CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

209203Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

EXCLUSIVITY SUMMARY

NDA # 209203 SUPPL # HFD #

Trade Name Duzallo

Generic Name lesinurad/allopurinol fixed-dose combination

Applicant Name Ardea Biosciences

Approval Date, If Known Goal date: August 18, 2017 (actual Sunday 8/20/17)

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)(2)

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.

This NDA submission include one pivotal bioequivalence (BE) study RDEA594-501 which demonstrated BE between lesinurad/allopurinol 200/300 mg and 200/200 fixed dose combination (FDC) tablets and co-administered single agents in healthy subjects in the fasted and fed states. The BE data from study RDEA594-501 provided the necessary pharmacokinetic data in support of a bridge between the combination studies contained in the lesinurad NDA (207988) to the lesinurad/allopurinol FDC NDA (209203)

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# 207988, lesinurad (Zurampic)
NDA# 016084, allopurinol (Zyloprim)
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:

The two replicate, phase 3 studies crossed-referenced in this NDA were studies RDEA594-301 and RDEA594-302 which were submitted and reviewed in support of NDA 207988 Lesinurad (Zurampic) 200 mg monotherapy.

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 RDEA594-301: A 12-month, phase 3, multicenter, randomized, double-blind, placebo-controlled, combination study evaluating 200 mg and 400 mg of lesinurad once daily with concomitant daily doses of 100-800 mg of allopurinol.

YES ☒ NO ☐

Investigation #2 RDEA594-302: A 12-month, phase 3, multicenter, randomized, double-blind, placebo-controlled combination study evaluating 200 mg and 400 mg of lesinurad once daily with concomitant daily doses of 100-800 mg of allopurinol.

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:

The approval of NDA 207988 Lesinurad (Zurampic) 200 mg monotherapy relied on both the efficacy and safety data from the two replicate, phase 3 studies RDEA5940301 and RDEA594-302.

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 RDEA594-301: A 12-month, phase 3, multicenter, randomized, double-blind, placebo-controlled, combination study evaluating 200 mg and 400 mg of lesinurad once daily with concomitant daily doses of 100-800 mg of allopurinol.

YES ☐ NO ☒

Investigation #2 RDEA594-302: A 12-month, phase 3, multicenter, randomized, double-blind, placebo-controlled, combination study evaluating 200 mg and 400 mg of lesinurad once daily with concomitant daily doses of 100-800 mg of allopurinol.

YES ☐ NO ☒

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

NDA 207988 lesinurad (Zurampic)

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 RDEA594-301 !

IND # 102128 YES ☒ ! NO ☐
! Explain:

Investigation #2 RDEA594-302 !

IND # 102128 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:

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Name of person completing form: Susan Rhee, RPM, DPARP Reviewer, DPARP
Date: July 21, 2017

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

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/

SUSAN RHEE
09/01/2017

BADRUL A CHOWDHURY
09/01/2017

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION[1]

NDA # 209203 BLA #	NDA Supplement # BLA Supplement #	If NDA, Efficacy Supplement Type: *(an action package is not required for SE8 or SE9 supplements)*
Proprietary Name: Duzallo Established/Proper Name: lesinurad/allopurinol Dosage Form: fixed-dose combination tablets 200mg/300mg and 200mg/200mg		Applicant: Ardea Biosciences Agent for Applicant (if applicable):
RPM: Susan Rhee		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 August 18, 2017 (actual Aug 20, 2017 – Saturday)	☐ 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 required 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 5 year NCE NDA 207988	☐ 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)
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 – 8/18/17
• Original applicant-proposed labeling	☒ Included – 10/20/16
❖ 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 – 8/1/17
• Original applicant-proposed labeling	☒ Included – 10/20/16
❖ 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 – 7/10/17
❖ Proprietary Name • Acceptability/non-acceptability letter(s) *(indicate date(s))* – • Review(s) *(indicate date(s)* - 1/23/17 Review, 11/18/19 Acknowledgement	Letter 1/25/17 Review 1/23/17 Acknowledgement 11/18/16
❖ Labeling reviews *(indicate dates of reviews)*	RPM: ☒ 1/31/2017 DMEPA: ☒ 7/19/17, 6/16/17 DMPP/PLT (DRISK): ☒8/1/17 OPDP: ☒ 7/26/17 SEALD: ☒ None CSS: ☒ None Product Quality ☒ None Other: ☒ 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	1/31/2017 ☐ Not a (b)(2) 8/16/17
❖ NDAs/NDA supplements only: Exclusivity Summary *(signed by Division Director)*	☐ Completed
❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
• Applicant is on the AIP	☐ Yes ☒ No
• This application is on the AIP ○ If yes, Center Director's Exception for Review memo *(indicate date)* ○ If yes, OC clearance for approval *(indicate date of clearance communication)*	☐ Yes ☒ No ☐ Not an AP action

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

❖ Pediatrics *(approvals only)* • Date reviewed by PeRC scheduled for 4/5/2017 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 OPDP letters regarding pre-launch promotional materials as these are non-disclosable; do not include Master File letters; do not include previous action letters, as these are located elsewhere in package)*	8/18/17, 8/17/17, 8/4/17, 7/20/17(2), 6/30/17, 6/16/17, 5/31/17, 5/22/17, 3/23/17, 3/15/17, 1/3/17, 12/23/16, 11/2/16
❖ 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
• EOP2 meeting *(indicate date of mtg)*	☐ No mtg
• Mid-cycle Communication *(indicate date of mtg)*	☐ N/A
• Late-cycle Meeting *(indicate date of mtg)*	☐ N/A
• Other milestone meetings (e.g., EOP2a, CMC focused milestone meetings) *(indicate dates of mtgs)*	
❖ Advisory Committee Meeting(s)	☒ No AC meeting
• Date(s) of Meeting(s)	
Decisional and Summary Memos	
❖ Office Director Decisional Memo *(indicate date for each review)*	☐ None
Division Director Summary Review *(indicate date for each review)*	☐ None 8/15/17
Cross-Discipline Team Leader Review *(indicate date for each review)*	☒ None
PMR/PMC Development Templates *(indicate total number)*	☐ None
Clinical	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) *(indicate date for each review)*	☒ No separate review
• Clinical review(s) *(indicate date for each review)*	7/14/16, 12/15/16

• 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)*	Page 63 of Multi-disciplinary Review and Evaluation
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers *(indicate date of each review)*[5]	☐ None DPMH 8/18/17
❖ 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
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
Statistical Review(s) *(indicate date for each review)*	☐ None
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 7/15/17, 12/21/16
❖ OSI Clinical Pharmacology Inspection Review Summary *(include copies of OSI letters)*	☐ None requested 5/31/17

[5] For Part 3 combination products, all reviews from the reviewing Center(s) should be entered into the official archive (for further instructions, see "Section 508 Compliant Documents: Process for Regulatory Project Managers" located in the CST electronic repository).

Nonclinical ☐ None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) *(indicate date for each review)*	☐ No separate review
• Supervisory Review(s) *(indicate date for each review)*	☐ No separate review 7/21/17
• Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	☐ None 7/5/17, 12/7/16
❖ 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
❖ ECAC/CAC report/memo of meeting	☒ None 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[6]	
• 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 7/20/17, 11/30/16, 10/26/16
❖ 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)*	
☐ Review & FONSI *(indicate date of review)*	
☐ Review & Environmental Impact Statement *(indicate date of each review)*	
❖ Facilities Review/Inspection	
☒ Facilities inspections (indicate date of recommendation; within one week of taking an approval action, confirm that there is an acceptable recommendation) *(only original applications and efficacy supplements that require a manufacturing facility inspection(e.g., new strength, manufacturing process, or manufacturing site change)*	☒ Acceptable 7/14/17 Re-evaluation date: ☐ Withhold recommendation ☐ Not applicable

[6] Do not include Master File (MF) reviews or communications to MF holders. However, these documents should be made available upon signatory request.

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

/s/

SUSAN RHEE
08/22/2017

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II

ELECTRONIC CORRESPONDENCE

DATE: August 18, 2017

To: Sonia Villegas, Ph.D. Regulatory Affairs	**From:** Susan Rhee, PharmD Regulatory Management Officer
Company: Ardea Biosciences	Division of Pulmonary, Allergy, and Rheumatology Products
email: SVillegas@ardeabio.com	**Fax number:** 301-796-9728
Phone number: 858-652-6624	**Phone number:** 301-796-2402

Subject: NDA 209203 Duzallo Labeling - Label IR #5

Total no. of pages including cover:

Comments: Please confirm receipt.

Document to be mailed: YES xNO

NDA 209203
Duzallo (lesinurad/allopurinol FDC)
Ardea Biosciences, Inc.

Your submission received on October 20, 2016, is currently under review. Attached are our revisions to your proposed label (submitted on 8/17/17). Be advised that these changes are not necessarily the Agency's final recommendations and that additional changed may be forthcoming as we continue to review.

Submit a clean copy and a track-changed version of the label incorporating our recommended changes as soon as possible. The information can be sent by electronic mail to susan.rhee@fda.hhs.gov, followed by an official submission to the NDA. If you have any questions, please contact Susan Rhee, Regulatory Project Manager, at 301-796-2402.

Drafted by: SRhee 8/18/17
Initialed by: LJafari for SBarnes 8/18/17
Finalized by: SRhee 8/18/17

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

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/s/

SUSAN RHEE
08/18/2017

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II

ELECTRONIC CORRESPONDENCE

DATE: August 17, 2017

To: Sonia Villegas, Ph.D. Regulatory Affairs	**From:** Susan Rhee, PharmD Regulatory Management Officer
Company: Ardea Biosciences	Division of Pulmonary, Allergy, and Rheumatology Products
email: SVillegas@ardeabio.com	**Fax number:** 301-796-9728
Phone number: 858-652-6624	**Phone number:** 301-796-2402

Subject: NDA 209203 Duzallo Labeling - Label IR #4

Total no. of pages including cover:

Comments: Please confirm receipt.

Document to be mailed: YES xNO

NDA 209203
Duzallo (lesinurad/allopurinol FDC)
Ardea Biosciences, Inc.

Your submission received on October 20, 2016, is currently under review. Attached are our revisions to your proposed label and Medication Guide (submitted on 8/14/17). Be advised that these changes are not necessarily the Agency's final recommendations and that additional changed may be forthcoming as we continue to review.

Submit a clean copy and a track-changed version of the label and Medication Guide incorporating our recommended changes as soon as possible. The information can be sent by electronic mail to susan.rhee@fda.hhs.gov, followed by an official submission to the NDA. If you have any questions, please contact Susan Rhee, Regulatory Project Manager, at 301-796-2402.

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

Drafted by: SRhee 8/17/17
Initialed by: LJafari for SBarnes 8/17/17
Finalized by: SRhee 8/17/17

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/s/

SUSAN RHEE
08/17/2017

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II

ELECTRONIC CORRESPONDENCE

DATE: August 4, 2017

To: Sonia Villegas, PhD Regulatory Affairs	**From:** Jessica Lee, PharmD Senior Regulatory Project Manager
Company: Ardea Biosciences	Division of Pulmonary, Allergy, and Rheumatology Products
Fax number:	**Fax number:** 301-796-9728
Phone number: 858-652-6624	**Phone number:** 301-796-3769

Subject: NDA 209203 Duzallo Labeling Information Request

Total no. of pages including cover:

Comments: Please confirm receipt.

Document to be mailed: YES xNO

Dear Dr. Villegas,

Your submission dated October 20, 2016, to NDA 209203, is currently under review. Attached are our revisions to your proposed package insert dated July 26, 2017. Be advised that these labeling changes are not necessarily the Agency's final recommendations and that additional labeling changes may be forthcoming as we continue to review the label.

Submit a clean copy and a tracked-change version of the label incorporating our recommended changes by Wednesday, August 9, 2017. If you have any questions, contact Susan Rhee, Regulatory Project Manager, at 301-796-2402.

Drafted by: JLee 8/4/17

Initialed by: SBarnes 8/4/17

Finalized by: JLee 8/4/17

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/s/

JESSICA K LEE
08/04/2017

Food and Drug Administration
Center for Drug Evaluation
and Research

Office of Drug Evaluation II

ELECTRONIC CORRESPONDENCE

DATE: July 20, 2017

To: Sonia Villegas, Ph.D. Regulatory Affairs	**From:** Susan Rhee, PharmD Regulatory Management Officer
Company: Ardea Biosciences	Division of Pulmonary, Allergy, and Rheumatology Products
email: SVillegas@ardeabio.com	**Fax number:** 301-796-9728
Phone number: 858-652-6624	**Phone number:** 301-796-2402

Subject: NDA 209203 Duzallo (lesinurad/allopurinol) labeling comments

Total no. of pages including cover:

Comments: Please confirm receipt and provide response by July 27, 2017

Document to be mailed: *Yes* x*No*

NDA 209203
lesinurad/allopurinol FDC
Ardea Biosciences, Inc.

We refer to NDA 209203 for Duzallo (lesinurad/allopurinol) FDC and to your proposed labeling submission dated October 20, 2016. We are providing our labeling comments and recommendation in the attached marked up labeling. The proposed insertions are underlined and deletions are in strike-out. Please be advised that these labeling comments are not necessarily the Agency's final recommendations and that additional labeling comments may be forthcoming.
Submit revised labeling incorporating the changes shown in the attached marked up label by **4pm July 27, 2017** via email to susan rhee@fda.hhs.gov, followed by an official submission to the NDA. If you have any questions, please contact Susan Rhee, Regulatory Project Manager, at 301-796-2402.

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

Drafted by: SRhee 7/19/17

Initialed by: SBarnes 7/19/17, NNikolov/RNeuner 7/20/17

Finalized by: SRhee 7/20/17

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/s/

SUSAN RHEE
07/20/2017

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 209203

GENERAL ADVICE

Ardea Biosciences
Attention: Sonia Villegas, Ph.D.
Senior Manager, Regulatory Affairs
9390 Towne Center Drive
San Diego, CA 92121

Dear Dr. Villegas:

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

We refer to the teleconference on July 06, 2017 for discussion on the proposed physiologically based pharmacokinetic (PBPK) model for your proposed fixed-dose combination (FDC) lesinurad and allopurinol immediate release (IR) tablets (200mg/200mg, and 200mg/300mg).

It was discussed if a FDC batch is available that is evaluated *in vivo* and is non-bioequivalent (non-BE) to the target FDC tablets that could be used to further challenge the developed PBPK model and thus defining dissolution safe space based on profile and/or specification. It was stated that such data is not available to challenge the PBPK model with non-BE FDC batch. Considering the above, since the PBPK model is not challenged by the non-BE FDC batch to define dissolution safe space, its application for post-approval changes may be limited. Note that the proposed dissolution acceptance criterion of Q = (b)(4)% in 45 min for lesinurad based on PBPK and Q = (b)(4)% in 20 min for allopurinol is acceptable. However, it is advised to further refine the proposed PBPK model possibly by challenging it with non-BE FDC batch for defining the dissolution safe space and broadening its application for lifecycle management of the proposed FDC IR tablets (e.g., supporting biowaiver for major post-approval manufacturing/formulation changes).

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

Sincerely,

{See appended electronic signature page}

Craig M. Bertha, Ph.D.
CMC Lead
Branch IV, Division II
Office of New Drug Products
Office of Pharmaceutical Quality

Craig Bertha

Digitally signed by Craig Bertha
Date: 7/20/2017 10:29:08AM
GUID: 50841a65000098a9383c817879a6a84d

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II

ELECTRONIC CORRESPONDENCE

DATE: June 30, 2017

To: Sonia Villegas, Ph.D. Regulatory Affairs	**From:** Susan Rhee, PharmD Regulatory Management Officer
Company: Ardea Biosciences	Division of Pulmonary, Allergy, and Rheumatology Products
email: SVillegas@ardeabio.com	**Fax number:** 301-796-9728
Phone number: 858-652-6624	**Phone number:** 301-796-2402

Subject: NDA 209203 (lesinurad/allopurinol) Container comments

Total no. of pages including cover:

Comments: Please confirm receipt.

Document to be mailed: YES xNO

NDA 209203
lesinurad/allopurinol FDC
Ardea Biosciences, Inc.

Your submission received on October 20, 2016, is currently under review. We have the following comments related to container label:

1. Move the manufacturer information to the side panel or reduce the size as it competes with the proprietary name for prominence and takes readers' attention away from important information such as proprietary and proper names and strength.

2. Ensure the lot number and expiration date is printed on the container labels.

Provide the requested information by noon Thursday, July 9, 2017. The information can be sent by electronic mail to susan.rhee@fda.hhs.gov, followed by an official submission to the IND. If you have any questions, please contact Susan Rhee, Regulatory Project Manager, at 301-796-2402.

Drafted by: SRhee 6/30/17

Initialed by: SBarnes 6/30/17

Finalized by: SRhee 6/30/17

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/s/

SUSAN RHEE
06/30/2017

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

Sent: 06/16/2017 11:51:29 AM
To: SVillegas@ardeabio.com
CC: Susan.Rhee@fda.hhs.gov
BCC: Bamidele.aisida@fda.hhs.gov
Subject: INFORMATION REQUEST NDA 209203

Hello Sonia,

I have received the following information request from our CMC review team. Please respond to the following with a submission to your NDA by Friday, June 23,2017.

Provide the calculation that estimates the introduction concentration into the aquatic environment to support your exclusion request for an environmental assessment.

Please confirm receipt of this email

Thanks,

Florence Aisida, Pharm.D,BCPS
RBPM, Office of Program and Regulatory Operations
Office of Pharmaceutical Quality/CDER/FDA.
(240) 402-2691 |Bamidele.aisida@fda.hhs.gov

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II

ELECTRONIC CORRESPONDENCE

DATE: May 31, 2017

To: Sonia Villegas, Ph.D. Senior Manager, Regulatory Affairs	**From:** Susan Rhee, PharmD Regulatory Management Officer
Company: Ardea Biosciences	Division of Pulmonary, Allergy, and Rheumatology Products
email: SVillegas@ardeabio.com	**Fax number:** 301-796-9728
Phone number: 858-652-6624	**Phone number:** 301-796-2402

Subject: NDA 209203 (lesinurad/allopurinol FDC) Information Request 2

Total no. of pages including cover: 3

Comments: Please confirm receipt.

Document to be mailed: YES xNO

NDA 209203
Lesinurad/allopurinol FDC

Your response to the Information Request received on May 25, 2017 is currently under review. We continue to review the clinical pharmacology information in your NDA submission and have the following information request:

1. With reference to your report 'Model of Uric Acid Handling' (Module 5.3.3.5)', justify why the EC_{50} values (6424 ng/mL in healthy subjects and 13690 ng/mL patients) are substantially higher as compared to EC_{50} values (974 ng/mL) reported in 'Population PK-PD Modeling of Serum Urate Following Administration of Lesinurad in Phase 3 Studies' (Module 5.3.3.5). The EC_{50} of 13690 ng/mL in patients is also much higher as compared to the observed therapeutic lesinurad concentrations. Additionally, justify whether this EC_{50} value is supported by the dose response observed in the phase 3 studies and preclinical receptor binding studies.

2. Perform sensitivity analysis for EC_{50} values vs serum uric acid for your model report 'Simulation of Uric Acid Lowering' (Module 5.3.3.5) at 0.1 times lower EC_{50} similar to that shown in Figure 14 of the report. Note the y-axis should be scaled appropriately to view the differences in serum uric acid response.

3. Conduct an analysis to assess correlation of C_{max} as well as AUC from plasma concentration-time profile of lesinurad versus E_{max} (maximum observed percentage change from baseline in serum urate concentrations) from food effect studies conducted for NDA 207988 and NDA 209203. Provide results for the following scenarios:
    a. Data from fasted state only
    b. Data from fed state only
    c. Data from fasted and fed states combined

4. With reference to Table 20 Module 2.7.2 Summary of Clinical Pharmacology Studies (NDA 207988, Page 104), provide a similar tabular listing for area under the serum/plasma uric acid curve and data from NDA 209203 included in the table. Conduct a correlation analysis for area under the serum uric acid curve versus C_{max} and AUC from plasma concentration-time profile of lesinurad similar to the one mentioned above for the following scenarios:
    a. Data from fasted state only
    b. Data from fed state only

Provide the requested information along with the datasets used for the analysis by 4pm Friday June 2, 2017. The information can be sent by electronic mail to susan.rhee@fda.hhs.gov, followed by an official submission to the IND. If you have any questions, please contact Susan Rhee, Regulatory Project Manager, at 301-796-2402.

Drafted by: SRhee 5/30/17

Initialed by: SBarnes 5/31/17

Finalized by: SRhee 5/31/17

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/s/

SUSAN RHEE
05/31/2017

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II

ELECTRONIC CORRESPONDENCE

DATE: May 22, 2017

To: Sonia Villegas, Ph.D. Senior Manager, Regulatory Affairs	**From:** Susan Rhee, PharmD Regulatory Management Officer
Company: Ardea Biosciences	Division of Pulmonary, Allergy, and Rheumatology Products
email: SVillegas@ardeabio.com	**Fax number:** 301-796-9728
Phone number: 858-652-6624	**Phone number:** 301-796-2402

Subject: NDA 209203 (lesinurad/allopurinol FDC) Information Request

Total no. of pages including cover: 3

Comments: Please confirm receipt.

Document to be mailed: YES xNO

NDA 209203
lesinurad/allopurinol FDC

Your submission dated October 20, 2016, is currently under review. We have the following comments:

We note that in the food effect study (RDEA594-501), C_{max} for lesinurad from the FDC tablet in the fed state was 46 % lower compared to the fasted state. The observed C_{max} reduction is more than the reported C_{max} reduction as per the approved lesinurad label. Provide justification for a greater difference in lesinurad C_{max} with FDC in the fed state as compared to the approved lesinurad tablet.

Additionally, provide justification on the choice of using plasma urate concentrations as opposed to serum uric acid as the pharmacodynamic measurement in study RDEA594-501.

Provide the requested information by 4:00 PM Friday, May 26, 2017. The information can be sent by electronic mail to susan.rhee@fda.hhs.gov, followed by an official submission to the IND. If you have any questions, please contact Susan Rhee, Regulatory Project Manager, at 301-796-2402.

Drafted by: SRhee 5/22/17

Initialed by: CJackson for SBarnes 5/22/17

Finalized by: SRhee 5/22/17

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/s/

SUSAN RHEE
05/22/2017

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PeRC Meeting Minutes
April 5, 2017

PeRC Members Attending:
Lynne Yao
Meshaun Payne
Robert “Skip” Nelson
Hari Cheryl Sachs
Lily Mulugeta
Gettie Audain
Susan McCune
Victor Baum
Shrikant Pagay
Maura Oleary
Thomas Smith
Raquel Tapia
Daiva Shetty
Darin Fegly
John Alexander
Gilbert Burkhart
Rosemary Addy
Julia Pinto
Dionna Greene
Adriene Hornatko-Munoz
Barbara Buch
Jinging Ye

`

Agenda

NON-RESPONSIVE

	NDA 209203	Lesinurad (allopurinol) Full Waiver	DPARP	Susan Rhee	(b) (4)

NON-RESPONSIVE

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NON-RESPONSIVE

Lesinurad/Allopurinol (Full Waiver)

- Proposed Indication: (b) (4)
- *PeRC Recommendations*:
  - The PeRC agreed with the plan for a full waiver

NON-RESPONSIVE

`

NON-RESPONSIVE

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/s/

MESHAUN L PAYNE
05/04/2017

From: Aisida, Bamidele (Florence)
To: "Sonia Villegas"
Cc: Rhee, Susan
Subject: RE: CMC IR NDA 209203
Date: Thursday, March 23, 2017 12:22:03 PM

Hello Sonia,

I meant April 6, 2017 for the response, sorry for the confusion.

Thanks,
Florence

From: Aisida, Bamidele (Florence)
Sent: Thursday, March 23, 2017 12:16 PM
To: 'Sonia Villegas'
Cc: Rhee, Susan
Subject: CMC IR NDA 209203

Hello Sonia,

I have received the following information requests from our CMC review team. Please respond to the following with a submission to your NDA by Wednesday, May 6,2017.

(b) (4)

7. *You have provided Equipment Type for the proposed commercial manufacturing process in* (b) (4)*. Please provide a summary table for equipment make, model and capacity for the proposed commercial manufacturing.*
8. *The maximum* (b) (4) *batch size for commercial batch will be* (b) (4) *of the exhibit batch size. Please provide a summary table to compare the* (b) (4) *parameters between the exhibit batches and the intended commercial batches with justification.*

Please confirm receipt of this email.

Thanks,

-Florence

Florence Aisida, Pharm.D,BCPS
Regulatory Business Process Manager, Office of Program and Regulatory Operations (OPRO)
Office of Pharmaceutical Quality/CDER/FDA. T: 240.402.2691

From: Aisida, Bamidele (Florence)
To: "Sonia Villegas"
Cc: Rhee, Susan
Subject: CMC IR NDA 209203
Date: Wednesday, March 15, 2017 9:28:21 AM

Hello Sonia,

I have received the following information requests from our CMC review team. Please respond to the following with a submission to your NDA by Wednesday, March 29, 2017.

1. It is noted that for the PBPK modeling approach, there are six drug records for each subject and for each drug entity (Lesinurad and Allopurinol). As an example for subject # 9001, refer the following Table for the drug records. Specifically for drug record #s 5 and 6 for both drug entities and for all subjects, clarify the purpose for which these drug records were employed in the modeling and simulation, and if employed for the proposal of particle size distribution and/or dissolution specification.

Drug Record #_Subject # 9001	Lesinurad	Allopurinol
1	RD594-SAAD-9001	Allo-SAAD-9001
2	RD594-Lesinurad-9001	Allo-Zyloprim-9001
3	Sub9001-DissoSpec	Sub9001-AlloDissoSpec
4	RD594_FDC-AAAD-9001	Allo-AAAD-9001
5	RD594-FDC-AAAD-9001z	Allo-AAAD-9001z
6	RD594_DissoSpec-9001z	Allo-DissoSpec-9001z

Please confirm receipt of this email.

Thanks,

Florence Aisida, Pharm.D,BCPS
Regulatory Business Process Manager
HHS | FDA | CDER
Office of Pharmaceutical Quality
Office of Program and Regulatory Operations
Bamidele.aisida@fda.hhs.gov | 240.402.2691

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 119031
NDA 209203

PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE

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

ATTENTION: Sonia Villegas, Ph.D.
Senior Manager, Regulatory Affairs Strategy

Dear Dr. Villegas:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) and your New Drug Application (NDA) dated and received October 20, 2016, submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Lesinurad and Allopurinol Tablets, 200 mg/200 mg and 200 mg/300 mg.

We also refer to:

- Your IND correspondence, dated and received August 5, 2016, requesting review of your proposed proprietary name, Duzallo
- Your NDA correspondence, dated and received November 8, 2016, requesting review of your proposed proprietary name, Duzallo.

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

If any of the proposed product characteristics as stated in your November 8, 2016 submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review. Additionally, if your application receives a complete response, a new request for name review for your proposed name should be submitted when you respond to the application deficiencies.

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 Michael Sinks in the Office of Surveillance and Epidemiology, at (240) 402-2684. For any other information regarding this application, contact Susan Rhee, Regulatory Project Manager, in the Office of New Drugs at (301) 796-2402.

Sincerely,

{See appended electronic signature page}

Todd Bridges, RPh
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/

DANIELLE M HARRIS on behalf of TODD D BRIDGES
01/25/2017

From: Sonia Villegas
To: Aisida, Bamidele (Florence)
Cc: Rhee, Susan
Subject: RE: CMC IR NDA 209203
Date: Tuesday, January 03, 2017 11:42:03 AM

Dear Florence:

Happy New Year and thank you for your email.

I can confirm receipt of these CMC IRs and will work with our FDC team to address and provide the information/data by February 3rd, 2017.

Kind Regards,

-Sonia

Sonia Villegas Pugsley, Ph.D.
Sr. Manager, Regulatory Affairs
Ardea Biosciences, Inc.
svillegas@ardeabio.com
Tel: 858-652-6624
Cell: (b) (6)

From: Aisida, Bamidele (Florence) [mailto:Bamidele.Aisida@fda.hhs.gov]
Sent: Tuesday, January 03, 2017 7:00 AM
To: Sonia Villegas
Cc: Rhee, Susan
Subject: CMC IR NDA 209203

Hello Ms. Villegas:

We are in the process of reviewing your NDA and have identified the lack of some relevant information. In order to continue reviewing your submission, provide the following information/data by February 3rd 2016.

1. It is noted that mean % dissolved data along with observed ranges obtained with the proposed QC dissolution method are submitted for the to-be-marketed batches of both fixed dose combination (FDC) strengths [200mg/200mg - Lot # AAAE, AAAF, AAAG, PAAB; 200mg/300mg – Lot # SAAF, SAAH, SAAG, RAAB; 0000(1), 3.2.P.5.4, Batch Analyses]; however, this is incomplete. Submit complete QC dissolution data (individual, mean, SD, %RSD, profiles) generated on these batches.

2. Include the dissolution medium sampling volume and (b) (4) that will be employed for

(b) (4) in the analytical procedure for dissolution (3.2.P.5.2). It is noted that dissolution method development report includes (b) (4) study in Appendix H (Method validation summary); however, details about (b) (4) is not included in the validation report of the current submission [0000(1), 3.2.P.5.3]. Include the above information and provide updated report on "Validation of Analytical Procedure for Dissolution".

3. Provide details on the change made in process parameters for manufacturing (b) (4) batch used to demonstrate discriminating ability of the proposed QC dissolution method.

4. Provide dissolution similarity (e.g., f2 values) for all batches (comparing test and reference) used in the dissolution method discriminating ability study [0000(1), 3.2.P.2., Dissolution Method (AR-594-FDCA-004-1.0)].

5. Several hyperlinks in the dissolution method development report [0000(1), 3.2.P.2., AR-594-FDCA-004-1.0] do not work (e.g., references 11.9 to 11.13). Provide an updated dissolution method development report with active hyperlinks.

(b) (4)

7. It is acknowledged that in silico PBPK datasets for the single agent Lesinurad drug product are submitted; however, the same is not submitted for the FDC drug product. In order to evaluate your modeling approach for particle size distribution and dissolution specifications, provide complete in silico PBPK datasets of the FDC product used for model development, optimization, validation, and application (e.g., Gastroplus compatible files including but not limited to *.mdb, *.cat, *.dsd, *.opd, *.spd, *.stc files). Include detailed model descriptions and raw data used for in silico modeling (model development, optimization, validation, and application) including but not limited to physicochemical parameters, in vitro dissolution

profiles, in vivo plasma drug concentration time profiles, and virtual BE trials. Submit this information in module 5.3.1.3. As experienced with NDA 207988, if there is validation error on placing *.mdb files under 5.3.1.3, consider placing these files in module 1 (e.g., module 1.11). It is noted that *.mdb Gastroplus file is not submitted for cross referenced NDA 207988 (Lesinurad IR tablets). Submit this file under module suggested above. Also, submit datasets used for BE analysis performed in Phoenix WinNonlin.

8. It is stated in the PBPK report for the FDC product [0000(1), 5.3.1.3., SR16-019] that virtual dissolution profile used in virtual trial simulation to justify the proposed dissolution specification was generated by adjusting the identified sensitive time scale parameter A of the Weibull release profile. Provide the entire virtual % dissolved-time data in tabular format used in the simulation.

9. Elaborate on the use of plasma drug concentration time profile and pharmacokinetic data only from three subjects (subject 9002, 9003, and 9016; 0000(1), 5.3.1.3., SR16-019) for parameter sensitivity analysis (PSA) and simulation for justification on both the proposed particle size distribution and dissolution specifications. It is stated in the PBPK report for the FDC product about high variability of stomach emptying and the clearance and varying systemic clearance in these subjects and Table 29 and Table 30 are referenced. However, this is not evident from Table 29 and Table 30 [e.g., Clearnace (CL) column of Table 29 and Table 30]. Explain clearly the rationale on the use of PK data from three subjects versus all subjects from study 501 (Pivotal BE study) for parameter sensitivity analysis and simulation.

Please confirm receipt of this IR.

Thanks,

Florence Aisida, Pharm.D,BCPS
Regulatory Business Process Manager
HHS | FDA | CDER
Office of Pharmaceutical Quality
Office of Program and Regulatory Operations
Bamidele.aisida@fda.hhs.gov | 240.402.2691

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 209203

FILING COMMUNICATION -
FILING REVIEW ISSUES IDENTIFIED

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

Attention: Sonia Villegas
Senior Manager, Regulatory Affairs

Dear Ms. Villegas:

Please refer to your New Drug Application (NDA) dated and received on October 20, 2016, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA), for Duzallo (lesinurad/allopurinol) fixed-dose combination tablets, 200mg/300mg and 200mg/200mg.

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 August 20, 2017.

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 July 21, 2016.

During our filing review of your application, we identified the following potential review issues:

Clinical

1. According to the draft labeling included in your submission, you are proposing to include under Section 14 Clinical Studies efficacy data generated from phase 3 studies previously reviewed and described in the lesinurad product labeling. Inclusion of these data in the

lesinurad/allopurinol fixed dose combination (FDC) tablet proposed labeling will be a review issue.

2. We have concerns that the information you have included under Subsection 2.1 Recommended Dosing of the draft label regarding patients who are taking [redacted] (b) (4) in the lesinurad/allopurinol FDC tablets may be confusing to healthcare providers and patients. The content of the information under Section 2 Dosing and Administration of the FDC tablet's label will also be a review issue.

Clinical Pharmacology

3. We note that the upper limit of 90% CI of allopurinol Cmax for 200/200 mg FDC tablet (study RDEA594-501) was outside the BE limits of 0.80 to 1.25. We also note that food effect study showed 46% lower Cmax for lesinurad from the FDC tablet in the fed state. The observed Cmax reduction is more than the reported Cmax reduction as per the approved lesinurad label. The acceptability of these results will be a review issue.

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. We cannot locate the master production batch records for the proposed commercial manufacturing in the submission. Please submit the master production batch records for our review in accordance to 21CFR314.54(a)(1)(i).

2. We noted that batch AAAD for the 200/200 mg formulation, and batch SAAD for the 200/300 mg formulation, have been manufactured and used for the bioavailability study. Please summarize the major differences between these executed batch records and the proposed master production records, and provide justification.

3. Please provide a full English translation of the executed batch records.

4. Lesinurad is reported to possess polymorphic forms. Please provide data to demonstrate the drug substance remains the same polymorphic form during drug product manufacturing process.

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. As you develop your proposed PI, we encourage you to review the labeling review resources on the *PLR Requirements for Prescribing Information* and *Pregnancy and Lactation Labeling Final Rule* websites, which include:

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

Please respond only to the above requests for information. 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), Medication Guide and Carton/Container Labeling. Submit consumer-directed, professional-directed, and television advertisement materials separately and send each submission to:

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

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry (available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf).

Do not submit launch materials until you have received our proposed revisions to the package insert (PI), Medication Guide, and Carton/Container Labeling, 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.

Pediatric studies conducted under the terms of section 505B of the Federal Food, Drug, and Cosmetic Act (the Act) may also qualify for pediatric exclusivity under the terms of section 505A of the Act. If you wish to qualify for pediatric exclusivity please consult Division of Pulmonary, Allergy, and Rheumatology Products. Please note that satisfaction of the requirements in section 505B of the Act alone may not qualify you for pediatric exclusivity under 505A of the Act.

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 Susan Rhee, Regulatory Project Manager, at (301) 796-2402.

Sincerely,

{See appended electronic signature page}

Badrul A. Chowdhury, MD, PhD
Division 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
12/23/2016

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 209203

PROPRIETARY NAME ACKNOWLEDGEMENT

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

ATTENTION: Sonia Villegas
Senior Manager, Regulatory Affairs

Dear Ms. Villegas:

Please refer to your New Drug Application (NDA) dated and received October 20, 2016, submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Lesinurad and Allopurinol Tablets, 200 mg/200 mg and 200 mg/300 mg.

We acknowledge receipt of your correspondence, dated and received November 8, 2016, requesting a review of your proposed proprietary name, Duzallo.

The user fee goal date is February 6, 2017.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact me in the Office of Surveillance and Epidemiology, at (240) 402-2684. For any other information regarding this application, contact Susan Rhee, Regulatory Project Manager, in the Office of New Drugs at (301) 796-2402.

Sincerely,

{See appended electronic signature page}

Michael Sinks, PharmD
Safety Regulatory Project Manager
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

MICHAEL A SINKS
11/18/2016

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 209203

NDA ACKNOWLEDGMENT

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

Attention: Sonia Villegas
Senior Manager, Regulatory Affairs

Dear Ms. Villegas:

We have received your New Drug Application (NDA) submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

Name of Drug Product: lesinurad/allopurinol tablets, 200mg/300mg and 200mg/200mg

Date of Application: October 20, 2016

Date of Receipt: October 20, 2016

Our Reference Number: NDA 209203

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 December 19, 2016, in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(1)(1)(i) in structured product labeling (SPL) format as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3). The content of labeling must confirm to the content and format requirements of revised 21 CFR 201.56-57.

You are also responsible for complying with the applicable provisions of sections 402(i) and 402(j) of the Public Health Service Act (PHS Act) [42 USC §§ 282 (i) and (j)], which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No, 110-85, 121 Stat. 904).

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

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 me, Regulatory Project Manager, at (301) 796-2402.

Sincerely,

{See appended electronic signature page}

Susan Rhee, Pharm.D.
LCDR, U.S. Public Health Service
Regulatory Project Manager
Division of Pulmonary, Allergy, and Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

SUSAN RHEE
11/02/2016

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 119031

MEETING PRELIMINARY COMMENTS

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

Attention: Sonia Villegas, Ph.D.,
Senior Regulatory Affairs Associate II

Dear Dr. Villegas:

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

We also refer to your June 16, 2016, correspondence, received June 16, 2016, requesting a meeting to discuss the clinical dataset in support of an NDA submission for your drug product, lesinurad/allopurinol.

Our preliminary responses to your meeting questions are enclosed.

You should provide, to the Regulatory Project Manager, a hardcopy or electronic version of any materials (i.e., slides or handouts) to be presented and/or discussed at the meeting.

In accordance with 21 CFR 10.65(e) and FDA policy, you may not electronically record the discussion at this meeting. The official record of this meeting will be the FDA-generated minutes.

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

Sincerely,

{See appended electronic signature page}

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

Center for Drug Evaluation and Research

ENCLOSURE:
Preliminary Meeting Comments

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PRELIMINARY MEETING COMMENTS

Meeting Type: B
Meeting Category: Pre-NDA

Meeting Date and Time: Tuesday, August 30, 2016, 2:00 PM-3:00 PM
Meeting Location: 10903 New Hampshire Avenue
White Oak Building 22, Conference Room: 4201
Silver Spring, Maryland 20903

Application Number: 119031
Product Name: lesinurad/allopurinol
Indication: Treatment of hyperuricemia associated with gout in patients who have not achieved target serum uric acid (sUA) levels (b) (4)

Sponsor/Applicant Name: Ardea Bioscience Inc.

FDA ATTENDEES

Badrul A. Chowdhury, M.D., Ph.D., Director, Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)
Sarah Yim, M.D., Supervisory Associate Director, DPARP
Rosemarie Neuner, M.D, M.P.H., Clinical Reviewer, DPARP
Timothy Robison, Ph.D., Nonclinical Team Leader, DPARP
Matthew Whittaker, Ph.D., Nonclinical Reviewer, DPARP
Anshu Marathe Ph.D., Clinical Pharmacology Team Leader, Division of Clinical Pharmacology II (DCPII)
Jianmeng Chen, Ph.D., Clinical Pharmacology Reviewer, DCP II
Julia Pinto, Ph.D., Acting Branch Chief, Office of Pharmaceutical Quality (OPQ), Division of New Drug Products II, (NDPD II)
Craig Bertha, Ph.D., Quality Assessment Lead, OPQ/NDPD II
Vincent (Peng) Duan, Ph.D., Biopharmaceutics Reviewer, OMPT/CDER/OPS/ONDQA

Introduction:

This material consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the teleconference scheduled for Tuesday, August 30, 2016, 2:00 PM-3:00 PM, White Oak Building 22, Conference Room: 4201 between Ardea Bioscience Inc. and the Division of Pulmonary, Allergy, and Rheumatology Products. We are sharing this material to promote a collaborative and successful discussion at the meeting. The meeting minutes will reflect agreements, important issues, and any action items discussed during the meeting and may not be identical to these preliminary comments following substantive

discussion at the meeting. However, if these answers and comments are clear to you and you determine that further discussion is not required, you have the option of cancelling the meeting (contact the regulatory project manager (RPM)). If you choose to cancel the meeting, this document will represent the official record of the meeting. If you determine that discussion is needed for only some of the original questions, you have the option of reducing the agenda and/or changing the format of the meeting (e.g., from face to face to teleconference). It is important to remember that some meetings, particularly milestone meetings, can be valuable even if the pre-meeting communications are considered sufficient to answer the questions. Contact the RPM if there are any major changes to your development plan, the purpose of the meeting, or the questions based on our preliminary responses, as we may not be prepared to discuss or reach agreement on such changes at the meeting.

1.0 BACKGROUND

On June 16, 2016, Ardea Biosciences, Inc. submitted a Pre-NDA meeting request. The purpose of the meeting request was to discuss the label, clinical dataset and the format and technical aspects of the eCTD for their drug product, lesinurad/allopurinol FDC in anticipation for the submission of their NDA application. Lesinurad is a uric acid transporter 1 (URAT1) inhibitor, and allopurinol, is a xanthine oxidase inhibitor (XOI). The proposed indication of their product is for the treatment of (b) (4) hyperuricemia associated with gout (b) (4) (b) (4)

2.0 DISCUSSION

2.1. Labeling

Question 1: ***The Sponsor plans to submit a label justification document in support of the proposed FDC prescribing information (PI) in Module 5, Section 5.3.5.4.***

a. Does the Agency agree with this proposed placement in Module 5?

FDA Response to Question 1a:
Your proposal is reasonable.

b. Does the Agency agree to the content proposed for the justification document?

FDA Response to Question 1b:
According to your meeting package, the label justification document for lesinurad/allopurinol FDC tentatively may contain an annotated allopurinol label which will direct the reader to the location in the draft proposed label for lesinurad/allopurinol FDC where text from the allopurinol label was incorporated. You are also tentatively planning to provide rationale for not including information from the allopurinol label due to its lack of relevance to the FDC

product or failure to meet PLLR criteria as well as additional background information supporting your proposed language in the draft FDC label. Overall, your approach to the contents of the justification document for the lesinurad/allopurinol FDC product label appears to be reasonable. The content of the lesinurad/allopurinol FDC product's label will be a review issue.

2.2. Statistics/Biometrics

Question 2: ***The Sponsor plans to include in the submission the datasets for the following individual studies: RDEA594-501 (Final Analysis), RDEA594-306 (12-Month Interim Analysis), and RDEA594-307 (12-Month Interim Analysis). Does the agency agree that these are sufficient to meet the data requirements for the lesinurad/allopurinol FDC NDA?***

FDA Response to Question 2:

We concur in principle that data from the phase 1 bioavailability and bioequivalence crossover study RDEA594-501 of the FDC with co-administered lesinurad and allopurinol in healthy volunteers as well as 12-month interim analysis data from the ongoing phase 3 long-term extension study RDEA594-306, which evaluated the safety of lesinurad in combination with allopurinol, should be sufficient to support submission of an NDA for lesinurad/allopurinol FDC. Submission of supportive data from study RDEA594-307, which evaluates lesinurad in combination with febuxostat, is not required in order for to conduct the review of your proposed application for lesinurad/allopurinol FDC. Additional analyses and data may be requested over the course of the review.

2.3 Regulatory

Question 3: ***The Sponsor plans to submit the lesinurad/allopurinol FDC NDA as a 505(b)(2) application. The Sponsor will rely on the Agency's findings and published literature on allopurinol in accordance with 21 CFR §314.54. In addition, as agreed to in pre-IND meeting correspondence (written responses dated 24 June 2013) and EOP2 meeting correspondence (written responses dated 2 May 2016), the Sponsor plans to rely on lesinurad NDA clinical, nonclinical, and quality information to support the lesinurad/allopurinol FDC NDA. Does the Agency agree that the FDC NDA submission as outlined is an acceptable approach?***

FDA Response to Question 3:

Your proposal appears reasonable.

Question 4: ***The Sponsor plans to provide lesinurad/allopurinol FDC drug product information in Module 3, Section 3.2.P of the FDC NDA; in addition, specific lesinurad drug substance information related to the FDC drug***

product will also be provided in Module 3, Section 3.2.P. Does the Agency agree with this submission proposal for Module 3 in support of the FDC NDA?

FDA Response to Question 4:
Yes, we agree.

Question5: ***Ardea plans to cross reference administrative, quality, nonclinical, and clinical information previously submitted to the lesinurad NDA in Modules 1, 2, 3, 4, and 5. Within the lesinurad/allopurinol FDC NDA, references to documents and data previously submitted to the lesinurad NDA will be hyperlinked to the appropriate document/page within the lesinurad NDA. In addition, documents originally submitted to the lesinurad NDA will be referred to in the lesinurad/allopurinol FDC NDA via cross-reference leafs in the XML backbone. Does the agency agree with the approach outlined?***

FDA Response to Question 5:
Your proposed formatting approach for the lesinurad/allopurinol NDA appears reasonable. As we had difficulties with the hyperlinks in the original lesinurad NDA, please make sure that the hyperlinks in your NDA are functional before you submit it for review.

Question6: ***Does the Agency agree that the proposed lesinurad/allopurinol FDC NDA package substantiates a review and decision on an NDA for FDC for the treatment of hyperuricemia associated with gout?***

FDA Response to Question 6:
As described in your meeting package, the proposed content of the lesinurad/allopurinol FDC NDA should be sufficient for us to conduct a review. Additional data and analyses may be requested over the course of our review. Final determination of approvability, however, remains a review issue.

Question 7: ***Does the Agency have any additional comments on the proposed lesinurad/allopurinol NDA submission?***

FDA Response to Question 7:
If you intend to request a waiver of the BE study for the lower strength tablets based on the in silico modeling approach and dissolution data (meeting minutes dated on January 19, 2016), you will need to submit the full report (e.g. model files and all supporting raw data) for the dissolution and absorption (ACAT) model along with the complete dissolution report to the Agency for review. The final acceptance of your biowaiver request will be determined during the NDA review process.

3.0 PREA REQUIREMENTS

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

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

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

DATA STANDARDS FOR STUDIES

Under section 745A(a) of the FD&C Act, electronic submissions "shall be submitted in such electronic format as specified by [FDA]." FDA has determined that study data contained in electronic submissions (i.e., NDAs, BLAs, ANDAs and INDs) must be in a format that the Agency can process, review, and archive. Currently, the Agency can process, review, and archive electronic submissions of clinical and nonclinical study data that use the standards specified in the Data Standards Catalog (Catalog) (See http://www.fda.gov/forindustry/datastandards/studydatastandards/default.htm).

On December 17, 2014, FDA issued final guidance, *Providing Electronic Submissions in Electronic Format--- Standardized Study Data* (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM292334.pdf). This guidance describes the submission types, the standardized study data requirements, and when standardized study data will be required. Further, it describes the availability of implementation support in the form of a technical specifications document, Study Data Technical Conformance Guide (Conformance Guide) (See

http://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM384744.pdf), as well as email access to the eData Team (cder-edata@fda.hhs.gov) for specific questions related to study data standards. Standardized study data will be required in marketing application submissions for clinical and nonclinical studies that start on or after December 17, 2016. Standardized study data will be required in commercial IND application submissions for clinical and nonclinical studies that start on or after December 17, 2017. CDER has produced a *Study Data Standards Resources* web page that provides specifications for sponsors regarding implementation and submission of clinical and nonclinical study data in a standardized format. This web page will be updated regularly to reflect CDER's growing experience in order to meet the needs of its reviewers.

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

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

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

LABORATORY TEST UNITS FOR CLINICAL TRIALS

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

CDER/CBER Position on Use of SI Units for Lab Tests website found at http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/ucm372553.htm.

SUBMISSION FORMAT REQUIREMENTS

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

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

/s/

LAURA MUSSE
08/25/2016

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 119031

MEETING PRELIMINARY COMMENTS

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

Attention: Sonia Villegas, Ph.D.
Senior Regulatory Affairs Associate II

Dear Dr. Villegas:

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

We also refer to your February 29, 2016, correspondence, received February 29, 2016, requesting an End Of Phase 2 meeting to discuss your clinical data package and in-vitro dissolution methods in support of a New Drug Application (NDA) for your product, lesinurad/allopurinol.

Our preliminary responses to your meeting questions are enclosed.

You should provide, to the Regulatory Project Manager, a hardcopy or electronic version of any materials (i.e., slides or handouts) to be presented and/or discussed at the meeting.

In accordance with 21 CFR 10.65(e) and FDA policy, you may not electronically record the discussion at this meeting. The official record of this meeting will be the FDA-generated minutes.

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

Sincerely,

{See appended electronic signature page}

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

ENCLOSURE:
Preliminary Meeting Comments

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PRELIMINARY MEETING COMMENTS

Meeting Type: B
Meeting Category: End of Phase 2

Meeting Date and Time: May 6, 2016, 3:00 PM-4:00 PM, Eastern Time
Meeting Location: 10903 New Hampshire Avenue
White Oak Building 22, Conference Room: 1311
Silver Spring, Maryland 20903

Application Number: 119031
Product Name: lesinurad/allopurinol
Indication: (b) (4)

Sponsor/Applicant Name: Ardea Biosciences, Inc.

FDA ATTENDEES (tentative)

Badrul A. Chowdhury, M.D., Ph.D., Director, Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)
Sarah Yim, M.D., Supervisory Associate Director, DPARP
Rosemarie Neuner, M.D, M.P.H., Clinical Reviewer, DPARP
Timothy Robison, Ph.D., Nonclinical Team Leader, DPARP
Matthew Whittaker, Ph.D., Nonclinical Reviewer, DPARP
Anshu Marathe Ph.D., Clinical Pharmacology Team Leader, Division of Clinical Pharmacology II (DCPII)
Jianmeng Chen, Ph.D., Clinical Pharmacology Reviewer, DCP II
Gregory Levin, Ph.D., Acting Team Leader Statistical Reviewer, Division of Biometrics II (DBII)
Craig Bertha, Ph.D., Quality Assessment Lead, Office of Pharmaceutical Quality, New Drug Products, Division of (OPQ), (NDPD II)
Kelly Kitchens, Ph.D., Acting Lead Biopharmacologist, OMPT/CDER/OPS/ONDQA
Vidula Kolhatkar, Ph.D., Biopharmaceutics Reviewer, New Drug Products
Laura Musse, R.N., M.S., C.R.N.P., Regulatory Health Project Manager, DPARP

Introduction:

This material consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the meeting scheduled for May 6, 2016, 3:00 PM-4:00 PM, White Oak, building 22, conference room: 1311 between Ardea Biosciences,

Inc. and the Division of Pulmonary, Allergy, and Rheumatology Products. We are sharing this material to promote a collaborative and successful discussion at the meeting. The meeting minutes will reflect agreements, important issues, and any action items discussed during the meeting and may not be identical to these preliminary comments following substantive discussion at the meeting. However, if these answers and comments are clear to you and you determine that further discussion is not required, you have the option of cancelling the meeting (contact the regulatory project manager (RPM)). If you choose to cancel the meeting, this document will represent the official record of the meeting. If you determine that discussion is needed for only some of the original questions, you have the option of reducing the agenda and/or changing the format of the meeting (e.g., from face to face to teleconference). It is important to remember that some meetings, particularly milestone meetings, can be valuable even if the pre-meeting communications are considered sufficient to answer the questions. Contact the RPM if there are any major changes to your development plan, the purpose of the meeting, or the questions based on our preliminary responses, as we may not be prepared to discuss or reach agreement on such changes at the meeting.

1.0 BACKGROUND

On February 29, 2016, Ardea Biosciences, Inc. submitted a Type-B Meeting request. The purpose of the meeting request was to discuss the development program for lesinurad/allopurinol, Fixed Dose Combination (FDC) tablets (200/200 and 200/300). The Sponsor is seeking acceptability from the Agency of their proposal in support of the New Drug Application (NDA) submission. Lesinurad is a uric acid transporter 1 (URAT1) inhibitor, and allopurinol, is a xanthine oxidase inhibitor (XOI). The proposed indication of their product is for (b) (4) treatment of hyperuricemia associated with gout (b) (4)

2.0 DISCUSSION

2.1 Chemistry, Manufacturing, and Controls

Question 1: ***Does the Agency agree that the proposed dissolution test method described in development report AR-594-FDCA-004 is acceptable to control the quality of lesinurad/allopurinol 200/200 and 200/300 FDC tablets?***

FDA Response to Question 1:

Your proposed dissolution test method appears reasonable.

Note that the final determination on the acceptability of the dissolution method is a review issue that can be determined during the IND or NDA. However, the acceptability of the proposed dissolution criterion for your product will be made during the NDA review process based on the totality of the provided dissolution data. Provide the complete dissolution profile data (*individual, mean, SD, profiles*) for n = 12 units for your products. The dissolution data should be reported as the cumulative percentage of drug dissolved with time (*the percentage is based on the product's label claim*).

2.2 Biopharmaceutics and Clinical Pharmacology

Question 2: ***Does the Agency agree with the Sponsor's proposal to refer to the clinical pharmacology and biopharmaceutical information in the lesinurad NDA, and submit only new information in the lesinurad/allopurinol FDC NDA?***

FDA Response to Question 2:

Yes, we agree.

2.3 Clinical Efficacy

Question 3: ***Does the agency agree that cross-referencing the Summary of Clinical Efficacy (SCE) and Integrated Summary of Efficacy (ISE) in the lesinurad NDA is acceptable and fulfills the requirements for an SCE and an ISE in the lesinurad/allopurinol FDC NDA under 21CFR §314.50(d)(5)(v)?***

FDA Response to Question 3:

We concur that your proposal to cross reference the Summary of Clinical Efficacy (SCE) and Integrated Summary of Efficacy (ISE) from NDA 207988 for lesinurad monotherapy in your NDA for the lesinurad/allopurinol FDC is acceptable.

2.4 Clinical Safety

Question 4: ***Does the agency agree with the proposed presentation of safety information in the lesinurad/allopurinol FDC NDA, including cross-reference to lesinurad NDA?***

FDA Response to Question 4:

We concur with your proposal to submit the second interim clinical study reports for the ongoing studies 306 and 307 in your NDA for lesinurad/allopurinol FDC as well as cross referencing the safety data in the Summary of Clinical Safety (SCS) and Integrated Summary of Safety (ISS), the 4-month safety update and the semi-annual Periodic Benefit-Risk Evaluation Reports (PBRERs) from the original lesinurad NDA 207988 for lesinurad monotherapy.

Question 5: ***Does the agency agree that a Risk Evaluation and Mitigation Strategy (REMS) is not required for the lesinurad/allopurinol FDC NDA?***

FDA Response to Question 5:

We agree that a REMS will not be necessary for your proposed lesinurad/allopurinol FDC NDA.

3.0 PREA REQUIREMENTS

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

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

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

DATA STANDARDS FOR STUDIES

Under section 745A(a) of the FD&C Act, electronic submissions "shall be submitted in such electronic format as specified by [FDA]." FDA has determined that study data contained in electronic submissions (i.e., NDAs, BLAs, ANDAs and INDs) must be in a format that the Agency can process, review, and archive. Currently, the Agency can process, review, and archive electronic submissions of clinical and nonclinical study data that use the standards specified in the Data Standards Catalog (Catalog) (See http://www.fda.gov/forindustry/datastandards/studydatastandards/default.htm).

On December 17, 2014, FDA issued final guidance, *Providing Electronic Submissions in Electronic Format--- Standardized Study Data* (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/

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

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

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

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

LABORATORY TEST UNITS FOR CLINICAL TRIALS

CDER strongly encourages IND sponsors to identify the laboratory test units that will be reported in clinical trials that support applications for investigational new drugs and product registration. Although Système International (SI) units may be the standard reporting mechanism globally, dual reporting of a reasonable subset of laboratory tests in U.S. conventional units and SI units might be necessary to minimize conversion needs during review. Identification of units to be used for laboratory tests in clinical trials and solicitation of input from the review divisions should occur as early as possible in the development process. For

more information, please see the FDA website entitled, Study Data Standards Resources and the CDER/CBER Position on Use of SI Units for Lab Tests website found at http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/ucm372553.htm.

SUBMISSION FORMAT REQUIREMENTS

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

505(b)(2) REGULATORY PATHWAY

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

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

If you intend to rely, in part, on literature or other studies for which you have no right of reference but that are necessary for approval, you also must establish that reliance on the studies described in the literature or on the other studies is scientifically appropriate. You should include a copy of such published literature in the 505(b)(2) application and identify any listed drug(s) described in the published literature (e.g., trade name(s)).

If you intend to rely, in part, on the Agency's finding of safety and/or effectiveness for a listed drug(s) or published literature describing a listed drug(s) (which is considered to be reliance on FDA's finding of safety and/or effectiveness for the listed drug(s)), you should identify the listed drug(s) in accordance with the Agency's regulations at 21 CFR 314.54. It should be noted that 21 CFR 314.54 requires identification of the "listed drug for which FDA has made a finding of safety and effectiveness," and thus an applicant may only rely upon a listed drug that was approved in an NDA under section 505(c) of the FD&C Act. The regulatory requirements for a

505(b)(2) application (including, but not limited to, an appropriate patent certification or statement) apply to each listed drug upon which a sponsor relies.

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

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

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

List the information essential to the approval of the proposed drug that is provided by reliance on the FDA's previous finding of safety and efficacy for a listed drug or by reliance on published literature	
Source of information (e.g., published literature, name of listed drug)	**Information Provided (e.g., specific sections of the 505(b)(2) application or labeling)**
1. Example: Published literature	*Nonclinical toxicology*
2. Example: NDA XXXXXX "TRADENAME"	*Previous finding of effectiveness for indication X*
3. Example: NDA YYYYYY "TRADENAME"	*Previous finding of safety for Carcinogenicity, labeling section XXX*
4.	

Please be advised that circumstances could change that would render a 505(b)(2) application for this product no longer appropriate. For example, if a pharmaceutically equivalent product were approved before your application is submitted, such that your proposed product would be a "duplicate" of a listed drug and eligible for approval under section 505(j) of the FD&C Act, then

it is FDA's policy to refuse to file your application as a 505(b)(2) application (21 CFR 314.101(d)(9)). In such a case, the appropriate submission would be an Abbreviated New Drug Application (ANDA) that cites the duplicate product as the reference listed drug.

Office of Scientific Investigations (OSI) Requests

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

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

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

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

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

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

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

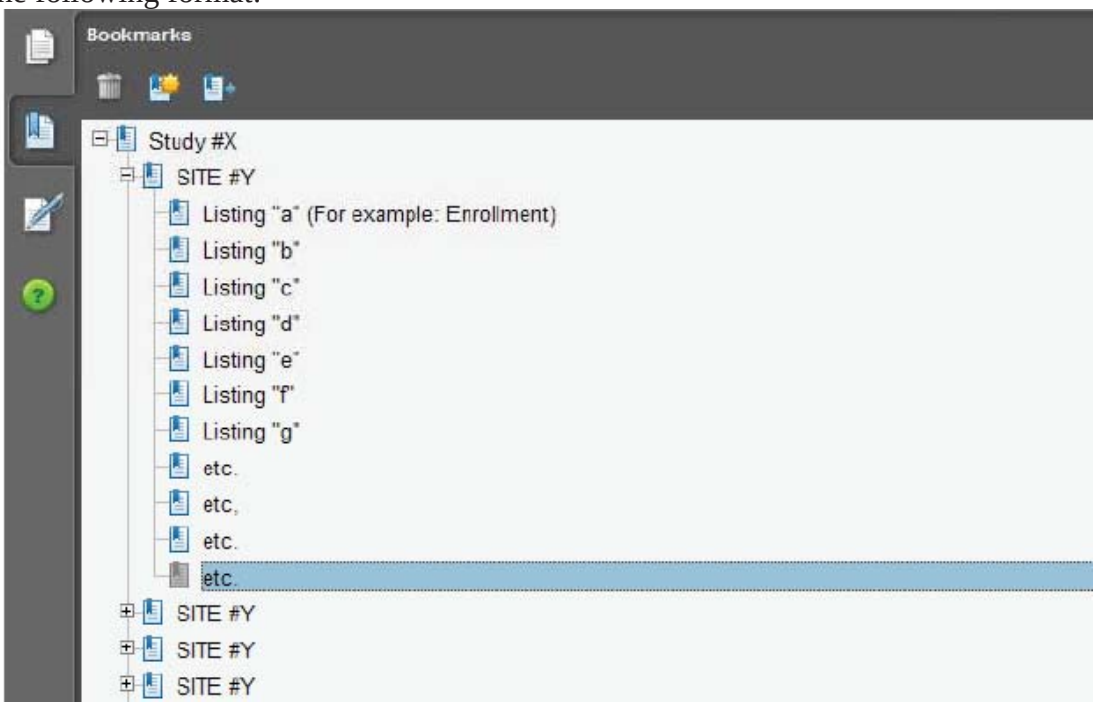
4. For each pivotal trial, provide a sample annotated Case Report Form (or identify the location and/or provide a link if provided elsewhere in the submission).

5. For each pivotal trial provide original protocol and all amendments ((or identify the location and/or provide a link if provided elsewhere in the submission).

II. Request for Subject Level Data Listings by Site

1. For each pivotal trial: Site-specific individual subject data listings (hereafter referred to as "line listings"). For each site, provide line listings for:
   a. Listing for each subject consented/enrolled; for subjects who were not randomized to treatment and/or treated with study therapy, include reason not randomized and/or treated
   b. Subject listing for treatment assignment (randomization)
   c. Listing of subjects that discontinued from study treatment and subjects that discontinued from the study completely (i.e., withdrew consent) with date and reason discontinued
   d. Listing of per protocol subjects/ non-per protocol subjects and reason not per protocol
   e. By subject listing of eligibility determination (i.e., inclusion and exclusion criteria)
   f. By subject listing, of AEs, SAEs, deaths and dates
   g. By subject listing of protocol violations and/or deviations reported in the NDA, including a description of the deviation/violation
   h. By subject listing of the primary and secondary endpoint efficacy parameters or events. For derived or calculated endpoints, provide the raw data listings used to generate the derived/calculated endpoint.
   i. By subject listing of concomitant medications (as appropriate to the pivotal clinical trials)
   j. By subject listing, of testing (e.g., laboratory, ECG) performed for safety monitoring

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



III. Request for Site Level Dataset:

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

Attachment 1

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

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

DSI Pre-NDA Request Item[1]	STF File Tag	Used For	Allowable File Formats
I	data-listing-dataset	Data listings, by study	.pdf
I	annotated-crf	Sample annotated case report form, by study	.pdf
II	data-listing-dataset	Data listings, by study (Line listings, by site)	.pdf
III	data-listing-dataset	Site-level datasets, across studies	.xpt
III	data-listing-data-definition	Define file	.pdf

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

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

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

References:

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

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

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

NEW PROTOCOLS AND CHANGES TO PROTOCOLS

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

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

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

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

/s/

LAURA MUSSE
05/02/2016