CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

207988Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

EXCLUSIVITY SUMMARY

NDA # 207988 SUPPL # HFD #

Trade Name Zurampic

Generic Name lesinurad

Applicant Name Ardea Biosciences, Inc.

Approval Date, If Known December 22, 2015

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES ☒ NO ☐

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

505(b)(1)

b) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES ☒ NO ☐

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

c) Did the applicant request exclusivity?

YES ☐ NO ☒

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

d) Has pediatric exclusivity been granted for this Active Moiety?

YES ☐ NO ☒

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES ☐ NO ☒

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES ☐ NO ☒

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES ☐ NO ☐

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)
IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a)

is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES ☐ NO ☐

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES ☐ NO ☐

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES ☐ NO ☐

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES ☐ NO ☐

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES ☐ NO ☐

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES ☐ NO ☐

Investigation #2 YES ☐ NO ☐

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES ☐ NO ☐

Investigation #2 YES ☐ NO ☐

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1 !
!
IND # YES ☐ ! NO ☐
! Explain:

Investigation #2 !
!
IND # YES ☐ ! NO ☐
! Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1 !
!

YES ☐ ! NO ☐
Explain: ! Explain:

Investigation #2 !
!
YES ☐ ! NO ☐
Explain: ! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES ☐ NO ☐

If yes, explain:

==========

Name of person completing form: Jessica Lee, PharmD
Title: Regulatory Project Manager
Date: 11/24/15

Name of Division Director signing form: Badrul A. Chowdhury, MD, PhD
Title: Director

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05; removed hidden data 8/22/12

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

/s/

JESSICA K LEE
12/22/2015

LYDIA I GILBERT MCCLAIN
12/22/2015
Signing for Dr. Badrul Chowdhury as Acting Division Director

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION[1]

NDA # 207988 BLA #	NDA Supplement # BLA Supplement #	If NDA, Efficacy Supplement Type: *(an action package is not required for SE8 or SE9 supplements)*
Proprietary Name: Zurampic Established/Proper Name: lesinurad Dosage Form: Tablet		Applicant: Ardea Biosciences Inc. Agent for Applicant (if applicable):
RPM: Jessica Lee		Division: DPARP

NDA Application Type: ☒ 505(b)(1) ☐ 505(b)(2)
Efficacy Supplement: ☐ 505(b)(1) ☐ 505(b)(2)

BLA Application Type: ☐ 351(k) ☐ 351(a)
Efficacy Supplement: ☐ 351(k) ☐ 351(a)

For ALL 505(b)(2) applications, two months prior to EVERY action:

- **Review the information in the 505(b)(2) Assessment and submit the draft[2] to CDER OND IO for clearance.**
- **Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)**

☐ No changes
☐ New patent/exclusivity *(notify CDER OND IO)*
Date of check:

Note: If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.

❖ Actions	
• Proposed action • User Fee Goal Date is 12/29/15	☒ AP ☐ TA ☐ CR
• Previous actions *(specify type and date for each action taken)*	☒ None
❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____	☐ Received
❖ Application Characteristics[3]	

[1] The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 2) lists the documents to be included in the Action Package.
[2] For resubmissions, 505(b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) Assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., new listed drug, patent certification revised).
[3] Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA.

Review priority: ☒ Standard ☐ Priority
Chemical classification (new NDAs only):
(confirm chemical classification at time of approval)

☐ Fast Track
☐ Rolling Review
☐ Orphan drug designation
☐ Breakthrough Therapy designation
☐ Rx-to-OTC full switch
☐ Rx-to-OTC partial switch
☐ Direct-to-OTC

(NOTE: Set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager; Refer to the "RPM BT Checklist for Considerations after Designation Granted" for other require actions: CST SharePoint)

NDAs: Subpart H
☐ Accelerated approval (21 CFR 314.510)
☐ Restricted distribution (21 CFR 314.520)
Subpart I
☐ Approval based on animal studies

BLAs: Subpart E
☐ Accelerated approval (21 CFR 601.41)
☐ Restricted distribution (21 CFR 601.42)
Subpart H
☐ Approval based on animal studies

☐ Submitted in response to a PMR
☐ Submitted in response to a PMC
☐ Submitted in response to a Pediatric Written Request

REMS: ☐ MedGuide
☐ Communication Plan
☐ ETASU
☐ MedGuide w/o REMS
☐ REMS not required

Comments:

❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 *(approvals only)*	☐ Yes ☐ No
❖ Public communications *(approvals only)*	
• Office of Executive Programs (OEP) liaison has been notified of action	☒ Yes ☐ No
• Indicate what types (if any) of information were issued	☐ None ☒ FDA Press Release ☐ FDA Talk Paper ☐ CDER Q&As ☐ Other
❖ Exclusivity	
• Is approval of this application blocked by any type of exclusivity (orphan, 5-year NCE, 3-year, pediatric exclusivity)? • If so, specify the type	☒ No ☐ Yes
❖ Patent Information (NDAs only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.	☒ Verified ☐ Not applicable because drug is an old antibiotic.

CONTENTS OF ACTION PACKAGE

Officer/Employee List

❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list *(approvals only)*	☒ Included
Documentation of consent/non-consent by officers/employees	☒ Included

Action Letters	
❖ Copies of all action letters *(including approval letter with final labeling)*	Action(s) and date(s) Approval 12/22/15
Labeling	
❖ Package Insert *(write submission/communication date at upper right of first page of PI)*	
• Most recent draft labeling *(if it is division-proposed labeling, it should be in track-changes format)*	☒ Included
• Original applicant-proposed labeling	☒ Included
❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling *(write submission/communication date at upper right of first page of each piece)*	☒ Medication Guide ☐ Patient Package Insert ☐ Instructions for Use ☐ Device Labeling ☐ None
• Most-recent draft labeling *(if it is division-proposed labeling, it should be in track-changes format)*	☒ Included
• Original applicant-proposed labeling	☒ Included
❖ Labels (**full color** carton and immediate-container labels) *(write submission/communication date on upper right of first page of each submission)*	
• Most-recent draft labeling	☒ Included
❖ Proprietary Name • Acceptability/non-acceptability letter(s) *(indicate date(s))* • Review(s) *(indicate date(s)*	Acceptable 3/17/15 3/6/15
❖ Labeling reviews *(indicate dates of reviews)*	RPM: 3/12/15 ☐ None DMEPA: 11/4/15 ☐ None DMPP/PLT (DRISK): ☐ None 12/20/15; 12/10/15 OPDP: ☐ None 12/7/15 SEALD: ☐ None CSS: ☐ None Product Quality ☐ None Other: 8/25/15 (PMHS) ☐ None
Administrative / Regulatory Documents	
❖ RPM Filing Review[4]/Memo of Filing Meeting *(indicate date of each review)* ❖ All NDA 505(b)(2) Actions: Date each action cleared by 505(b)(2) Clearance Committee	3/12/15 ☒ Not a (b)(2)
❖ NDAs only: Exclusivity Summary *(signed by Division Director)*	☒ Included
❖ Application Integrity Policy (AIP) Status and Related Documents http://www fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
• Applicant is on the AIP	☐ Yes ☒ No

[4] Filing reviews for scientific disciplines are NOT required to be included in the action package.

• This application is on the AIP o If yes, Center Director's Exception for Review memo *(indicate date)* o If yes, OC clearance for approval *(indicate date of clearance communication)*	☐ Yes ☒ No ☐ Not an AP action
❖ Pediatrics *(approvals only)* • Date reviewed by PeRC 7/8/15 If PeRC review not necessary, explain: _____	
❖ Breakthrough Therapy Designation	☒ N/A
• Breakthrough Therapy Designation Letter(s) (granted, denied, an/or rescinded)	
• CDER Medical Policy Council Breakthrough Therapy Designation Determination Review Template(s) *(include only the completed template(s) and not the meeting minutes)*	
• CDER Medical Policy Council Brief – Evaluating a Breakthrough Therapy Designation for Rescission Template(s) *(include only the completed template(s) and not the meeting minutes)* *(completed CDER MPC templates can be found in DARRTS as clinical reviews or on the MPC SharePoint Site)*	
❖ Outgoing communications: letters, emails, and faxes considered important to include in the action package by the reviewing office/division (e.g., clinical SPA letters, RTF letter, Formal Dispute Resolution Request decisional letters, etc.) *(do not include previous action letters, as these are located elsewhere in package)*	12/22/15; 12/21/15; 12/18/15 (2); 12/16/15; 12/15/15(2); 11/23/15; 11/16/15;11/3/15; 10/15/15; 10/9/15; 10/7/15; 10/2/15; 9/9/15; 8/21/15; 8/20/15; 8/14/15; 8/12/15; 8/12/15; 8/7/15; 8/7/15; 7/30/15; 6/4/15; 6/3/15; 5/21/15; 5/19/15; 4/24/15; 3/12/15; 2/27/15; 1/12/15; 1/8/15
❖ Internal documents: memoranda, telecons, emails, and other documents considered important to include in the action package by the reviewing office/division (e.g., Regulatory Briefing minutes, Medical Policy Council meeting minutes)	
❖ Minutes of Meetings	
• If not the first review cycle, any end-of-review meeting *(indicate date of mtg)*	☐ N/A or no mtg
• Pre-NDA/BLA meeting *(indicate date of mtg)*	☐ No mtg 9/26/14
• EOP2 meeting *(indicate date of mtg)*	☐ No mtg 7/21/11
• Mid-cycle Communication *(indicate date of mtg)*	☐ N/A 6/10/15
• Late-cycle Meeting *(indicate date of mtg)*	☐ N/A 9/18/15
• Other milestone meetings (e.g., EOP2a, CMC focused milestone meetings) *(indicate dates of mtgs)*	7/6/11 (CMC)

❖ Advisory Committee Meeting(s)	☐ No AC meeting
• Date(s) of Meeting(s)	10/23/15
Decisional and Summary Memos	
❖ Office Director Decisional Memo *(indicate date for each review)*	☐ None 12/22/15
Division Director Summary Review *(indicate date for each review)*	☐ None 11/23/15
Cross-Discipline Team Leader Review *(indicate date for each review)*	☐ None 11/22/15
PMR/PMC Development Templates *(indicate total number)*	☐ None 12/21/15
Clinical	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) *(indicate date for each review)*	☒ No separate review
• Clinical review(s) *(indicate date for each review)*	9/17/15; 2/26/15
• Social scientist review(s) (if OTC drug) *(indicate date for each review)*	☐ None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here ☐ and include a review/memo explaining why not *(indicate date of review/memo)*	9/17/15 (Clinical Review) Pg 248
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers *(indicate date of each review)*	☒ None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation *(indicate date of each review)*	☒ N/A
❖ Risk Management • REMS Documents and REMS Supporting Document *(indicate date(s) of submission(s))* • REMS Memo(s) and letter(s) *(indicate date(s))* • Risk management review(s) and recommendations (including those by OSE and CSS) *(indicate date of each review and indicate location/date if incorporated into another review)*	☒ None
❖ OSI Clinical Inspection Review Summary(ies) *(include copies of OSI letters to investigators)*	☐ None requested 12/16/15; 11/6/15 (2); 8/20/15
Clinical Microbiology ☒ None	
❖ Clinical Microbiology Team Leader Review(s) *(indicate date for each review)*	☐ No separate review
Clinical Microbiology Review(s) *(indicate date for each review)*	☐ None
Biostatistics ☐ None	
❖ Statistical Division Director Review(s) *(indicate date for each review)*	☒ No separate review
Statistical Team Leader Review(s) *(indicate date for each review)*	☐ No separate review 12/15/15
Statistical Review(s) *(indicate date for each review)*	☐ None 10/8/15; 2/20/15
Clinical Pharmacology ☐ None	
❖ Clinical Pharmacology Division Director Review(s) *(indicate date for each review)*	☒ No separate review
Clinical Pharmacology Team Leader Review(s) *(indicate date for each review)*	☒ No separate review
Clinical Pharmacology review(s) *(indicate date for each review)*	☐ None 9/3/15; 2/20/15
❖ OSI Clinical Pharmacology Inspection Review Summary *(include copies of OSI letters)*	☒ None requested

Nonclinical ☐ None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) *(indicate date for each review)*	☐ No separate review 12/18/15
• Supervisory Review(s) *(indicate date for each review)*	☐ No separate review 11\24\15
• Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	☐ None 9/25/15; 9/10/15; 9/3/15; 9/1/15; 7/29/15; 2/17/15
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer *(indicate date for each review)*	☒ None
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	☐ No carc 11/17/15
❖ ECAC/CAC report/memo of meeting	☐ None 7/1/15; 5/25/15 Included in P/T review, page
❖ OSI Nonclinical Inspection Review Summary *(include copies of OSI letters)*	☒ None requested
Product Quality ☐ None	
❖ Product Quality Discipline Reviews	
• Tertiary review (*indicate date for each review*)	☒ None
• Secondary review (e.g., Branch Chief) *(indicate date for each review)*	☒ None
• Integrated Quality Assessment (contains the Executive Summary and the primary reviews from each product quality review discipline) *(indicate date for each review)*	☐ None 9/8/15
❖ Reviews by other disciplines/divisions/Centers requested by product quality review team *(indicate date of each review)*	☐ None
❖ Environmental Assessment (check one) (original and supplemental applications)	
☒ Categorical Exclusion *(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)*	12/1/15
☐ Review & FONSI *(indicate date of review)*	
☐ Review & Environmental Impact Statement *(indicate date of each review)*	
❖ Facilities Review/Inspection	
☒ Facilities inspections (*action must be taken prior to the re-evaluation date*) *(only original applications and efficacy supplements that require a manufacturing facility inspection(e.g., new strength, manufacturing process, or manufacturing site change)*	☒ Acceptable 3/24/15 Re-evaluation date: ☐ Withhold recommendation ☐ Not applicable

Day of Approval Activities	
❖ For all 505(b)(2) applications: • Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)	☐ No changes ☐ New patent/exclusivity *(Notify CDER OND IO)*
• Finalize 505(b)(2) assessment	☐ Done
❖ For Breakthrough Therapy (BT) Designated drugs: • Notify the CDER BT Program Manager	☐ Done *(Send email to CDER OND IO)*
❖ For products that need to be added to the flush list (generally opioids): Flush List • Notify the Division of Online Communications, Office of Communications	☐ Done
❖ Send a courtesy copy of approval letter and all attachments to applicant by fax or secure email	☒ Done
❖ If an FDA communication will issue, notify Press Office of approval action after confirming that applicant received courtesy copy of approval letter	☐ Done
❖ Ensure that proprietary name, if any, and established name are listed in the *Application Product Names* section of DARRTS, and that the proprietary name is identified as the "preferred" name	☐ Done
❖ Ensure Pediatric Record is accurate	☐ Done
❖ Send approval email within one business day to CDER-APPROVALS	☐ Done

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/s/

JESSICA K LEE
12/22/2015

Your submission dated December 25, 2014, to NDA 207988, is currently under review. Attached are the edits to your proposed package insert (PI) submitted on December 21, 2015. Be advised that these labeling changes are not necessarily the Agency's final recommendations and that additional labeling changes may be forthcoming as the label is continued to be reviewed.

Submit a clean copy and a tracked-change version of the label incorporating our recommended changes to the NDA as soon as possible today, December 22, 2015. The information can be sent by electronic mail to Jessica.Lee@fda.hhs.gov, followed by an official submission to the NDA. If you have any questions, please contact Jessica Lee, Regulatory Project Manager, at 301-796-3769.

18 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

JESSICA K LEE
12/22/2015

Your submission dated December 25, 2014, to NDA 207988, is currently under review. Attached are the edits to your proposed package insert (PI) submitted on December 17, 2015. Be advised that these labeling changes are not necessarily the Agency's final recommendations and that additional labeling changes may be forthcoming as the label is continued to be reviewed.

Submit a clean copy and a tracked-change version of the label incorporating our recommended changes to the NDA by noon, Tuesday, December 22, 2015. The information can be sent by electronic mail to Jessica.Lee@fda.hhs.gov, followed by an official submission to the NDA. If you have any questions, please contact Jessica Lee, Regulatory Project Manager, at 301-796-3769.

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/s/

JESSICA K LEE
12/21/2015

Your submission dated December 25, 2014, to NDA 207988 is currently under review. We have the following request for information:

As discussed in the teleconference on December 17, 2015, regarding a Post Marketing Requirement (PMR) for renal safety for NDA 207988, provide agreement for the following revised clinical trial:

A randomized, controlled, clinical trial to evaluate the safety of lesinurad 200mg on a background of concomitant xanthine oxidase inhibitor, with respect to renal function and renal adverse events in gout patients who have not achieved target serum uric acid with a xanthine oxidase inhibitor alone. Enrollment should be enriched with patients with moderate renal impairment (creatinine clearance 30 to 60 mL/min). The minimum treatment duration should be 2 years. The trial must also include an assessment of cardiovascular (CV) safety based on an independent adjudication of prospectively defined and collected CV events.

Provide dates for the following PMR schedule:

Final Protocol Submission:	MM/YY
Trial Completion:	MM/YY
Final Report Submission:	MM/YY

Submit your agreement and the PMR schedule dates by 12:00 pm (EST), Monday, December 21, 2015. The information can be sent by electronic mail to Jessica.Lee@fda.hhs.gov, followed by an official submission to the NDA. If you have any questions, please contact Jessica Lee, Regulatory Project Manager, at 301-796-3769.

Drafted by: JLee 12/18/15

Initialed by: SBarnes 12/18/15
SYim 12/1815

Finalized by: JLee 12/1815

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

/s/

JESSICA K LEE
12/18/2015

Dear Ms. Manhard,

Please refer to your submission dated, December 25, 2014, to NDA 207988. We are requesting your assistance in populating the attached tables for your New Molecular Entity, lesinurad, currently under review in the Division.

As part of FDASIA 2012, information on demographic subgroups in clinical trials for newly-approved drugs and biologics will be made publicly available on www.fda.gov/drugtrialssnapshot.

The website will include information on study design, results of efficacy and safety studies, and whether there were any differences in efficacy and side effects within sex, race, and age subgroups. The website is not intended to replace or replicate the package insert (PI), which is intended for health care practitioners, and will contain the following:

- Information written in consumer-friendly language
- "MORE INFORMATION" sections that provide more technical, data-heavy information
- Information that focuses on subgroup data and analyses
- Links to the PI for the product and to the FDA reviews at Drugs@FDA

Submit the requested information no later than, Monday, December 28, 2015. The information can be sent by electronic mail to Jessica.Lee@fda.hhs.gov, followed by an official submission to the NDA. If you have any questions, please contact Jessica Lee, Regulatory Project Manager, at 301-796-3769.

Attachments:

1. Table for Lesinurad
2. Instructions for completion of Table for Effect of Lesinurad on Serum Uric Acid Response by Subgroup

Drafted by:	NLowry 12/18/15 JLee 12/18/15
Initialed by:	RNeuner 12/18/15 SBarnes 12/18/15
Finalized by:	JLee 12/18/15

Demographics for Pooled Population (Trials 301, 302, and 304)--shoud not include any data regarding patients who received ZURAMPIC 400 mg

Demographic Parameters	ZURAMPIC 200 mg	Placebo	Total
Sex			
Men			
Women			
Age			
Mean years (SD)			
Median (years)			
Min, Max (years)			
Age Group			
below 65 years			
65 and above			
Race (please modify according to your program)			
White			
African American or Black			
Asian			
American Indian or Alaska Native			
Native Hawaiian or Other Pacific Islander			
Other			
Region			
United States			
European Union			
Asia			
Other			

Subgroup	ZURAMPIC 200 mg (N=511)	Placebo (N=516)
Overall Treatment -Emergent Adverse Events		
Sex		
Male		
Female		
Age Group		
<17 years		
17 - 64 years		
>=65 years		
Race (modify according to the program)		
White		
Black or African American		
Asian		
American Indian or Alaska Native		
Native Hawaiian or Other Pacific Islander		
Other		

Subgroup	ZURAMPIC 200 mg (N=511)	Placebo (N=516)
Overall Treatment -Emergent Serious Adverse Events		
Sex		
Male		
Female		
Age Group		
<17 years		
17 - 64 years		
>=65 years		
Race (modify according to the program)		
White		
Black or African American		
Asian		
American Indian or Alaska Native		
Native Hawaiian or Other Pacific Islander		
Other		

Table X. Effect of Lesinurad on Serum Uric Acid Response by Subgroup (see special instructions in W

Demographic Parameters		CONTROL	
	N	Number (%) of Serum Uric Acid Responders (sUA < 6 mg/dL in studies 301 and 302, sUA < 5 mg/dL in study 304) at Month 6	N
Sex			
Male			
Female			
Age Group			
below 65 years			
65 years and above			
Race			
White			
Black or African American			
Asian			
American Indian or Alaska Native			
Native Hawaiian or Other Pacific Islander			
Other			
Ethnicity			
Hispanic or Latino			
Not Hispanic or Latino			

ord document)

LESINURAD 200 **Number (%) of Serum Uric Acid Responders (sUA < 6 mg/dL in studies 301 and 302, sUA < 5 mg/dL in study 304) at Month 6**	**Difference (95% Confidence Interval) in Proportion of Serum Uric Acid Responders (Lesinurad 200 minus placebo)**	**Test for Treatment by Subgroup Interaction (p-value)**
		insert
		insert
		insert
		insert

Instructions for completion of Table for Effect of Lesinurad on Serum Uric Acid Response by Subgroup:

With respect to the request for completion of the shell table for serum uric acid responders by subgroup, please complete the table based on analyses in each of the studies or combinations of studies listed below. For the individual studies estimate the treatment effect of Lesinurad relative to placebo within subgroups and test for the difference in overall treatment effect across subgroups. For combinations of studies, estimate the treatment effect of Lesinurad relative to placebo within subgroups and test for the difference in overall treatment effect across subgroups by combining the estimates from the individual studies.

- Studies 301 and 302, each individually
- Studies 301 and 302 combined
- Study 304 individually

With respect to the interaction tests of the treatment effect by race. For an individual study the model should include the following factors/terms:

- race (as a categorical factor)
- treatment
- treatment by race interaction term
- the covariates used in the primary analysis

When performing an interaction test of the treatment effect by race for a combination of studies, additionally include the following factors/terms:

- race by study interaction term
- treatment by study interaction term
- interaction terms with study for each covariate used in the primary analysis

Please provide the code and a description of the statistical methods used to generate these analyses.

Your submission dated December 25, 2014, to NDA 207988, is currently under review. Attached are the edits to your proposed Medication Guide (MG) submitted on November 23, 2015. Be advised that these labeling changes are not necessarily the Agency's final recommendations and that additional labeling changes may be forthcoming as the label is continued to be reviewed.

Submit a clean copy and a tracked-change version of the label incorporating our recommended changes to the NDA by Thursday, December 17, 2015. The information can be sent by electronic mail to Jessica.Lee@fda.hhs.gov, followed by an official submission to the NDA. If you have any questions, please contact Jessica Lee, Regulatory Project Manager, at 301-796-3769.

3 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

JESSICA K LEE
12/16/2015

Your submission dated December 25, 2014, to NDA 207988, is currently under review. Attached are the edits to your proposed package insert (PI) submitted on November 23, 2015. Be advised that these labeling changes are not necessarily the Agency's final recommendations and that additional labeling changes may be forthcoming as the label is continued to be reviewed.

Submit a clean copy and a tracked-change version of the label incorporating our recommended changes to the NDA by Thursday, December 17, 2015. The information can be sent by electronic mail to Jessica.Lee@fda.hhs.gov, followed by an official submission to the NDA. If you have any questions, please contact Jessica Lee, Regulatory Project Manager, at 301-796-3769.

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/s/

JESSICA K LEE
12/15/2015

Your submissions dated December 25, 2014, to NDA 207988 is currently under review. We have the following request for information:

As discussed in the teleconference on December 15, 2015, there will be a Post Marketing Requirement (PMR) for renal safety for NDA 207988. Provide agreement for the following clinical trial:

A 2-year, randomized, controlled, clinical trial to evaluate the safety of lesinurad 200mg on a background of concomitant xanthine oxidase inhibitor, with respect to renal function and renal adverse events in gout patients with moderate to severe renal impairment (creatinine clearance 30 to 60 mL/min) who have not achieved target serum uric acid with a xanthine oxidase inhibitor alone. The trial must also include an assessment of cardiovascular (CV) safety based on an independent adjudication of prospectively defined and collected CV events.

Provide dates for the following PMR schedule:

Final Protocol Submission:	MM/YY
Trial Completion:	MM/YY
Final Report Submission:	MM/YY

Submit your agreement and the PMR schedule dates by Thursday, December 17, 2015. The information can be sent by electronic mail to Jessica.Lee@fda.hhs.gov, followed by an official submission to the NDA. If you have any questions, please contact Jessica Lee, Regulatory Project Manager, at 301-796-3769.

Drafted by: JLee 12/15/15

Initialed by: SBarnes 12/15/15

Finalized by: JLee 12/15/15

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/s/

JESSICA K LEE
12/15/2015

Your submissions dated December 25, 2014 and November 19, 2015, to NDA 207988, are currently under review. We have the following comments regarding your container labels and request that you submit container labels to the NDA with the changes below. Be advised that these labeling changes are not necessarily the Agency's final recommendations and that additional labeling changes may be forthcoming as the label is continued to be reviewed.

Container Labels (All)

1. We recommend capitalizing only the first letter in the proprietary name because words written in all-capital letters are less legible than words written in mixed case letters. Revise the proposed proprietary name "ZURAMPIC" to "Zurampic".

Submit the revised container labels incorporating our recommended changes to the NDA by November 30, 2015. The information can be sent by electronic mail to Jessica.Lee@fda.hhs.gov, followed by an official submission to the NDA. If you have any questions, please contact Jessica Lee, Regulatory Project Manager, at 301-796-3769.

Drafted by: TMcMillan 11/20/15
JLee 11/23/15

Initialed by: SBarnes 11/23/15

Finalized by: JLee 11/23/15

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/s/

JESSICA K LEE
11/23/2015

Your submissions dated December 25, 2014 and May 21, 2015, to NDA 207988, are currently under review. We have the following comments regarding your container labels and request that you submit container labels to the NDA with the changes below. Be advised that these labeling changes are not necessarily the Agency's final recommendations and that additional labeling changes may be forthcoming as the label is continued to be reviewed.

Container Labels (All)

1. Replace the NDC number placeholders with the actual NDC numbers.

2. Revise the Usual Adult Dosage statement to the following: "See full prescribing information"

3. You have designated a placeholder (XXXX-XX) that is in close proximity to the lot and expiration number and may be mistaken as the lot and/or expiration number. Ensure that this placeholder (XXXX-XX) is clearly differentiated, distinguishable, and in reasonable proximity away from the lot and expiration numbers to avoid misinterpretation.

Professional Sample Container Label

4. Relocate the "PROFESSIONAL SAMPLE-NOT FOR SALE" statement to the principal display panel under the "Rx only" statement. Relocate the AstraZeneca name and logo to the side panel to ensure there is adequate space on the principal display panel for more important information.

Submit the revised container labels incorporating our recommended changes to the NDA by November 20, 2015. The information can be sent by electronic mail to Jessica.Lee@fda.hhs.gov, followed by an official submission to the NDA. If you have any questions, please contact Jessica Lee, Regulatory Project Manager, at 301-796-3769.

Drafted by: TMcMillan 11/4/15
JLee 11/10/15

Initialed by: SBarnes 11/12/15

Finalized by: JLee 11/16/15

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/s/

JESSICA K LEE
11/16/2015

NDA 207988

Your submissions dated December 25, 2014 and September 16, 2015, to NDA 207988, are currently under review. We have the following comments regarding your label and request that you submit the label to the NDA with the changes below. Be advised that these labeling changes are not necessarily the Agency's final recommendations and that additional labeling changes may be forthcoming as the label is continued to be reviewed.

(b) (4)

[redacted]

Comment [A1]: Note to Sponsor: Major revisions necessary

NDA 207988

(b) (4)

[redacted]

Comment [A2]: Note to Sponsor: Major Revisions necessary

Submit a clean copy and a tracked-change version of the label incorporating our recommended changes to the NDA by November 17, 2015. The information can be sent by electronic mail to Jessica.Lee@fda hhs.gov, followed by an official submission to the NDA. If you have any questions, please contact Jessica Lee, Regulatory Project Manager, at 301-796-3769.

NDA 207988

Drafted by: SYim 10/29/15
JLee 10/29/15

Initialed by: MWhittaker; TRobison 10/30/15
YWang; GLevin 11/2/15
JChen 11/2/15
SBarnes 11/3/15
JMaynard 11/3/15

Finalized by: JLee 11/3/15

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/s/

JESSICA K LEE
11/03/2015

Your NDA 207988 submitted on Dec 29, 2014, is currently under review. We have the following requests for information:

Reference is made to study protocols and study reports for study 301, 302, 303, and 304 under section 5.3.5.

1. Clarify whether the sampling time point for serum uric acid for the primary endpoint assessment is pre-specified in the phase 3 protocols.

2. Provide a summary of actual sampling time points relative to dose for the primary endpoint assessments for each treatment arm in the phase 3 studies.

3. Regarding the daily variation of serum uric acid relative to lesinurad dose, explain whether the sampling timepoint in phase 3 studies may affect the efficacy result/outcome, for both the responder analysis and absolute change in serum uric acid.

Source data, model codes or control streams, and scripts used to generate the corresponding analyses should be provided with your response. Data files should be submitted as SAS transport files with *.xpt extension (eg. Data1.xpt), and other files should be submitted as ASCII text files with *.txt extension (e.g.:myfile_ctl.txt, myfile_out.txt.

Submit to me via email at michelle.jordan@fda.hhs.gov, and officially to the NDA by **4:00p.m. EST, October 16, 2015.** If you have any questions, please contact Michelle Jordan Garner, Senior Regulatory Project Manager, at 301-796-4786.

Drafted by: MichelleJG10/15/15

Concurrence by: SBarnes10/15/15
Finalized by: MichelleJG 8/15/15

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/s/

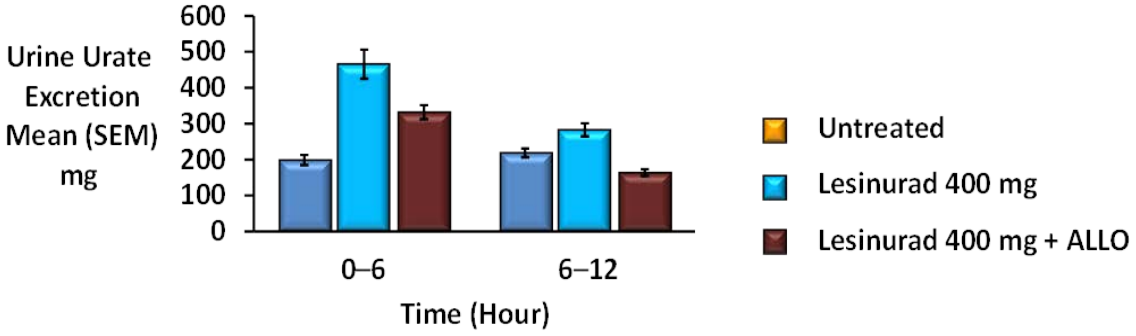
MICHELLE Y JORDAN GARNER
10/15/2015

ZURAMPIC (lesinurad) NDA 207988
Questions on Stats Information Request Received 7 October 2015

1. During the teleconference today, we understood that the request was for analyses using Risk Differences; (b) (4) [redacted] . **Do you agree with our proposal to provide analyses using** (b) (4) [redacted] **instead of Incidence Rate Ratios?**

2. With respect to the request in Item 1 to provide analyses on integrated data for the Phase 3 studies, we agree that it is appropriate to integrate data from all phase 3 combination studies, Studies 301, 302 and 304 to assess adjudicated major adverse cardiovascular events (MACE), mortality, and serious renal adverse events (AEs). We also agree to integrate data from all Phase 3 studies including the monotherapy study 303 to assess adjudicated major adverse cardiovascular events (MACE) and mortality. (b) (4) [redacted] **Does the Agency agree with this proposal?**

Urinary uric acid excretion in gout patients following lesinurad 400mg alone and with allopurinol (Study 110)



Jordan Garner, Michelle

From: Jordan Garner, Michelle
Sent: Friday, October 09, 2015 2:02 PM
To: Meghan O'Neill; Kimberly Manhard
Cc: Jordan Garner, Michelle
Subject: RE: Stats IR/Zurampic/NDA 207988

Hi,

See below.

(1) We do not agree with your proposal. We believe that calculation of incidence rates, which take into account the amount of follow-up time per person, is more appropriate than calculation of cumulative incidence proportions because a considerable proportion of patients dropped out of the studies early. In addition, estimation of the potential treatment effect on a relative scale is important, given the fact that effects tend to be more consistent on the relative rather than absolute difference scale across populations. Therefore, a potential increase in risk on the absolute difference scale may be underestimated from these clinical trials, which likely had lower baseline rates of MACE than that expected in gout patients in clinical practice (see, e.g., the NHANES estimated rate you cited in the Cardiovascular Study Report of 2.31 CV deaths/100 person-years). We understand your concern about the instability and uncertainty in the rate ratio due to the small numbers of events, although the statistical uncertainty should be conveyed by the width of the confidence interval. You may submit results on both relative and absolute difference scales if you wish (although estimates of absolute differences should take into account the amount of follow-up per person); we will consider the concerns you have expressed in determining what to present at the AC meeting.

(2) We do not agree with your proposal. For very rare adverse events of special interest, it is important to integrate as much (reliable) information as possible to evaluate potential increases in risk. You may present results from Study 303 separately from Studies 301, 302, and 304, and we will consider your argument and that data in determining what to present at the AC meeting. But we additionally continue to request analyses based on integrated data from all four studies.

Let me know if you need any additional days to respond to the IR. I can grant you until 4pm on Friday (10/16/15), but will need to alert the team when to expect Ardea's response, if it's going to be later than the original due date.

Michelle JGarner

Michelle Jordan Garner, MS, OTR/L
CDR, U.S. Public Health Service
Sr. Regulatory Management Officer
Food and Drug Administration
Center for Drug Evaluation and Research/ODEII
Division of Pulmonary, Allergy, and Rheumatology Products
10903 New Hampshire Ave., Bldg 22, Room 3200
Silver Spring, MD 20993

Telephone: 301-796-4786
Fax: 301-796-9728
Email: michelle.jordan@.fda.hhs.gov

From: Meghan O'Neill [mailto:moneill@ardeabio.com]
Sent: Friday, October 09, 2015 12:54 PM
To: Jordan Garner, Michelle; Kimberly Manhard
Subject: RE: Stats IR/Zurampic/NDA 207988
Importance: High

Hi Michelle,

Have you heard anything from the stats team leader?
Thanks for all your help.

Best,

Meghan

From: Jordan Garner, Michelle [mailto:Michelle.Jordan@fda.hhs.gov]
Sent: Thursday, October 08, 2015 1:44 PM
To: Kimberly Manhard
Cc: Meghan O'Neill
Subject: RE: Stats IR/Zurampic/NDA 207988

The stats team leader who spoke about the IR is on leave. Therefore, I may not get a reply until tomorrow.

Michelle JGarner

Michelle Jordan Garner, MS, OTR/L
CDR, U.S. Public Health Service
Sr. Regulatory Management Officer
Food and Drug Administration
Center for Drug Evaluation and Research/ODEII
Division of Pulmonary, Allergy, and Rheumatology Products
10903 New Hampshire Ave., Bldg 22, Room 3200
Silver Spring, MD 20993

Telephone: 301-796-4786
Fax: 301-796-9728
Email: michelle.jordan@.fda.hhs.gov

From: Kimberly Manhard [mailto:KManhard@ardeabio.com]
Sent: Thursday, October 08, 2015 12:52 PM
To: Jordan Garner, Michelle
Cc: Meghan O'Neill
Subject: RE: Stats IR/Zurampic/NDA 207988

Hi Michelle,
Due to the limited time for us to respond to the Stats IR, can you please estimate when we might have a response to our questions sent yesterday as the responses will impact our programming?
Also, we did not submit the questions to the NDA, but please let me know if we should.
Thanks for your help!
Kimberly

From: Kimberly Manhard
Sent: Wednesday, October 07, 2015 4:02 PM
To: 'Jordan Garner, Michelle'

Cc: Meghan O'Neill
Subject: RE: Stats IR/Zurampic/NDA 207988

Hi Michelle,
Attached please find an MS Word file with 2 questions on Item 1 in the Stats IR received today. Please let me know if we should also submit officially to the NDA. If preferable, we would be happy to have a brief teleconference tomorrow at the Agency's convenience to help further explain our proposals.
Thanks in advance.
Kind regards,
Kimberly

From: Kimberly Manhard
Sent: Wednesday, October 07, 2015 1:16 PM
To: 'Jordan Garner, Michelle'
Cc: Meghan O'Neill
Subject: RE: Stats IR/Zurampic/NDA 207988

Thanks, Michelle. We will provide by the end of the day.

From: Jordan Garner, Michelle [mailto:Michelle.Jordan@fda.hhs.gov]
Sent: Wednesday, October 07, 2015 1:02 PM
To: Kimberly Manhard
Subject: RE: Stats IR/Zurampic/NDA 207988

Please provide a list of questions. Our schedules are very packed, and we can expeditiously assist you with responses if you provide them in writing via email.

Michelle JGarner

Michelle Jordan Garner, MS, OTR/L
CDR, U.S. Public Health Service
Sr. Regulatory Management Officer
Food and Drug Administration
Center for Drug Evaluation and Research/ODEII
Division of Pulmonary, Allergy, and Rheumatology Products
10903 New Hampshire Ave., Bldg 22, Room 3200
Silver Spring, MD 20993

Telephone: 301-796-4786
Fax: 301-796-9728
Email: michelle.jordan@.fda.hhs.gov

From: Kimberly Manhard [mailto:KManhard@ardeabio.com]
Sent: Wednesday, October 07, 2015 4:00 PM
To: Jordan Garner, Michelle
Cc: Meghan O'Neill
Subject: RE: Stats IR/Zurampic/NDA 207988

Hi Michelle,
The team does have a couple of questions regarding the Stat IR. Can we set up a brief call?
Thanks,
Kimberly

From: Kimberly Manhard
Sent: Wednesday, October 07, 2015 11:15 AM

To: 'Jordan Garner, Michelle'
Cc: Meghan O'Neill
Subject: RE: Stats IR/Zurampic/NDA 207988

Thank you, Michelle. We have received the Stats IR and will let you know if we have any questions.

From: Jordan Garner, Michelle [mailto:Michelle.Jordan@fda.hhs.gov]
Sent: Wednesday, October 07, 2015 10:26 AM
To: Kimberly Manhard
Cc: Meghan O'Neill
Subject: Stats IR/Zurampic/NDA 207988

Kimberly,

Attached is the IR that was mentioned during today's tcon. Let me know if you have any questions/concerns, and that you have received.

Michelle JGarner

Michelle Jordan Garner, MS, OTR/L
CDR, U.S. Public Health Service
Sr. Regulatory Management Officer
Food and Drug Administration
Center for Drug Evaluation and Research/ODEII
Division of Pulmonary, Allergy, and Rheumatology Products
10903 New Hampshire Ave., Bldg 22, Room 3200
Silver Spring, MD 20993

Telephone: 301-796-4786
Fax: 301-796-9728
Email: michelle.jordan@.fda.hhs.gov

Please note: Ardea Biosciences Inc. has moved! Effective December 8, 2014, our new address is 9390 Towne Centre Drive, San Diego CA 92121. This email message is for the sole use of the intended recipient(s) and may contain confidential and privileged information. Any unauthorized review, use, disclosure or distribution is proh bited. If you are not the intended recipient, please contact the sender by reply email and destroy all copies of the original message. If you are the intended recipient, please be advised that the content of this message is subject to access, review and disclosure by the sender's Email System Administrator.

Please note: Ardea Biosciences Inc. has moved! Effective December 8, 2014, our new address is 9390 Towne Centre Drive, San Diego CA 92121. This email message is for the sole use of the intended recipient(s) and may contain confidential and privileged information. Any unauthorized review, use, disclosure or distribution is proh bited. If you are not the intended recipient, please contact the sender by reply email and destroy all copies of the original message. If you are the intended recipient, please be advised that the content of this message is subject to access, review and disclosure by the sender's Email System Administrator.

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/s/

MICHELLE Y JORDAN GARNER
10/09/2015

Your NDA submission dated December 29, 2014, is currently under review. We have the following requests for additional analyses and information to help support the safety evaluation of lesinurad:

1. We request additional integrated safety analyses that compare treatment groups with respect to the following endpoints: adjudicated major adverse cardiovascular events (MACE), mortality, and serious renal adverse events. Please perform analyses based on integrated data from Studies 301, 302, and 304, as well as analyses based on integrated data from Studies 301, 302, 304, and 303. Analyses should estimate both incidence rates within treatment groups as well as incidence rate ratios (IRRs) comparing treatment groups (lesinurad 200 mg vs. placebo, lesinurad 400 mg vs. placebo, and total lesinurad vs. placebo), along with 95% confidence intervals (CIs) for the IRRs. Analyses should consider only the first event per person. The calculation of estimated rate ratios and corresponding CIs comparing treatment groups helps provide best estimates of potential increases in risk, along with estimates of the statistical uncertainty in the magnitude of the potential increases in risk. These results may be presented at the Advisory Committee meeting for discussion.

2. Clarify how person-time at risk was defined for patients who had a MACE in your calculation of exposure-adjusted incidence rates of MACE (e.g., Table 19, Cardiovascular Safety Report). For estimates of the incidence rates of first MACE, as is requested in (1) above, the person-years at risk for a patient who had a MACE should be calculated as (date of MACE – date of first dose of study drug + 1) / 365.25.

3. Submit the integrated analysis datasets and programming code used to conduct the requested analyses.

Submit to me via email at michelle.jordan@fda.hhs.gov, and officially to the NDA by **4:00p.m. EST, October 14, 2015.** If you have any questions, please contact Michelle Jordan Garner, Senior Regulatory Project Manager, at 301-796-4786.

Drafted by: MichelleJG10/7/15

Concurrence by: SBarnes10/7/15
Finalized by: MichelleJG 8/13/15

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/s/

MICHELLE Y JORDAN GARNER
10/07/2015

We are currently reviewing your pending NDA 207988. Submit revised labeling incorporating changes shown in the attached marked up PI. Additional labeling changes will be forthcoming.

Submit your response to me via email at michelle.jordan@fda.hhs.gov on or by COB (4:00p.m.) Wednesday September 16, 2015. Your response will subsequently need to be submitted officially to the NDA.

If you have any questions, please contact me at 301-796-4786.

Drafted by: MichelleJG9/9/15

Concurrence by: CFord for SBarnes 9/9/15
Finalized by: MichelleJG 9/9/15

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/s/

MICHELLE Y JORDAN GARNER
09/09/2015

NDA 207988
Lesinurad
Ardea Biosciences, Inc.

Dear Ms. Manhard:

We are currently reviewing your submission dated December 25, 2014, and have the following requests for information.

1. Supply the missing data in the table below:

Exposure-Adjusted Incidence of Death in Studies 301, 302, 303, and 304

	Combined 12-M, Studies 301, 302 and 304				6-M, Monotherapy Study 303	
	PBO+ XOI	**LESU200 mg + XOI**	**LESU400 mg + XOI**	**Total Lesinurad + XOI**	**PBO**	**LESU400 mg**
Number of Subjects	516	511	510	1021	107	107
Subject-Year	421.3	414.6	413			
Number of deaths	0	2	3	5	0	1
Death Rate/100 Subject-Years	0	0.48	0.73			
95% Confidence Intervals	(0.00, 0.88)	(0.06,1.74)	(0.15, 2.12)			

2. Submit the following 3 death narratives (they were not found in the submission in the corresponding clinical study reports):

   Subject 203-0401-111 (link to narrative is not functional)
   Subject 203-0309-005
   Subject 118-001-009

In order to facilitate the review of your submission, provide the requested information no later than the close of business Wednesday, August 26, 2015. You may submit your response via telephone facsimile at 301-796-9728, or by email to phuong.ton@fda.hhs.gov, followed by an official submission to your NDA.

If you have any questions, please contact Nina Ton, Regulatory Project Manager, at 301-796-1648.

NDA 207988
Lesinurad
Ardea Biosciences, Inc.

Drafted by: NTon/August 21, 2015
Cleared by: RNeuner/August 21, 2015
SYim/August 21, 2015
SBarnes/August 21, 2015
Finalized by: NTon/August 21, 2015

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/s/

PHUONG N TON
08/21/2015

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 207988

METHODS VALIDATION
MATERIALS RECEIVED

Ardea Biosciences, Inc.
Attention: Kimberly Manhard
9390 Towne Centre Drive
San Diego, CA 92121

Dear Kimberly Manhard:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Zurampic (lesinurad) Tablets, 200 mg and to our August 7, 2015, letter requesting sample materials for methods validation testing.

We acknowledge receipt on August 18, 2015, of the sample materials and documentation that you sent to the Division of Pharmaceutical Analysis (DPA) in St. Louis.

If you have questions, you may contact me by telephone (314-539-2155), FAX (314-539-2113), or email (Laura.Pogue@fda.hhs.gov).

Sincerely,

{See appended electronic signature page}

Laura C. Pogue, Ph.D.
MVP Coordinator
Division of Pharmaceutical Analysis
Office of Testing and Research
Office of Pharmaceutical Science
Center for Drug Evaluation and Research

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

/s/

LAURA POGUE
08/20/2015

Your NDA submission dated December 29, 2014, is currently under review. We have the following request for information:

1. There were a total of 4 more deaths reported in the ongoing extension studies in your 120-day safety update. Provide updated MACE rates, per 100 PYE, for each treatment group for the pooled analysis of all studies in the phase 3 program (studies 301 through 307) that includes the 3 out of 4 deaths attributed to MACE by the CEAC.

2. Provide overall death incidence rates per 100 PYE for each treatment group of the pooled analysis for the 12-month controlled period of the phase 3 pivotal studies (301, 302, and 304).

Submit to me via email at michelle.jordan@fda.hhs.gov, and officially to the NDA by **4:00p.m. EST, August 19, 2015.** If you have any questions, please contact Michelle Jordan Garner, Senior Regulatory Project Manager, at 301-796-4786.

Drafted by: MichelleJG8/13/15

Concurrence by: SBarnes8/13/15
Finalized by: MichelleJG 8/13/15

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/s/

MICHELLE Y JORDAN GARNER
08/14/2015

Your NDA submission dated December 29, 2014, is currently under review.

1. We refer to your June 8, 2015 response to the statistical IR, issued on June 3, 2015, requesting the analysis program of Mean Rate of Gout Flares Requiring Treatment per Subject for the 6-Month Period from the End of Month 6 to the End of Month 12. In your response you used "log follow-up time" in your text description, and variable logoff set in your sample SAS program. We have the following request for information:

   Clarify the exposure variable name you used in deriving the offset.

2. When you submitted your NDA, you did not include the DMFs on item #30, *"Cross References (List related BLAs, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, MAFs, and DMFs referenced in the current application.),"* of Form FDA 356h. Therefore, include this information on the 356h that you will include in your official submission response to this information request.

Submit to me via email at michelle.jordan@fda.hhs.gov, and officially to the NDA by **4:00p.m. EST, August 13, 2015.** If you have any questions, please contact Michelle Jordan Garner, Senior Regulatory Project Manager, at 301-796-4786.

Drafted by: MJordanGarner/8/7/15

Concurrence by: SBarnes8/12/15
Finalized by: MichelleJG8/12/15

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/s/

MICHELLE Y JORDAN GARNER
08/12/2015

Aisida, Bamidele (Florence)

From: Aisida, Bamidele (Florence)
Sent: Wednesday, August 12, 2015 9:52 AM
To: 'moneill@ardeabio.com'
Cc: 'KManhard@ardeabio.com'
Subject: NDA 207988

Dear Ms. O'Neil,

We are reviewing the CMC section of your submission and have the following comments and information requests. We request a prompt written response by August 19, 2015 in order to continue our evaluation of your NDA.

1. In response to CMC Information Request dated June 4, 2015, you proposed the following drug substance (DS) particle size distribution (PSD) specification limits:

   - D(v, 0.5) NMT (b)(4) µm
   - D(v, 0.9) NMT (b)(4) µm

   The submitted PSD specification limit exceeds the limits of distribution used in clinical batches of Lesinurad (pg.9 Table 3). It is recommended to set DS PSD ranges based on batches tested in the clinical trials and confirmed by in vitro dissolution testing. Additionally, it is recommended to set a lower bound for the D(v, 0.5) based on the provided data. Therefore the following PSD specification limits are recommended:

   - D(v, 0.5) (b)(4) µm
   - D(v, 0.9) NMT (b)(4) µm

   The FDA is in agreement that a specification limit for D(v, 0.1) is unnecessary.

If I can provide you with any further information, please let me know.

Thanks,

Florence Aisida, Pharm.D,BCPS
Regulatory Business Process Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research
Food and Drug Administration
Phone: (240) 402-2691
Email: bamidele.aisida@fda.hhs.gov

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

REQUEST FOR METHODS VALIDATION MATERIALS

NDA 207988 August 7, 2015

Ardea Biosciences, Inc.
Attention: Kimberly Manhard
9390 Towne Centre Drive
San Diego, CA 92121

Dear Kimberly Manhard:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Zurampic (lesinurad) Tablets, 200 mg.

We will be performing methods validation studies on Zurampic (lesinurad) Tablets, 200 mg, as described in NDA 207988.

In order to perform the necessary testing, we request the following sample materials and equipments:

Method, current version

3.2.S.4.2	Analytical Procedure for Lesinurad Identity by HPLC
3.2.S.4.2	Analytical Procedure for Lesinurad Assay by HPLC
3.2.S.4.2	Analytical Procedure for Lesinurad Organic Impurities Content by HPLC
3.2.P.5.2	Analytical Procedure for Lesinurad Identification by HPLC/UV Spectrum and Retention Time
3.2.P.5.2	Analytical Procedure for Lesinurad Assay by HPLC
3.2.P.5.2	Analytical Procedure for Lesinurad Degradation Products Content by HPLC

Samples and Reference Standards

2	500 mg Lesinurad reference standard
2	500 mg Lesinurad drug substance
2	60 tablets Lesinurad drug product
1	200 mg of each Impurity: (b) (4)

Equipment

1	(b) (4)

Please include the MSDSs and the Certificates of Analysis for the sample and reference materials.

Forward these materials via express or overnight mail to:

Food and Drug Administration
Division of Pharmaceutical Analysis
Attn: MVP Sample Custodian
645 S Newstead
St. Louis, MO 63110

Please notify me upon receipt of this email. You may contact me by telephone (314-539-2155), FAX (314-539-2113), or email (Laura.Pogue@fda.hhs.gov).

Sincerely,

{See appended electronic signature page}

Laura C. Pogue, Ph.D.
MVP coordinator
Division of Pharmaceutical Analysis
Office of Testing and Research
Office of Pharmaceutical Science
Center for Drug Evaluation and Research

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/s/

LAURA POGUE
08/07/2015

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

Sent: 08/07/2015 09:22:02 AM
To: KManhard@ardeabio.com
CC:
BCC: bamidele.aisida@fda.hhs.gov
Subject: NDA INFORMATION REQUEST

Please see attached and confirm receipt

Florence Aisida, Pharm.D,BCPS
Regulatory Business Process Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research
Food and Drug Administration
Phone: (240) 402-2691
Email: bamidele.aisida@fda.hhs.gov

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 207988

INFORMATION REQUEST

Ardea Biosciences, Inc.
Attn: Kimberly Manhard
Senior Vice President, Regulatory Affairs and Development Operations
9390 Towne Centre Drive
San Diego, CA 92121

Dear Ms. Manhard:

Please refer to your New Drug Application (NDA) dated and received December 29, 2014, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA), for Zurampic (lesinurad) Tablet.

We are reviewing the CMC section of your submission and have the following comments and information requests. We request a prompt written response by August 14, 2015 in order to continue our evaluation of your NDA.

Film Coat Specification (Opadry Blue product number [redacted] (b) (4)):

1. Include your test procedure "identification (ID) by color difference" in Section P.4.2.
2. Provide a Letter of Authorization for DMF [redacted] (b) (4) that includes a specific page and date reference to the test methods and the method validation.
3. Amend the specifications to include a requirement for a COA, as requested in our Information request letter dated June 3, 2015.

Biopharmaceutics:

1. The submitted dissolution profiles of lesinurad tablets 200 mg (lots used in clinical studies) with the proposed dissolution testing method (50 mM Acetate Buffer, pH 4.5 plus 1% SLS, Apparatus 2 (paddles) at 75 rpm) do not provide adequate support of the proposed 30-minute time point dissolution specification for the following reasons:

[redacted] (b) (4)

2. The strategy of using [redacted] (b) (4) is never used by the FDA to set in vitro dissolution acceptance criteria.
3. To aid in the regulatory-decision making in terms of setting the appropriate dissolution acceptance criterion for your proposed product, provide the following information/data:
    a. Batch numbers 12E058 and MPAC behave as outliers (e.g. [redacted] (b) (4) [redacted] (b) (4)). Provide an explanation for the observed dissolution behavior, including data on [redacted] (b) (4) [redacted] etc.
    b. If available, submit in vivo data (e.g. PK data) demonstrating that batches with a similar dissolution profile to batches 12E058 and MPAC do not have an impact on systemic exposure.
    c. If in vivo data are not available, consider providing in *silico* predictions (e.g. GastroPlus predictions) on the impact of lower dissolution profiles (e.g. comparable to those observed for batch 12E058) on the systemic exposure of your drug product.

If you have any questions, call Florence Aisida, Regulatory Process business Manager, at (240) 402-2691.

Sincerely,

Craig M. Bertha -S

Digitally signed by Craig M. Bertha -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300103470, cn=Craig M. Bertha -S
Date: 2015.08.07 05:43:13 -04'00'

Craig M. Bertha, Ph.D.
Application Technical Lead
Branch IV, Division II
Office of New Drug Products
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

Your NDA submission dated December 29, 2014, is currently under review. We have the following request for information:

> Submit the database lock dates for the following studies: RDEA594-301, RDEA594-302, RDEA594-303, and RDEA594-304. If you have provided this information in a previous submission, identify the submission(s) where this information may be found.

Submit to me via email at michelle.jordan@fda.hhs.gov, and officially to the NDA by **4:00p.m. EST, August 3, 2015.** If you have any questions, please contact Michelle Jordan Garner, Senior Regulatory Project Manager, at 301-796-4786.

Drafted by: MichelleJG7/29/15

Concurrence by: SBarnes7/29/15
Finalized by: MichelleJG 7/29/15

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/s/

MICHELLE Y JORDAN GARNER
07/30/2015

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 207988

MID-CYCLE COMMUNICATION

Ardea Biosciences, Inc.
9390 Towne Centre Drive
San Diego, CA 92121

Attention: Kimberly Manhard,
Senior Vice President, Regulatory Affairs and Development Operations

Dear Ms. Manhard:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Zurampic (lesinurad) 200 mg tablets.

We also refer to the teleconference between representatives of your firm and the FDA on June 10, 2015. The purpose of the teleconference was to provide you an update on the status of the review of your application.

A record of the teleconference is enclosed for your information.

If you have any questions, call me at (301) 796-4786.

Sincerely,

{See appended electronic signature page}

Michelle Jordan Garner, MS, OTR/L
Senior Regulatory Management Officer
Division of Pulmonary, Allergy, and Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure:
Mid-Cycle Communication

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MID-CYCLE COMMUNICATION

Meeting Date and Time: June 10, 2015; 12:00 P.M.

Application Number: NDA 207988
Product Name: Zurampic (lesinurad)
Indication: Treatment of hyperuricemia associated with gout
Applicant Name: Ardea Biosciences, Inc.

Meeting Chair: Sarah Yim, MD
Meeting Recorder: Michelle Jordan Garner, MS, OTR/L

FDA ATTENDEES

Division of Pulmonary, Allergy, and Rheumatology Products
Badrul A. Chowdhury, MD, PhD, Division Director
Sarah Yim, MD, Supervisory Associate Director
Rosemarie Neuner, MD, Clinical Reviewer,
Timothy Robison, PhD, Pharmacology/Toxicology Team Leader
Matthew Whittaker, PhD, Pharmacology/Toxicology Reviewer
Michelle Jordan Garner, MS, OTR/L, Senior Regulatory Management Officer
LeAnn Brodhead, PharmD, Regulatory Health Project Manager
Division of Clinical Pharmacology 2
Ping Ji, PhD, Clinical Pharmacology (acting) Team Leader
Jianmeng Chen, PhD, Clinical Pharmacology Reviewer
Anuradha Ramamoorthy, PhD, Clinical Pharmacology Reviewer
Office of Pharmaceutical Quality
Craig Bertha, PhD, Quality Assessment Lead
Division of Biometrics II
Ruthanna Davi, PhD, Biostatistics Team Leader
Yu Wang, PhD, Biostatistics Reviewer
Office of Surveillance and Epidemiology
Jamie Wilkins Parker, Risk Management Team Leader
Jasminder Kumar, Risk Management Reviewer
Teresa McMilan, Medication Error Prevention and Analysis Reviewer
Neil Vora, Regulatory Health Project Manager
Division of Scientific Inspections
Anthony Orencia, MD, Medical Officer

APPLICANT ATTENDEES

James Mackay, PhD, President and Chief Operating Officer, Ardea

Kimberly Manhard, Senior Vice President, Regulatory Affairs and Development Operations, Ardea
Chris Storgard, MD, Vice President, Clinical Research and Development, Ardea
Nihar Bhakta, MD, Executive Medical Director, Clinical Development, Ardea
Maple Fung, MD, Senior Medical Director, Clinical Development, Ardea
Scott Adler, MD, Senior Medical Director, Inflammation, Clinical Development, AstraZeneca
Lalitha Aiyer, MD, Executive Director, Pharmacovigilance, Ardea
William Bushnell, MS, Global Project Statistician, AstraZeneca
Jeff Kopicko, MSPH, Senior Director, Biometrics, Ardea
Clynn Wilker, PhD, DVM, DACT, Executive Director, Toxicology, Ardea
Caroline Lee, PhD, Senior Director, Drug Metabolism and Pharmacokinetics, Ardea
(b) (4) Clinical Pharmacokineticist, Consultant to Ardea
Colin Rowlings, PhD, Senior Vice President, Pharmaceutical Sciences, Ardea
Jean-Luc Girardet, Vice President, Chemistry and Translational Sciences, Ardea
Sonia Villegas, PhD, Senior Regulatory Affairs Associate II, Ardea
Diane Alleva, PhD, Director, Global Regulatory Affairs, CMC, AstraZeneca
Meghan O'Neill, Manager, Regulatory Affairs,

1.0 INTRODUCTION

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may or may not be able to consider your response before we take an action on your application during this review cycle.

2.0 SIGNIFICANT ISSUES

Clinical:

1. We have identified the following efficacy and safety issues based on our ongoing review of the data submitted in support of this NDA:

    a. Efficacy issues: Lesinurad has a modest treatment effect on lowering serum uric acid (i.e., approximate mean decrease of 1 mg/dl for the 200 mg dose). This raises at least 2 concerns:

        i. It is unclear whether the treatment effect seen when lesinurad is administered with 300 mg of allopurinol would persist if patients were treated with higher doses of allopurinol.

ii. Because the treatment effect is modest, the risk-benefit profile of lesinurad is not clearly favorable in light of potential safety concerns (mentioned below) and will require further discussion, including discussion by the Arthritis Advisory Committee.

b. Safety issues include:

i. Renal toxicity: In addition to urolithiasis and elevations in serum creatinine, particularly at higher doses, the lesinurad safety database contains cases of acute renal failure that resulted in subjects initiating hemodialysis. Additionally, it is unclear whether the safety precautions implemented in your trials ameliorated this concern.

ii. Continued concerns regarding a potential cardiovascular signal in view of the imbalance in deaths and number of dose dependent MACE events that occurred in subjects treated with lesinurad

iii. Due to the small number of subjects who took concomitant doses of allopurinol > 300 mg per day, we are unable to determine if higher doses of allopurinol will have a negative impact on lesinurad's safety profile

2. In view of the above efficacy and safety issues that have been identified thus far, if the risk/benefit profile is determined to be acceptable for the 200 mg once a day dose of lesinurad, it is likely your proposed labeling will be inadequate, and a boxed warning may be needed. Additionally, Warnings and Precautions may need to include cardiovascular adverse outcomes. Furthermore, it is unclear whether the data support a general description of "XOI" in light of the limited data on higher doses of allopurinol and failed primary analysis for Study 304. However, we will defer detailed discussion of labeling pending more definitive determination regarding the acceptability of the overall risk-benefit profile of lesinurad.

CMC/Biopharm:
See information request section below.

Pharmacology/Toxicology:
No significant issues have been identified at this time.

Clinical Pharmacology:
Lesinurad should not be recommended for patients with moderate or severe renal impairment, based on preliminary review for PK, efficacy, and safety in these patients.

3.0 INFORMATION REQUESTS

CMC IR sent June 4, 2015 due prior to July 17, 2015. TCON discussion with product quality team took place June 10, 2015.

4.0 MAJOR SAFETY CONCERNS/RISK MANAGEMENT

At this time, the Office of New Drugs and the Office of Surveillance and Epidemiology have insufficient information to conclusively determine whether a risk evaluation and mitigation strategy (REMS) will be necessary to ensure that the benefits of the drug outweigh the risks. However, based on the information currently available, we do not believe that a REMS will be necessary. We will make a final determination for the need for a REMS at the completion of the review cycle.

5.0 ADVISORY COMMITTEE MEETING

An Advisory Committee meeting is scheduled for October 23, 2015. More details to follow as they are developed.

6.0 LATE-CYCLE MEETING /OTHER PROJECTED MILESTONES

- Labeling negotiations begin September 9, 2015
- Labeling and LCM tcon scheduled September 17, 2015
    - Agency Briefing Package due to applicant - Sept 11, 2015
- PDUFA goal date: December 29, 2015

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/s/

MICHELLE Y JORDAN GARNER
07/09/2015

NDA 207988 **INFORMATION REQUEST**

Ardea Biosciences
Attention: Kimberly J. Manhard
Senior Vice President
Regulatory Affairs and Developmental Operations
9390 Towne Centre Drive
San Diego CA 92121

Dear Vice President Manhard:

Please refer to your original New Drug Application received December 29, 2014, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Zurampic (lesinurad).

We are reviewing your submission and have the following comment. We request a prompt written response in order to continue our evaluation of your supplement. Please submit your response prior to **July 17, 2015.**

1. Provide data to show that the Identification test for the blue film coating, Opadry Blue (b) (4) is specific for that particular coating. Amend the receiving specifications for the film coating to include a requirement for a COA from the supplier.
2. Regarding the test method for the Assay and Degradation Products
    a. Include directions for storage conditions and times for the standard and test solutions in the test procedure.
    b. Specify the blank to be used.
    c. Provide data to show the effect of (b) (4) on recovery of the drug substance or degradants.
3. Regarding the Specifications
    a. Revise the acceptance criterion for the degradant (b) (4) in the drug product to NMT (b) (4)%.
    b. Revise the acceptance criterion for "total degradation products" to NMT (b) (4)%, since this parameter should only reflect the sum of known (b) (4) and individual unspecified degradation products (b) (4)
4. Provide a commitment to continue the long-term studies through the proposed shelf life.
5. Amend the tablet composition to show the different composition of (b) (4) (b) (4) consistent with the batch record.
6. Amend the batch formula to show the different composition of (b) (4) consistent with the batch record.
7. Amend the tablet manufacturing process description to show (b) (4) in making a batch of tablets, consistent with the batch record.

8. Amend the tablet manufacturing process flow diagram to show [redacted], consistent with the batch record.
9. Provide a test for particle size distribution (PSD) in the drug substance specification and associated acceptance criteria that are representative of PSD data ranges from drug substance used in pivotal clinical batches. We do not agree [redacted]
10. The proposed dissolution acceptance criterion of [redacted]% Q in [redacted] minutes is unacceptable as it lacks discriminatory capability between formulations that did not demonstrate bioequivalency in clinical study (Study 109). A data-driven dissolution acceptance criterion of [redacted]% Q in [redacted] minutes is recommended for lesinurad tablets 200 mg.
Implement the recommended dissolution acceptance criterion for your proposed product and provide the revised specifications table.

Sincerely,

Andrew Shiber -A

Digitally signed by Andrew Shiber -A
DN: c=US, e=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Andrew Shiber -A, 0.9.2342.19200300.100.1.1=00142621 41
Date: 2015.06.04 11:26:39 -04'00'

CDR Andrew Shiber, Pharm.D.
United States Public Health Service
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

Jordan Garner, Michelle

From: Jordan Garner, Michelle
Sent: Wednesday, June 03, 2015 12:40 PM
To: Kimberly Manhard
Cc: Meghan O'Neill; Jordan Garner, Michelle
Subject: RE: Stats IR: Zurampic/NDA 207988 - URGENT CLARIFICATIION REQUESTED

Hi Kimberly,

While our IR required the submission of stats programs related to key efficacy endpoints analysis, you only submitted programs for the primary efficacy endpoint. We also need you to submit key secondary endpoint analysis programs too. Specifically, for study 301, 302, and 304, submit

1. Programs for rate of Gout Flare analysis,
2. Programs for proportion of Tophi CR (or partial in 304) analysis;

and, for study 304, submit

3. Program for proportion of improvement in HAQ-DI.

Therefore, please submit this information ASAP.

Michelle JGarner

Michelle Jordan Garner, MS, OTR/L
CDR, U.S. Public Health Service
Sr. Regulatory Management Officer
Food and Drug Administration
Center for Drug Evaluation and Research/ODEII
Division of Pulmonary, Allergy, and Rheumatology Products
10903 New Hampshire Ave., Bldg 22, Room 3200
Silver Spring, MD 20993

Telephone: 301-796-4786
Fax: 301-796-9728
Email: michelle.jordan@.fda.hhs.gov

From: Kimberly Manhard [mailto:KManhard@ardeabio.com]
Sent: Tuesday, June 02, 2015 5:37 PM
To: Jordan Garner, Michelle
Cc: Meghan O'Neill
Subject: RE: Stats IR: Zurampic/NDA 207988 - URGENT CLARIFICATIION REQUESTED

Hi Michelle,
Hope all is going well. I am sure it is an extremely busy time for you now.

Last Tuesday we had submitted the response to the Stats IR, which included the statistical analysis programs for the primary endpoint for each of the pivotal studies and the additional secondary endpoints (b) (4) Since the request was not very specific (statistical programs for key efficacy endpoints) we asked for confirmation that these program met the needs.

Please confirm that the response provided in Sequence 0013 adequately addresses the Stats Information Request. We are happy to send additional statistical programs (ie, key secondary endpoints), if needed.

Thank you in advance for your assistance.

Kind regards,
Kimberly

From: Jordan Garner, Michelle [mailto:Michelle.Jordan@fda.hhs.gov]
Sent: Tuesday, May 26, 2015 1:00 PM
To: Kimberly Manhard
Subject: RE: Stats IR: Zurampic/NDA 207988 - URGENT CLARIFICATIION REQUESTED

Thanks for the clarification. Therefore, I can delete this email because I received the Gateway submission of the same.

Michelle JGarner

Michelle Jordan Garner, MS, OTR/L
CDR, U.S. Public Health Service
Sr. Regulatory Management Officer
Food and Drug Administration
Center for Drug Evaluation and Research/ODEII
Division of Pulmonary, Allergy, and Rheumatology Products
10903 New Hampshire Ave., Bldg 22, Room 3200
Silver Spring, MD 20993

Telephone: 301-796-4786
Fax: 301-796-9728
Email: michelle.jordan@.fda.hhs.gov

From: Kimberly Manhard [mailto:KManhard@ardeabio.com]
Sent: Tuesday, May 26, 2015 3:58 PM
To: Jordan Garner, Michelle
Cc: Meghan O'Neill
Subject: RE: Stats IR: Zurampic/NDA 207988 - URGENT CLARIFICATIION REQUESTED

Hi Michelle,
This information is the same as what was submitted today in Sequence 0013 to address the **Stats IR** with the exception that I did not include form 356h with the e-mail. This Stats IR response was due today by 4pm EST.

This is not the same as what was submitted on May 22nd. On May 22nd in Sequence 0012 we submitted the response to the **OSI Facilities Inspection IR** that was due on May 29th. I also sent the information from Sequence 0012 via e-mail to you on that same day for the OSI IR.

Please let me know if you have any further questions.

Kind regards,
Kimberly

From: Jordan Garner, Michelle [mailto:Michelle.Jordan@fda.hhs.gov]
Sent: Tuesday, May 26, 2015 12:31 PM
To: Kimberly Manhard

Cc: Meghan O'Neill
Subject: RE: Stats IR: Zurampic/NDA 207988 - URGENT CLARIFICATIION REQUESTED

Is this information in addition to what was sent to the NDA, and what was sent via email 5/22/15?

Michelle JGarner

Michelle Jordan Garner, MS, OTR/L
CDR, U.S. Public Health Service
Sr. Regulatory Management Officer
Food and Drug Administration
Center for Drug Evaluation and Research/ODEII
Division of Pulmonary, Allergy, and Rheumatology Products
10903 New Hampshire Ave., Bldg 22, Room 3200
Silver Spring, MD 20993

Telephone: 301-796-4786
Fax: 301-796-9728
Email: michelle.jordan@.fda.hhs.gov

From: Kimberly Manhard [mailto:KManhard@ardeabio.com]
Sent: Tuesday, May 26, 2015 2:41 PM
To: Jordan Garner, Michelle
Cc: Meghan O'Neill
Subject: RE: Stats IR: Zurampic/NDA 207988 - URGENT CLARIFICATIION REQUESTED

Dear Michelle,
Please find attached the following 10 files submitted today in Sequence 0013 in response to the Statistical Information Request asking for the statistical analysis programs for the key efficacy endpoints.

- Cover letter
- Response document
- Zip file including 2 statistical analysis programs as .txt files for Study 301
- Zip file including 2 statistical analysis programs as .txt files for Study 302
- Zip file including 3 statistical analysis programs as .txt files for Study 304
- Define.pdf file

The key efficacy endpoints were not defined in the request. Ardea has provided the statistical analysis programs for the primary endpoint for each of the studies and the additional secondary endpoints (b) (4)

Please confirm that this response adequately addresses the Information Request.

Kind regards,
Kimberly

From: Jordan Garner, Michelle [mailto:Michelle.Jordan@fda.hhs.gov]
Sent: Thursday, May 21, 2015 2:02 PM
To: Kimberly Manhard
Subject: RE: Stats IR: Zurampic/NDA 207988 - URGENT CLARIFICATIION REQUESTED

Yes, presenting as .txt files is acceptable.

Michelle JGarner

Michelle Jordan Garner, MS, OTR/L
CDR, U.S. Public Health Service
Sr. Regulatory Management Officer
Food and Drug Administration
Center for Drug Evaluation and Research/ODEII
Division of Pulmonary, Allergy, and Rheumatology Products
10903 New Hampshire Ave., Bldg 22, Room 3200
Silver Spring, MD 20993

Telephone: 301-796-4786
Fax: 301-796-9728
Email: michelle.jordan@.fda.hhs.gov

From: Kimberly Manhard [mailto:KManhard@ardeabio.com]
Sent: Thursday, May 21, 2015 4:47 PM
To: Jordan Garner, Michelle
Cc: Meghan O'Neill
Subject: RE: Stats IR: Zurampic/NDA 207988 - URGENT CLARIFICATIION REQUESTED
Importance: High

Dear Michelle,
Our statistical contractor has a question for the Agency. To meet the timeline a response is needed urgently.

> Agency Request:
> Submit statistical analysis programs for the main analysis of the key efficacy endpoints in the pivotal phase 3 studies. Provide sufficient coding, so that we may understand how you used the derived variables and records included in your analysis datasets for these analyses.
>
> Ardea Question:
> **To address this request, we intend to provide the requested statistical analysis programs as .txt files. Does the Agency agree this is acceptable?**

Thank you in advance.

Kind regards,
Kimberly

From: Jordan Garner, Michelle [mailto:Michelle.Jordan@fda.hhs.gov]
Sent: Thursday, May 21, 2015 9:42 AM
To: Kimberly Manhard
Cc: Meghan O'Neill
Subject: Stats IR: Zurampic/NDA 207988

Hi Kimberly,

Attached please find a stats IR. Note the response date of May 26, 2015. Please let me know that you have received this correspondence, and if you have any questions/concerns.

Michelle JGarner

Michelle Jordan Garner, MS, OTR/L

CDR, U.S. Public Health Service
Sr. Regulatory Management Officer
Food and Drug Administration
Center for Drug Evaluation and Research/ODEII
Division of Pulmonary, Allergy, and Rheumatology Products
10903 New Hampshire Ave., Bldg 22, Room 3200
Silver Spring, MD 20993

Telephone: 301-796-4786
Fax: 301-796-9728
Email: michelle.jordan@.fda.hhs.gov

Please note: Ardea Biosciences Inc. has moved! Effective December 8, 2014, our new address is 9390 Towne Centre Drive, San Diego CA 92121. This email message is for the sole use of the intended recipient(s) and may contain confidential and privileged information. Any unauthorized review, use, disclosure or distribution is proh bited. If you are not the intended recipient, please contact the sender by reply email and destroy all copies of the original message. If you are the intended recipient, please be advised that the content of this message is subject to access, review and disclosure by the sender's Email System Administrator.

Please note: Ardea Biosciences Inc. has moved! Effective December 8, 2014, our new address is 9390 Towne Centre Drive, San Diego CA 92121. This email message is for the sole use of the intended recipient(s) and may contain confidential and privileged information. Any unauthorized review, use, disclosure or distribution is proh bited. If you are not the intended recipient, please contact the sender by reply email and destroy all copies of the original message. If you are the intended recipient, please be advised that the content of this message is subject to access, review and disclosure by the sender's Email System Administrator.

Please note: Ardea Biosciences Inc. has moved! Effective December 8, 2014, our new address is 9390 Towne Centre Drive, San Diego CA 92121. This email message is for the sole use of the intended recipient(s) and may contain confidential and privileged information. Any unauthorized review, use, disclosure or distribution is proh bited. If you are not the intended recipient, please contact the sender by reply email and destroy all copies of the original message. If you are the intended recipient, please be advised that the content of this message is subject to access, review and disclosure by the sender's Email System Administrator.

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/s/

MICHELLE Y JORDAN GARNER
06/03/2015

Your NDA submission dated December 29, 2014, is currently under review. We have the following request for information:

> Submit statistical analysis programs for the main analysis of the key efficacy endpoints in the pivotal phase 3 studies. Provide sufficient coding, so that we may understand how you used the derived variables and records included in your analysis datasets for these analyses.

Submit to me via email at michelle.jordan@fda.hhs.gov, and officially to the NDA by **4:00p.m. EST, May 26, 2015.** If you have any questions, please contact Michelle Jordan Garner, Senior Regulatory Project Manager, at 301-796-4786.

Drafted by: MichelleJG5/20/15

Concurrence by: CFord (for SandyB)/ May 21, 2015
Finalized by: MichelleJG 5/21/15

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/s/

MICHELLE Y JORDAN GARNER
05/21/2015

Your NDA submission dated December 29, 2014, is currently under review. We have the following request for information:

Provide the clinical study site subject data listings to capture the following, as applicable, for Douglas Radman, MD (Study 301 Site 05335), Wymon Drummond, MD (Study 301 Site 05185), and Alan Miller, MD (Study 302 Site 5394):

a. Subject discontinuations (If applicable sorted by treatment group and including the following variables: site subject number, screening visit date, randomization date (if applicable), date of first dose/last dose, date of discontinuation, reason for discontinuation).

b. Subject assignment per treatment arm (randomization group, as applicable).

c. Concomitant medication list (non-study medications).

d. All adverse events (If applicable per treatment group: preferred term/investigator entry, date start/stopped, severity/resolution, serious adverse event (SAE [yes/no], death [yes/no]).

e. Primary study efficacy endpoint.

f. Any protocol deviations or violations.

Submit to me via email at michelle.jordan@fda.hhs.gov, and officially to the NDA by **4:00p.m. EST, May 29, 2015.** If you have any questions, please contact Michelle Jordan Garner, Senior Regulatory Project Manager, at 301-796-4786.

Drafted by: MichelleJG5/18/15

Concurrence by: CJackson (for SandyB)/ May 18, 2015
Finalized by: MichelleJG 5/19/15

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/s/

MICHELLE Y JORDAN GARNER
05/19/2015

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 207988

INFORMATION REQUEST

Ardea Biosciences, Inc.
Attn: Kimberly Manhard
Senior Vice President
Regulatory Affairs and Development Operations
9390 Towne Centre Drive
San Diego, CA 92121

Dear Ms. Manhard:

Please refer to your New Drug Application (NDA) dated and received December 29, 2014, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA), for Zurampic (lesinurad) Tablets, 200 mg.

We are reviewing the CMC section of your submission and have the following comments and information requests. We request a prompt written response by May 15, 2015 in order to continue our evaluation of your NDA.

A. The Drug Substance:

1. Provide identification numbers for all non-compendial analytical methods used in the drug substance specifications.

2. Provide identification numbers for all non-compendial validation protocols used in the testing of the lesinurad drug substance.

B. The Manufacturing Process.

1. Specify the (b) (4) quantity of hypromellose used (b) (4).
2. Specify the (b) (4) quantity of crospovidone used (b) (4)
3. Specify the quantity of (b) (4) magnesium stearate, (b) (4)
4. Tighten the (b) (4) limits for tablet hardness (b) (4) or provide further justification.

If you have any questions, call Youbang Liu, Regulatory Project Manager, at (301) 796-1926.

Sincerely,

Craig M. Bertha -S

Digitally signed by Craig M. Bertha -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=13001034 70, cn=Craig M. Bertha -S
Date: 2015.04.24 13:34:58 -04'00'

Craig M. Bertha, Ph.D.
Application Technical Lead
Branch IV, Division II
Office of New Drug Products
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 207988

PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE

Ardea Biosciences, Inc.
9390 Towne Centre Drive
San Diego, CA 92121

ATTENTION: Kimberly J. Manhard
Senior Vice President, Regulatory Affairs and Development Operations

Dear Ms. Manhard:

Please refer to your New Drug Application (NDA) dated December 25, 2014, received December 29, 2014, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Lesinurad Tablets, 200 mg.

We also refer to your correspondence, dated and received January 12, 2015, requesting review of your proposed proprietary name, Zurampic.

We have completed our review of the proposed proprietary name, Zurampic and have concluded that this name is conditionally acceptable.

If any of the proposed product characteristics as stated in your January 12, 2015, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

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 2013 through 2017, (http://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM270412.pdf)

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Sarah Harris, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (240) 402-4774. For any other information regarding this application, contact Michelle Jordan Garner, Regulatory Project Manager, in the Office of New Drugs at (301) 796-4786.

Sincerely,

{See appended electronic signature page}

Todd Bridges, RPh
Deputy Director
Division of Medication Error Prevention and Analysis
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

TODD D BRIDGES
03/17/2015

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 207988

FILING COMMUNICATION -
FILING REVIEW ISSUES IDENTIFIED

Ardea Biosciences, Inc.
9390 Towne Centre Drive
San Diego, CA 92121

Attention: Kimberly Manhard,
Senior Vice President, Regulatory Affairs and Development Operations

Dear Ms. Manhard:

Please refer to your New Drug Application (NDA) dated December 25, 2014, received December 29, 2014, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA), for Zurampic (lesinurad) 200 mg tablets.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is Standard. Therefore, the user fee goal date is December 29, 2015. This application is also subject to the provisions of "the Program" under the Prescription Drug User Fee Act (PDUFA) V (refer to http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm272170.htm.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing commitment requests by September 9, 2015.
In addition, the planned date for our internal mid-cycle review meeting is May 26, 2015. We are currently planning to hold an advisory committee meeting to discuss this application. During our filing review of your application, we identified the following potential review issues:

Clinical

1. We refer you to the minutes from the July 21, 2011 end-of-phase 2 meeting, our written responses to you dated February 28, 2014 and May 8, 2014 as well as the minutes from the October 24, 2014 pre-NDA meeting, in which we have raised concerns regarding both the safety and efficacy of lesinurad. These specific concerns include:

    a. Adequacy of dose ranging/dosing interval selection, in light of apparent dose-related safety concerns.

    b. Renal and cardiovascular safety profile of lesinurad.

    c. The interpretability of the safety data in light of the timing of the safety-related protocol amendments implemented in the then ongoing confirmatory phase 3 studies.

    d. Adequacy of the overall risk-benefit profile, especially in light of the primary efficacy results for your third pivotal study, RDEA594-304, as well as the lack of secondary outcome support in that study and in your two, replicate pivotal studies, RDEA594-301 and-302. Final determination of the drug's overall risk/benefit will be a review issue.

2. According to the labeling included in your submission, you are proposing that lesinurad be indicated for the treatment of hyperuricemia associated with gout in combination with a xanthine oxidase inhibitor. As noted in the pre-NDA filing meeting minutes, you do not appear to have the data necessary to support this expanded indication in view of the equivocal results from study RDEA594-304, which assessed the safety and efficacy of 200 mg/day of lesinurad when co-administered with 80 mg/day of febuxostat. Additionally, determination of a second line therapy indication with allopurinol in gout patients with hyperuricemia will depend upon the robustness of results from safety and efficacy subanalyses of subjects who participated in the pivotal phase 3 studies, RDEA594-301 and-302, while taking > 300 mg/day of allopurinol.

Pharmacology/Toxicology

3. There is currently no Established Pharmacologic Class for URAT1 specific inhibitors (http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/ucm162549.htm). Therefore, the suitability of the proposed language in the Indications and Usage Section of the labeling will be a review issue.

4. We acknowledge your explanation regarding the safety qualification of the M3c epoxide intermediate and the M4 metabolite in section 4.7.1 of the Nonclinical Overview. However, the safety qualification of the M3c metabolite with respect to carcinogenicity will be a review issue. We note that nonclinical exposure multiples over calculated human M3c exposures are computed on a mg/m^2 basis.

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of

deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application. If you respond to these issues during this review cycle, we may not consider your response before we take an action on your application.

We request that you submit the following information:

1. Your submitted materials provide a high level description of AstraZeneca's proposed Risk Evaluation and Mitigation Strategy (REMS). The proposed REMS includes:

    A. Communication Plan targeted to HCP though the use of a
        i. Dear Health Care Professional Letter
        ii. Zurampic REMS Website
        iii. Letters to Professional Organizations

    B. Timetable for Submission of Assessments

You submitted a single Dear Healthcare Provider (DHCP) letter (b) (4) .

    A. Provide a separate DCHP letter for each target audience with risk messaging specific to the respective target audience, and reflect these letters in the REMS document.

    B. Additionally, provide all other materials necessary to implement your proposal referred to in your REMS document (e.g., proposed communication and education materials and forms, including REMS Letters for Healthcare Providers, REMS Letters for Professional Societies, and REMS Program Website screenshots). A REMS Supporting Document outlining the program should also be provided.

For further clarification on the format and contents of proposed REMS, see FDA Guidance, "*Format and Content of Proposed Risk Evaluation and Mitigation Strategies (REMS), REMS Assessments, and Proposed REMS Modifications*" as well as a recently approved REMS found on the FDA website.

2. We acknowledge the data that you submitted to determine the impact of the Critical Material Attributes (CMA) and Critical Process Parameters (CPP) affecting dissolution.

    A. Provide data - e.g., dissolution profiles - in a graphical and tabular format as a function of the critical attributes identified.

    B. Use the proposed QC method, which supports your conclusions regarding the impact (or lack of impact) of these attributes on the dissolution profile of your proposed product, to show the discriminating power of the proposed QC dissolution method. In general the testing, conducted to demonstrate the discriminating ability of the dissolution method, should compare the dissolution profiles of the drug product manufactured under targeted conditions versus the drug products that are

intentionally manufactured with meaningful variations (i.e. [redacted] (b) (4)) for the most relevant manufacturing variables ([redacted] (b) (4) .).

C. If available, submit data showing the capability of the selected dissolution method to reject batches that are not bioequivalent. Note that the discriminating ability is not only determined by the dissolution method settings but also by the selected specification-sampling time point and specification value.

3. Your proposed dissolution acceptance criterion of "Not less than [redacted] (b) (4) % (Q) of the labeled amount of lesinurad is dissolved in [redacted] (b) (4) minutes," is not supported by the data provided and does not discriminate for aberrant batches [redacted] (b) (4) . We recommend you implement a dissolution acceptance criterion of Q= [redacted] (b) (4) % in [redacted] (b) (4) min. To further support the recommended dissolution acceptance criterion, submit the following information/data:

A. Individual and mean dissolution profiles (in tabular and graphical form) from all pivotal phase 3 batches.

B. The drug substance PSD (D10, D50, D90) and coating weight gain for all batches tested in pivotal phase 3 clinical trials.

4. Provide dissolution profile comparisons with similarity testing (e.g. *f2* testing) between 2*200mg IR tablet and 400 mg IR tablet, [redacted] (b) (4) using the proposed QC dissolution method and additional media tested.

5. Provide supplier information for each of the proposed starting materials [redacted] (b) (4) used to manufacture the lesinurad drug substance. In addition, provide Certificates of Analysis from the manufacturers, and in-house acceptance criteria for each of the starting materials.

6. Provide updated structural characterization data/spectra (elemental analysis, high-resolution mass spectrum, FTIR, ^{1}H and ^{13}C NMR, UV and X-ray powder diffraction) from the most recent lesinurad lot used as the analytical reference standard (17JL02.HE00016) or another comparable lot of the drug substance manufactured by [redacted] (b) (4) at the commercial manufacturing facility. The structural characterization data submitted in the NDA for the lesinurad drug substance was obtained from the lesinurad analytical reference standard, Lot A10085-38-2 manufactured by [redacted] (b) (4) by Ardea Biosciences; which is not representative of the commercial drug substance.

7. Provide identification numbers for all non-compendial analytical methods used in the drug substance specifications.

8. Provide identification numbers for all non-compendial validation protocols used in the testing of the lesinurad drug substance.

9. Provide study data to demonstrate that the desired lesinurad (b) (4) did not change in the drug product manufacturing process, or during shelf-life storage.

PRESCRIBING INFORMATION

Your proposed prescribing information (PI) must conform to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57. We encourage you to review the labeling review resources on the *PLR Requirements for Prescribing Information* website including:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- 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 42 important format items from labeling regulations and guidances.

During our preliminary review of your submitted labeling, we have identified the following labeling issues and have the following labeling comments:

1. The Highlights (HL) section headings are not in two-column format. HL must be in a minimum of 8-point font and should be in a two-column format, with ½ inch margins on all sides and between columns.

2. The length of the HL is longer than a 1/2 page due to a lack of a two-column listing of HL headings and possibly due to the large font. The length of HL must be ½ page or less unless a waiver has been granted.

3. There is no horizontal line separating HL from the Table of Contents (TOC); or between the TOC and the Full Prescribing Information (FPI). A horizontal line must separate the HL from the TOC, and the separate the TOC from the FPI.

4. There is no horizontal line separating HL from the Table of Contents (TOC); or between the TOC and the Full Prescribing Information (FPI). A horizontal line must separate the HL from the TOC, and the separate the TOC from the FPI.

5. There is no horizontal line separating HL from the Table of Contents (TOC); or between the TOC and the Full Prescribing Information (FPI). A horizontal line must separate the HL from the TOC, and the separate the TOC from the FPI.

6. The year (2015) needs to be added after the statement, "**Initial U.S. Approval:**"

7. The revision date needs to be included at the end of the HL, bolded and right justified: "**Revised: 12/2015**"

8. The TOC is in one-column, and should be in a two-column format.

9. None of the TOC section headings are bolded, but are all in UPPER CASE. However, all section headings in the TOC must be bolded and in UPPER CASE.

10. All subsections should be indented under heading titles, in the TOC.

11. There is no "*", and no sections have been omitted. In the TOC, when a section or subsection is omitted, the numbering must not change. If a section or subsection from 201.56(d)(1) is omitted from the FPI and the TOC, the heading "FULL PRESCRIBING INFORMATION: CONTENTS" must be followed by an asterisk and the following statement must appear at the end of the TOC: "*Sections or subsections omitted from the full prescribing information are not listed."

12. Remove sections 8.2, 9, and 15 in the HL, TOC, and FPI.

13. Remove the error message located in the following: TOC –section 17, FPI- sections 4, 7.2, 8.3, 8.7, and 8.8.

14. Provide the Med Guide in Word format.

We request that you resubmit labeling (in Microsoft Word format) that addresses these issues by April 13, 2015. The resubmitted labeling will be used for further labeling discussions. Use the SRPI checklist to correct any formatting errors to ensure conformance with the format items in regulations and guidances.

At the end of labeling discussions, use the SRPI checklist to ensure that the PI conforms with format items in regulations and guidances.

Please respond to the above requests for information, no later than 30 days from the date of this letter. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

PROMOTIONAL MATERIAL

You may request advisory comments on proposed introductory advertising and promotional labeling. Please submit, in triplicate, a detailed cover letter requesting advisory comments (list each proposed promotional piece in the cover letter along with the material type and material identification code, if applicable), the proposed promotional materials in draft or mock-up form with annotated references, and the proposed package insert (PI), and Medication Guide. Submit consumer-directed, professional-directed, and television advertisement materials separately and send each submission to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

Do not submit launch materials until you have received our proposed revisions to the package insert (PI), and Medication Guide, and you believe the labeling is close to the final version.

For more information regarding OPDP submissions, please see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm. If you have any questions, call OPDP at 301-796-1200.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, 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.

We acknowledge receipt of your request for a full waiver of pediatric studies for this application. Once we have reviewed your request, we will notify you if the full waiver request is denied and a pediatric drug development plan is required.

If you have any questions, call Michelle Jordan Garner, Regulatory Project Manager, at (301) 796-4786.

Sincerely,

{See appended electronic signature page}

Badrul A. Chowdhury, MD, PhD
Director
Division of Pulmonary, Allergy, and Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

BADRUL A CHOWDHURY
03/12/2015

Your NDA submission dated December 29, 2014 is currently under review. We have the following request for information:

> To facilitate statistical review of Study SR10-019, "RDEA594: 26-Week Oral Gavage Carcinogenicity and Toxicokinetic Study in CBYB6F1-Tg(HRAS)2Jic Mice", submit the tumor data sets in conformance to the electronic format specified in *Study Data Specifications, Version 2.0* (July 18, 2012). This document is available at: http://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM312964.pdf).

Submit the tumor data sets to me via email at michelle.jordan@fda.hhs.gov, and officially to the NDA by **4:00p.m. EST, March 20, 2015.** If you have any questions, please contact Michelle Jordan Garner, Senior Regulatory Project Manager, at 301-796-4786.

Drafted by: MichelleJG2/27/15

Concurrence by: SandyB 2/27/15
Finalized by: MichelleJG 2/27/15

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/s/

MICHELLE Y JORDAN GARNER
02/27/2015

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 207988

NDA ACKNOWLEDGMENT

Ardea Biosciences, Inc.
9390 Towne Centre Drive
San Diego, CA 92121

Attention: Kimberly Manhard,
Senior Vice President, Regulatory Affairs and Development Operations

Dear Ms. Manhard:

We have received your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

Name of Drug Product: Zurampic (lesinurad)
Tablets/200 mg

Date of Application: December 25, 2014

Date of Receipt: December 29, 2014

Our Reference Number: NDA 207988

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on February 27, 2015 in accordance with 21 CFR 314.101(a).

Title VIII of FDAAA amended the PHS Act by adding new section 402(j) [42 USC § 282(j)], which expanded the current database known as ClinicalTrials.gov to include mandatory registration and reporting of results for applicable clinical trials of human drugs (including biological products) and devices.

In addition to the registration and reporting requirements described above, FDAAA requires that, at the time of submission of an application under section 505 of the FDCA, the application must be accompanied by a certification that all applicable requirements of 42 USC § 282(j) have been met. Where available, the certification must include the appropriate National Clinical Trial (NCT) numbers [42 USC § 282(j)(5)(B)].

You did not include such certification when you submitted this application. You may use Form FDA 3674, "Certification of Compliance, under 42 U.S.C. § 282(j)(5)(B), with Requirements of

ClinicalTrials.gov Data Bank," [42 U.S.C. § 282(j)] to comply with the certification requirement. The form may be found at http://www.fda.gov/opacom/morechoices/fdaforms/default.html.

In completing Form FDA 3674, you should review 42 USC § 282(j) to determine whether the requirements of FDAAA apply to any clinical trial(s) referenced in this application. Please note that FDA published a guidance in January 2009, "Certifications To Accompany Drug, Biological Product, and Device Applications/Submissions: Compliance with Section 402(j) of The Public Health Service Act, Added By Title VIII of the Food and Drug Administration Amendments Act of 2007," that describes the Agency's current thinking regarding the types of applications and submissions that sponsors, industry, researchers, and investigators submit to the Agency and accompanying certifications. Additional information regarding the certification form is available at: http://www.fda.gov/RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticActFDCAct/SignificantAmendmentstotheFDCAct/FoodandDrugAdministrationAmendmentsActof2007/ucm095442.htm. Additional information regarding Title VIII of FDAAA is available at: http://grants.nih.gov/grants/guide/notice-files/NOT-OD-08-014.html. Additional information for registering your clinical trials is available at the Protocol Registration System website http://prsinfo.clinicaltrials.gov/.

When submitting the certification for this application, **do not** include the certification with other submissions to the application. Submit the certification within 30 days of the date of this letter. In the cover letter of the certification submission clearly identify that it pertains to **NDA 207988** submitted on December 25, 2014, and that it contains the FDA Form 3674 that was to accompany that application.

If you have already submitted the certification for this application, please disregard the above.

The NDA number provided above should be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Pulmonary, Allergy, and Rheumatology Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, please see

http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm.

Secure email between CDER and applicants is useful for informal communications when confidential information may be included in the message (for example, trade secrets or patient information). If you have not already established secure email with the FDA and would like to set it up, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications.

If you have any questions, call Michelle Jordan Garner, Regulatory Project Manager, at (301) 796-4786.

Sincerely,

{See appended electronic signature page}

Michelle Jordan Garner, MS, OTR/L
Senior Regulatory Management Consultant
Division of Pulmonary, Allergy, and Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

MICHELLE Y JORDAN GARNER
01/12/2015

Harris, Sarah

From: Kimberly Manhard <KManhard@ardeabio.com>
Sent: Thursday, January 08, 2015 11:28 AM
To: Harris, Sarah
Cc: Jordan Garner, Michelle; Meghan O'Neill
Subject: RE: NDA 207988 Proprietary Name Information Request

Categories: DPARP

Dear Sarah,
Thank you for your e-mail and the guidance on the Proprietary Name Request submission to NDA 207988. We intend to submit the request for the proprietary name "Zurampic" to the NDA within 2 weeks.

With kind regards,
Kimberly

Kimberly Manhard
Senior Vice President
Regulatory Affairs and Development Operations
Ardea Biosciences, Inc.
4939 Directors Place
San Diego, CA 92121
kmanhard@ardeabio.com
Work: 858.652-6522
Cell: (b) (6)
Fax: 858.625.0745
www.ardeabio.com

From: Harris, Sarah [mailto:Sarah.Harris@fda.hhs.gov]
Sent: Thursday, January 08, 2015 7:28 AM
To: Kimberly Manhard
Cc: Jordan Garner, Michelle
Subject: NDA 207988 Proprietary Name Information Request

Dear Kimberly,

In reference to NDA 207988, submitted December 25, 2014 received December 29, 2014, the Agency would like to provide the following advice:

If you intend to use the proprietary name "Zurampic", you will need to formally submit a Proprietary Name Request in accordance with current FDA guidance. Links to the guidances are provided below. Although the name "Zurampic" was conditionally approved under IND 102128 on July 18, 2014, you will need to submit a **new** "**REQUEST FOR PROPRIETARY NAME REVIEW**" to your NDA. Additionally, include the statement "**REQUEST FOR PROPRIETARY NAME REVIEW**" in bold capital letters on the first page of the submission. You should also reference the date, SDN, and eCTD sequence of the original request.

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

Best Practices in Developing Proprietary Names for Drugs – Draft Guidance:
http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm398997.pdf.

Kindly confirm receipt of this email.

Thanks,
Sarah

Sarah Harris, PharmD
Safety Regulatory Project Manager | OSE | CDER | FDA
sarah.harris@fda.hhs.gov | 240.402.4774

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

/s/

SARAH J HARRIS
01/08/2015

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 102128

MEETING MINUTES

Ardea Biosciences, Inc.
4939 Directors Place
San Diego, CA 92121

Attention: Kimberly Manhard,
Sr. Vice President, Regulatory Affairs and Development Operations

Dear Ms. Manhard:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Zurampic (lesinurad tablet). We also refer to the meeting between representatives of your firm and the FDA on September 26, 2014. The purpose of the meeting was to discuss the phase 3 efficacy and safety data for lesinurad, and gain Agency agreement on the format and technical aspects of the NDA.

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) 796-4786.

Sincerely,

{See appended electronic signature page}

Michelle Jordan Garner, MS, OTR/L
Senior Regulatory Management Officer
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:	Meeting Type: Type B
Meeting Category:	Pre-NDA
Meeting Date and Time:	September 26, 2014; 10:00 A.M.
Meeting Location:	FDA/WO/Bldg 22, Conf. Rm. 1309
Application Number:	IND 102128
Product Name:	Zurampic (lesinurad)
Indication:	Treatment of hyperuricemia in patients with gout
Sponsor/Applicant Name:	Ardea Biosciences, Inc.
Meeting Chair:	Badrul A. Chowdhury, MD, PhD
Meeting Recorder:	Michelle Jordan Garner, MS, OTR/L

FDA ATTENDEES

Division of Pulmonary, Allergy, and Rheumatology Products
Badrul A. Chowdhury, MD, Ph.D., Director
Sarah Yim, MD, Supervisory Associate Director
Susan Limb, MD, Clinical Team Leader
Rosemarie Neuner, MD, Clinical Reviewer
Sally Seymour, MD, Deputy Director for Safety
Timothy Robision, Ph.D., Pharmacology/Toxicology Team Leader
Matthew Whittaker, Ph.D., Pharmacology/Toxicology Reviewer
Michelle Jordan Garner, MS, OTR/L, Senior Regulatory Management Officer
Division of New Drug Quality Assessment
Craig Bertha, PhD, Product Quality Lead
Edwin Jao, PhD, Product Quality Reviewer
John Duan, PhD, Product Quality Reviewer
Division of Clinical Pharmacology 2
Satjit Brar, PhD, Deputy Director
Jianmeng Chen, Ph.D., Clinical Pharmacology Reviewer
Division of Biometrics II
Thomas Permutt, PhD, Director
Division of Risk Management
Jamie Wilkins Parker, Team Leader

EASTERN RESEARCH GROUP ATTENDEES

So Hyun Kim, Independent Assessor

SPONSOR ATTENDEES

James Mackay, President and Chief Operating Officer, Ardea
Kimberly Manhard, Senior VP, Regulatory Affairs and Development Operations, Ardea
Chris Storgard, MD, Vice President, Clinical Research & Development, Ardea
William Mezzanotte, MD, Vice President, Global Medicine Development, AstraZeneca
Lalitha Aiyer, MD, Executive Director, Pharmacovigilance, Ardea
Mark A. DeSiato, Vice President, Global Regulatory Affairs, US Region, AstraZeneca
Jeff Kopicko, MSPH, Sr Director, Biometrics, Ardea
William Bushnell, MS, Global Project Statistician, AstraZeneca
Michael Gillen, Director, Clinical Pharmacology, AstraZeneca
Mark Longer, PhD, Executive Director, Regulatory Affairs, Ardea
Colin Rowlings, PhD, Sr Vice President, Pharmaceutical Sciences, Ardea
By Teleconference:
Scott Adler, MD, Senior Medical Director, Inflammation, Clinical Development, AstraZeneca
Nihar Bhakta, MD, Executive Medical Director, Clinical Development, Ardea
Maple Fung, MD, Senior Medical Director, Clinical Development, Ardea

1.0 BACKGROUND

Zurampic (lesinurad) is a uric acid transporter 1 (URAT1) inhibitor, indicated for the treatment of hyperuricemia associated with gout in combination with a xanthine oxidase inhibitor. Lesinurad has been developed, in all phase 3 clinical studies, as a crystalline free acid. During the development of lesinurad, Ardea has received the following interactions from FDA: response to 2 SPAs – 1) rat carcinogenicity study (December 22, 2009), and 2) mouse carcinogenicity study (April 28, 2011); CMC EOP2 meeting (minutes August 4, 2011) and EOP2 meeting (minutes August 19, 2011); and written responses to Type C meeting request (minutes February 28, 2014) and clarification responses (dated May 8, 2014).

The purpose of this meeting was to discuss all content and technical formatting of a complete NDA submission for Zurampic (lesinurad, 200 mg tablets). The meeting discussion focused on clarification of the introductory comments, and preliminary responses to questions 7, 11, and 14.

2.0 DISCUSSION

INTRODUCTORY COMMENTS:

We concur that no additional studies are required to support the filing of the NDA. However, we highlight the following major review issues that were first raised in the EOP2 meeting minutes dated July 21, 2011, and our written responses to you dated February 28, and May 8, 2014:

- *Appropriate dosing frequency for lesinurad*
- *Renal safety of lesinurad*
- *Type of data necessary for potential labeling indications and instructions for use*

Based on the limited data contained in your meeting package, these safety concerns persist in view of the dose-related renal and cardiac adverse event analyses. The interpretability of lesinurad's safety data is also questionable due to the timing of the safety-related protocol amendments implemented in the ongoing confirmatory studies.

These safety issues are coupled with equivocal efficacy. We note the questionable results from your third pivotal study, RDEA594-304, that assessed the safety and efficacy of lesinurad 200 mg once daily when co-administered with 80 mg/day of febuxostat to achieve a reduction in serum uric acid (sUA) $\leq$ 5 mg/dL, as well as the lack of secondary outcome support for the surrogate primary endpoint of the reduction in sUA $\leq$ 6 mg/dL in your two, replicate, pivotal studies, RDEA594-301 and -302, that assessed co-administration of lesinurad 200 mg once daily with $\geq$ 300 mg/day of allopurinol. At this time, the drug's overall risk/benefit ratio is uncertain, although final determination will be a review issue.

Given the equivocal results of RDEA594-304, you do not have the data necessary to support the proposed broader indication for the treatment of hyperuricemia associated with gout in combination with a xanthine oxidase inhibitor. Determination of a second line therapy indication with allopurinol in gout patients with hyperuricemia will be a review issue, taking into consideration the limited number of subjects who participated in the pivotal phase 3 studies while taking > 300 mg/day of allopurinol.

Discussion:

Ardea sought clarification of the statements regarding equivocal efficacy results; dosing frequency; renal safety of lesinurad; adequacy of the number of subjects taking allopurinol > 300 mg/day; assessment of the impact of protocol amendments; and the type of data necessary for potential labeling indications and instructions for use.

1. Equivocal efficacy results

Ardea acknowledged that the primary endpoint evaluating the proportion of subjects who achieved an sUA < 5 mg/dL by Month 6 with the 200 mg dose level of lesinurad in study RDEA594-304 was missed; however, at every other time point the combination of lesinurad 200 mg and febuxostat resulted in a greater proportion of subjects achieving the recommend treatment target for patients with tophi of sUA < 5 mg/dL with p-values ranging from 0.0002 to 0.028. Ardea questioned if the comment, that they do not have the data necessary to support the proposed broader indication in combination with an XO inhibitor, is based only on missing the primary endpoint at month 6 and if sUA lowering remains a valid primary endpoint. Ardea also requested clarification of the comment regarding equivocal efficacy as it relates to the combination studies of lesinurad with allopurinol in studies RDEA594-301 and RDEA594-302.

FDA confirmed that the comment about equivocal efficacy for febuxostat study RDEA594-304 was based on missing the primary endpoint at the pre-specified time point and stated that the broader indication will be a review issue.

FDA agreed that sUA lowering is still an acceptable endpoint but reminded Ardea that it is a surrogate marker for efficacy. For this reason, FDA considers the secondary endpoints of flare reduction and tophi resolution to be clinically important. FDA's comments about not achieving the secondary endpoints in studies RDEA594-301 and RDEA594-302 were related to the overall benefit-risk assessment for lesinurad 200 mg and questioned whether the efficacy achieved may be the same as up-titrated allopurinol.

2. Dosing frequency

Ardea asked for clarification of the persistent concerns related to the dosing frequency of lesinurad. At the EOP2, Ardea indicated theoretical concerns that evening dosing could be expected to increase the risk of kidney stones based on decreased urine volume leading to increase urinary uric acid concentration and increased urine pH resulting in increased undissociated urinary uric acid, both important factors resulting in increased risk of stone formation. A further justification for QD dosing was submitted after the EOP2 meeting. In a March 2012 correspondence, FDA expressed concern that QD dosing and the resultant intra-day sUA fluctuations may result in increased gout flares after flare prophylaxis is discontinued. Ardea believes that the Phase 3 data has demonstrated that there is no increase in the incidence of kidney stone when lesinurad is given once daily (QD) in the morning. In addition, in each of the core Phase 3 studies the rate of gout flares requiring treatment after prophylaxis withdrawal was higher in the placebo treatment groups than in the lesinurad monotherapy and combination therapy treatment groups.

FDA stated that the purported improved safety profile for QD dosing versus more frequent dosing remains hypothetical in the absence of clinical data evaluating different dosing regimens. The PK characteristics of lesinurad support more frequent dosing. Given the dose-related safety concerns identified on preliminary review, FDA questions whether lower nominal doses administered more frequently might have a better safety profile with similar or better efficacy. Ardea intends to submit a complete justification for the proposed dosing regimen in the NDA. The adequacy of the information will be a major review issue.

3. Renal safety of lesinurad

Ardea has performed analyses evaluating multiple renal parameters that will be included in the NDA. Other than an increase in the rate of serum creatinine elevations, the renal profile of following treatment with lesinurad 200 mg in combination with either allopurinol or febuxostat is similar to treatment with a xanthine oxidase (XO) inhibitor alone. The observed serum creatinine elevations were often single, transient and reversible with the majority resolving without treatment interruption. In the 12-month core Phase 3 studies with lesinurad 200mg with an XO inhibitor, there were no SAEs of acute renal failure reported, no evidence of worsening of kidney function, as the mean serum creatinine was unchanged when comparing baseline to last visit, no evidence of alterations in the urine protein to urine creatinine ratio, and no elevations associated with hyperkalemia or alterations in bicarbonate, calcium, potassium, phosphate or sodium. Based these analyses, Ardea considers the renal safety profile of lesinurad 200 mg to be acceptable especially when coupled with the marked sUA lowering resulting in a positive benefit risk assessment.

FDA is unable to agree at this time that the renal safety profile of the 200 mg dose is acceptable. The safety concerns, coupled with the concerns about the adequacy of dose frequency selection and the range of concomitant allopurinol doses assessed in the program, raise questions about the overall risk-benefit and will likely require public discussion.

4. Adequacy of the number of subjects taking allopurinol > 300 mg/day

Ardea asked for clarification if the comment, that determination of a second line therapy indication taking into account the Phase 3 studies had limited subjects >300 mg will be a review issue, was related to a safety concern. The efficacy analysis in this subgroup demonstrates a similar treatment effect and a safety analysis will be conducted. Ardea referred to the Phase 4 interventional study ALLO-401 (LASSO), which included the largest cohort of subjects treated with allopurinol at daily doses > 300 mg that demonstrate comparable safety to the cohort treated with allopurinol at daily doses of 300 mg. Also, in the Phase 3 lesinurad combination studies, approximately half the subjects with moderate renal impairment were receiving allopurinol at daily doses >200, which for that population represents high dose allopurinol.

The FDA confirmed that the need for sufficient data on subjects receiving allopurinol at a dose > 300 mg/day was related to safety and to assess for any overlapping toxicities.

5. Assessment of the impact of protocol amendments

Ardea agreed with the importance of assessing the impact of the protocol amendments on the renal and cardiac safety profile of lesinurad in combination with an XO inhibitor. Because the amendments were implemented late in the core Phase 3 trials, Ardea proposed to include the analysis in the 4-month safety update to better assess the impact of the amendments in the core and extension studies.

Ardea asked for an explanation of the statement that the "type of data necessary for potential labeling indications and instructions for use" was a major review issue. The FDA clarified that the comment referred to the dosing and administration changes in the protocol related to safety as well as the issue of a broader versus more specific indication statement. Ardea stated that they plan to incorporate ongoing data on more subjects, and plan to submit findings as a 4 month safety update. FDA stated that the requested analysis on renal and cardiovascular safety following the protocol amendments should be presented in the initial NDA to consider it a complete application. FDA stated the decision to update the NDA with data from the ongoing extension studies in the 4-month safety update was at Ardea's discretion, but cautioned that the timelimes for advisory committee (AC) preparation may make it difficult to ensure review of supplementary materials prior to the AC meeting. Therefore, Ardea should ensure that the NDA is complete at the time of the original submission.

Labeling

Question 1:

Does the Agency agree with a text and tabular presentation of the pharmacokinetic data or intrinsic factors and drug-drug interaction studies, respectively, in Section 12 Clinical Pharmacology of the proposed Prescribing Information for lesinurad?

Response:

Yes, we agree. Also refer to the draft guidance "Clinical Pharmacology Labeling for Human Prescription Drug and Biological Products—Considerations, Content and Format." *(http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM109739.pdf)*

Discussion:

None.

Question 2:

Does the Agency agree that the proposed lesinurad label statements for Section 13 Nonclinical Toxicology of the proposed Prescribing Information for lesinurad are acceptable?

Response:

We cannot comment on your proposed labeling for sections 8.1, 13.1, and 13.2 at this time. The acceptability of these sections of the label will be review issues. It is unlikely that Section 13.2 would be needed.

Discussion:

None.

Question 3:

Does the Agency have comments or suggestions on the other proposed label statements presented in the Target Product Profile for lesinurad, including the Indications for Use, Dosage and Administration, Contraindications, Warnings and Precautions, Drug Interactions, and Use in Specific Populations sections?

Response:

It is premature at this juncture to comment on proposed labeling statements for lesinurad. Refer to the Introductory Comments.

Discussion:

None.

Chemistry, Manufacturing, and Controls

Question 4:

Does the Agency agree that, based on new information available since the CMC End of Phase 2 meeting, the compound known as (b) (4) *can be designated as a starting material in the manufacturing process for lesinurad drug substance?*

Response:

Yes, we agree. For all structure alert impurities (including those related to the starting materials and process generated) provide in the NDA, in a tabular form the structure, in-silico test results, point of occurrence, summary with link to details of toxicological assessment, and chemical assessment (control, purge and fate). Impurities that are identified as structural alerts should be at or below acceptable qualification thresholds to support an NDA as described in the ICH M7 Guideline. See the response to Question 8.

We also note that any non-genotoxic impurities or degradants of the active ingredient exceeding qualification limits per the ICH Q3A (R2) and Q3B (R2) Guidances, respectively, should be appropriately qualified in a toxicology study with minimum duration of 13 weeks. Batch analysis of impurities in drug substance lots used in toxicology studies with lesinurad can be considered in the qualification process as needed. Levels of impurities and degradants in the drug product exceeding qualification limits should be supported by No Observed Adverse Effect Levels (NOAELs) identified in toxicology studies with an appropriate safety margin (e.g., (b) (4) fold on mg/m^2 basis).

Discussion:

None.

Question 5:

Does the Agency agree that the revised proposed dissolution method utilizing USP <711> Apparatus 2 (paddle) at 75 rpm in pH 4.5 acetate buffer plus 1% SLS is an acceptable method for lesinurad tablets?

Response:

Yes, we agree.

Discussion:

None.

Question 6:

Does the Agency agree that a biowaiver request for the 200 mg strength lesinurad tablet, the proposed commercial product, is not needed based on the level of changes associated with the manufacture of lesinurad tablets at the proposed commercial manufacturing site relative to the Phase 3 clinical manufacturing site?

Response:

No, we do not agree. A biowaiver request is needed. In the biowaiver request, you have two choices: 1) provide the composition similarity and dissolution similarity between the proposed commercial 200 mg strength and the 400 mg strength, which was used in the bioequivalence study, and supporting data; or 2) provide a side-by-side comparison between the proposed commercial 200 mg strength and the 200 mg strength used in phase 3 studies, including composition, manufacturing and dissolution profiles. For both options, f2 results for dissolution profile comparisons should be provided.

Discussion:

None.

Question 7:

Does the Agency agree that data from physicochemical testing of debossed tablets is not required to be presented in the original NDA or as an additional component within 30 days after the original submission?

Response:

No, we do not agree. If the debossed tablet is the to-be-marketed formulation, the data from physicochemical testing of debossed tablets should be provided in the NDA. In addition, dissolution profile comparison between debossed tablets and the non-debossed tablet using the proposed regulatory method should be provided.

Discussion:

Ardea clarified that they intend to provide the physicochemical testing data on a development batch of debossed tablets containing (b) (4) in Module 3.2.P.2 at the time of the original NDA, and proposed to submit the data from the physicochemical testing of the debossed tablets produced by the commercial process as an additional component not later than 30 days after the original submission in accordance with PDUFA V. FDA agreed to accept data on a commercial batch as an additional component within 30 days of the original NDA submission.

Nonclinical

Question 8:

Does the Agency agree with the process used for assessment of the potential genotoxic impurities in the lesinurad drug substance?

Response:

The process used for assessment of potential genotoxic impurities generally appears to be acceptable per the ICH M7 Guideline. A final decision regarding the assessment and control of genotoxic impurities will be made upon review of the NDA submission.

Discussion:

None.

Question 9:

Does the Agency agree that the completed nonclinical package is sufficient to support an NDA for lesinurad?

Response:

The sufficiency of the nonclinical package will be a review issue. We note the presence of the disproportionate human metabolite M4, formed via the epoxide intermediate M3c.

Provide justification in your NDA that the M3c/M4 metabolites have been adequately assessed and are qualified with respect to general toxicity, genetic toxicity, carcinogenicity, and reproductive toxicity. This should include information that the M3c epoxide intermediate was formed in a nonclinical species at sufficient levels to permit assessments of potential toxicity. If this is not possible, the M3c metabolite should be qualified for safety according to the ICH M3 (R2) Guidance and *FDA Guidance for Industry: Safety testing of drug metabolites (February, 2008).*

Discussion:

None.

Clinical

Question 10:

Ardea believes that the weight of the evidence from pre-specified analyses of sUA lowering supports a claim for lesinurad in combination with febuxostat for the treatment of hyperuricemia in association with gout. Does the Agency propose any additional analyses in support of this claim at the recommended dose of 200 mg qd?

Response:

Based on our review of your meeting package, no additional efficacy analyses are necessary to support submission of an NDA for lesinurad.

Discussion:

None.

Question 11:

The cardiovascular safety profile of lesinurad will be described in a Cardiovascular Safety Report that will be included in the Integrated Summary of Safety. Does the Agency have any additional recommendations for information that should be presented in the Cardiovascular Safety Report?

Response:

In view of the safety-related changes you made to the protocols for the five ongoing phase 3 studies (RDEA 594-301, -302, -304, -306, and -307) in order to minimize the risk of nephrotoxicity in participating patients, we recommend that you include the results from analyses of cardiac and renal adverse events pre- and post-implementation of these safety changes in your NDA submission. Additionally, you should expand your cardiovascular safety analyses to include adverse events such as congestive heart failure, pulmonary edema, left ventricular failure, cardiac arrhythmia, and volume overload. Since the recommended dose range for allopurinol is up to 800 mg/day, safety subanalyses should also be conducted in patients taking >300 mg/day of allopurinol.

Discussion:

Ardea stated that they would include the suggested analyses in the cardiovascular (CV) safety report, and asked if the request was to look at the adverse event terms in a combined fashion, such as a custom preferred term list or if the request was to combine the MACE evaluation with the new terms, for a MACE-plus analysis. Lastly, Ardea added that they are planning a safety subanalysis in patients taking a daily dose of allopurinol > 300 mg and would like to confirm that this subanalysis should be focused on the renal and CV safety.

FDA clarified that Ardea should look at cardiac safety beyond those terms included in a typical MACE analysis, given concerns related to potential cardiac overload that may be associated with the 2L fluid intake requirements. The MACE analysis as originally planned should remain separate. Exploration of underlying pathophysiology is welcome but not required in the NDA. The safety analysis in patients taking >300 mg allopurinol should include renal and CV safety in addition to overall general safety.

Question 12:

Does the Agency agree that the Phase 3 data package provides adequate safety and efficacy information to substantiate a review and decision on an NDA for lesinurad for the treatment of hyperuricemia associated with gout in combination with a xanthine oxidase inhibitor?

Response:

Based on our review of your meeting package, there appears to be adequate safety and efficacy data to support filing and review of an NDA.

Discussion:

None.

Question 13:

Does the Agency agree with the plan for providing safety data from the completed clinical studies and ongoing open-label extension studies in the NDA and 4-month safety update?

Response:

At the time of submission, the lesinurad NDA will include safety data from the completed 12-month, pivotal phase 3 studies (RDEA594-301, -302, and -304) in addition to safety data from the completed phase 1 and 2a PK/PD studies, completed periods of the two phase 2b studies (RDEA594-202 and -203), and the phase 3 monotherapy and extension studies (RDEA594-303 and -305). You also plan to include safety data from an ongoing phase 2b extension study (RDEA594-203) and two ongoing phase 3 extension studies (RDEA-306 and -307) to support the safety profile of the drug. The 4-month safety update will include approximately 20 weeks of additional safety data from the three ongoing extension studies RDEA594-203, -306, and -307). Based on exposure projections included in your meeting package, your proposal appears adequate to support filing and to satisfy the requirements outlined in the ICH E1 guideline for the safety evaluation of drugs intended for chronic administration. However, final determination of safety will be a review issue. Additional data may be required if unexpected safety signals are identified. Refer to the Introductory Comments.

Discussion:

None.

Question 14:

Does the Agency have comments or suggestions on the proposed goals for the Risk Management Plan for lesinurad?

Response:

It is difficult to comment on details of the proposed Risk Management Plan prior to our review of the safety data. However, based on our preliminary review, we are uncertain as to whether a REMS will be sufficient to address the safety concerns outlined in the Introductory Comments and to assure safe use of lesinurad. The need for a REMS will be a review issue.

Discussion:

Ardea stated that a comprehensive safety analysis will be provided in the submission which they believe demonstrates that lesinurad 200 mg in combination has an acceptable and manageable

safety profile, when used in combination with either allopurinol or febuxostat, and asked what approach FDA would consider sufficient to ensure the safe use of lesinurad 200 mg. FDA clarified that the comment was based on the limited data in the briefing book, and that a final decision regarding a REMS will be determined after a complete review of the safety and assessment of the benefit-risk profile. While FDA acknowledged the typical morbidity associated with a gout population at baseline, FDA is uncertain whether a REMS can compensate for the preliminary safety issues identified. They advised Ardea to address each raised concern, from the Introductory Comments, in the benefit-risk assessment in the NDA and indicated that the type of REMS would be discussed later.

Format and Technical

Question 15:

Does the Agency agree that the proposed Table of Contents constitutes a complete submission?

Response:

The proposed comprehensive Table of Contents included in your meeting package appears to be an adequate presentation of the data necessary for a complete NDA submission. However, the adequacy of the data remains a review issue. Keep in mind, additional data may be requested over the course of the review process.

Discussion:

None.

Question 16:

Does the Agency agree that it is acceptable to provide method validation reports only for lesinurad and its metabolites in the submission and not the method validation reports for analytes for the drug products included in drug interaction studies?

Response:

Yes, it is acceptable.

Discussion:

None.

Question 17:

Does the Agency agree that it is appropriate to include the clinical study reports for the monotherapy Phase 2b and Phase 3 studies that do not support the claimed indication in Module 5, Section 5.3.5.4?

Response:

We concur with your proposal to include the clinical study reports for the lesinurad monotherapy phase 2b and 3 studies in Section 5.3.5.4 of Module 5 for completeness of your application as these data do not support your proposed drug indication.

Discussion:

None.

Question 18:

Does the Agency agree with the proposed presentation of the Integrated Summary of Efficacy, which will consist of an integrated data review of efficacy within Module 2, Section 2.7.3 Summary of Clinical Efficacy and the supporting Tables, Figures, and Listings and Datasets in Module 5, Section 5.3.5.3 Integrated Analyses?

Response:

Your proposal to include a narrative summary of efficacy data within Section 2.7.3 Summary of Clinical Efficacy in Module 2 that will be hyperlinked to supporting analyses and datasets in Section 5.3.5.3 Integrated Analyses in Module 5, thus obviating the need for a separate Integrate Summary of Efficacy narrative is acceptable.

Discussion:

None.

Question 19:

Does the Agency agree with the proposed presentation of the Integrated Summary of Safety in Module 5.3.5.3 that will rely on the integrated data review of safety within Module 2, Section 2.7.4 and include additional focused reports on safety topics of interest?

Response:

Your proposal to include narrative portions of the Integrated Summary of Safety within Section 2.7.4 Summary of Clinical Safety in Module 2 that will also contain various safety analyses including the assessments by the independent Renal Event Adjudication and Cardiovascular Endpoints Adjudication Committees which will be hyperlinked to supporting analyses and datasets within Section 5.3.5.3 in Module 5 that will also include brief summaries of key safety topics presented in Section 2.7.4 Summary of Clinical Safety is acceptable, provided that the additional safety analyses listed in the response to Question 12 are included.

Discussion:

None.

Question 20:

Does the Agency agree that the proposed eCTD submission format is acceptable?

Response:

From a technical standpoint the proposed format for the planned NDA is acceptable. However, we have the following comments:

- Do not use eCTD Backbone Files Specification for Module 1 (07 February 2014 v2.3) as v2.3 is not yet implemented. Please use The eCTD Backbone Files Specification For Module 1 (13 December 2006), located at:- http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM315024.pdf

- Do not provide placeholders for sections that will not be submitted (e.g. m1.3.1 – Applicant Information, N/A).

- Module 2 Literature References should be provided under m2.7.5 (References) and Non-clinical Literature References should be provided under m4.3 (Literature References)

- The tabular listing in module 5.2 and synopsis of individual studies in module 2.7.6, should be provided in tabular format and linked to the referenced studies in m5.

- If a study supports multiple eCTD heading elements (e.g. both m4.2.2.6 and m5.3.2.2), provide the document in one heading element (e.g. m4.2.2.6). The leaf title of the cross referenced section (e.g.m.5.3.2.2.), should state where the actual document resides in the eCTD structure (e.g. cross ref to m4.2.2.6- SR11-054.pdf; or something similar) and a link to the document should also be provided, for ease of review. This helps the reviewer only review the study once and also makes them aware that a single study supports multiple sections of the eCTD.

- Regarding use of the m5-3-7 heading element, FDA doesn't use module 5.3.7 CRFs. If case report forms should be submitted in the future, they should be referenced under the appropriate study's Study Tagging File (STF) to which they belong, organized by site as per the specifications and tagged as “case report form”. Do not use m5.3.7 as a heading element in the index.xml

Discussion:

None.

Question 21:

Does the Agency agree that datasets larger than 1 gigabyte in size (without splitting) are acceptable for the NDA submission?

Response:

No we do not agree. If datasets are greater than 1 gb in size, split the datasets into smaller datasets no larger than 1 gb in size. Datasets should be resized to the maximum length used prior to splitting. This will ensure split datasets have matching variable lengths for future merges. Split data should be noted in the data definition document, clearly identifying the method used for the dataset splitting. See CDER Common Data Standards Issues Document (pg. 12). http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM254113.pdf

Discussion:

None.

Question 22:

Does the Agency agree with the proposed plan for the submission of nonclinical datasets, which will only include electronic Statistical Analysis System transport files for the 2 carcinogenicity studies?

Response:

Yes, we agree.

Discussion:

None.

Discussion:

None.

Question 23:

Does the Agency agree with the proposal for provision of the clinical datasets as described?

Response:

Yes, the proposal is acceptable.

Discussion:

None.

3.0 OTHER IMPORTANT INFORMATION

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

- A preliminary discussion on the need of a REMS was held and it was concluded that a final decision regarding a REMS will be determined after a complete review of the safety and assessment of the benefit-risk profile.
- Major components of the application are expected to be submitted with the original application and are not subject to agreement for late submission. We agreed that the following minor application components may be submitted within 30 calendar days after the submission of the original application: data on a commercial batch as an additional component.

- Prominently identify each submission containing your late component with the following wording in bold capital letters at the top of the first page of the submission:

  NDA/BLA NUMBER: LATE COMPONENT - QUALITY

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, 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 (PSP) within 60 days of an End of Phase (EOP2) meeting. 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.

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 Pediatric and Maternal Health Staff 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.

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. As you develop your proposed PI, we encourage you to review the labeling review resources on the *PLR Requirements for Prescribing Information* website including:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- 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 42 important format items from labeling regulations and guidances.

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.				

4.0 ISSUES REQUIRING FURTHER DISCUSSION

No issues requiring further discussion.

5.0 ACTION ITEMS

No action items.

6.0 ATTACHMENTS AND HANDOUTS

None.

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

/s/

MICHELLE Y JORDAN GARNER
10/24/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 102128

MEETING MINUTES

Ardea Biosciences, Inc.
4939 Directors Place
San Diego, CA 92121

Attention: Kimberly Manhard, Senior Vice President,
Regulatory Affairs and Development Operations

Dear Ms. Manhard:

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

We also refer to the meeting between representatives of your firm and the FDA on July 21, 2011. The purpose of the meeting was to evaluate plans for the phase 3 program and registration activities to support a new drug application.

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) 796-4786.

Sincerely,

{See appended electronic signature page}

Michelle Jordan Garner, MS, OTR/L
Senior Regulatory Management Officer
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:	Type B
Meeting Category:	End of Phase 2
Meeting Date and Time:	July 21, 2011; 2:00 PM -3:00 PM
Meeting Location:	WO Building 22, Conference Room 1309
Application Number:	IND 102128
Product Name:	Lesinurad
Proposed Indication:	Treatment of Gout
Sponsor/Applicant Name:	Ardea Biosciences, Ltd.
Meeting Chair:	Badrul A. Chowdhury, MD, PhD
Meeting Recorder:	Michelle Jordan Garner, MS, OTR/L

FDA ATTENDEES

Badrul A. Chowdhury, MD, Ph.D., Division Director, Division of Pulmonary, Allergy, and Rheumatology Products

Sarah Yim, MD, Clinical Team Leader, Division of Pulmonary, Allergy, and Rheumatology Products

Susan Limb, MD, Clinical Team Leader, Division of Pulmonary, Allergy, and Rheumatology Products

Rosemarie Neuner, M.D., Clinical Reviewer, Division of Pulmonary, Allergy, and Rheumatology Products

Molly Topper, Ph.D., Nonclinical Supervisor, Division of Pulmonary, Allergy, and Rheumatology Products

Janet Maynard, MD, Clinical Reviewer, Division of Pulmonary, Allergy, and Rheumatology Products

Ping Ji, Ph.D., Clinical Pharmacology Reviewer, Division of Clinical Pharmacology 2, Office of Clinical Pharmacology

Elizabeth Shang, Clinical Pharmacology Reviewer, Division of Clinical Pharmacology 2, Office of Clinical Pharmacology

Joan Buenconsejo, Ph.D., Biostatistics Team Leader, Division of Biometrics II

Michelle Jordan Garner, MS, OTR/L, Senior Regulatory Management Officer, Division of Pulmonary, Allergy, and Rheumatology Products

ARDEA BIOSCIENCES ATTENDEES

Barry Quart, President/CEO
Kimberly Manhard, Sr VP, Regulatory Affairs and Development Operations
David Hagerty, MD, CMO and Sr VP, Clinical Development
Vijay Hingorani, MD, Medical Monitor
Matthew Cravets, MSc, Sr Director, Biostatistics
Matthew Suster, Associate Director, Clinical Operations
(b) (4) Clinical Pharmacology Consultant
Li-Tian Yeh, PhD, VP, Translational Science
Clynn Wilker, DVM, PhD, DACT, Sr Director, Toxicology
Jeffrey Miner, PhD, Sr Director, Oncology & Inflammation Biology
Meghan Gallagher, Regulatory Affairs Associate
(b) (4) Medical Consultant
(b) (4) Medical Consultant

1.0 BACKGROUND

Ardea Biosciences submitted an End-of-Phase-2 meeting request dated April 8, 2011, to evaluate plans for the phase 3 program and registration activities to support a new drug application. The Agency reviewed the briefing package dated June 17, 2011. In an email dated July 20, 2011, the Agency responded to the questions contained in Ardea Biosciences meeting package.

Any discussion that took place at the meeting is captured directly under the original response. Ardea Biosciences' questions are in **bold**; the Agency's response is in *italics*; and the discussion is in normal font. Ardea Biosciences provided a slide presentation (attached in 5.0 of these minutes) which were used as Ardea's talking points during the meeting.

2.0 DISCUSSION

Question 1:

Does the FDA agree that the completed nonclinical safety pharmacology studies with lesinurad are sufficient to support the NDA?

Response:

We agree that the completed nonclinical safety pharmacology studies with lesinurad are sufficient to support the NDA.

Discussion:

None

Question 2:

Does the FDA agree that the single-agent, repeat-dose chronic toxicity studies of lesinurad in rats and monkeys are sufficient to support the proposed Phase 3 studies of lesinurad and the NDA?

Response:

We agree that your completed nonclinical rat and monkey chronic oral toxicology studies support your proposed Phase 3 clinical trials and an NDA for lesinurad administered orally once daily up to 400 mg per day.

Discussion:

None

Question 3:

Does the FDA agree that the ongoing 13-week lesinurad and allopurinol combination repeat-dose toxicity study in rats is sufficient to support the proposed Phase 3 studies of lesinurad in combination with allopurinol and the NDA?

Response:

As your Phase 3 clinical studies propose the co-administration of lesinurad and allopurinol products, not a fixed-dose combination product, and the toxicology profile of allopurinol is well characterized, the 13-week lesinurad and allopurional combination repeat-dose toxicology study is not essential to support your Phase 3 clinical studies or the NDA. However, submit the completed 13-week combination repeat-dose toxicity study as supportive data to your IND.

Discussion:

None

Question 4:

Does the FDA agree that the ongoing 13-week combination repeat-dose toxicity study in rats with lesinurad and allopurinol, the most widely used drug in the xanthine oxidase inhibitor class, is also sufficient to support the proposed Phase 3 study of lesinurad in combination with febuxostat, a member of the same class?

Response:

No nonclinical combination toxicology study is required to support the clinical co-administration of lesinurad and febuxostat. (Refer to our response to question 3)

Discussion:

None

Question 5:

Does the FDA agree that the completed genotoxicity studies with lesinurad, its metabolites and drug substance starting materials/intermediates are sufficient to support the proposed Phase 3 studies and the NDA?

Response:

We agree that the completed genotoxicity studies with lesinurad and its metabolites support the proposed Phase 3 studies and the NDA.

As was discussed in your July 6, 2011 EOP2 CMC meeting, you proposed to complete bacterial reverse mutation assays (Ames assays) for starting materials or impurities that contain structural alerts. For those impurities that are positive in the Ames assay or are known carcinogens, you proposed to control these impurities to < (b) (4) mcg/day. We agree with your proposed approach to qualify or control impurities containing structural alerts.

We also remind you for impurities that do not contain structural alerts, Monitor impurities and degradation products of all active ingredients and refer to ICH Guidance [ICH Q3A(R) and ICH Q3B(R)] for possible qualification requirements.

Discussion:

None

Question 6:

Does the FDA agree that the ongoing transgenic mouse and rat carcinogenicity studies are sufficient to support the NDA?

Response:

We acknowledge that completion of the transgenic mouse and rat carcinogenicity studies may fulfill the carcinogenicity assessment requirement to support an NDA filing for lesinurad. However, review and discussions with the Executive Carcinogenicity Assessment Committee of the completed carcinogenicity study reports are necessary prior to concurring with the validity of your carcinogenicity studies.

Discussion:

None

Question 7:

Does the FDA agree that the completed fertility and early embryonic development study and the embryo-fetal development studies with lesinurad along with the planned prenatal and postnatal development study are sufficient to allow the inclusion of women of child bearing potential (WOCBP) in the proposed Phase 3 studies and to support the NDA?

Response:

We agree that your currently completed and planned (Pre- and Post-natal development toxicity) reproductive toxicology studies are sufficient to allow the inclusion of WOCBP in the proposed Phase 3 studies and to support an NDA. The adequacy of the pre- and post-natal development study will be a review issue.

Discussion:

None

CLINICAL PHARMACOLOGY

Question 8:

Does the agency agree that Ardea has adequately characterized the systemic elimination of lesinurad in humans and no further studies to identify human clearance pathways or human metabolite structures are required for Phase 3 or registration?

Response:

Based on the information in the meeting package, it appears that you have sufficient information characterizing the systemic elimination of lesinurad in humans before the start of Phase 3 clinical trials or for filing of the NDA. However, adequacy of these data will be a review issue.

Discussion:

None

Question 9:

Does the FDA agree that the pharmacokinetic (PK), safety and efficacy data in individuals with mild to moderate renal impairment available from the single-dose Phase 1 renal impairment study and multiple-dose Phase 2 studies of lesinurad given as monotherapy and as an add-on to allopurinol in gout patients are adequate to support the proposed Phase 3 clinical trials of lesinurad that will include patients with mild to moderate renal impairment?

Response:

No, we do not agree. Your proposed dose of lesinurad in Phase 3 studies is up to 400 mg. The numbers of patients with moderate renal impairment exposed to 400 mg and 600 mg of your product in Phase 1 and 2 studies were too small (6 in 400 mg and 5 in 600 mg) to draw any meaningful conclusion with respect to safety and efficacy. We note that in moderate renal impairment subjects, exposure of the drug is doubled relative to that in healthy controls. Whether you adjust the dose or not in phase 3 clinical trials, we recommend that you conduct subgroup analysis based on degree of renal impairment so as to be able to obtain a clear understanding of the risk benefit in subject with renal impairment. In addition, please note that in general you need to characterize PK in subjects with severe renal impairment, including End-Stage Renal Disease on dialysis if these patients represent significant proportion of the target patient population. Contraindication of use in subject with severe renal impairment when the drug has potential use in these subjects in the absence of otherwise mitigating factors is not reasonable.

Discussion:

Ardea agreed to conduct subgroup analysis (as recommended by FDA) based on the degree of renal impairment in Phase 3 studies, to evaluate risk benefit in subjects with severe renal impairment. Ardea also agreed to characterize PK in subjects with severe renal impairment. FDA expressed that patients with end-stage renal on dialysis, could be at greater risk for kidney stones due to their low urine output

Question 10:

Does the FDA agree that the Phase 1 PK study in hepatically-impaired subjects can be conducted during Phase 3 and that it is acceptable to exclude patients with hepatic impairment in Phase 3?

Response:

Please note that in general patients with hepatic impairment should be included in clinical trials if these patients represent significant proportion of the target patient population. If you can justify that this is not the case, you may conduct the PK study during phase 3 and not include patients in phase 3. If patients with hepatic insufficiency are included in phase 3 trials, you need to evaluate the impact of hepatic insufficiency upon the PK so that any needed dose adjustments and/or safety measures can be incorporated.

Discussion:

Ardea expressed that due to the absence of adequate epidemiology data, patients with hepatic impairment represent a significant proportion of the target patient population would be an overestimation, and therefore would be excluded in Phase 3 studies. FDA agreed that this exclusion would be acceptable.

Question 11:

Does the FDA agree that the completed and planned drug interaction studies with lesinurad and drugs that are substrates of CYP3A4, CYP2C9 and CY2C8 are adequate to support the proposed Phase 3 clinical trials and the NDA?

Response:

It appears that your completed and planned drug interaction studies with lesinurad are adequate to support the proposed Phase 3 clinical trials and filing of the NDA. However, whether further information in regard to drug interaction is needed for registration will be a review issue. We also have the following comments on your planned drug interaction study with lesinurad.

Lesinurad as a Substrate

You stated that lesinurad is a CYP2C9 substrate. Your cross-study analysis on effect of CY2C9 genotype on PK of lesinurad indicated that lesinurad systemic exposures may double when CYP2C9 activity is impaired. However, you have based this on only one subject identified as a CYP2C9 poor metabolizer. We suggest that you conduct a dedicated drug-drug interaction study to evaluate the effect of potent inhibitor and inducer of CYP2C9 upon the PK of your drug product.

Discussion:

Ardea stated they will conduct studies using CYP2C9 inhibitor (fluconazole) and CYP2C9 inducer (rifampin), as recommended by FDA guidance on, *"Drug Interaction Studies – Study Design, Data Analysis, and Implications for Dosing and Labeling."* FDA agreed with Ardea's proposal to conduct studies using the CYP2C9 inhibitor, fluconaole, and the CYP2C9 inducer, rifampin, to address FDA's concerns.

Lesinurad as an Inhibitor and/or Inducer

a. *You proposed to use repaglinide as a marker to study the effect of lesinurad upon CYP2C8. Repaglinide is also a substrate for OATP1B1. In vitro study results showed that your product inhibits OATP1B1 as well. We recommend that you select a sensitive CYP2C8 substrate that is not a substrate of OATP1B1 or OATP1B3.*

Discussion:

Ardea expressed that lesinurad has minimal in vivo inhibitory effect on OATP1B1 by presenting additional preliminary results from an on-going clinical drug drug interaction study of lesinurad and atorastatin. Therefore, they believe repaglinide is a suitable CYP2C8 probe in the planned lesinurad-CYP2C8 DDI study. They continued that rosiglitazone is another CYP2C8 substrate recommended in the FDA guidance on drug interaction studies; however, it was not chosen due to safety concerns and restricted access. FDA expressed that if preliminary results from the atorvastatin study are confirmed and OATP1B1 inhibition is ruled out, then repaglinide is an acceptable substrate for evaluating lesinurad's effect on CYP2C8.

b. *You proposed to use tolbutamide as a marker to study the effect of lesinurad upon CYP2C9. Tolbutamide is not a sensitive CYP2C9 substrate. We recommend that you select a sensitive CYP2C9 substrate for this drug-drug interaction study.*

Discussion:

Ardea expressed two CYP2C9 probe substrates, tolbutamide and warfarin; which are recommended in the FDA guidance regarding drug interaction studies. Ardea presented their justification on why tolbutamide is a sensitive probe substrate. Ardea asked FDA to clarify which CYP2C9 substrate is preferred as a sensitive probe substrate for a PK interaction study. FDA advised Ardea that Celebrex is a sensitive CYP2C9 substrate based on literature data. FDA also expressed that warfarin could also be used and would be clinically relevant in the gout

population that includes elderly patients. Ardea expressed concern regarding the use of warfarin for a drug-drug interaction study, due to the need to also investigate pharmacodynamic activity and the complexity of enantiomeric disposition of warfarin that would require investigation. FDA cautioned that Ardea would not be able to make a label statement about the concomitant use of warfarin without the study. Ardea committed to providing a justification for selecting a CYP2C9 probe substrate.

c. *You stated that in vitro human hepatocytes study showed that lesinurad has limited potential to induce CYP2B6, CYP2C8, CYP2C9, and CYP2C19. You planned to assess potential induction or inhibition of CYP2C8 and CYP2C9, but not CYP2B6 or CYP2C19. Please provide the justification as to why such assessments are not needed. Alternatively, in vivo testing of the potential for your product to induce CYP2B6 and CYP2C19 metabolism is warranted.*

Discussion:

Ardea agreed with FDA's preliminary comments, and stated that they will provide a justification or conduct in vivo testing to evaluate induction of CYP2B6 and CYP2C19 by lesinurad.

d. *You stated that your product has inhibitory effect (based upon in vitro study) upon hepatic uptake transporter OATP1B1 (IC50=9.3 uM). The in vivo testing of the potential for your product to inhibit OATP1B1 is warranted if [I]/Ki >=0.1. Your planned study of evaluating your product's effect upon atorvastatin (a CYP3A and OATP1B1 substrate) does not adequately address the inhibition potential upon OATP1B1 due to the induction potential of your product upon CYP3A4.*

Discussion:

Ardea clarified the design of the study, to be a study to assess inhibition of OATP1B1 prior to the onset of induction effects. Ardea continued that single doses of atorvastatin are administered alone (as a baseline); in combination with the first dose of lesinurad (to assess OATP1B1 inhibition); and after 11 days of lesinurad QD dosing (to assess CYP3A4) induction). FDA stated that based on the information presented at the meeting, which clarified the design of the ongoing atorvastatin drug-drug interatction study, Ardea's study design appears acceptable for evaluating lesinurad's potential of OATP1B1 inhibition and CYP3A4 induction.

Question 12:

Does the FDA agree that the analysis of lesinurad pharmacokinetic dependence on gender, age, race, and ethnicity may be assessed with population pharmacokinetics in the proposed Phase 3 clinical trials?

Response:

Yes, we agree that effect of gender, age, race and ethnicity upon lesinurad PK may be assessed with population PK in the proposed Phase 3 clinical trials. Please note that quality covariates

information will depend on having adequate number of patients in these demographic characteristics.

Discussion:

None

Question 13:

Does the FDA agree that a pediatric waiver for lesinurad would be granted since gout is extremely rare in individuals below 18 years of age?

Response:

We agree in principle that granting a waiver for conducting studies with lesinurad in children less than 18 years of age would be reasonable due to the rarity of this disease in the pediatric population. However, a final determination will be made under the Pediatric Research Equity Act (PREA) during the review of your NDA based on the appropriateness of your request for a waiver.

Discussion:

None

Question 14:

Does the FDA agree that based on the lack of signal of an ECG effect in the completed thorough ECG study of the parent compound, RDEA806, and the lack of an ECG signal in Phase 1 and Phase 2 clinical trials of lesinurad that a thorough ECG study can be conducted prior to registration and included in the NDA?

Response:

No, we do not agree. Although lesinurad showed no effect on ECG in your TQT study for parent molecule REDA806, you acknowledged that the concentrations of lesinurad were much lower than would be achievable in its use in gout. Even though ECG data from Phase 1 and 2 trials with lesinurad showed no clear signal of a likely ECG effect and no signal of any exposure-QTc relationship, these type ECG data can not replace TQT study, which is dedicated to evaluating your product's effect on cardiac repolarization and requires you to study the effect of your product and its metabolites at higher exposures with a positive control arm in the trial. Data from the literature suggest that hyperuricemia may be a risk factor for cardiovascular events, and many patients with gout have multiple risk factors for cardiac disease which include but are not limited to metabolic syndrome, hypertension, congestive heart failure, diabetes mellitus.

Taken together, we have concerns about a potential increase in risk for these events to occur during the trial as a result of long term dosing with lesinurad. Therefore, we suggest that you

follow the guidance provided in the ICH E14 document and conduct a TQT study prior to initiating your pivotal Phase 3 studies.

Discussion:

Ardea agreed to conduct a TQT study prior to the initiation of their Phase 3 studies. The proposed design includes 2 study segments: Segment A for the supratherapeutic dose determination and Segment B for the TQT investigation. Prior to Phase 3, Ardea proposes to complete dosing in both segments and to provide ECG and PK data from Segment A. Then they proposed to provide the ECG report for Segment B within 3 months after Phase 3 begins. FDA stated that a completed TQT study of lesinurad is preferred prior to dosing in Phase 3. FDA continued that if Ardea chooses to initiate Phase 3 prior to providing the final ECG report from the TQT study (Segment B), then Ardea must provide a justification for doing so, when the Phase 3 protocols are submitted. Ardea indicated that they plan to submit the TQT study protocol to FDA for review by the Interdisciplinary Review Team soon. FDA stated that the toxicology data will be needed to support the planned single doses up to the (b) (4) mg dose in Segment A. Ardea provided slides to support that the toxicology studies support the proposed clinical single oral doses of (b) (4) mg. FDA stated that these data would be reviewed at the time of the TQT protocol submission. (Note: 2 back-up slides, which are attached, were provided which showed that there was a safety margin in both rats and monkeys based on the toxicokinetic data from Day 1 across all the repeat-dose toxicity studies).

CLINICAL (Safety and Efficacy)

Question 15:

Does the FDA agree with the definition of an inadequate responder to allopurinol in the two identical proposed Phase 3 lesinurad add-on studies (Study 301 and Study 302) in gout patients who have had an inadequate hypouricemic response to allopurinol?

Response:

We have concerns that patients who are suboptimally treated with allopurinol could potentially qualify as inadequate responders based on the minimally therapeutic dose of 200 mg/day of allopurinol required for study entry. In view of the approved broad dose range (e.g., 100-800 mg/day) for allopurinol, modify the entry criteria for Studies 301 and 302 to include subjects who failed to normalize serum uric acid following ≥ 3 months treatment with allopurinol at the maximum labeled dose (800 mg QD) or at a medically appropriate lower dose based on dose-limiting toxicity or dose-limiting co-morbidity (i.e., renal impairment).

Discussion:

Ardea agreed that the term 'inadequate responders' may be confusing, but they felt it was consistent with guidance and approvals for other rheumatology products. They would like to study patients who have not achieved the target sUA ≤ 6.5 mg/dL with a prescribed dose of

allopurinol of at least 200 mg per day. Ardea stated that lesinurad provides the opportunity to treat the underlying physiological abnormality in gout, inadequate renal excretion of uric acid, with a complementary mechanism of action to xanthine oxidase inhibitors (XOI). Co-administration of lesinurad in these patients would potentate the urate lowering activity of XOI. Ardea explained that standard of care of hyperuricemic gout patients in clinical practice is 100-300 mg/day of allopurinol, and no large, randomized studies with allopurinol at doses higher than 300 mg/day have been conducted. Ardea pointed out that some studies suggest markedly increased risk of Stevens-Johnson syndrome at higher doses. Therefore, they believed that requiring patients to be on allopurinol doses greater than 300 mg per day would not reflect or be relevant to current clinical practice. Ardea continued that because the majority of clinicians are unwilling to increase the dose of allopurinol above 300 mg per day, many of these patients will continue to have multiple flares of gout. Ardea also stated that steady state sUA reduction is achieved within 4 weeks with allopurinol, and the proposed study requires failure to achieve this targeted goal reduction in sUA after receiving a stable dose of allopurinol for at least 7 weeks. Ardea expressed that the patient population they would like to study in Studies 301 and 302 are those patients not achieving a sUA less than 6.5 mg/dL at their prescribed allopurinol dose for at least 7 weeks and experiencing 2 flares within the previous year. Ardea believes this approach is consistent with FDA guidance on the development of RA products specifically defining the population based on their prior inadequate responses to standard therapy. They also believed that it is also consistent with precedence for approval of DMARDs as an add-on to MTX, without requiring the use of the highest approved dose of MTX.

Ardea then asked if FDA agreed with the intended patient population for Studies 301 and 302. FDA responded that there were concerns regarding the pursuit of a second line claim in inadequate responders to address an unmet need without requiring patients to have received the maximum dose of allopurinol or first failing therapy with first-line agents. FDA then asked the sponsor why they were proposing to study such a wide dose range of lesinurad. Ardea stated that most of the patients who would be participating in the proposed trials are taking multiple medications which increases the risk of SAEs. Ardea continued that patients could have either dose limiting toxicity or have a co-morbid condition such as renal impairment that would restrict the doses evaluated. FDA agreed that it was a matter of semantics regarding the term ‘inadequate responders’ and that add-on studies with allopurinol would be acceptable. . The description of the target population in the drug’s label could be discussed at a later time.

Ardea has submitted the following post-meeting comments:

1. **“The 200 mg dose level was proposed as the lowest dose allowed in the proposed studies due to its use in patients with moderate renal impairment. Both the previously conducted CONFIRMS trial and the on-going CARES trial of febuxostat in patients with cardiovascular co-morbidities included the 200 mg/day dose of allopurinol for patients with moderate renal impairment.**

2. **We greatly appreciate the clarification by the FDA and are re-evaluating the entry criteria for Studies 301 and 302 to bring them more in-line with the FDA suggestions.”**

Question 16:

Does the FDA agree that it is acceptable to allow a history (by medical record or patient interview) of intolerance or a contraindication to allopurinol or febuxostat for entry into the planned Phase 3 lesinurad monotherapy study (Study 303) in gout patients who are intolerant or have or a contraindication to a xanthine oxidase inhibitor?

Response:

Your proposed approach to document intolerance or a contraindication to treatment with approved xanthine oxidase inhibitors by reviewing potential study candidates' medical records or from information obtained during the study screening interview of potential trial candidates is acceptable.

Discussion:

None

Question 17:

Does the FDA agree with the proposed primary endpoint of *proportion of patients whose sUA levels are <6.0 mg/dL by 6 months (or the final visit)*for demonstration of efficacy in gout patients in the two identical proposed Phase 3 lesinurad add-on studies in gout patients who have had an inadequate hypouricemic response to allopurinol (Study 301 and Study 302) and lesinurad monotherapy study in gout patients who are intolerant or have a contraindication to a xanthine oxidase inhibitor (Study 303)?

Response:

We concur that the proportion of patients whose sUA levels are <6.0 mg/dL by Month 6 or the final study visit is an acceptable primary endpoint for your proposed Phase 3 studies in patients who are inadequate responders to medically appropriate doses of concomitant allopurinol, who are intolerant or have a contraindication to xanthine oxidase inhibitors. Refer to Question 15 response regarding the definition of inadequate responders to medically appropriate doses of concomitant allopurinol for Studies 301 and 302.

Discussion:

None

Question 18:

Does the FDA agree with the proposed primary endpoint of *proportion of patients whose sUA levels are <5.0 mg/dL by 6 months* for demonstration of efficacy in tophaceous gout patients with hyperuricemia in the Phase 3 febuxostat combination study (Study 304)?

Response:

(b) (4)

Discussion:

(b) (4)

Ardea has submitted the following post-meeting comment:

"We greatly appreciate the clarification by the FDA and are re-evaluating the entry criteria for Study 304 to bring them more in-line with the FDA suggestions. As noted under Question 31, we have agreed to include the lesinurad 200 mg dose group, as such, we need to determine whether it is feasible to conduct the entire expanded study in patients not adequately responding to febuxostat 80 mg/day (the highest approved dose)."

Question 19:

Does the FDA agree with the key secondary efficacy endpoints included in the two identical proposed Phase 3 lesinurad add-on studies (Study 301 and Study 302) in gout patients who have had an inadequate hypouricemic response to allopurinol:

- ***sUA:***

    1. ***Proportion of subjects with an sUA level that is <5.0 mg/dL by Month 6***

2. ***Proportion of renally impaired (creatinine clearance <90 mL/min by Cockcroft-Gaultformula) subjects whose sUA level is <6.0 mg/dL by Month 6***

- ***Flare:***

1. ***Proportion of subjects requiring treatment for a gout flare during Month 12***

2. ***Proportion of subjects requiring treatment for a gout flare during Month 6***

- ***Tophi:***

Mean percent change from Baseline in the sum of the longest diameters for all target tophi by Month 12

- ***Patient Reported Outcomes:***

1. ***Proportion of subjects with an improvement in HAQ-DI of at least 0.25 at Month 12***

2. ***Mean change from Baseline to Month 12 in the SF-36 physical summary (PCS)***

(b) (4)

<u>*Response:*</u>

All of these secondary endpoints would be supportive of your primary endpoint which is a surrogate endpoint. However, the decision concerning what information will be included in product labels as labeling claims depends on a number of factors, including statistical significance, clinical significance and whether the information is redundant with other information.

(b) (4)

Discussion:

None

Question 20:

Does the FDA agree with the proposed hypothesis testing approach for the key secondary efficacy endpoints proposed in the replicate Phase 3 lesinurad add-on studies, Study 301 and Study 302, that of which each include 3 treatment arms?

Response:

In Studies 301 and 302, you propose to (b) (4) *This approach is not acceptable. In your statistical analysis plan, provide a strategy or a correction method to account for multiple comparison tests in key secondary endpoints that will control the type 1 error.*

(b) (4)

Discussion:

Ardea proposed to (b) (4) . FDA did not agree (b) (4) and stated that they would need to account for multiplicity when evaluating key secondary endpoints. Ardea agreed to submit a statistical analysis plan with a detailed description and justification (b) (4) to the IND for FDA comment.

Question 21:

Does the FDA agree that the proposed key secondary efficacy endpoints included in the Phase 3 febuxostat combination study in tophaceous gout patients (Study 304):

- ***Tophi***

Mean percent change from Baseline in the sum of the longest diameters for all target tophi by Month 12

- ***sUA***

Proportion of renally impaired (creatinine clearance <90 mL/min by Cockcroft-Gaultformula) subjects whose sUA level is <6.0 mg/dL by Month 6

- ***Flare***

Proportion of subjects requiring treatment for a gout flare during Month 12

- ***PRO***

    1. ***Proportion of subjects with an improvement in HA Q-DI of at least 0.25 at Month 12***

    2. ***Mean change from Baseline to Month 12 in the SF-36 physical component summary (PCS)***

(b) (4)

Response:

Refer to the response to Question 19.

Discussion:

None

Question 22:

Does the FDA agree that the proposed key secondary efficacy endpoints included in the Phase 3 lesinurad monotherapy study in gout patients who are intolerant or have a contraindication to a xanthine oxidase inhibitor (Study 303):

- ***sUA***

Proportion of renally impaired (creatinine clearance <90 mL/min by Cockcroft-Gaultformula) subjects whose sUA level is <6.0 mg/dL at the final visit

- ***PRO***

    1. ***Proportion of subjects with an improvement in HAQ-DI of at least 0.25***

2. Mean change from baseline in the SF-36 physical component summary

(b) (4)

Response:

Refer to the response to Question 19.

Discussion:

None

Question 23:

Does the FDA agree with the proposed hypothesis testing approach for the key secondary efficacy endpoints proposed in the Phase 3 lesinurad studies, Study 303 and Study 304, that each includes 2 treatment arms?

Response:

Your proposed hypothesis testing approach for the key secondary efficacy endpoints in Studies 303 and 304 appears reasonable.

Additional Statistics Comments:

Given the high dropout rates observed in both the ULORIC and KRYSTEXXA trials (18% - 33%), and most of these dropouts were due to treatment-related adverse events, and because it is unclear how many patients are expected to discontinue in your proposed trials, applying last observation carried forward for patients who have missing Month 6 data is not acceptable. Patients with missing data for the primary efficacy analysis (i.e. those who discontinues from the study or treatment prior to month 6, regardless of reasons) should be considered treatment failures or non-responders.

It is unclear from the protocol synopses how you plan to handle missing data on secondary endpoints. In your statistical analysis plan, outline how you plan to handle missing data on each of the secondary endpoints (e.g. sUA, flare, tophi, and the PRO endpoints). Discuss potential mechanisms which may cause secondary endpoints data to be missing, and the proportion of dropouts expected in each treatment group at Month 6 or at Month 12 (if applicable). We also recommend that you outline additional analyses to gauge the sensitivity of your analysis method to violations of the assumed missing data mechanism. In addition, provide a plan on how you will integrate and explain the results from all these sensitivity analyses; in particular, if the results are in different direction from the result of the primary analysis.

We also recommend that the reasons for discontinuation be clearly documented to avoid less informative terms such as 'lost to follow-up', 'patient/investigator decision,' 'withdraw consent', etc. If a patient is 'lost to follow-up,' you should provide a plan for attempting to contact the patient so that a more informative category can be assigned.

Refer to the National Research Council of the National Academy's report, titled "The Prevention and Treatment of Missing Data in Clinical Trials" for further information.

Discussion:

None

Question 24:

Does the FDA agree with the proposed collection method and definition of a gout flare and that the proposed collection method for gout flares is adequate to support the key secondary efficacy endpoint of Proportion of subjects requiring treatment for a gout flare in the proposed Phase 3 studies?

Response:

According to your meeting package, subjects participating in the proposed Phase 3 trials will be required to self-report via an electronic diary or an interactive voice- or web-based response system each gout flare they experience and any medication used to treat the flare. The analysis for the secondary endpoint of gout flares will only include clinically relevant disease flares which are defined as patient-reported gout flares that required the use of either prescribed or self-medicated treatment. Additional signs and symptom data regarding each gout flare will be collected as specified in a pending Outcome Evaluation in Gout Special Interest Group of OMERACT publication and includes overall pain at rest via a 10-point numeric rating scale, and the presence of warm and swollen joints. In principle we agree with both the proposed collection method and definition of a gout flare as well as the proposed collection of gout flare data.

Discussion:

None

Question 25:

Does the FDA agree with the proposed method of measuring tophi with digital calipers and the proposed definition of tophus reduction and resolution (b) (4) **in Phase 3 studies?**

Response:

We concur in principle with your proposed method of measuring tophi with digital calipers. [redacted] *We recommend that you analyze the tophi measurement data from your Phase 3 trials using either a binary response (yes/no) or categorical response scale (e.g., complete response: 100% decrease in tophus area, marked response: at least 75% decrease in area, improved: approximately ≥ 50% reduction from baseline in size of unmeasured tophi, partial response: at least 50% decrease in are, stable disease: neither a 50% decrease not a 25% increase in area and/or improvement or progression from baseline in area of unmeasurable tophi, progressive disease: >25% increase in ar**ea or > 50% increase from baseline in area in unmeasurable tophi or unable to evaluate).***

Discussion:

None, as time did not permit discussion.

Question 26:

Does the FDA agree that the two proposed Phase 3 allopurinol add-on studies in gout patients with hyperuricemia who are inadequate responders to allopurinol (Study 301 and Study 302) are adequate to support the proposed indication for the [redacted] **treatment of gout in combination with allopurinol in patients who have had an inadequate response to allopurinol?**

Response:

As stated in the response to Question 15, we have concerns that patients who are suboptimally treated with allopurinol could potentially qualify as inadequate responders based on the minimally therapeutic dose of 200 mg/day of allopurinol required for study entry. Presuming this issue is addressed, we concur in principle that the two proposed Phase 3 allopurinol add-on studies (Studies 301 and 302) in hyperuricemic patients with gout who are inadequate responders to allopurinol should be sufficient to support the proposed indication for the [redacted] *treatment of gout in combination with allopurinol in hyperuricemic patients who have had an inadequate response to allopurinol provided that the primary endpoint is met in both studies and no new safety signals are identified. However, the final determination of the efficacy and safety of lesinurad is a review issue.*

Discussion:

None

Question 27:

Does the FDA agree that the proposed Phase 3 combination study with febuxostat in tophaceous gout patients (Study 304) is adequate to expand the proposed indication to the (b) (4) treatment of gout in combination with a xanthine oxidase (XO) inhibitor in patients who have had an inadequate response to one or more XO inhibitors is supported?

Response:

We agree in principle, that positive results from your proposed Phase 3 combination study with febuxostat in tophaceous gout patients (Study 304) should be adequate to support expanding the proposed indication to the (b) (4) treatment of gout in combination with a XO inhibitor in hyperuricemic patients who have had an inadequate response to one or more XO inhibitors provided that no new safety signals are identified. The final determination of the efficacy and safety of lesinurad for this expanded claim will again be a review issue.

Discussion:

None

Question 28:

(b) (4)

(b) (4)

(b) (4)

Discussion:

None

Question 29:

Does the FDA agree that the 200 mg qd and 400 mg qd dose levels of lesinurad chosen for the proposed Phase 3 add-on studies with allopurinol (Study 301 and Study 302) are

adequately supported by the concluded Phase 2b add-on study of lesinurad in the similar patient population of patients with an inadequate hypouricemic response to allopurinol?

Response:

It is not clear to us that the dosing regimens, you explored in Phase 1, Phase 2, and the proposed Phase 3 program, are optimal. For example, we have no information on PK, PD, dose/exposure-response, and safety of your product following different dosing intervals (e.g., 100 mg or 200 mg PO BID). Please provide information on alternative dosing scenarios and justification on why the QD is the best regimen for this patient population.

Discussion:

Ardea expressed that once daily dosing was selected based on:

- a sustained biologic effect after a single dose of lesinurad; half-life for sUA lowering was 33-43 hrs after a single dose of lesinurad in Study 109.
- Serum urate lowering at trough and intra-day changes are almost identical with lesinurad 400 mg to febuxostat 40 mg, a once daily product;
- PK modeling indicates that using twice daily dosing versus once daily would produce only a minimal increase in urate lowering;
- Urine volume is substantially reduced at night (approx. 1/5 of morning), so twice daily dosing would result in the highest concentrations of urinary uric acid, which would increase the potential for crystallization; and
- Dosing once daily is the easiest for patients to use and has the best compliance; since gout already has the poorest compliance of any chronic disease evaluated, the slight potential benefit of BID dosing is not worth the predicted decline in compliance.

FDA stated that there was concern about Ardea's proposed QD dosing regimen based on 1.) the lack of information included in the meeting package and 2,) the sponsor would select a higher nominal dose than needed for a QD regimen without investigating a BID regimen. FDA continued that if the 400 mg QD dosing is too high and if patients take the drug at night, then it could be more harmful and result in a compliance issue. FDA also stated that Ardea would have to provide data to justify a large sample size. In response, Ardea presented results from a single dose administration of their proposed Phase 3 table showing a sustained PD effect (sUA) out beyond 48 hours, with a half-life of 33-43 hours. They also showed a table of urine volumes and projected urinary uric acid concentrations for once versus twice daily dosing; dosing at night which produced the highest urinary uric acid concentrations due to the lower urine volume at that time. FDA also questioned whether the sustained PD effect also affected safety. Due to time constraints, it was agreed that Ardea could provide a package of information for FDA review prior to initiation of the Phase 3 studies, with adequate justification and supporting data for QD dosing and an explanation why BID dosing would not be pursued due to safety concerns.

Question 30:

Does the FDA agree that the dose level of lesinurad, 400 mg qd, chosen for the proposed Phase 3 monotherapy study in gout patients with intolerance or a contraindication to a xanthine oxidase inhibitor (Study 303) is adequately supported by the concluded Phase 1b (Study 110) and Phase 2b monotherapy dose-response study of lesinurad (Study 202)?

Response:

See response to Question #29.

Discussion:

See "Discussion" for Question 29, as they were discussed together.

Question 31:

Does the FDA agree that the dose level of lesinurad, 400 mg qd, chosen for the proposed Phase 3 febuxostat combination study in tophaceous gout patients (Study 304) is adequately supported by the concluded Phase 1 studies of febuxostat in combination with lesinurad?

Response:

See response to Question #29.

In addition, we recommend evaluating the same dose levels in Study 304 as proposed in Studies 301 and 302. In the event that similar efficacy or a dose-related safety signal is observed for the two doses in the allopurinol add-on trials, we may question whether a dose lower than the single proposed dose in Study 304 would also be appropriate as add-on treatment to febuxostat since this was not explored in the Phase 2 program.

Discussion:

None

Question 32:

Does the FDA agree that the planned total number of individuals exposed to lesinurad and the number of patients administered lesinurad 200 mg qd and 400 mg qd for 6 months and for 1 year in Phase 2 and Phase 3 clinical trials will be adequate for the planned NDA to support the second-line indication for the (b) (4) ***treatment of gout in combination with a xanthine oxidase (XO) inhibitor in patients who have had an inadequate response to one or more XO inhibitors*** (b) (4) **?**

Response:

According to the projected exposures contained in your meeting package, the lesinurad safety database will contain approximately 1100 patients treated for 6 months and approximately 200 patients treated for one year with daily doses of 200 mg to 400 mg given in combination with a xanthine oxidase inhibitor or as monotherapy. These exposure projections also included approximately 650 patients treated for 6 months and approximately 130 patients treated for one year with 400 mg/day of lesinurad which is the highest dose of the drug undergoing evaluation. The number of chronically exposed patients to lesinurad will increase to approximately 850 patients treated for one year at doses of 200 mg to 400 mg/day given in combination with a XO inhibitor or as monotherapy, out of which approximately 500 patients will have been treated with 400 mg/day for one year at the time of the 120-day safety update submission. Based on these projected exposures there should be an adequate numbers of patients exposed to lesinuard in the overall safety database to support the submission of an NDA. However, the final determination of the safety of the drug remains a review issue. Be advised that if unexpected safety issues arise in the Phase 3 study, additional safety data may be necessary.

Additional comment:

According to your meeting package, you intend to submit an NDA for lesinurad containing analyzed efficacy data supporting the 6-month primary endpoints for the 12-month Studies 301, 302 and 304. For the purpose of this analysis, blind will be maintained to protect the integrity of these on-going trials. However analyses results, of many of the secondary endpoints necessary to support the clinical meaningfulness of the surrogate primary endpoint, will not be available for inclusion in your NDA. In view of this, we recommend that you do not submit your NDA until all of the data necessary to support the efficacy and safety of lesinurad for the indications you are interested in obtaining are available for review.

Discussion:

None

3.0 DATA STANDARDS FOR STUDIES

CDER strongly encourages IND sponsors to consider the implementation and use of data standards for the submission of applications for product registration. Such implementation 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 studies. CDER has produced a web page that provides specifications for sponsors regarding implementation and submission of 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. The web page may be found at the following link:
http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm

4.0 ISSUES REQUIRING FURTHER DISCUSSION

There are no issues for further discussion.

5.0 ACTION ITEMS

There are no action items.

6.0 ATTACHMENTS AND HANDOUTS

Slides presented by Ardea, serving as their talking points, and referred to during discussion

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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/

SADAF NABAVIAN
08/19/2011

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 102,128

MEETING MINUTES

Ardea Biosciences, Inc.
Attention: Kimberly Manhard
Senior VP, Reg. Affairs & Development Operations
4939 Directors Place
San Diego, CA 92121

Dear Ms. Manhard:

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

We also refer to the meeting between representatives of your firm and the FDA on July 6, 2011. The purpose of the meeting was to discuss lesinurad Phase 3 program and registration activities to support the proposed NDA.

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

If you have any questions, call Swati Patwardhan, Regulatory Project Manager, at 301-796-4085.

Sincerely,

{See appended electronic signature page}

Prasad Peri, Ph.D.
Branch Chief
Division of New Drug Quality Assessment III
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

Enclosure: Meeting minutes

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF NEW DRUG OUALITY ASSESSMENT

Sponsor Name:	Ardea Biosciences, Inc.
Application Number:	IND 102,128
Product Name:	Lesinurad
Meeting Requestor:	Kimberly Joan Manhard
Meeting Type:	Type B
Meeting Category:	Chemistry, Manufacturing and Controls (CMC) End of Phase 2 (EOP 2) Meeting
Meeting Date and Time:	July 6, 2011, 3:00 to 4:00 pm
Meeting Location:	Food and Drug Administration, White Oak Campus, Building 22, Conference Room: 1415, Silver Spring, MD
Received Briefing Package	June 6, 2011
Meeting Chair:	Prasad Peri
Meeting Recorder:	Swati Patwardhan

FDA ATTENDEES:

CENTER OF DRUG EVALUATION AND RESEARCH

Office of New Drug Quality Assessment:

- Prasad Peri, Branch Chief, Branch VIII
- Alan Schroeder, CMC Lead, Branch VIII
- Edwin Jao, CMC Reviewer, Branch VIII
- Suarez Sandra, Biopharmaceutics reviewer
- Swati Patwardhan, Regulatory Project Manager

Division of Pulmonary, Allergy and Rheumatology Products:

- Rosemarie Neuner, Medical Officer

EXTERNAL ATTENDEES:

- Barry David Quart, PharmD, President and CEO
- Colin Edward Rowlings, PhD, Senior VP, Pharmaceutical Sciences
- Jean-Luc Samuel Girardet, PhD, VP, Research Operations
- Irina Zamansky, PhD, Senior Director, Analytical Sciences
- (b) (4) CMC Regulatory Consultant
- Pushpa Ganapathi Shao, PhD, Senior Regulatory Associate
- Li-Tain Yeh, PhD, VP, Translational Science
- Clynn Elwood Wilker, DVM, PhD, DACT
- Kimberly Joan Manhard, Senior VP, Regulatory Affairs and Development Operations

BACKGROUND

Lesinurad is being developed for the (b) (4) treatment of gout in combination with xanthine oxidese (XO) inhibitor in patients who have has an inadequate response to one or more XO inhibitors (b) (4) The objectives for the meeting are as follows:

- To verify the acceptability of the drug substance and drug product manufacturing plans to support Phase 3 and registration
- To identify any additional information necessary to support a marketing application

2.0 DISCUSSION

2.1 Drug Substance

2.1.1 Does the FDA agree with the designation of (b) (4) as one of the regulatory starting materials in the drug substance synthesis?

FDA Pre-meeting Response:

No, we do not agree. (b) (4) is recommended as a starting material. All impurities that contain structural alerts and possible toxic impurities associated with the process should be adequately investigated and controlled.

Meeting Discussion:

Ardea proposed (b) (4), as the starting material. The proposed starting material, (b) (4) is well characterized and commercially available (b) (4) They presented slides 3-6 to support their rationale. Ardea wanted to know if the choice of (b) (4) was acceptable. The Agency acknowledged Ardea's efforts in identifying a different starting material. However, the adequacy of

[redacted] as a starting material can be determined only after the application is reviewed. Ardea should provide a revised [redacted] route using the newly proposed starting material and create appropriate specifications for the new starting material. Ardea is considering 3 different vendors for the starting material. The Agency cautioned Ardea about choosing different vendors as it may result in different impurity profiles. Ardea assured the Agency that they will identify starting materials with [redacted]% purity and then set the specification.

Ardea agreed to develop adequate starting material specifications and submit the data as an amendment to the IND.

There was a question raised from the Agency as to how the [redacted] for the drug substance. Ardea responded that [redacted]

2.1.2 Does the FDA agree with the proposed strategy to allow the use of [redacted] as the regulatory starting material?

FDA Pre-meeting Response:

[redacted] can be used for the synthesis of the drug substance, provided that the resultant drug substance is equivalent; however, it is not appropriate to designate [redacted] as starting materials (see our response to 2.1.1, above).

Meeting Discussion:

No discussion occurred on this topic, as the preliminary responses were found satisfactory.

2.1.3 Does the FDA agree with the designation of [redacted] as one of the drug substance regulatory starting materials?

FDA Pre-meeting Response:

Yes. Since this compound is a structural alert, all possible toxic impurities in this starting material should be adequately investigated and controlled based on data and toxicological evaluation.

Meeting Discussion:

No discussion occurred on this topic, as the preliminary responses were found satisfactory.

2.1.4 Does the FDA agree with the designation of [redacted] as one of the drug substance regulatory starting materials?

FDA Pre-meeting Response:

Yes. As mentioned above, all possible toxic impurities in this starting material should be adequately investigated and controlled based on data and toxicological evaluation.

Meeting Discussion:

No discussion occurred on this topic, as the preliminary responses were found satisfactory.

2.1.5 Does the FDA agree with the proposed strategy to [redacted (b) (4)]?

FDA Pre-meeting Response:

Yes. All possible toxic impurities in an alternative synthesis should be adequately investigated and controlled based on data and toxicological evaluation, and the resultant drug substance should be shown to be the same in terms of identity, strength, quality and purity as drug substance produced by the current route.

Meeting Discussion:

No discussion occurred on this topic, as the preliminary responses were found satisfactory.

2.1.6 Does the FDA agree with the plan to initiate Phase 3 clinical studies using drug substance synthesized with [redacted (b) (4)] route?

FDA Pre-meeting Response:

Yes, as long as batch data demonstrate that the drug substances manufactured using different routes are chemically (impurity profile) and physically equivalent.

Meeting Discussion:

No discussion occurred on this topic, as the preliminary responses were found satisfactory.

2.1.7 Does the FDA have any comments on the proposed quality attributes for lesinurad drug substance?

FDA Pre-meeting Response:

Depending on the outcome of toxicological evaluation and purging studies, more impurities/degradants may have to be controlled at the drug substance level. This includes data and safety supported acceptance criteria and validated analytical methods.

Meeting Discussion:

No discussion occurred on this topic, as the preliminary responses were found satisfactory.

2.1.8 Does the FDA agree with the proposed Drug Substance Registration Stability Plan for the (b) (4) route?

FDA Pre-meeting Response:

Yes, with the following comments:

a. Stress testing should be conducted to investigate the susceptibility of the drug substance (b) (4) and to validate the stability indicating power of the analytical methods. This should also include testing with (b) (4)

b. Stability specifications and testing attributes may need to be revised pending on possible revision of release specifications.

Meeting Discussion:

No discussion occurred on this topic, as the preliminary responses were found satisfactory.

2.1.9 Does the FDA agree with the plan to use registration batch sizes between (b) (4)% of the anticipated commercial batch size for drug substance registration stability?

FDA Pre-meeting Response:

Yes, as long as the pilot batches are manufactured using equipment of the same design or operating principles and the same process as the future commercial production.

Meeting Discussion:

No discussion occurred on this topic, as the preliminary responses were found satisfactory.

2.2 Drug Product

2.2.1 Does the FDA have any comments on the proposed quality attributes for lesinurad tablets?

FDA Pre-meeting Response:

Depending on the outcome of toxicological evaluation of all the possible impurities/degradants, more impurities/degradants may have to be controlled at the drug product level. This includes data and safety supported acceptance criteria and validated analytical methods.

Meeting Discussion:

No discussion occurred on this topic, as the preliminary responses were found satisfactory.

2.2.2 Does the FDA have any comments on the proposed analytical method for dissolution testing of lesinurad tablets?

FDA Pre-meeting Response:

In general, it appears that the 75 rpm speed is more adequate than the (b) (4) rpm speed based on the dissolution profiles for the different strengths (b) (4) The use of (b) (4) pm may require beyond (b) (4) min testing to reach more than (b) (4) % dissolution.

- The FDA acknowledges the sponsor's efforts in developing a clinically relevant dissolution method. However, the data provided in the meeting package is insufficient to reach a conclusion about the discriminating power of the method. It appears that your statement about the 75 rpm paddle speed as being more clinically relevant (not over-discriminating) compared to the (b) (4) rpm speed is based on a BA study conducted in three different periods using both fasted and fed conditions. Under these circumstances it is not possible to reach a final conclusion on the discriminating power of your proposed method due to the possible confounded effect by the presence of food. Please clarify.
- Provide a full pharmacokinetic (PK) study report including 90% confidence intervals (CI) comparing the three different formulations used in the study (b) (4).
- Provide a dissolution method report including the complete dissolution profile data (individual, mean, SD, profiles) collected during the development and validation of the proposed dissolution method for both components.

Meeting Discussion:

Ardea clarified that the pharmacokinetic data was collected with the film coated tablet formulation. (b) (4) They are in the process of compiling a dissolution development method and they intend to send the method and draft protocol to the Agency for their review and comments.

As part of the in vitro-in vivo relationship analysis, the Agency suggested the calculation of 90 % confidence intervals for PK data analysis to determine the degree of sameness between formulations.. Further a clinical relevance should be established and link with in-vitro data. In this case, a biorelevant dissolution method is established when equivalence or inequivalence in vivo is also reflected in vitro conditions by the passing or failing of F2 testing, respectively.

Ardea agreed to submit the clinical PK report including the relevant statistical analysis for the purpose of evaluating the establishment of a biorelevant dissolution method and a proposed outline of the validation method as an amendment to IND. The Agency emphasized that the sponsor submit the

amendment to the IND after the fasted study data has been completed and to include the in vitro/in vivo relationship analysis described above.

2.2.3 Does the FDA agree with the proposed drug product registration stability plan?

FDA Pre-meeting Response:

Stability specification and testing attributes may need to be revised pending a possible revision of release specifications.

Meeting Discussion:

No discussion occurred on this topic, as the preliminary responses were found satisfactory.

2.2.4 Does the FDA agree with the proposed comparative testing to qualify debossed lesinurad tablets planned for commercialization?

FDA Pre-meeting Response:

Yes, dissolution profile comparisons provided for both proposed strengths, 200 and 400 mg in the appropriate QC media are acceptable.

Meeting Discussion:

No discussion occurred on this topic, as the preliminary responses were found satisfactory.

3.0 Additional Comments

a. Provide in tabulated form a list of specified, identified impurities/degradants indicating if they are structural alerts along with levels observed and/or their maximum acceptance criteria. This includes potential impurities with structural alerts such as those from the starting materials, process, and intermediates which have the potential to appear in the drug substance.

b. Provide data and toxicological evaluation supported assurance that all structural alert containing impurities/degradants in all batches to be used in the phase III clinical trial are adequately controlled and impose no safety concerns. Please note that additional comments and/or discussion on the drug substance impurities/degradants may be forthcoming or may be discussed at the meeting scheduled with the non-clinical and clinical review teams.

Meeting Discussion:

In response to "Additional Comment", bullet items a and b, Ardea stated that there are (b) (4) The phase 3 product will be synthesized (b) (4) All impurities will be tracked. Ardea presented slides 8-13 to describe and discuss their approach (b) (4)

Ardea would submit the impurities in tabulated format for [redacted] as requested by the Agency. The methods will identify impurities at ppm level. The Agency agreed with Ardea's approach [redacted] However, due to absence the pharmacology/toxicology representation at this meeting, additional comments from pharmacology should be expected.

Ardea has conducted the Ames test with early lot material [redacted]. The results were negative at [redacted] mcg/plate. Ardea intends to run the Ames test for any newly identified impurities. The Agency reiterated that there might be comments from the pharmacology group which will be provided later.

Post-meeting comment: An EOP2 meeting was held between Ardea and the clinical and nonclinical disciplines on July 21, 2011. Preliminary comments were provided to Ardea for this meeting which included the following, "*As was discussed in your July 6, 2011 EOP2 CMC meeting, you proposed to complete bacterial reverse mutation assays (Ames assays) for starting materials or impurities that contain structural alerts. For those impurities that are positive in the Ames assay or are known carcinogens, you proposed to control these impurities to <* [redacted] *mcg/day. We agree with your proposed approach to qualify or control impurities containing structural alerts. We also remind you that for impurities that do not contain structural alerts, monitor impurities and degradation products of all active ingredients and refer to ICH Guidances [ICH Q3A(R) and ICH Q3B(R)] for possible qualification requirements.*"

There was no discussion about this response.

c. Provide the following information/data as part of the preNDA meeting package or at the time of NDA submission:

   1) Data on the effect of the particle size of drug substance [redacted] on dissolution.
   2) Data on the effect of [redacted] in the drug substance on dissolution.
   3) Dissolution profile comparisons for the 200 mg tablet to support a waiver of the in vivo BA/BE studies for this strength if no plasma levels are included.
   4) Complete dissolution profile data (raw data and mean values) from the clinical and primary stability batches supporting the selection of the dissolution acceptance criterion (i.e., specification-sampling time point and specification value) for the proposed product.

d. It is not clear whether the formulation proposed to be evaluated in the phase 3 trials is film coated. If no plasma levels are provided then dissolution profile comparisons will be needed to support the link.

e. We note that you mention the use of QbD and DOE studies [redacted] on specific unit operations in manufacture [redacted]. We also note that you will continue to use these elements of a risk-based quality by design approach in the ongoing scale up of the manufacturing process.

   While we encourage these approaches, in order for us to provide you with guidance on such approaches, we strongly recommend that you provide us with complete details of

your proposed QbD approaches and DOE studies (as soon as available) that you plan to use for the development of your drug product.

Meeting Discussion:

Ardea agreed to submit the QbD outline and proposal as per the Agency's comments in the preliminary response. It should be noted that the Agency makes every attempt to respond to the applicant's queries in the timely manner, but can not commit to the timeline for the response. If needed, the Agency agreed to have a formal dialogue via a teleconference.

4.0 CONCURRENCE:

{See appended electronic signature page}

Swati Patwardhan.
Regulatory Health Project Manager for Quality
Division of New Drug Quality Assessment III
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

{See appended electronic signature page}

Prasad Peri
Branch Chief, Branch VIII
Division of New Drug Quality Assessment III
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

5.0 ATTACHMENTS AND HANDOUTS

Attached

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/s/

PRASAD PERI
08/04/2011

LATE-CYCLE COMMUNICATION DOCUMENTS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 207988

LATE-CYCLE MEETING MINUTES

Ardea Biosciences, Inc.
9390 Towne Centre Drive
San Diego, CA 92121

Attention: Kimberly Manhard,
Senior Vice President, Regulatory Affairs and Development Operations

Dear Ms. Manhard:

Please refer to your New Drug Application (NDA) dated December 25, 2014, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Zurampic (lesinurad) 200 mg tablets.

We also refer to the Late-Cycle Meeting (LCM) between representatives of your firm and the FDA on September 18, 2015.

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

If you have any questions, call Michelle Jordan Garner, Regulatory Project Manager at (301) 796-4786.

Sincerely,

{See appended electronic signature page}

Sarah Yim, MD,
Supervisory Associate Director
Division of Pulmonary, Allergy, and Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure:
Late Cycle Meeting Minutes

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF LATE-CYCLE MEETING MINUTES

Meeting Date and Time: September 18, 2015; 1:00 P.M.
Meeting Location: Teleconference

Application Number: NDA 207988
Product Name: Zurampic (lesinurad)
Applicant Name: Ardea Biosciences, Inc.

Meeting Chair: Sarah Yim, MD
Meeting Recorder: Michelle Jordan Garner, MS, OTR/L

FDA ATTENDEES

Office Drug Evaluation II
Mary Parks, MD, Deputy Director
Division of Pulmonary, Allergy, and Rheumatology Products
Badrul A. Chowdhury, MD, PhD, Director
Sarah Yim, MD, Supervisory Associate Director
Rosemarie Neuner, MD, Clinical Reviewer
Tim Robison, PhD, Pharmacology Toxicology Team Leader
Matthew Whittaker, PhD, Pharmacology Toxicology Reviewer
Office of Product Quality
Craig Bertha, PhD, Product Quality Lead
Division of Clinical Pharmacology 2, Office of Clinical Pharmacology
Ping Ji, Ph.D., Clinical Pharmacology, Team Leader (Acting)
Jianmeng Chen, PhD, Clinical Pharmacology Reviewer
Office of Surveillance and Epidemiology
Jamie Wilkins Parker, PhD, Team Leader
Jasminder Kumar, PhD, DRISK Reviewer
Teresa McMillan, PhD, DMEPA Reviewer

EASTERN RESEARCH GROUP ATTENDEES

Peggah Khorrami

APPLICANT ATTENDEES

James Mackay, PhD, President and Chief Operating Officer, Ardea
Kimberly Manhard, Senior Vice President, Regulatory Affairs and Development Operations, Ardea
Chris Storgard, MD, Vice President, Clinical Research and Development, Ardea
Nihar Bhakta, MD, Executive Medical Director, Clinical Development, Ardea
Maple Fung, MD, Senior Medical Director, Clinical Development, Ardea
Scott Adler, MD, Senior Medical Director, Inflammation, Clinical Development, AstraZeneca

William Bushnell, MS, Global Project Statistician, AstraZeneca
Jeff Miner, PhD, Executive Director, Biology, Ardea
(b) (4), Clinical Pharmacokineticist, Consultant to Ardea
Michael Gillen, Director, Clinical Pharmacology, AstraZeneca
Meghan O'Neill, Manager, Regulatory Affairs, Ardea
Leslie Bennett, Executive Director, Regulatory Strategy, Ardea
Fredrik Nyberg, MPH, PhD, MD, Group Director, Epidemiology, AstraZeneca

1.0 BACKGROUND

NDA 207988 was submitted on December 25, 2014, for Zurampic (lesinurad).

Proposed indication(s): Treatment of hyperuricemia associated with gout

PDUFA goal date: December 29, 2015

FDA issued a Background Package in preparation for this meeting on September 11, 2015.

2.0 DISCUSSION

1. Introductory Comments

Discussion:
There were no new issues from the mid-cycle review communication. However, FDA acknowledges receipt of the protocol of an observational study, and counter-proposed labeling submitted by the applicant. Although FDA was unable to provide any comments on the labeling submitted, it was expressed that they will more than likely agree with some of the counter-proposed labeling, but not all of it. FDA plans to wait until the outcome of the Advisory Committee (AC) meeting before proceeding with labeling negotiations.

2. Discussion of Substantive Review Issues

Clinical: Safety
Renal
Cardiovascular
Risk Benefit

Discussion:
FDA expressed having no new issues since the mid-cycle communication with Ardea. The 200 mg dose appears to be a reasonable dose for renal and cardiovascular safety; however, the 400 mg dose causes safety concerns. Ardea asked for clarification about renal stone events, and FDA responded that although the imbalance in renal stones was with the 400 mg dose, it is an expected concern related to the mechanism of action, and is considered part of the overall renal safety signal.

Ardea referred to their counter-proposed labeling including the boxed-warning regarding the risk of acute renal failure when used as monotherapy, and changes to the Warnings and Precaution sections of the label, which included responses to FDA initial comments and a cardiovascular event warning. Ardea expressed uncertainty regarding the possible MACE signal with the 400 mg dose given the low number of events. FDA acknowledged that the numbers are low; however, the exposure in the lesinurad groups was equal to slightly lower than the exposure in the placebo group. Therefore the imbalance is not an artifact of lower exposure in the placebo group. In the case of a potential serious safety concern, FDA would tend to take a conservative approach and treat the imbalance as a signal until proven otherwise. At this point, given that the imbalance is with the 400 mg dose and not with the 200 mg dose proposed for marketing, it is possible that a cardiovascular warning would be adequate to address this concern. If the sponsor wants to address this issue with additional data post-marketing, a non-interventional/observational study would likely not be adequate.

In order to address the risk-benefit concern, Ardea proposed to revise their indication statement to limit the use of lesinurad to those patients who have not achieved their target serum urate with xanthine oxidase inhibitors alone. FDA noted that this is recommended use of uricosurics in the American College of Rheumatology treatment guidelines, so it is not clear whether a change to the initially proposed indication would impact at all on the risk-benefit profile of the product. FDA also noted that all of the AC meeting documents will continue to reflect the initial proposed indication.

3. Discussion of Upcoming Advisory Committee Meeting

- Potential questions and discussion topics for AC Meeting are as follows:
  - Discussion question on efficacy
  - Discussion question on safety with focus on renal and CV events
  - Voting questions: adequacy of efficacy data, adequacy of safety data, approval recommendation

Discussion:

FDA reiterated that the main focus of the meeting is on the relative safety of lesinurad at the 200 and 400 mg doses, and in particular, the renal and cardiovascular events. The question, given the limited decrease in sUA at the 200 mg dose, is whether the risks of the 200 mg dose are sufficiently low to make the risk-benefit favorable. Part of this determination also depends on whether the AC believes the availability of another treatment option would be helpful.

Ardea asked what issues might be raised in terms of efficacy. FDA noted that studies 301, 302, and 303 all met their primary endpoint, and although study 304 did not meet its primary endpoint, the observed decrease in sUA appeared to be consistent with studies 301 and 302. FDA noted that 50% of patients were already meeting their target serum uric acid level at baseline in study 304, so a lack of power to show statistical significance in the difference between the lesinurad groups and placebo was not surprising.

4. REMS or Other Risk Management Actions

Based on the benefit-risk evaluation under consideration by the division for lesinurad, DRISK will complete a full evaluation of the need for a REMS for lesinurad after receiving input from the Arthritis Advisory Committee regarding the efficacy and safety of lesinurad.

Discussion:
FDA noted that the FDA presentations at the AC will not be addressing Ardea's proposed REMS.

5. Major Labeling Issues

- Established pharmacologic class: "Uricosuric" rather than "URAT1 Inhibitor"
- Renal-related labeling: language needs strengthening and should include safety data with 400 mg and monotherapy to emphasize why 400 mg and monotherapy should not be used. Although still under some discussion, the Division is leaning toward labeling that cautions against use in patients with eGFR<45 ml/min
- Cardiovascular: need warning about increased risk with higher doses
- Section 6 and 14 and other additional edits to be forthcoming after AC

Discussion:
FDA offered Ardea an opportunity to ask questions about the concerns that FDA noted within their initial labeling comments. Ardea expressed that their rationale for using "URAT1 Inhibitor" rather than "Uricosuric," as the pharmacologic class. This includes the fact that URAT1 inhibitor is commonly used in the published literature, and that there is precedence for using the specific mechanism as the pharmacologic class rather than the pharmacodynamic effect; examples include the various classes of agents used to lower blood sugar in diabetes. FDA responded that they will discuss the pharmacologic class further internally.

Ardea expressed that their position is (b) (4) FDA stated they will respond to Ardea's counter-proposed labeling after having internal discussions.

6. Review Plans

- AC meeting
- Labeling
- REMS Assessment

Discussion:
FDA reiterated that they would use the outcome of the upcoming AC meeting to determine labeling, and if there would be a need for a REMS.

7. Wrap-up and Action Items

No wrap-up or action items discussed.

This application has not yet been fully reviewed by the signatory authority, division director, and Cross-Discipline Team Leader (CDTL) and therefore, this meeting did not address the final regulatory decision for the application.

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/s/

MICHELLE Y JORDAN GARNER
11/01/2015

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 207988

LATE CYCLE MEETING
BACKGROUND PACKAGE

Ardea Biosciences, Inc.
9390 Towne Centre Drive
San Diego, CA 92121

Attention: Kimberly Manhard,
Senior Vice President, Regulatory Affairs and Development Operations

Dear Ms. Manhard:

Please refer to your New Drug Application (NDA) dated December 25, 2014, received December 29, 2014, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA), for Zurampic (lesinurad) 200 mg tablets.

We also refer to the Late-Cycle Meeting (LCM) scheduled for September 18, 2015. Attached is our background package, including our agenda, for this meeting.

If you have any questions, call Michelle Jordan Garner, Regulatory Project Manager, at (301) 796-4786.

Sincerely,

{See appended electronic signature page}

Badrul A. Chowdhury, MD, PhD
Director
Division of Pulmonary, Allergy, and Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

ENCLOSURE:
Late-Cycle Meeting Background Package

LATE-CYCLE MEETING BACKGROUND PACKAGE

Meeting Date and Time: September 18, 2015; 1:00 P.M. – 2:00 P.M.
Meeting Location: Teleconference

Application Number: NDA 207988
Product Name: Zurampic (lesinurad)
Indication: Treatment of hyperuricemia associated with gout
Sponsor/Applicant Name: Ardea Biosciences, Inc.

INTRODUCTION

The purpose of a Late-Cycle Meeting (LCM) is to share information and to discuss any substantive review issues that we have identified to date, Advisory Committee (AC) meeting plans, and our objectives for the remainder of the review. The application has not yet been fully reviewed by the signatory authority, Division Director, and Cross-Discipline Team Leader (CDTL) and therefore, the meeting will not address the final regulatory decision for the application. We are sharing this material to promote a collaborative and successful discussion at the meeting.

During the meeting, we may discuss additional information that may be needed to address the identified issues and whether it would be expected to trigger an extension of the PDUFA goal date if the review team should decide, upon receipt of the information, to review it during the current review cycle. If you submit any new information in response to the issues identified in this background package prior to this LCM or the AC meeting, if an AC is planned, we may not be prepared to discuss that new information at this meeting.

BRIEF MEMORANDUM OF SUBSTANTIVE REVIEW ISSUES IDENTIFIED TO DATE

1. Discipline Review Letters

No Discipline Review letters have been issued to date.

2. Substantive Review Issues

The following substantive review issues have been identified to date:

Clinical: Safety

- **Renal:** Lesinurad is associated with an increased risk of serious and non-serious renal adverse events, serious and non-serious renal stone events, reversible and non-reversible serum creatinine elevations which were not limited to initial treatment with lesinurad. These imbalances appeared to be larger, and events more severe, with the 400 mg dose

and with monotherapy. Imbalances were present in some renal adverse event categories for the 200 mg dose, but incidences were closer to those found in the control group and there were no serious renal adverse events in the 200 mg dose group during the controlled period of the studies.

- **Cardiovascular:** Lesinurad is associated with an increased risk of MACE with 400 mg dose. Even though imbalances were not consistently present with 200 mg dose, this concern likely merits a warning so that prescribers are aware that concerns are present with the 400 mg dose.
- **Risk Benefit:** As previously mentioned at the Midcycle Communication Meeting, because of the modest treatment effect, the risk-benefit profile of lesinurad is not clearly favorable in light of the aforementioned safety concerns and will require further discussion at the Arthritis Advisory Committee meeting on October 23, 2015.

ADVISORY COMMITTEE MEETING

Date of AC meeting: October 23, 2015

Date AC briefing package sent under separate cover by the Division of Advisory Committee and Consultant Management: Ardea: September 22, 2015; Division: September 25, 2015

Potential questions and discussion topics for AC Meeting are as follows:

- Discussion question on efficacy
- Discussion question on safety with focus on renal and CV events
- Voting questions: adequacy of efficacy data, adequacy of safety data, approval recommendation

We look forward to discussing our plans for the presentations of the data and issues for the upcoming AC meeting. Final questions for the Advisory Committee are expected to be posted two days prior to the meeting at this location:
http://www.fda.gov/AdvisoryCommittees/Calendar/default.htm

REMS OR OTHER RISK MANAGEMENT ACTIONS

Based on the benefit-risk evaluation under consideration by the division for lesinurad, DRISK will complete a full evaluation of the need for a REMS for lesinurad after receiving input from the Arthritis Advisory Committee regarding the efficacy and safety of leisnuard.

LCM AGENDA

1. **Introductory Comments** – 5 minutes
   - Welcome, Introductions, Ground rules, Objectives of the meeting

2. **Discussion of Substantive Review Issues** – 5 minutes
   Clinical: Safety
   - **Renal**
   - **Cardiovascular**
   - **Risk Benefit**

3. **Additional Applicant Data**
   No additional data needed at this time.

4. **Discussion of Upcoming Advisory Committee Meeting** – 5 minutes
   - Potential questions and discussion topics for AC Meeting are as follows:
     - Discussion question on efficacy
     - Discussion question on safety with focus on renal and CV events
     - Voting questions: adequacy of efficacy data, adequacy of safety data, approval recommendation

5. **REMS or Other Risk Management Actions -** 5 minutes
   Based on the benefit-risk evaluation under consideration by the division for lesinurad, DRISK will complete a full evaluation of the need for a REMS for lesinurad after receiving input from the Arthritis Advisory Committee regarding the efficacy and safety of leisnuard.

6. **Major Labeling Issues** – 30 minutes
   - Established pharmacologic class: "Uricosuric" rather than "URAT1 Inhibitor"
   - Renal-related labeling: language needs strengthening and should include safety data with 400 mg and monotherapy to emphasize why 400 mg and monotherapy should not be used. Although still under some discussion, the Division is leaning toward labeling that cautions against use in patients with eGFR<45 ml/min
   - Cardiovascular: need warning about increased risk with higher doses
   - Section 6 and 14 and other additional edits to be forthcoming after AC

7. **Review Plans** – 5 minutes
   - AC meeting
   - Labeling
   - REMS Assessment

8. **Wrap-up and Action Items** – 5 minutes

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/s/

BADRUL A CHOWDHURY
09/11/2015