to the listed drug(s). You should establish a "bridge" (e.g., via comparative bioavailability data) between your proposed drug product and each listed drug upon which you propose to rely to demonstrate that such reliance is scientifically justified.

If you intend to rely, in part, on literature or other studies for which you have no right of reference but that are necessary for approval, you also must establish that reliance on the studies described in the literature or on the other studies is scientifically appropriate. You should

include a copy of such published literature in the 505(b)(2) application and identify any listed drug(s) described in the published literature (e.g., trade name(s)).

If you intend to rely, in part, on the Agency's finding of safety and/or effectiveness for a listed drug(s) or published literature describing a listed drug(s) (which is considered to be reliance on FDA's finding of safety and/or effectiveness for the listed drug(s)), you should identify the listed drug(s) in accordance with the Agency's regulations at 21 CFR 314.54. It should be noted that 21 CFR 314.54 requires identification of the "listed drug for which FDA has made a finding of safety and effectiveness," and thus an applicant may only rely upon a listed drug that was approved in an NDA under section 505(c) of the FD&C Act. The regulatory requirements for a 505(b)(2) application (including, but not limited to, an appropriate patent certification or statement) apply to each listed drug upon which a sponsor relies.

If you propose to rely on FDA's finding of safety and/or effectiveness for a listed drug that has been discontinued from marketing, the acceptability of this approach will be contingent on FDA's consideration of whether the drug was discontinued for reasons of safety or effectiveness.

We encourage you to identify each section of your proposed 505(b)(2) application that relies on FDA's finding of safety and/or effectiveness for a listed drug(s) or on published literature. In your 505(b)(2) application, we encourage you to clearly identify (for each section of the application, including the labeling): (1) the information for the proposed drug product that is provided by reliance on FDA's finding of safety and/or effectiveness for the listed drug or by reliance on published literature; (2) the "bridge" that supports the scientific appropriateness of such reliance; and (3) the specific name (e.g., proprietary name) of each listed drug named in any published literature on which your marketing application relies for approval. If you are proposing to rely on published literature, include copies of the article(s) in your submission.

In addition to identifying in your annotated labeling the source(s) of information essential to the approval of your proposed drug that is provided by reliance on FDA's previous finding of safety and efficacy for a listed drug or by reliance on published literature, we encourage you to also include that information in the cover letter for your marketing application in a table similar to the one below.

List the information essential to the approval of the proposed drug that is provided by reliance on the FDA's previous finding of safety and efficacy for a listed drug or by reliance on published literature	
Source of information (e.g., published literature, name of listed drug)	**Information Provided (e.g., specific sections of the 505(b)(2) application or labeling)**
1. Example: Published literature	*Nonclinical toxicology*
2. Example: NDA XXXXXX "TRADENAME"	*Previous finding of effectiveness for indication X*

3. Example: NDA YYYYYY "TRADENAME"	*Previous finding of safety for Carcinogenicity, labeling section XXX*
4.	

Please be advised that circumstances could change that would render a 505(b)(2) application for this product no longer appropriate. For example, if a pharmaceutically equivalent product were approved before your application is submitted, such that your proposed product would be a "duplicate" of a listed drug and eligible for approval under section 505(j) of the FD&C Act, then it is FDA's policy to refuse to file your application as a 505(b)(2) application (21 CFR 314.101(d)(9)). In such a case, the appropriate submission would be an Abbreviated New Drug Application (ANDA) that cites the duplicate product as the reference listed drug.

Office of Scientific Investigations (OSI) Requests

The Office of Scientific Investigations (OSI) requests that the following items be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA field investigators who conduct those inspections (Item I and II). This information is requested for all major trials used to support safety and efficacy in the application (i.e., phase 2/3 pivotal trials). Please note that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe location or provide a link to the requested information.

The dataset that is requested in Item III below is for use in a clinical site selection model that is being piloted in CDER. Electronic submission of the site level dataset is voluntary and is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process.

This request also provides instructions for where OSI requested items should be placed within an eCTD submission (Attachment 1, Technical Instructions: Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format).

I. Request for general study related information and comprehensive clinical investigator information (if items are provided elsewhere in submission, describe location or provide link to requested information).

1. Please include the following information in a tabular format in the original NDA for each of the completed pivotal clinical trials:
   a. Site number
   b. Principal investigator
   c. Site Location: Address (e.g., Street, City, State, Country) and contact information (i.e., phone, fax, email)
   d. Location of Principal Investigator: Address (e.g., Street, City, State, and Country) and contact information (i.e., phone, fax, email). If the Applicant is aware of changes to a clinical investigator's site address or contact information since the time of the clinical

investigator's participation in the study, we request that this updated information also be provided.

2. Please include the following information in a tabular format, *by site,* in the original NDA for each of the completed pivotal clinical trials:
   a. Number of subjects screened at each site
   b. Number of subjects randomized at each site
   c. Number of subjects treated who prematurely discontinued for each site by site

3. Please include the following information in a tabular format in the NDA for each of the completed pivotal clinical trials:
   a. Location at which sponsor trial documentation is maintained (e.g., , monitoring plans and reports, training records, data management plans, drug accountability records, IND safety reports, or other sponsor records as described ICH E6, Section 8). This is the actual physical site(s) where documents are maintained and would be available for inspection
   b. Name, address and contact information of all Contract Research Organization (CROs) used in the conduct of the clinical trials and brief statement of trial related functions transferred to them. If this information has been submitted in eCTD format previously (e.g., as an addendum to a Form FDA 1571, you may identify the location(s) and/or provide link(s) to information previously provided.
   c. The location at which trial documentation and records generated by the CROs with respect to their roles and responsibilities in conduct of respective studies is maintained. As above, this is the actual physical site where documents would be available for inspection.

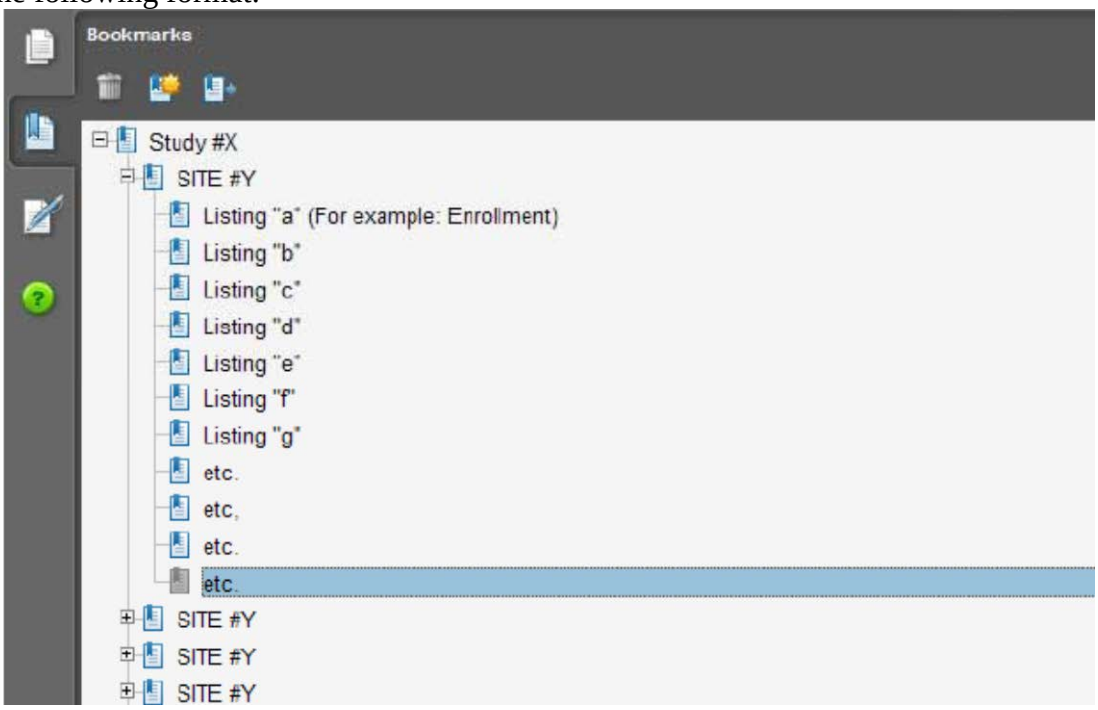
4. For each pivotal trial, provide a sample annotated Case Report Form (or identify the location and/or provide a link if provided elsewhere in the submission).
5. For each pivotal trial provide original protocol and all amendments ((or identify the location and/or provide a link if provided elsewhere in the submission).

II. Request for Subject Level Data Listings by Site

1. For each pivotal trial: Site-specific individual subject data listings (hereafter referred to as "line listings"). For each site, provide line listings for:
   a. Listing for each subject consented/enrolled; for subjects who were not randomized to treatment and/or treated with study therapy, include reason not randomized and/or treated
   b. Subject listing for treatment assignment (randomization)
   c. Listing of subjects that discontinued from study treatment and subjects that discontinued from the study completely (i.e., withdrew consent) with date and reason discontinued
   d. Listing of per protocol subjects/ non-per protocol subjects and reason not per protocol
   e. By subject listing of eligibility determination (i.e., inclusion and exclusion criteria)
   f. By subject listing, of AEs, SAEs, deaths and dates

g. By subject listing of protocol violations and/or deviations reported in the NDA, including a description of the deviation/violation
h. By subject listing of the primary and secondary endpoint efficacy parameters or events. For derived or calculated endpoints, provide the raw data listings used to generate the derived/calculated endpoint.
i. By subject listing of concomitant medications (as appropriate to the pivotal clinical trials)
j. By subject listing, of testing (e.g., laboratory, ECG) performed for safety monitoring

2. We request that one PDF file be created for each pivotal Phase 2 and Phase 3 study using the following format:



III. Request for Site Level Dataset:

OSI is piloting a risk based model for site selection. Voluntary electronic submission of site level datasets is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process. If you wish to voluntarily provide a dataset, please refer to the draft Guidance for Industry Providing Submissions in Electronic Format – Summary Level Clinical Site Data for CDER's Inspection Planning" (available at the following link http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332468.pdf) for the structure and format of this data set.

Attachment 1

Technical Instructions:
Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format

A. Data submitted for OSI review belongs in Module 5 of the eCTD. For items I and II in the chart below, the files should be linked into the Study Tagging File (STF) for each study. Leaf titles for this data should be named "BIMO [list study ID, followed by brief description of file being submitted]." In addition, a BIMO STF should be constructed and placed in Module 5.3.5.4, Other Study reports and related information. The study ID for this STF should be "bimo." Files for items I, II and III below should be linked into this BIMO STF, using file tags indicated below. The item III site-level dataset filename should be "clinsite.xpt."

DSI Pre-NDA Request Item[2]	STF File Tag	Used For	Allowable File Formats
I	data-listing-dataset	Data listings, by study	.pdf
I	annotated-crf	Sample annotated case report form, by study	.pdf
II	data-listing-dataset	Data listings, by study (Line listings, by site)	.pdf
III	data-listing-dataset	Site-level datasets, across studies	.xpt
III	data-listing-data-definition	Define file	.pdf

B. In addition, within the directory structure, the item III site-level dataset should be placed in the M5 folder as follows:

C. It is recommended, but not required, that a Reviewer's Guide in PDF format be included. If this Guide is included, it should be included in the BIMO STF. The leaf title should be "BIMO Reviewer Guide." The guide should contain a description of the BIMO elements being submitted with hyperlinks to those elements in Module 5.

[2] Please see the OSI Pre-NDA/BLA Request document for a full description of requested data files

References:

eCTD Backbone Specification for Study Tagging Files v. 2.6.1
(http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163560.pdf)

FDA eCTD web page
(http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm153574.htm)

For general help with eCTD submissions: ESUB@fda.hhs.gov

NEW PROTOCOLS AND CHANGES TO PROTOCOLS

To ensure that the Division is aware of your continued drug development plans and to facilitate successful interactions with the Division, including provision of advice and timely responses to your questions, we request that the cover letter for all new phase 2 or phase 3 protocol submissions to your IND or changes to these protocols include the following information:

1. Study phase
2. Statement of whether the study is intended to support marketing and/or labeling changes
3. Study objectives (e.g., dose finding)
4. Population
5. A brief description of the study design (e.g., placebo or active controlled)
6. Specific concerns for which you anticipate the Division will have comments
7. For changes to protocols only, also include the following information:
    - A brief summary of the substantive change(s) to the protocol (e.g., changes to endpoint measures, dose, and/or population)
    - Other significant changes
    - Proposed implementation date

We recommend you consider requesting a meeting to facilitate discussion of multiple and/or complex issues.

4.0 ISSUES REQUIRING FURTHER DISCUSSION

There were no issues requiring further discussion.

5.0 ACTION ITEMS

There were no action items.

6.0 ATTACHMENTS AND HANDOUTS

Attached are the slides presented by Aurinia Pharmaceuticals Inc.

13 Page(s) have been Withheld in Full as b4 (CCI/TS) immediately following this page

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This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

LAURA MUSSE
12/06/2016