

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

207533Orig1s000

ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS

EXCLUSIVITY SUMMARY

NDA # 207533

SUPPL # 000

HFD # 130

Trade Name Aristada

Generic Name Aripiprazole lauroxil extended-release injectable suspension

Applicant Name Alkermes

Approval Date, If Known 10/5/2015

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

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

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

YES NO

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

505(b)(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.

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?

5-year NCE exclusivity under 21 CFR 314.108(b)(2)

OR

3-year exclusivity

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?

N/A

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.)

N/A YES NO

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

NDA#

NDA#

NDA#

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

IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

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

1. Does the application contain reports of clinical investigations? (The Agency interprets

"clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES NO

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

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

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

YES NO

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

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

YES NO

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

YES NO

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted

or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES NO

If yes, explain:

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

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

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

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

Investigation #1 YES NO

Investigation #2 YES NO

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

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

Investigation #1	YES <input type="checkbox"/>	NO <input type="checkbox"/>
Investigation #2	YES <input type="checkbox"/>	NO <input type="checkbox"/>

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

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

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

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

Investigation #1		!
		!
IND #	YES <input type="checkbox"/>	! NO <input type="checkbox"/>
		! Explain:

Investigation #2		!
		!
IND #	YES <input type="checkbox"/>	! NO <input type="checkbox"/>
		! Explain:

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

in interest provided substantial support for the study?

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

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

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

YES NO

If yes, explain:

=====

Name of person completing form: Sharonjit Sagoo, Pharm.D.
Title: Regulatory Project Manager
Date: 10/5/2015

Name of Office/Division Director signing form: CAPT Mitchell Mathis, M.D.
Title: Director, Division of Psychiatry Products

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/

SHARONJIT K SAGOO
10/05/2015

MITCHELL V Mathis
10/05/2015

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION ¹		
NDA # 207533	NDA Supplement # 000	If NDA, Efficacy Supplement Type: <i>(an action package is not required for SE8 or SE9 supplements)</i>
Proprietary Name: Aristada Established/Proper Name: aripiprazole lauroxil Dosage Form: Extended-release injectable suspension		Applicant: Alkermes Agent for Applicant (if applicable):
RPM: Sharonjit Sagoo, Pharm.D.		Division: Division of Psychiatry Products
NDA Application Type: <input type="checkbox"/> 505(b)(1) <input checked="" type="checkbox"/> 505(b)(2) Efficacy Supplement: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) BLA Application Type: <input type="checkbox"/> 351(k) <input type="checkbox"/> 351(a) Efficacy Supplement: <input type="checkbox"/> 351(k) <input type="checkbox"/> 351(a)		<p><u>For ALL 505(b)(2) applications, two months prior to EVERY action:</u></p> <ul style="list-style-type: none"> Review the information in the 505(b)(2) Assessment and submit the draft² to CDER OND IO for clearance. Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity) <p><input checked="" type="checkbox"/> No changes <input type="checkbox"/> New patent/exclusivity (<i>notify CDER OND IO</i>) Date of check:</p> <p><i>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.</i></p>
❖ Actions		
<ul style="list-style-type: none"> Proposed action User Fee Goal Date is 8/22/2015 / Approval Date 10/5/2015 		<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> CR
<ul style="list-style-type: none"> Previous actions (<i>specify type and date for each action taken</i>) 		<input checked="" type="checkbox"/> 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 _____		N/A
❖ 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): NME
 (*confirm chemical classification at time of approval*)

- | | |
|---|---|
| <input type="checkbox"/> Fast Track | <input type="checkbox"/> Rx-to-OTC full switch |
| <input type="checkbox"/> Rolling Review | <input type="checkbox"/> Rx-to-OTC partial switch |
| <input type="checkbox"/> Orphan drug designation | <input type="checkbox"/> Direct-to-OTC |
| <input type="checkbox"/> Breakthrough Therapy designation | |

NDAs: Subpart H

- Accelerated approval (21 CFR 314.510)
 Restricted distribution (21 CFR 314.520)

Subpart I

- 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

BLAs: Subpart E

- Accelerated approval (21 CFR 601.41)
 Restricted distribution (21 CFR 601.42)

Subpart H

- Approval based on animal studies

- 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 (<i>approvals only</i>)	<input type="checkbox"/> Yes <input type="checkbox"/> No
❖ Public communications (<i>approvals only</i>)	
• Office of Executive Programs (OEP) liaison has been notified of action	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
• Indicate what types (if any) of information were issued	<input type="checkbox"/> None <input checked="" type="checkbox"/> FDA Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input type="checkbox"/> 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	<input checked="" type="checkbox"/> No <input type="checkbox"/> 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.	<input checked="" type="checkbox"/> Verified <input type="checkbox"/> 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 (<i>approvals only</i>)	<input checked="" type="checkbox"/> Included
Documentation of consent/non-consent by officers/employees	<input checked="" type="checkbox"/> Included

Action Letters	
❖ Copies of all action letters (including approval letter with final labeling)	AP 10/5/15
Labeling	
❖ Package Insert (write submission/communication date at upper right of first page of PI)	
• Most recent draft labeling (if it is division-proposed labeling, it should be in track-changes format)	<input checked="" type="checkbox"/> Included
• Original applicant-proposed labeling	<input checked="" type="checkbox"/> Included
❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling (write submission/communication date at upper right of first page of each piece)	<input checked="" type="checkbox"/> Medication Guide <input type="checkbox"/> Patient Package Insert <input type="checkbox"/> Instructions for Use <input type="checkbox"/> Device Labeling <input type="checkbox"/> None
• Most-recent draft labeling (if it is division-proposed labeling, it should be in track-changes format)	<input checked="" type="checkbox"/> Included
• Original applicant-proposed labeling	<input checked="" type="checkbox"/> Included
❖ Labels (full color carton and immediate-container labels) (write submission/communication date on upper right of first page of each submission)	
• Most-recent draft labeling	<input checked="" type="checkbox"/> Included
❖ Proprietary Name	Granted Letter: 11/17/2014 Review: 11/12/2014
• Acceptability/non-acceptability letter(s) (indicate date(s))	
• Review(s) (indicate date(s))	
❖ Labeling reviews (indicate dates of reviews)	RPM: <input checked="" type="checkbox"/> 10/29/14 DMEPA: <input checked="" type="checkbox"/> 7/1/2015; 1/21/2015 DMPP/PLT (DRISK): <input checked="" type="checkbox"/> 6/12/2015 OPDP: <input checked="" type="checkbox"/> 6/26/2015 SEALD: <input checked="" type="checkbox"/> None CSS: <input checked="" type="checkbox"/> None Product Quality <input checked="" type="checkbox"/> None Other: <input checked="" type="checkbox"/> DPMH 7/7/2015
Administrative / Regulatory Documents	
❖ RPM Filing Review ⁴ /Memo of Filing Meeting (indicate date of each review)	RPM Filing Review: 10/21/2014
❖ All NDA 505(b)(2) Actions: Date each action cleared by 505(b)(2) Clearance Committee	505(b)(2) Clearance Date: 10/5/2015
❖ NDAs only: Exclusivity Summary (signed by Division Director)	<input checked="" type="checkbox"/> Included
❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
• Applicant is on the AIP	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No

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

<ul style="list-style-type: none"> • This application is on the AIP <ul style="list-style-type: none"> ○ If yes, Center Director's Exception for Review memo (<i>indicate date</i>) ○ If yes, OC clearance for approval (<i>indicate date of clearance communication</i>) 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No N/A N/A <input type="checkbox"/> Not an AP action
❖ Pediatrics (<i>approvals only</i>) <ul style="list-style-type: none"> • Date reviewed by PeRC <u>April 1, 2015</u> 	
❖ Breakthrough Therapy Designation	<input checked="" type="checkbox"/> N/A
<ul style="list-style-type: none"> • Breakthrough Therapy Designation Letter(s) (granted, denied, an/or rescinded) 	
<ul style="list-style-type: none"> • CDER Medical Policy Council Breakthrough Therapy Designation Determination Review Template(s) (<i>include only the completed template(s) and not the meeting minutes</i>) 	
<ul style="list-style-type: none"> • CDER Medical Policy Council Brief – Evaluating a Breakthrough Therapy Designation for Rescission Template(s) (<i>include only the completed template(s) and not the meeting minutes</i>) <p>(<i>completed CDER MPC templates can be found in DARRTS as clinical reviews or on the MPC SharePoint Site</i>)</p>	
❖ 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.) (<i>do not include previous action letters, as these are located elsewhere in package</i>)	
❖ 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	
<ul style="list-style-type: none"> • If not the first review cycle, any end-of-review meeting (<i>indicate date of mtg</i>) 	<input checked="" type="checkbox"/> N/A or no mtg
<ul style="list-style-type: none"> • Pre-NDA/BLA meeting (<i>indicate date of mtg</i>) 	<input checked="" type="checkbox"/> No mtg 5/19/2014
<ul style="list-style-type: none"> • EOP2 meeting (<i>indicate date of mtg</i>) 	<input checked="" type="checkbox"/> CMC: 9/12/2011 Clinical/Nonclinical: 9/15/2011
<ul style="list-style-type: none"> • Mid-cycle Communication (<i>indicate date of mtg</i>) 	<input checked="" type="checkbox"/> February 9, 2015
<ul style="list-style-type: none"> • Late-cycle Meeting (<i>indicate date of mtg</i>) 	<input checked="" type="checkbox"/> June 1, 2015
<ul style="list-style-type: none"> • Other milestone meetings (e.g., EOP2a, CMC focused milestone meetings) (<i>indicate dates of mtgs</i>) 	N/A
❖ Advisory Committee Meeting(s)	<input checked="" type="checkbox"/> No AC meeting
<ul style="list-style-type: none"> • Date(s) of Meeting(s) 	N/A
Decisional and Summary Memos	
❖ Office Director Decisional Memo (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> 10/5/2015
Division Director Summary Review (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> 10/2/2015
Cross-Discipline Team Leader Review (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> See Clinical Review
PMR/PMC Development Templates (<i>indicate total number</i>)	<input type="checkbox"/> N/A
Clinical	
❖ Clinical Reviews	

<ul style="list-style-type: none"> Clinical Team Leader Review(s) (<i>indicate date for each review</i>) 	<input checked="" type="checkbox"/> No separate review
<ul style="list-style-type: none"> Clinical review(s) (<i>indicate date for each review</i>) 	10/2/15
<ul style="list-style-type: none"> Social scientist review(s) (if OTC drug) (<i>indicate date for each review</i>) 	<input checked="" type="checkbox"/> None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here <input type="checkbox"/> and include a review/memo explaining why not (<i>indicate date of review/memo</i>)	Addressed in Section 3.3 of Clinical Review 10/2/15
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers (<i>indicate date of each review</i>)	<input checked="" type="checkbox"/> None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation (<i>indicate date of each review</i>)	<input checked="" type="checkbox"/> N/A
❖ Risk Management <ul style="list-style-type: none"> REMS Documents and REMS Supporting Document (<i>indicate date(s) of submission(s)</i>) REMS Memo(s) and letter(s) (<i>indicate date(s)</i>) Risk management review(s) and recommendations (including those by OSE and CSS) (<i>indicate date of each review and indicate location/date if incorporated into another review</i>) 	N/A 10/2/2015 <input type="checkbox"/> None
❖ OSI Clinical Inspection Review Summary(ies) (<i>include copies of OSI letters to investigators</i>)	<input checked="" type="checkbox"/> 6/5/15; 9/11/15; 4/22/15; 3/9/15
Clinical Microbiology <input checked="" type="checkbox"/> None	
❖ Clinical Microbiology Team Leader Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> No separate review
Clinical Microbiology Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/>
Biostatistics <input type="checkbox"/> None	
❖ Statistical Division Director Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> No separate review
Statistical Team Leader Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> No separate review
Statistical Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> 6/8/15
Clinical Pharmacology <input type="checkbox"/> None	
❖ Clinical Pharmacology Division Director Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> No separate review
Clinical Pharmacology Team Leader Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> No separate review
Clinical Pharmacology review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> 10/1/15; 7/1/15; 6/10/15; 4/29/15; 4/22/15; 4/20/15
❖ OSI Clinical Pharmacology Inspection Review Summary (<i>include copies of OSI letters</i>)	<input checked="" type="checkbox"/> None requested

Nonclinical <input type="checkbox"/> None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> 8/13/15
• Supervisory Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> No separate review
• Pharm/tox review(s), including referenced IND reviews (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> 9/28/15; 4/30/15
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
❖ Statistical review(s) of carcinogenicity studies (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> No carc
❖ ECAC/CAC report/memo of meeting	<input checked="" type="checkbox"/> None Included in P/T review, page
❖ OSI Nonclinical Inspection Review Summary (<i>include copies of OSI letters</i>)	<input checked="" type="checkbox"/> None requested
Product Quality <input type="checkbox"/> None	
❖ Product Quality Discipline Reviews	
• Tertiary review (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
• Secondary review (e.g., Branch Chief) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> Office of Process and Facilities Review 10/1/15
• Integrated Quality Assessment (contains the Executive Summary and the primary reviews from each product quality review discipline) (<i>indicate date for each review</i>)	<input type="checkbox"/> None 8/7/15; 6/18/15; 4/22/15;
❖ Reviews by other disciplines/divisions/Centers requested by product quality review team (<i>indicate date of each review</i>)	<input checked="" type="checkbox"/> CDRH Review: 7/9/2015 Micro Review:
❖ Environmental Assessment (check one) (original and supplemental applications)	
<input checked="" type="checkbox"/> Categorical Exclusion (<i>indicate review date</i>)(<i>all original applications and all efficacy supplements that could increase the patient population</i>)	Granted 4/20/15
<input type="checkbox"/> Review & FONSI (<i>indicate date of review</i>)	
<input type="checkbox"/> Review & Environmental Impact Statement (<i>indicate date of each review</i>)	
❖ Facilities Review/Inspection	
<input checked="" type="checkbox"/> Facilities inspections (<i>action must be taken prior to the re-evaluation date</i>) (<i>only original applications and efficacy supplements that require a manufacturing facility inspection(e.g., new strength, manufacturing process, or manufacturing site change)</i>)	<input checked="" type="checkbox"/> Acceptable Re-evaluation date: <input type="checkbox"/> Withhold recommendation <input type="checkbox"/> Not applicable

Day of Approval Activities	
❖ For all 505(b)(2) applications: <ul style="list-style-type: none"> • Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity) 	<input checked="" type="checkbox"/> No changes <input type="checkbox"/> New patent/exclusivity (<i>Notify CDER OND IO</i>)
<ul style="list-style-type: none"> • Finalize 505(b)(2) assessment 	<input checked="" type="checkbox"/> Done
❖ For Breakthrough Therapy (BT) Designated drugs: <ul style="list-style-type: none"> • Notify the CDER BT Program Manager 	<input type="checkbox"/> Done (<i>Send email to CDER OND IO</i>)
❖ For products that need to be added to the flush list (generally opioids): Flush List <ul style="list-style-type: none"> • Notify the Division of Online Communications, Office of Communications 	<input type="checkbox"/> Done
❖ Send a courtesy copy of approval letter and all attachments to applicant by fax or secure email	<input checked="" type="checkbox"/> Done
❖ If an FDA communication will issue, notify Press Office of approval action after confirming that applicant received courtesy copy of approval letter	<input checked="" type="checkbox"/> Done
❖ Ensure that proprietary name, if any, and established name are listed in the <i>Application Product Names</i> section of DARRTS, and that the proprietary name is identified as the “preferred” name	<input checked="" type="checkbox"/> Done
❖ Ensure Pediatric Record is accurate	<input type="checkbox"/> Done
❖ Send approval email within one business day to CDER-APPROVALS	<input type="checkbox"/> Done

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

/s/

SHARONJIT K SAGOO
10/05/2015

MEMORANDUM OF TELECONFERENCES

Teleconference Dates: See below

Application Number: NDA 207533

Product Name: Aristada (aripiprazole lauroxil) extended-release injectable suspension

Sponsor/Applicant Name: Alkermes

Subject: Overdue PDUFA Date

1.0 BACKGROUND/DISCUSSION

This memorandum documents certain communications via teleconference between representatives of the Food and Drug Administration (FDA) and Alkermes Inc. and its counsel (together Alkermes) regarding issues related to Alkermes's New Drug Application (NDA 207553) for Aristada (aripiprazole lauroxil) extended-release injectable suspension.

On the dates listed below, representatives of FDA and of Alkermes participated in a teleconference, as described.

Friday, August 21, 2015: Alkermes and FDA discuss outstanding issues related to Alkermes's NDA 207553 and the impending PDUFA goal date.

Friday, August 28, 2015: Alkermes and FDA discuss the status of ongoing reviews related to Alkermes's NDA 207553.

Wednesday, September 9, 2015: Alkermes and FDA discuss the status of FDA's ongoing labeling review for NDA 207553.

Friday, September 18, 2015: Alkermes and FDA discuss outstanding issues related to FDA's review of Alkermes's NDA 207553.

Wednesday, September 30, 2015: Alkermes and FDA discuss the status of FDA's review of NDA 207553.

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/s/

SHARONJIT K SAGOO
10/02/2015

Sagoo, Sharonjit

From: Sagoo, Sharonjit
Sent: Wednesday, September 02, 2015 8:17 AM
To: Ann Kurowski (Ann.Kurowski@Alkermes.com)
Subject: NDA 207533 Aristada - Information Request

Good Morning Ann,

Under 21 CFR 314.54(a)(1)(vi), a 505(b)(2) application must contain a patent certification or statement with respect to any relevant patents that claim the listed drug or that claim any other drugs on which the investigations relied on for approval of the application were conducted, or that claim a use for the listed or other drug. Your 505(b)(2) application relies upon the Agency's finding of safety and effectiveness for NDA 21436 for Abilify oral tablets, but does not contain a patent certification or statement with respect to each patent listed in FDA's "Approved Drug Products with Therapeutic Equivalence Evaluations" (the Orange Book) for the listed drug upon which you rely. After you submitted your 505(b)(2) application, the NDA holder for Abilify oral tablets timely filed information on U.S. Patent No. 9089567 ("567" patent) for listing in the Orange book. In accordance with section 505(b)(2) of the FDCA and 21 CFR 314.50(i), you must submit an appropriate patent certification or statement with respect to the "567" patent.

Please note that if you elect to provide a paragraph IV certification (21 CFR 314.50(i)(1)(i)(A)(4)) with respect to this patent, the certification is to be accompanied by a statement that you will comply with the requirements under 314.52(a) with respect to providing a notice to each owner of the patent or their representatives and to the holder of the approved application for the drug product which is claimed by the patent or a use of which is claimed by the patent and with the requirements under 314.52(c) and 314.52(e) with respect to the content and documentation of receipt of the notice, respectively.

Best regards,
Sharon

Sharonjit Sagoo, Pharm.D., R.Ph.
LCDR, U.S. Public Health Service
Regulatory Project Manager
Division of Psychiatry Products
Center for Drug Evaluation and Research, FDA
Office of Drug Evaluation 1
Ph: (301) 796-0431
Email: sharonjit.sagoo@fda.hhs.gov

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/s/

SHARONJIT K SAGOO
09/02/2015

Sagoo, Sharonjit

From: Sagoo, Sharonjit
Sent: Tuesday, August 04, 2015 8:04 AM
To: Ann Kurowski (Ann.Kurowski@Alkermes.com)
Subject: Shell Tables for NDA 207533
Attachments: aripiprazole shells tables.xls

Hi Ann,

We are requesting your assistance in populating the attached tables for your New Molecular Entity, Aristada (aripiprazole lauroxil), currently under review in the Division.

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

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

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

We are requesting you submit this information no later than August 14, 2015.

Thank you in advance for your cooperation. Please feel free to respond with any questions.

Best Regards,
Sharon

Sharonjit Sagoo, Pharm.D.
LCDR, U.S. Public Health Service
Regulatory Project Manager
Division of Psychiatry Products
Center for Drug Evaluation and Research, FDA
Office of Drug Evaluation 1
Ph: (301) 796-0431
Email: sharonjit.sagoo@fda.hhs.gov

Table 7.5.3-a. Subgroup Analysis of Akathisia AE, Phase 3 safety population

Subgroup	Treatment 1 (N=50) n(%)		Treatment 2 (N=50) n(%)		Placebo (N=50) n(%)		Relative Risk***	95% CI	
	x (%)**	Total, n	x (%)**	Total, n	x (%)**	Total, n		LL	UL
Akathisia	40 (80.0)	50	45 (90.0)	50	40 (80.0)	50			
Sex									
Male									
Female									
Race									
White									
Black or African American									
Asian									
American Indian or Alaska Native									
Native Hawaiian or Other Pacific Islander									

Source:

*Designate per review, other options are SAEs or AEs of special interest (for instance, an HLT, SOC, or user-designated group of PTs)

** Percentages are calculated based on the number of subjects in the subgroup per arm. For example, percentage of males with TEAEs in treatment group = 25/30

***Designated per review, other options are Risk Difference, Hazard Ratios, etc

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/s/

SHARONJIT K SAGOO
08/04/2015



NDA 207533

DISCIPLINE REVIEW LETTER

Alkermes, Inc.
Attention: Georgianna Harris, Ph.D.
Vice President, Regulatory Affairs
852 Winter Street
Waltham, MA 02451-1420

Dear Dr. Harris:

Please refer to your August 22, 2014 New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for ARISTADA (aripiprazole lauroxil) injectable suspension, extended-release 441 mg, 662 mg, and 882 mg.

We also refer to your amendment(s) dated:

Amendment Sequence # 0017	10-APR-2015
Amendment Sequence # 0015	01-APR-2015
Amendment Sequence # 0014	13-MAR-2015
Amendment Sequence # 0013	06-MAR-2015
Amendment Sequence # 0012	02-FEB-2015
Amendment Sequence # 0008	19-DEC-2014
Amendment Sequence #0006	25-NOV-2014

Our review of the product quality (Chemistry, Manufacturing, and Controls and Biopharmaceutics) section of your submission is complete, and we have identified the following deficiencies:

1. Revise the post-approval stability protocol to include testing at accelerated conditions ^{(b) (4)} at accelerated conditions for the first three production batches for ^{(b) (4)}. Revise the proposed testing schedule for the long-term condition to include testing ^{(b) (4)}. In accordance with ICH Q1A(R2) Stability Testing of New Drug Substances and Products, the post-approval stability protocol should include a commitment to test the first three production batches at long-term conditions through the proposed shelf life and at accelerated conditions through six months. In addition, ICH Q1A(R2) also states that the

frequency of testing at the long-term condition should normally be every three (3) months over the first year.

2. Provide justification for the proposed (b) (4) (b) (4) hold time for the bulk (b) (4) drug substance. Provide additional bulk stability data, if available, for other bulk (b) (4) drug substance batches stored through (b) (4) at the proposed bulk hold storage condition along with results from the stacked stability protocol for the drug product batch manufactured using the (b) (4) bulk (b) (4) drug substance. Include as part of the justification, a statistical analysis of the available hold time stability data to support the proposed bulk hold time. The information provided in the submission represents one data point at the proposed bulk hold time and does not provide sufficient evidence that (b) (4) bulk hold time will not negatively impact product quality. Additional justification and data is required to support the proposed bulk hold time.
3. The proposed drug product shelf life of (b) (4) months is not in accordance with ICH Q1E. The submission contained fifteen (15) months of long-term, primary stability data for the drug product. Based on ICH Q1E, the drug product expiry cannot exceed the time period covered by primary stability data plus twelve (12) months, in this case 27 months. Additional justification and drug product stability data is required to support the proposed (b) (4) month drug product shelf life.
4. Provide executed batch records for each batch of drug product used to conduct the primary stability study. 21 CFR 314.50(d)(1)(ii)(b) requires submission of batch records for each drug product primary stability batch. The submission includes an executed batch record for Lot 453-0023 but did not include batch records for Lots 453-0020 453-0021 and 453-0018.
5. As per FDA and ICH recommendations the dissolution acceptance ranges should be mean (b) (4)% for the initial and middle time point, and NLT (b) (4)% at the final time point. Specifically, based on the provided dissolution data, we recommend that the dissolution acceptance criteria range for the 24 hours sampling time point be revised to (b) (4)%.

Implement the following acceptance criteria for the dissolution test of your product for release and on stability.

FDA's Recommended Dissolution Acceptance Criteria for ARISTADA™ (aripiprazole lauroxil) extended release injectable suspension	
Sampling Time	% Drug Dissolved
6 hours	(b) (4) %
24 hours	(b) (4) %
96 hours	NLT (b) (4) %

Revise the specifications table accordingly and provide a copy of the updated specifications table of the proposed drug product.

6. Clarify what is meant by the terms (b) (4) and (b) (4), used to describe the control strategy in Section 3.2.P.2.3 Manufacturing Process Development. The meaning of these terms was not clearly defined in the submission. It is unclear based on the information provided in the submission if these terms refer to (b) (4)
(b) (4)
7. Clarify how the “defined design space” for the (b) (4) will be implemented as part of commercial manufacturing. It is unclear from the information provided in the submission if the “defined design space” represents a proposal for regulatory flexibility with respect to making changes to the (b) (4) without notification to the Agency.
8. Comment on the expected product performance in cases where (b) (4)
(b) (4) Provide any available data demonstrating suitable product performance under these conditions. (b) (4)
(b) (4) It was not clear from the development studies or human factors evaluations if this potential in-use scenario was evaluated.
9. Provide updated drug product photostability results that include results for the dark control (b) (4)
(b) (4) The results provided in the submission did not include the dark control data and included the data for the (b) (4). We cannot determine if (b) (4) impacts stability or compare the results to a control sample based on the data in the submission.
10. Update the SPL data elements package description to denote that the product is a combination product containing a pre-filled syringe (Type 2, prefilled drug delivery device/system). Also provide SPL data elements for the intended commercial kit. The proposed SPL data elements do not include information on the commercial kit or accurately reflect that the drug product is a combination product.

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

and in conformance with the user fee reauthorization agreements, we may or may not be able to consider your response before we take an action on your application during this review cycle.

If you have any questions, call Teshara Bouie, Regulatory Business Project Manager, at (301) 796-1649.

Sincerely,

Olen
Stephens -S

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Date: 2015.04.29 09:27:43 -04'00'

Olen Stephens, Ph.D.
Branch Chief (acting)
Division of New Drug Products I
Office of New Drug Products
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

PeRC Meeting Minutes
April 1, 2015

PeRC Members Attending:

Lynne Yao

Jane Inglese

Hari Cheryl Sachs

Tom Smith

Karen Davis-Bruno

Peter Starke (did not review Efinaconazole and Tavaborole)

Andrew Mulberg

Gregory Reaman

Shrikant Pagay

Andrew Mosholder

Freda Cooner

Kevin Krudys

Lily Mulugeta

Michelle Roth-Cline (for Robert Nelson)

Kristiana Brugger

Agenda

NDA	Non-Responsive		
NDA	Non-Responsive		
PIND	Non-Responsive		
IND	Non-Responsive		
NDA	Non-Responsive		
IND	Non-Responsive		
IND	Non-Responsive		
NDA	Non-Responsive		
NDA	207533	Aristada (aripiprazole lauroxil) Full Waiver *Agreed iPSP	Treatment of schizophrenia
NDA	Non-Responsive		
BLA	Non-Responsive		
IND	Non-Responsive		

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Non Responsive

Aristada (aripiprazole lauroxil) Full Waiver

- NDA 207533 seeks marketing approval for Aristada (aripiprazole lauroxil) for treatment of schizophrenia.
- The application triggers PREA as directed to a new active ingredient. This is also an extended-release injectable product
- The application has a PDUFA goal date of August 22, 2015.
- *PeRC Recommendations:*
 - The PeRC agreed with a full waiver for all pediatric patients because studies would be impossible or highly impracticable

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/s/

JANE E INGLESE
04/13/2015



NDA 207533

INFORMATION REQUEST

Alkermes, Inc.
Attention: Ann Kurowski
Associate Director, Regulatory Affairs
852 Winter Street
Waltham, MA 02451-1420

Dear Ms. Kurowski:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Aripiprazole Lauroxil Extended-Release Injectable Suspension.

We are reviewing the Chemistry, Manufacturing, and Controls section of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

1. Revise all relevant sections of the submission to reflect that the drug product expiration date will be determined from (b) (4).
(b) (4) Section 3.2.P.8.1 indicates that drug product expiration date will be calculated from (b) (4). This approach is not acceptable.
(b) (4)
2. Revise the proposed regulatory drug product specification to include a control for (b) (4) at release and on stability. Alternatively, provide justification, supported by data, for not including a control (b) (4) in the drug product specification. We consider (b) (4) a critical quality attribute of the drug product that could impact both patient safety and efficacy of the drug product due to inaccurate dosing. The proposed drug product specification does not include a direct control of (b) (4) at release or on stability.

3. Revise the proposed regulatory drug product acceptance criteria for the description test to include the criterion “free from visual defects” for the syringe package. Results observed during development indicate that (b) (4).
The addition of this criterion will provide additional assurance that the drug product is not grossly compromised. In addition, comment on the need for including a (b) (4) as part of the product description acceptance criterion.
4. Include an in-process control for (b) (4) or justify the absence of these controls. We acknowledge that (b) (4) is monitored throughout the (b) (4) operation and that a (b) (4) on (b) (4) samples is in place at release.
5. Provide a description of the container closure system used for the bulk (b) (4) drug substance. Include information on the regulatory status of the materials of construction. Include information on the recommended storage condition and any special storage instructions for the bulk (b) (4) drug substance. We could not locate this information in the submission.
6. Provide representative certificates of analyses for all starting materials and reagents used in the manufacture of the drug substance.
7. Update the specification for (b) (4) to include a test for assay.
8. Provide a description of the closures for the primary (b) (4) and secondary (b) (4) container closure systems for the drug substance.
9. The acceptance criterion for each of the specified impurities and for the single unidentified impurity in the stability table is NMT (b) (4)%. The acceptance criteria for each of the specified impurities and for the single unidentified impurity in the drug substance specification are NMT (b) (4)% and NMT (b) (4)%, respectively. Be advised that release and stability specification for the drug substance must be congruent. As such we request that you provide a consolidated specification table with release and stability limits.
10. Provide the results of the forced degradation studies for the drug substance.

If you have any questions, contact Teshara G. Bouie, Regulatory Project Manager, at (301) 796-1649.

Sincerely,

Olen Stephens, Ph.D.
Acting Branch Chief
Branch II, Division of New Drug Products I
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

Olen
Stephens -S

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ou=HHS, ou=FDA, ou=People,
cn=Olen Stephens -S,
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NDA 207533

MID-CYCLE COMMUNICATION

Alkermes, Inc.
Attention: Ann Kurowski, M.S.
Associate Director, Regulatory Affairs
852 Winter Street
Waltham, MA 02451-2417

Dear Ms. Kurowski:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for ARISTADA (aripiprazole lauroxil) extended release injectable suspension 441 mg, 662 mg, and 882 mg.

We also refer to the teleconference between representatives of your firm and the FDA on February 9, 2015. The purpose of the teleconference was to provide you an update on the status of the review of your application.

A record of the teleconference is enclosed for your information.

If you have any questions, call me, at (301) 796-0431.

Sincerely,

{See appended electronic signature page}

LT Sharonjit Sagoo, Pharm.D.
Regulatory Project Manager
Division of Psychiatry Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure:
Mid-Cycle Communication



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MID-CYCLE COMMUNICATION

Meeting Date and Time: February 9, 2015 at 11:00 AM – 12:00 PM EST

Application Number: NDA 207533

Product Name: ARISTADA (aripiprazole lauroxil) extended release injectable suspension

Indication: Schizophrenia

Applicant Name: Alkermes

FDA ATTENDEES

Mitchell Mathis, M.D.	Director, Division of Psychiatry Products (DPP)
Tiffany Farchione, M.D.	Deputy Director, DPP
Robert Temple, M.D.	Deputy Director, Office of Drug Evaluation I
Praveen Balimane, Ph.D.	Clinical Pharmacology Reviewer, Office of Clinical Pharmacology (OCP)
Kevin Krudys, Ph.D.	Pharmacometrics Team Leader, OCP
Xiaofeng Wang, Ph.D.	Pharmacometrics Reviewer, OCP
Jeffrey Kraft, Ph.D.	Pharmacogenomics Reviewer, OCP
Amy Avila, Ph.D.	Pharmacology/Toxicology Reviewer, DPP
Aisar Atrakchi, Ph.D.	Pharmacology/Toxicology Supervisor, DPP
Jinglin Zhong, Ph.D.	Biometrics Reviewer
Peiling Yang, Ph.D.	Biometrics Team Leader
Lucas Kemp, M.D.	Clinical Team Leader, DPP
Wendy Wilson-Lee, Ph.D.	Branch Chief, Office of Pharmaceutical Quality
Cathy Miller M.P.H., BSN	Risk Management Analyst, DRISK
Susannah O'Donnell, MPH	Reviewer, Office of Prescription Drug Promotion
Jenn Sellers, M.D., Ph.D, F.A.A.P.	Senior Medical Officer, Office of Compliance, Office of Scientific Investigations (OSI)
Susan Thompson, M.D.	Team Leader, Office of Compliance, OSI
Patrick J. Zhou	Eastern Research Group
Sharonjit Sagoo, Pharm.D.	Regulatory Project Manager, DPP

APPLICANT ATTENDEES

Elliot Ehrich, M.D.	Sr. VP, Research and Development and Chief Medical Officer
Srdjan Stankovic, M.D.	Sr. VP, Clinical Development and Medical Affairs
Georgianna Harris, Ph.D.	VP, Regulatory Affairs
Bernard Silverman, M.D.	VP, Clinical Development
Anjana Bose, Ph.D.	VP, Clinical Biometrics
Daniel Deaver, Ph.D.	VP, Nonclinical Development

Robert Risinger, MD	Senior Medical Director
Ryan Turncliff, Ph.D.	Director Translational Medicine
Marjie Hard, Ph.D.	Staff Scientist, Translational Medicine
Lawrence Dahm, Ph.D.	Principal Toxicologist
Magali Hickey, Ph.D.	Director, Formulation Development
Yangchun Du, Ph.D.	Associate Director, Biostatistics
Colleen Ellwanger	Director Project Management
John Lally	Senior Director, Regulatory CMC
Ann Kurowski, M.S.	Associate Director, Regulatory Affairs

1.0 INTRODUCTION

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

2.0 SIGNIFICANT ISSUES

As previously stated, the purpose of this meeting is to provide a status update on the review of your application. The application is still under review and no regulatory decisions have been determined.

The following issues were discussed:

Pharmaceutical Quality

- Establishment of the drug product expiry – we do not agree with your proposal to assign the expiry (b) (4)
- Control for resuspendability – you did not propose controls at release or on stability and did not provide adequate justification to support not including this test
- Bulk (b) (4) drug substance – we require information on the container closure used to store the bulk drug

3.0 INFORMATION REQUESTS

Pharmaceutical Quality

- An information request addressing the issues listed in Section 2.0 is forthcoming.

Clinical Pharmacology

- Pending information request delivered via email 2/6/2015 regarding missed doses.

Pharmacology/Toxicology

- Pending information request delivered via email 2/6/2015 regarding genotoxic impurities.

Device Evaluation

- Pending information request delivered via email 2/5/2015 for constituent part requirements and verification studies.

Surveillance and Epidemiology

- Pending information request delivered via email 2/2/2015 for a pharmacovigilance plan.

4.0 MILESTONES IN THE REVIEW CYCLE

PMR/PMC/Labeling Goal is April 22, 2015.

5.0 MAJOR SAFETY CONCERNS/RISK MANAGEMENT

At this time, we have not identified any major safety concerns.

At this time, we have not identified any risk associated with ARISTADA (aripiprazole lauroxil) extended-release injectable suspension that would require a Risk Evaluation and Mitigation Strategy (REMS).

5.0 ADVISORY COMMITTEE MEETING

We do not anticipate the need to convene an Advisory Committee Meeting for this application.

6.0 LATE-CYCLE MEETING /OTHER PROJECTED MILESTONES

1. A face-to-face Late-Cycle Meeting is scheduled for Thursday, May 21, 2015 at 3:00 – 4:00 PM EST.
2. The face-to-face meeting may be changed to a teleconference per Alkermes' request.
3. The internal Pre-Meeting for the Late-Cycle Meeting will take place on April 16, 2015.
4. We plan to issue Discipline Review Letters by April 29, 2015.
5. We plan to deliver the Agency Late-Cycle Meeting Briefing Package no later than May 7, 2015.
6. We plan to take action by the PDUFA goal date of August 22, 2015.

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/s/

SHARONJIT K SAGOO
02/18/2015



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 207533

**PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE**

Alkermes, Inc.
852 Winter Street,
Waltham, MA 02451-1420

ATTENTION: Ann Kurowski, M.S.
Associate Director Regulatory Affairs

Dear Ms. Kurowski:

Please refer to your New Drug Application (NDA), dated and received August 22, 2014, submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Aripiprazole Lauroxil, Extended-release Injectable Suspension, 441 mg, 662 mg, and 882 mg.

We also refer to your correspondence, dated and received August 22, 2014, requesting review of your proposed proprietary name, Aristada. We have completed our review of the proposed proprietary name, Aristada, and have concluded that this name is acceptable.

If any of the proposed product characteristics as stated in your August 22, 2014, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Vasantha Ayalasomayajula, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (240) 402-5035. For any other information regarding this application, contact Sharonjit Sagoo, Regulatory Project Manager in the Office of New Drugs, at (301) 796-0431.

Sincerely,

{See appended electronic signature page}

Kellie A. Taylor, Pharm.D., MPH
Deputy Director
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

TODD D BRIDGES on behalf of KELLIE A TAYLOR
11/17/2014



NDA 207533

NDA ACKNOWLEDGMENT

Alkermes, Inc.
Attention: Georgianna Harris, Ph.D.
Vice President, Regulatory Affairs
852 Winter Street
Waltham, MA 02451-2417

Dear Dr. Harris:

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

Name of Drug Product: ARISTADA (aripiprazole lauroxil) extended release injectable suspension 441 mg, 662 mg, and 882 mg

Date of Application: August 22, 2014

Date of Receipt: August 22, 2014

Our Reference Number: NDA 207533

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 October 21, 2014, 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(l)(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 conform 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 Psychiatry Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

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If you have any questions, contact Sharonjit Sagoo, Pharm.D., Regulatory Project Manager, at sharonjit.sagoo@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

LT Sharonjit Sagoo, Pharm.D.
Regulatory Project Manager
Division of Psychiatry Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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

/s/

SHARONJIT K SAGOO
08/27/2014



IND 107249

MEETING MINUTES

Alkermes, Inc.
Attention: Mark Machado
Manager, Regulatory Affairs
852 Winter Street
Waltham, MA 02451-1420

Dear Mr. Machado:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for ALKS 9072.

We also refer to the meeting between representatives of your firm and the FDA on Monday, May 19, 2014. The purpose of the meeting was to discuss the adequacy of the clinical, nonclinical and CMC programs to support an NDA filing of aripiprazole lauroxil for the treatment of schizophrenia; acceptability of the format and presentation of data in the NDA; and contents of the application to support the proposed indication.

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

If you have any questions, contact Sharonjit Sagoo, Pharm.D., Regulatory Project Manager at sharonjit.sagoo@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Mitchell V. Mathis, M.D.
CAPT, USPHS
Director
Division of Psychiatry Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B
Meeting Category: Pre-NDA

Meeting Date and Time: Monday, May 19, 2014 at 1:00 PM – 2:00 PM EST
Meeting Location: FDA, White Oak

Application Number: IND 107249
Product Name: ALKS 9072
Indication: Schizophrenia
Sponsor/Applicant Name: Alkermes, Inc.

FDA ATTENDEES

Mitchell Mathis, M.D.	Director, Division of Psychiatry Products (DPP)
Jing Zhang, M.D.	Medical Team Leader, DPP
Gregory Dubitsky, M.D.	Medical Reviewer, DPP
Hao Zhu, Ph.D.	Clinical Pharmacology Team Leader, Office of Clinical Pharmacology (OCP)
Huixia Zhang, Ph.D.	Clinical Pharmacology Reviewer, OCP
Kevin Krudys, Ph.D.	Pharmacometrics Reviewer, OCP
Ping Zhao, Ph.D.	Senior Clinical Pharmacologist, OCP
Aisar Atrakchi, Ph.D.	Pharmacology/Toxicology Supervisor, DPP
Amy Avila, Ph.D.	Pharmacology/Toxicology Reviewer, DPP
David Claffey, Ph.D.	Chemistry, Manufacturing and Controls Team Lead
Pei-I Chu, Ph.D.	Chemistry, Manufacturing and Controls Reviewer
Yeh-Fong Chen, Ph.D.	Biometrics Reviewer
Peiling Yang, Ph.D.	Biometrics Team Lead
Sharonjit Sagoo, Pharm.D.	Regulatory Project Manager, DPP

EASTERN RESEARCH GROUP ATTENDEES

Patrick Zhou, Independent Assessor

SPONSOR ATTENDEES

Ann Kurowski, M.S.	Associate Director, Regulatory Affairs
Georgianna Harris, Ph.D.	VP, Regulatory Affairs
John Lally	Senior Director, Regulatory CMC
Elliot Ehrich, M.D.	Sr. VP, Research and Development and Chief Medical Officer
Srdjan Stankovic, M.D.	Sr. VP, Clinical Development and Medical Affairs

Bernard Silverman, M.D.	VP, Clinical Development
Robert Risinger, M.D.	Senior Medical Director
Anjana Bose, Ph.D.	VP, Clinical Biometrics
Yangchun Du, Ph.D.	Associate Director, Biostatistics
Marjie Hard, Ph.D.	Staff Scientist, Translational Medicine, CMC Team Leader
Ryan Turncliff, Ph.D.	Director, Translational Medicine
Daniel Deaver, Ph.D.	VP, Nonclinical Development
Lawrence Dahm, Ph.D.	Principal Toxicologist
Magali Hickey, Ph.D.	Director, Formulation Development
Michael Palmieri, Ph.D.	Senior Director, Analytical Development
Paul Herbert, M. Eng.	VP, Process Development
Bob Edmonston, M.S.	Director, Chemical Development

1.0 BACKGROUND

Aripiprazole lauroxil (Aristada™) is a prodrug of the atypical antipsychotic, aripiprazole, that has been developed as an extended-release intramuscular injection for once monthly administration in the treatment of schizophrenia. After injection, aripiprazole lauroxil is converted to aripiprazole. Alkermes is also considering alternative dosing frequencies to offer patients greater flexibility in achieving treatment optimization.

Alkermes intends to submit an NDA for aripiprazole lauroxil in the second half of 2014. Aripiprazole lauroxil will be marketed as an aqueous suspension in a single-use pre-filled syringe for injection into either the deltoid or gluteal muscle. It is planned that doses of 441mg (for deltoid and gluteal injection) and 662mg and 882mg (for gluteal administration) will be available. Equivalent doses of aripiprazole are as follows:

Aripiprazole Lauroxil Dose	Equivalent Aripiprazole Dose
(b) (4)	(b) (4)
441mg	300mg
(b) (4)	(b) (4)
662mg	450mg
882mg	600mg

Aripiprazole lauroxil has been developed under section 505(b)(2) using aripiprazole tablets as the Reference Listed Drug (RLD). The safety and efficacy data to support this formulation will rely, in part, on the data derived from studies with aripiprazole tablets. (Coincidentally, another extended-release formulation of aripiprazole for once monthly intramuscular injection, Abilify Maintena, was approved during the development of aripiprazole lauroxil.)

In preparation for that submission, the sponsor has requested a face-to-face pre-NDA meeting with the Division of Psychiatry Products (DPP) to discuss the clinical, nonclinical, and chemistry, manufacturing, and controls programs; data format and presentation, and NDA contents.

Clinical Program

The aripiprazole lauroxil clinical program consists of the 7 clinical trials presented in Table 1 below. The first 5 trials listed in this table have been completed and the last 2 are ongoing.

Table 1: Clinical Trials	
Study Number	Study Design
Phase 1	
ALK9072-001	Single, ascending dose trial in 32 stable, chronic schizophrenic subjects. Doses were 221mg, 441mg, 588mg, or placebo injected into the gluteal muscle.
ALK9072-101	Single dose trial comparing gluteal vs deltoid injections in 46 stable, chronic schizophrenic subjects. Primary doses were 441mg (deltoid) and 441mg (gluteal).
ALK9072-002	Multiple, ascending dose trial in 76 stable, chronic schizophrenic subjects. Doses were 441mg, 662mg, 882mg, or placebo given as 4 monthly injections into the gluteal muscle.
ALK9072-102	Multiple dose safety trial of deltoid injections in 53 stable, chronic schizophrenic subjects. Doses were 441mg or placebo given as 4 monthly injections.
Phase 3	
ALK9072-003	Randomized, double-blind, placebo-controlled trial in 623 subjects with acute, exacerbated schizophrenia. Doses were 441mg, 882mg, or placebo (about 200 subjects each) given as 3 monthly gluteal injections with oral study drug for the first 3 weeks after randomization.
ALK9072-003EXT	Long-term, open label extension of ALK9072-003. This trial is ongoing, with 478 subjects to date. Gluteal injections of 441mg or 882mg are given monthly for up to 52 weeks.
ALK9072-003EXT2	Long-term, open label extension of ALK9072-003EXT. This trial is ongoing, with about 10 subjects to date. Gluteal injections of 441mg or 882mg are given monthly. This trial will run until January 2016.

2. DISCUSSION

2.1. Clinical

Question 1: Does the Agency agree with the presentation of the primary efficacy endpoint and secondary efficacy endpoint results?

The demonstration of efficacy is based on a single multicenter, randomized, double-blind, placebo-controlled trial (ALK9072-003). Schizophrenic patients in acute exacerbation were randomized in a 2:2:1:1 ratio to aripiprazole lauroxil 441mg, aripiprazole lauroxil 882mg, low volume placebo, or high volume placebo, respectively, by gluteal intramuscular injection every 28 days for 3 doses (study days 1, 29, and 57). Also, oral aripiprazole or oral placebo was administered during the first 3 weeks after randomization. The primary endpoint was the change from baseline to day 85 in the PANSS total score. The key secondary endpoint was the CGI-Improvement score at day 85. An unblinded interim analysis was conducted by a firewalled independent statistical center in June 2013 for the sole purpose of sample size re-

estimation based on the primary efficacy variable. The sample size was not changed based on this analysis. The full database analysis is ongoing at this time but preliminary findings show statistical superiority of both aripiprazole lauroxil doses over placebo. Sample data displays for the primary and key secondary efficacy variables are provided.

FDA Response to Question 1:

The display of results for the primary and key secondary efficacy variables appears to be acceptable.

Discussion at Meeting:

No further discussion.

Question 2: Does the Agency agree with the proposed presentation of the data in the Summary of Clinical Efficacy (SCE)?

Because this application will contain only one key efficacy trial (ALK9072-003), no Integrated Summary of Efficacy (ISE) will be provided in Module 5. Instead, a summary of all efficacy data will be presented in the Summary of Clinical Efficacy (SCE) under Module 2. The SCE will include the efficacy assessments and statistical methods, summary of results, subgroup analyses from the controlled trial, and information relevant to dosing. Subgroups will include gender, race (white, non-white), age (<55, ≥55), and region (U.S., Europe, and Asia). [REDACTED] (b) (4)

FDA Response to Question 2:

The general content outline for the SCE is acceptable except for the data regarding persistence of efficacy. [REDACTED] (b) (4)

Thus, because of the limited usefulness of this information, it need not be included in the SCE.

Discussion at Meeting:

No further discussion.

Question 3: Does the Agency agree with the proposed presentation of the Integrated Summary of Safety (ISS)? Specifically, does the Agency agree with the:

- a. Proposed [REDACTED] (b) (4)
- b. Proposed categorization and planned baseline for summarizing long-term safety data,
- c. Organization and presentation for safety variables, and
- d. Proposed approach for the ALK9072-003EXT2 study?

The Integrated Summary of Safety (ISS) will present safety data categorized into 3 groups:

Group 1 = double-blind, placebo-controlled trial ALK9072-003.

Group 2 = long-term, open-label extension trial ALK9072-003EXT with a cut-off of April 30, 2014. This will integrate data from patients who received aripiprazole lauroxil during the double-blind lead-in trial ALK9072-003.

(b) (4)

Safety data from the extension of trial ALK9072-003EXT, ALK9072-003EXT2, will be based on only about 10 subjects as of April 30, 2014. These data will include lists of subjects who experienced serious adverse events (SAEs) or adverse events that led to dropout. Exposure will be summarized by the number of injections received by dose (441mg and 882mg) for Group 1, Group 2, and Groups 1 and 2 combined as of April 30, 2014. All safety data will be summarized using descriptive statistics for all subjects who received at least one injection of study drug. Baseline characteristics, treatment-emergent adverse events (TEAEs), SAEs (including deaths), adverse events leading to dropout, and data from the Columbia-Suicide Severity rating Scale (C-SSRS) will be provided (b) (4). In addition, data regarding TEAEs of special interest, injection site reactions, laboratory tests, vital signs, ECG, and extrapyramidal symptoms scales will be presented for Groups 1 and 2. For Groups 1 and 2, safety information will be presented separately for the Treatment Period and the Follow-up Period. Baseline is defined as the last value on or before the first injection of study drug for trial ALK9072-003. For trial ALK9072-003EXT, baseline will be the baseline value for ALK9072-003 for subjects who received active drug in the double-blind lead-in trial and the baseline for ALK9072-003EXT for subjects who received placebo in the double-blind lead-in trial. The incidence of common TEAEs will be presented by various subgroups: age (<55, ≥55), race (white, non-white), gender, region (U.S., Europe, Asia), CYP metabolizer status (PM, IM, EM), and BMI category (<18.5, ≥18.5 to <25, ≥25 to <30, and ≥30). Adverse events of special interest will include the following: liver safety, metabolic changes, suicidality, injection site reactions, seizures, CPK increases, deep vein thrombosis and pulmonary embolism, hypersensitivity reactions, weight changes, and QT prolongation. Laboratory, vital sign, and body weight data will include change from baseline data and the percentage of subjects with Potentially Clinically Significant (PCS) values at any post-baseline visit. Shift tables will be provided for metabolic parameters. ECG data will include the number and percentage of patients with any of the following: QTcB or QTcF >500msec, change from baseline in QTcB/QTcF ≥30msec but <60msec, and change from baseline ≥60msec. (b) (4)

Injection site reaction findings will include adverse event reports as well as specific symptoms (e.g., pain, redness, swelling). An outline for the ISS structure was provided by the sponsor.

FDA Response to Question 3:

a. The (b) (4) is not acceptable. (b) (4)

An additional source of safety data will be the published literature. The ISS must include a literature search for any publications containing safety data pertaining to aripiprazole lauroxil. It appears that you plan to provide literature findings in section 13 of the ISS. We request the following information

pertaining to your search: search terms, databases searched, start and end dates of the search, the methodology for identifying important articles, the level of review of identified articles (e.g., entire text versus abstract only), and the name and credentials of the individual(s) who conducted the search and examined the resulting articles. In addition, we will need a warrant signed and dated by the person(s) responsible for evaluating the results of the search that the reviewed publications either a) revealed no new adverse safety findings associated with aripiprazole lauroxil or b) revealed new adverse safety findings associated with aripiprazole lauroxil. In the latter case, a detailed description of the findings with complete copies of the relevant articles should be provided to us. Please note that important articles in foreign languages should be translated into standard English.

- b. *The proposed plan for presenting safety data from the long-term trials is generally acceptable. However, subjects from trials ALK9072-003, ALK9072-003EXT, and ALK9072-003EXT2 must have assigned unique subject identification numbers (a number that remains the same for a given patient regardless of the trial) so that data from each subject can be tracked across these 3 trials.*
- c. *We have the following comments on the presentation of specific safety data: 1) The presentation of C-SSRS data is not acceptable. Findings from the C-SSRS should be mapped to one of the categories of suicidal ideation or behavior according to the Columbia-Classification Algorithm of Suicide Assessment (C-CASA). These categories are described in Appendix A to the Guidance for Industry-Suicidal Ideation and Behavior: Prospective Assessment of Occurrence in Clinical Trials (August 2012). The number and percentage of subjects by treatment group in trial ALK9072-003 who met the criterion for each category should be provided in a table for our review. 2) Standard analyses of numerical safety data (i.e., change from baseline and percentage of subjects meeting PCS criteria for laboratory, vital sign, and ECG parameters as well as C-SSRS data) should be restricted to trial ALK9072-003.*

(b) (4)
3)
(b) (4)

- d. *The proposed approach for ALK9072-003EXT2 is acceptable.*

Discussion at Meeting:

Prior to the meeting, Alkermes had provided an email with a proposed table for displaying C-CASA data from trial ALK9072-003. The FDA Clinical Review Team stated that the proposed table may be included in the NDA submission but requested that a specific table for presenting these data also be provided. This table as well as a slide created by (b) (6) Ph.D., which depicts the scheme for mapping C-SSRS items to C-CASA categories was provided in hardcopy to the sponsor during the meeting. These items are reproduced in Section 6.0 of these meeting minutes. Alkermes accepted our request without further discussion.

Question 4: Does the Agency agree with the proposed presentation of clinical datasets; including electronic data sets, case report forms and patient narratives?

The sponsor will provide datasets which comply with the Clinical Data Interchange Standards Consortium (CDISC) for the 5 completed trials. SAS programs will be provided for primary and secondary efficacy tables. In addition, Case Report Forms (CRFs) and narrative descriptions will be provided for subjects who died, had any non-fatal SAE, or who discontinued treatment due to an adverse event.

FDA Response to Question 4:

Clarify if raw variables were collected using CDSIC. If not, you will also need to submit raw variables in addition to datasets in CDISC.

Subjects from trials ALK9072-003, ALK9072-003EXT, and ALK9072-003EXT2 must have a unique subject identification number (USUBJID) included in the datasets. Otherwise, from a clinical standpoint, the proposed datasets are acceptable.

From a statistical standpoint, please also include the following in your submission:

- a. SAS programs by which the derived variables were produced from the raw variables;*
- b. A list of serial numbers and submission dates of the protocols, SAPs, amendments, and any relevant meetings.*
- c. The interim analysis results and minutes of meetings of the independent statistical center.*

Discussion at Meeting: *The sponsor clarified that raw variables were not collected using the CDSIC, but they did not find any discrepancy between those raw variables and those converted to the CDISC format. Nevertheless, they agree to include raw variables in their future NDA submission.*

Question 5: Does the Agency agree with the proposed population PK (PopPK) modeling and simulation plans?

FDA Response to Question 5:

Yes. The proposed population PK modeling and simulation plans are acceptable.

Discussion at Meeting:

No further discussion.

Question 6: Does the Agency agree that modeling and simulation may be used to support recommendations for different dose schedules?

FDA Response to Question 6:

We recommend that you conduct simulations and submit your rationale for different dose schedules. Recommendations for different dose schedules than those studied in clinical trials will need to be justified based on totality of data which involves benefit-risk assessment as well as adequacy of the population PK model.

Discussion at Meeting:

No further discussion.

Question 7: Does the Agency agree with the proposal for the submission of files and datasets from the PopPK analysis, and for the physiologically-based pharmacokinetics (PBPK) simulations conducted using the Simcyp Population-based Simulator?

FDA Response to Question 7:

Yes, the proposal for submitting files and datasets from the PopPK analysis is acceptable.

Your strategy of using PBPK to address drug and genetic interaction potential for aripiprazole lauroxil is reasonable.

A. *We also have the following comments regarding your PBPK modeling and simulation:*

1. *PBPK model development and verification:*

a) *Your PBPK model should be constructed and verified using available clinical drug interaction and CYP2D6 pharmacogenetic study results for aripiprazole. Recent simulations by Vieira et al revealed under prediction of the effect of several CYP3A inhibitors on aripiprazole using SimCYP software. Points brought up by this publication should be considered. Besides drug model, you should establish virtual CYP2D6 intermediate metabolizers and ultra-rapid metabolizers (IMs and URM), and verify aripiprazole PK in IMs or URM, whenever such data are available.*

b) *PBPK model of aripiprazole lauroxil should be verified or optimized based on available clinical PK data. Simulations should be conducted in subjects with specific CYP2D6 phenotypes (URMs, extensive metabolizers (EMs), IMs, or PMs), whenever such data are available.*

2. *Application of aripiprazole lauroxil PBPK model. Besides conducting simulations in CYP2D6 PMs and pooled non-PM subjects, you should individually evaluate the effects of CYP2D6 or CYP3A inhibitors on aripiprazole PK in subjects with a specific CYP2D6 phenotype (URMs, EMs, IMs or PMs) administered with different doses of aripiprazole lauroxil.*

3. *Submission. You should submit formal PBPK study report. The study report should include the purpose of the simulations, assumptions being made, detailed process of PBPK model building and verification, a summary of model input parameters of drugs, version of SimCYP being used, simulation results, and conclusions. The parameters can be compiled in the table format with parameter name, parameter values (mean and/or variability), source of the parameter values and assumptions being made. In addition, any modification of the default values of the system and/or drug parameter input of a particular version of the software should be declared and justified. Besides files outlined in your question, include workspace files for final simulations.*

B. *In addition to your proposed PBPK modeling, we recommend you to use population PK simulation to independently derive the doses in subgroups of patients and in patients receiving concomitant medications. Please refer to our review for population PK approach as utilized for Abilify Maintena (http://www.accessdata.fda.gov/drugsatfda_docs/nda/2013/202971Orig1s000ClinPharmR.pdf).*

C. Please provide a table summarizing your final proposal on dosage adjustments for patients who are CYP2D6 poor metabolizers and for patients taking CYP2D6 inhibitors, CYP3A4 inhibitors, or CYP3A4 inducers. The table should be in the same format as that in the Ability Maintena Kit label.

Reference:

Vieira MD, Kim MJ, Apparaju S, Sinha V, Zineh I, Huang SM, Zhao P. PBPK Model Describes the Effects of Comedication and Genetic Polymorphism on Systemic Exposure of Drugs That Undergo Multiple Clearance Pathways. *Clin Pharmacol Ther.* 2014, 95(5):550-7

Discussion at Meeting:

Sponsor believes that their PBPK model has been adequately verified and they plan to use simulation results to support product label with regard to drug-drug interaction potential. Sponsor requested clarification on the extent of simulations in CYP2D6 IMs and URM and whether dosing recommendations under various scenarios should be provided in PBPK submission. The reviewer recommended that the sponsor comprehensively simulate all potential interaction scenarios and include dosing recommendations in the submission. The review team may or may not request additional information during NDA review. Sponsor also sought advice on timing of PBPK submissions on CYP2D6 IMs and URM, and initially proposed submission by day 120 safety review (sponsor stated other simulation scenarios will be included in the original NDA submission). If priority review designation is granted, sponsor agrees to make sure there is sufficient time for the reviewer to perform review for those two simulation scenarios.

Post Meeting Comments:

We request you to submit any PBPK data and relevant report that are not included in the original submission within 30 days after the application submission.

2.2. Nonclinical

Question 8: Does the Agency agree that the completed nonclinical program is adequate to support review of the NDA?

FDA Response to Question 8:

Yes, the completed nonclinical program appears adequate to support review of the NDA. However, the final adequacy of all data will be a matter of review.

Please note that a 505(b)(2) applicant that seeks to rely upon the Agency's finding of safety and/or effectiveness for a listed drug may rely on FDA's finding of safety and effectiveness only as reflected in the FDA-approved labeling for the listed drug.

Discussion at Meeting:

No further discussion.

Question 9: Does the Agency agree that completed nonclinical studies evaluating sorbitan monolaurate, together with the literature review provided, are adequate to support the review of the NDA?

FDA Response to Question 9:

Yes, the completed nonclinical studies and literature for sorbitan monolaurate appear adequate to support the review of the NDA. However, the final adequacy of all data will be a matter of review.

Please note that a b2 applicant may not rely on information from the Summary Basis of Approval (SBA) or FDA reviewers' public summaries to justify a safe level of an impurity/excipient; however, a b2 applicant may rely on the labeling of a listed drug if that labeling indicates the level of the impurity/excipient. To rely, in part, on the Agency's finding of safety and/or effectiveness for a listed drug(s), the b2 applicant should identify the listed drug(s) in accordance with the Agency's regulations at 21 CFR 314.54. 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 on which a b2 applicant relies.

A b2 applicant may be able to rely on identified published literature about an impurity/excipient that supports the safe use of a proposed level of an impurity/excipient. If the published literature describes a specific listed drug, the b2 applicant should identify the listed drug in accordance with the Agency's regulations at 21 CFR 314.54. As noted above, 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 on which a b2 applicant relies.

Discussion at Meeting:

No further discussion.

Question 10: Alkermes does not plan to include nonclinical datasets (SEND) in the aripiprazole lauroxil NDA. Does the Agency agree?

FDA Response to Question 10:

Nonclinical datasets (SEND) are not required at this time. However, CDER strongly encourages IND sponsors to consider the implementation and use of data standards for the submission of applications for investigational new drugs and product registration. Such implementation should occur as early as possible in the product development lifecycle, so that data standards are accounted for in the design, conduct, and analysis of clinical and nonclinical studies. CDER has produced a 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. The web page may be found at: <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm>

Discussion at Meeting:
No further discussion.

2.3. Chemistry, Manufacturing and Control (CMC)

Question 11: Does the Agency agree with the presentation and content for drug substance control strategy?

FDA Response to Question 11:

*No, we do not agree. We stated in our EOP2 meeting (b) (4)
All CMC information provided in
DMF (b) (4) including your justification (b) (4)
will be evaluated at the time of NDA review.*

Discussion at Meeting: *The applicant stated that the proposed regulatory starting materials will be identified and documented in DMF (b) (4) FDA agreed that this approach was acceptable and the data will be reviewed at the NDA stage.*

Question 12: Does the Agency agree with the presentation and content for drug product control strategy?

FDA Response to Question 12:

In principle, we agree. However, agreement on specifications and their limits will occur at the time of NDA review. Addition of tests and acceptance criteria for polymorphic form identification (b) (4) should be considered at release and over the proposed expiry period or justification provided for their absence.

Discussion at Meeting:
No further discussion.

Question 13: Does the Agency agree with the approach to the post approval stability commitment?

FDA Response to Question 13:

According to ICHQ1A(R2), if the submission does not include stability data on production batches, a commitment should be made to place the first three production batches on both long term stability studies through the proposed shelf life and on accelerated studies for 6 months. The stability protocol used for studies on commitment batches should be the same as that for the primary batches. Annually thereafter, your proposal to conduct long-term stability (b) (4) is acceptable.

Discussion at Meeting:
No further discussion.

Question 14: Does the Agency agree with the presentation and content [REDACTED] (b) (4) [REDACTED] ?

FDA Response to Question 14:

In principle, we agree. However, you need to provide development data [REDACTED] (b) (4) [REDACTED]. The adequacy of the data provided will be evaluated at the time of NDA review.

Discussion at Meeting:

No further discussion.

2.4. Administrative Questions

Question 15: Does the Agency agree with Alkermes filing the aripiprazole lauroxil NDA under section 505(b)(2) using oral aripiprazole tablets as the Reference Listed Drug (RLD) as previously agreed at the Pre-IND meeting and confirmed at the EOP2 meeting?

FDA Response to Question 15:

At this time, based on the available information, a (b)(2) application seems acceptable. Please refer to the information specific to 505(b)(2) applications provided in the responses to the other questions in this document and to the general information on 505(b)(2) applications provided at the end of this document.

Discussion at Meeting:

No further discussion.

Question 16: Does the Agency agree that the rationale that led to the new molecular entity (NME) determination for aripiprazole lauroxil also supports a determination that aripiprazole lauroxil is a new chemical entity (NCE)? Is there any additional information needed by the Agency to make a determination that the NME, aripiprazole lauroxil, will also qualify as an NCE?

FDA Response to Question 16:

The final NCE determination will be made at the time of NDA approval. We have requested feedback from the CDER Exclusivity Board and we will forward any additional information or preliminary decisions we receive from the Board.

Discussion at Meeting:

No further discussion.

Question 17: Please confirm the timing of NDA review activities under PDUFA V. Specifically Alkermes would like responses to the following:

- a. Does the Agency agree with Alkermes' plan to submit a safety update at Day 120?
- b. Does the Agency expect to convene an Advisory Committee to review aripiprazole lauroxil?

- c. Does the Agency agree with the proposal to submit additional stability data within 30 days of filing the NDA?

At the time of the NDA filing, trials ALK9072-003EXT and ALK9072-EXT2 will be ongoing. Additional exposure and safety data from these trials will be submitted in a 120-Day Safety Update, with a cut-off date 120 days after the NDA safety cut-off date. New safety data will be presented in a cumulative manner, that is, combined with the original NDA data. Data will be summarized in the same manner as in the NDA submission but for trial ALK9072-003EXT2, data will be limited to exposure, SAEs, and adverse events leading to dropout.

FDA Response to Question 17:

- a. *The proposed plan for a 120-Day Safety Update is acceptable with one exception: separate line listings for new deaths, non-fatal SAEs, and adverse events leading to dropout should be provided in addition to the planned data.*
- b. *The decision about a need for an Advisory Committee Meeting will be made during the NDA review process.*
- c. *Your proposal is unclear. We remind you that as per the ICH Q1A(R2) guidance that the long-term testing should cover a minimum of 12 months' duration on at least three primary batches at the time of submission. The proposal to provide additional stability data within 30 days of filing is acceptable.*

Discussion at Meeting:

The applicant clarified that at least 12 months of stability data will be submitted at the time of NDA filing. Additional data will be available within 30 days of filing.

Question 18: Based on FDA's previous findings of safety and efficacy for aripiprazole as well as supportive nonclinical and clinical data from aripiprazole lauroxil, a Risk Evaluation and Mitigation Strategy (REMS) will not be included in the NDA. Does the Agency agree with this plan?

FDA Response to Question 18:

At this time, yes, we agree.

Discussion at Meeting:

No further discussion.

Question 19: Does the Agency agree with the proposed table of contents (TOC) of the NDA for aripiprazole lauroxil?

FDA Response to Question 19:

From a clinical standpoint, the TOC appears to be acceptable.

Discussion at Meeting:

No further discussion.

Additional OCP Comments:

1. *You should provide relative BA information comparing your product with oral aripiprazole.*
2. *You should also provide steady state concentrations of all major moieties for your product for different dose levels.*
3. *Please address the concern for potential dose dumping, especially when the drug product is accidentally injected into blood instead of the muscle. You may address the issue through in vitro approach (e.g., provide comparative solubility data on both aripiprazole lauroxil and aripiprazole in aqueous buffers, blood and/or plasma). In addition, please also look for signs of potential dose dumping using concentration data from finished clinical trials (e.g., unexpected change in concentrations).*
4. *We would like you to conduct additional simulations evaluating the scenario where a patient might be transitioned from Abilify Maintena to Aripiprazole Lauroxil. You can use the population pharmacokinetic model for Abilify Maintena in the FDA review posted online (http://www.accessdata.fda.gov/drugsatfda_docs/nda/2013/202971Orig1s000ClinPharmR.pdf). Steady state plasma concentrations of aripiprazole after administration of Abilify Maintena can be simulated using the model from the FDA review. You can then use the pharmacokinetic model that you are developing for Aripiprazole Lauroxil to evaluate the appropriate transition strategy from Ability Maintena to Aripiprazole Lauroxil. Any differences in concentrations after switching patients from Ability Maintena to Aripiprazole Lauroxil should be justified.*
5. *Please submit a clinical pharmacology summary using the template attached at the time of NDA submission.*

3.0 Discussion of the Content of a Complete Application

- The content of a complete application was discussed. Alkermes indicated their intention to request priority review status for their application based primarily on the possibility of using a longer dosing interval (6 to 8 weeks) with aripiprazole lauroxil compared to other extended-release injectable antipsychotic products, which may lead to improved treatment compliance and, in turn, reduce the occurrence of aggression and hostility in schizophrenic patients. FDA advised the sponsor to include a clear justification for priority status in the application based on criteria described in the relevant Guidance for Industry. Otherwise, the clinical content of the application, as described in the meeting package and with the revisions requested in the FDA Preliminary Comments and during the meeting, were deemed to be acceptable.

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

- A preliminary discussion on the need for a REMS was held and it was concluded that a REMS is not anticipated at this time.

- Major components of the application are expected to be submitted with the original application and are not subject to agreement for late submission. We agreed that the following minor application components may be submitted within 30 calendar days after the submission of the original application: PBPK modeling.

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

NDA NUMBER: LATE COMPONENT - CLINICAL PHARMACOLOGY

3.1 PREA REQUIREMENTS

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

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

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

3.2 PRESCRIBING INFORMATION

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 [CFR 201.56\(a\) and \(d\)](#) and [201.57](#). As you develop your proposed PI, we encourage you to review the labeling review resources on the [PLR Requirements for Prescribing Information](#) website including:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) – a checklist of 42 important format items from labeling regulations and guidances.

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

3.3 505(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)
<i>1. Example: Published literature</i>	<i>Nonclinical toxicology</i>
<i>2. Example: NDA XXXXXX “TRADENAME”</i>	<i>Previous finding of effectiveness for indication X</i>
<i>3. Example: NDA YYYYYY “TRADENAME”</i>	<i>Previous finding of safety for Carcinogenicity, labeling section XXX</i>
<i>4.</i>	

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.

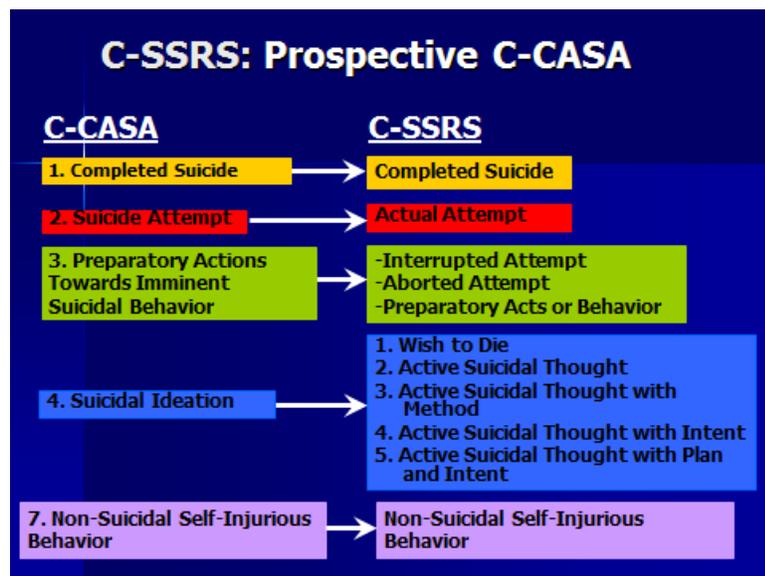
6.0 FDA Requested Data Display of C-CASA Data and Mapping Scheme

Table - Number (Percentage) of Subjects with Suicidal Ideation and/or Suicidal Behavior based on C-SSRS at any Post baseline visit

C-CASA Category	<i>AL 441</i> <i>n/N (%)</i>	<i>AL 882 mg</i> <i>n/N (%)</i>	<i>Placebo</i> <i>n/N (%)</i>
Completed Suicide			
Suicide Attempt			
Preparatory Actions Toward Imminent Suicidal Behavior			
Suicidal Ideation			
Self-Injurious Behavior Without Suicidal Intent			

n= number of subjects with an event

N= number of subjects with at least one post baseline assessment



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

/s/

MITCHELL V Mathis
06/03/2014



IND 107249

MEETING MINUTES

Alkermes, Inc.
Attention: Mark Machado
Manager, Regulatory Affairs
852 Winter Street
Waltham, MA 02451-1420

Dear Mr. Machado:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for ALKS 9072.

We also refer to the meeting between representatives of your firm and the FDA on September 15, 2011. The purpose of the meeting was to further discuss the nonclinical and clinical development plan for ALKS 9072.

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

If you have any questions, call Sharonjit Sagoo, Regulatory Project Manager at (301) 796-0431.

Sincerely,

{See appended electronic signature page}

Thomas Laughren, M.D.
Division Director
Division of Psychiatry Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

ENCLOSURE:
Meeting Minutes



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B
Meeting Category: End of Phase 2

Meeting Date and Time: Thursday, September 15, 2011, 10:00am
Meeting Location: White Oak CDER Building #22, Conference Room 1315

Application Number: 107249
Product Name: ALKS 9072
Indication: Treatment of schizophrenia in adults
Sponsor/Applicant Name: Alkermes

Meeting Chair: Mitchell Mathis, M.D.

FDA ATTENDEES

Mitchell Mathis, M.D.	Deputy Director, Division of Psychiatry Products
Jing Zhang, M.D.	Clinical Team Leader
Gregory Dubitsky, M.D.	Clinical Reviewer
Barry Rosloff, Ph.D.	Pharmacology/Toxicology Supervisor
Aisar Atrakchi, Ph.D.	Pharmacology/Toxicology Team Leader
Elzbieta Chalecka-Franaszek, Ph.D.	Pharmacology/Toxicology Reviewer
Huixia Zhang, Ph.D.	Clinical Pharmacology Reviewer, OCP
Tele Chhagan, Ph.D.	Pharmaceutical Assessment Lead
Peiling Yang, Ph.D.	Statistical Team Leader, OB
Yeh-Fong Chen, Ph.D.	Statistical Reviewer
Sue-Jane Wang, Ph.D.	Associate Director, Office of Biostatistics
Sharonjit Sagoo, Pharm.D.	Regulatory Project Manager

SPONSOR ATTENDEES

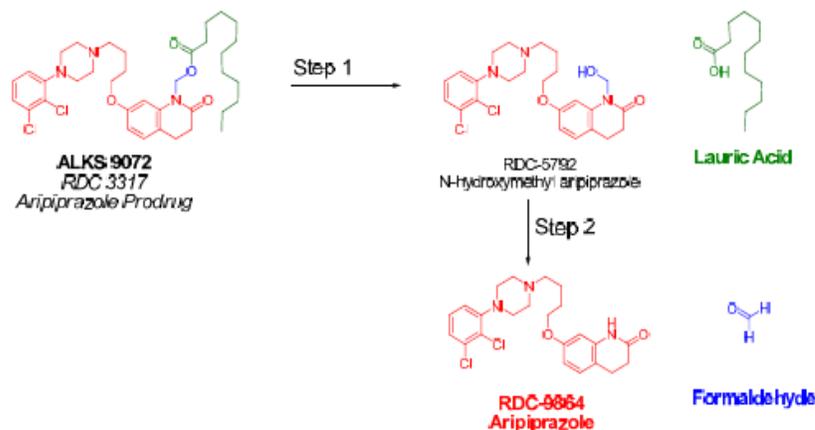
Dennis Bucceri, Ph.D.	VP, Regulatory Affairs
Dan Deaver, Ph.D.	VP, Non-Clinical Development
Lawrence Dahm, Ph.D.	Principal Toxicologist
Örn Almarsson, Ph.D.	VP, Pharmaceutical Research and Development
Elliot Ehrich, M.D.	Sr. VP, Research and Development and Chief Medical Officer
Robert Risinger, M.D.	Senior Medical Director
Marc De Somer, M.D.	VP, Clinical Development and Med Affairs
Ryan Turncliff, Ph.D.	Director, Translational Medicine
Yangchun Du, Ph.D.	Senior Biostatistician
Mark Machado, M.D.	Manager, Regulatory Affairs
Nannette Ciampa, RAC	Senior Regulator Affairs Associate

1.0 BACKGROUND

Introduction

Alkermes is developing ALKS 9072 (RDC-3317) for the treatment of schizophrenia in adults.

ALKS 9072 is an N-lauroyloxymethyl prodrug of aripiprazole for extended-release administered via intramuscular (IM) injection. Conversion of ALKS 9072 to aripiprazole is governed by the following processes, depicted in the figure below: dissolution of the prodrug from the injection site and subsequent enzyme-mediated cleavage, generating lauric acid and an N-hydroxymethyl aripiprazole intermediate (RDC-5792) (Step 1); then, the covalently bonded hydroxymethyl group dissociates, releasing aripiprazole and formaldehyde (Step 2). Aripiprazole is approved for the treatment of schizophrenia in the oral dose range 10-30 mg/day.



The sponsor states that ALKS 9072 may offer advantages over currently available treatments for schizophrenia, such as passive compliance with once-monthly administration, a distinctly favorable tolerability profile, little potential for dose dumping, a gradual rise in plasma levels to minimize intolerance, no requirement for a loading dose, less fluctuation in drug levels at steady state, less potential for injection site reactions, and no need for reconstitution before administration.

ALKS 9072 Development Plan

The sponsor's development plan is summarized in the following table.

Study Number (Phase) ^a	Objective	Dose Levels ^b	No. of Subjects ^c	Status
<i>Studies to be included in NDA submission</i>				
ALK9072-001 (Phase 1)	Safety, Tolerability, Single Ascending-Dose PK	ALKS 9072: 150, 300, 400 mg, or placebo	32 (26 active, 6 placebo)	Completed
ALK9072-002 (Phase 1)	Safety, Tolerability, Multiple Fixed-Dose PK	ALKS 9072: 300, 450, 600 mg, or placebo	96 (target 72 active, 24 placebo)	Planned
ALK9072-003 (Phase 3)	Efficacy, Safety, Tolerability, (treatment of acute exacerbation of schizophrenia symptoms)	ALK 9072: 300, 600 mg, or placebo	540 (target 360 active, 180 placebo)	Planned
ALK9072-005 (Phase 3)	Open Label Safety Extension of Study ALK9072-003	ALKS 9072: 300, 600 mg	TBD	Planned
<i>Study to be submitted after NDA approval</i>				
(b) (4)				

The formulation used in the completed Phase 1 trial (ALK9072-001) contained (b) (4)



At the time of NDA submission, it is anticipated that 140 patients will have received at least 6 monthly injections and 50 patients will have received at least 12 monthly injections of ALKS 9072. Overall, about 500 patients will have received at least one dose of ALKS 9072.

The Briefing Package for this meeting contains a summary of the results of trial ALK9072-001, protocols for trials ALK9072-002 and ALK9072-003, and a Statistical Analysis Plan for trial ALK9072-003.

Regulatory History

On 6 April 2010, a pre-IND meeting was held between Alkermes and the Division of Psychiatry Products (DPP). The objective of the meeting was to reach agreement on the initial development plan for ALKS 9072. We informed the sponsor that the 505(b)(2) pathway, with Abilify Tablets as the Reference Listed Drug, would likely be acceptable for ALKS 9072. We stressed the importance of measuring concentrations of the N-hydroxymethyl intermediate *in vivo* and the potential need to address the safety and pharmacokinetics of this moiety if it remains in the body

for any appreciable length of time. We also indicated that a 12-week efficacy trial would be adequate to support approval for the treatment of schizophrenia. Other topics included the adequacy of the nonclinical safety assessment strategy and a proposed ascending single-dose trial in patients with schizophrenia.

More recently (via email on 01 June 2011), Alkermes received feedback from DPP relative to the prerequisites for, and the timing of, single-dose and multiple-dose pharmacokinetics (PK) data prior to entering Phase 3. The Division agreed that the multiple-dose PK study could be run in parallel with the Phase 3 study under the assumption that full results from the Phase 1 single-dose PK study and modeling of the data be made available to DPP prior to the initiation of the Phase 3 study.

Alkermes requested and was granted a Type B, End of Phase 2 (EoP2), meeting with DPP to be held on September 15, 2011, to further discuss the nonclinical and clinical development plan for ALKS 9072 for the indication of treatment of schizophrenia.

Results of Trial ALK9072-001

The sponsor conducted this randomized, double-blind, placebo-controlled, ascending single dose trial in patients with chronic, stable schizophrenia. Patients were enrolled in three sequential dose cohorts (150mg, 300mg, and 400mg), with a total of 12, 10 and 10 patients, respectively. In each cohort, all patients received oral aripiprazole 10 mg/day on days 1-5. On day 27, patients were randomized in a 4:1 ratio to receive a single IM injection of ALKS 9072 or placebo, followed by an 8-week evaluation of safety, tolerability, and pharmacokinetics. Patients were allowed to continue current medications that were not specifically excluded.

Patients were in the age range of 21-55 years (mean 43 years) and all were Black. All patients who received active drug were CYP2D6 extensive or intermediate metabolizers. After IM administration of ALKS 9072, aripiprazole concentrations increased steadily for 4-8 weeks across all dose cohorts (T_{max} 29-58 days) and declined in a linear fashion through 88 days post-dose (half-life 17-22 days). There was no evidence of early release. Confidence intervals revealed considerable variability but C_{max} and AUC_{∞} values were, on average, dose-proportional. Concentrations of the active metabolite, dehydroaripiprazole, paralleled those of aripiprazole, with exposure (AUC_{last}) approximately 30% of aripiprazole exposure across all doses.

There were no measurable concentrations of the prodrug ALKS 9072 (LLOQ 1 ng/ml). Concentrations of the N-hydroxymethyl intermediate were measured under cold conditions in all 8 patients who received the 400mg dose. (The intermediate was stable at low temperature but this assay methodology has not been validated.) Concentrations were measurable but low in all 8 patients, with a mean C_{max} of 11.2 ± 2.6 ng/ml and a median T_{max} of 33.5 days (range 24-58 days). Mean exposure of the intermediate was 10.4% and 7.5% of aripiprazole on C_{max} and AUC_{last} , respectively. The sponsor asserts that concentrations of the intermediate in the rat and dog provide safety margins of 3.4 and 2.5 for human exposure, respectively.

ALKS 9072 appeared to be well tolerated. There was one serious adverse event (cocaine relapse after a 400mg IM dose) and one adverse event that led to dropout (priapism after oral aripiprazole). Injection site reactions were reported by two patients in the 150mg cohort; both reported mild injection site pain within hours of injection and both resolved within 5 days. Otherwise, the most common adverse events included abdominal discomfort, dyspepsia, vomiting, nasopharyngitis, and headache.

Pharmacokinetic Modeling and Simulation Based on Data from ALK9072-001

A compartmental pharmacokinetic model was constructed to estimate aripiprazole bioavailability at steady state after ALKS 9072 IM injection and to simulate aripiprazole concentrations produced by ALKS 9072 in planned clinical trials. In addition, the model was used to explore strategies for conversion of oral aripiprazole therapy to ALKS 9072 IM treatment. The model was evaluated by using data from the 150mg and 300mg cohorts from study ALK9072-001 to predict concentrations and exposure for the 400mg cohort in that study. This demonstrated that the model was adequate.

Based on model predictions, steady state concentrations of aripiprazole and dehydroaripiprazole will be attained after the fourth monthly injection of ALKS 9072. ALKS 9072 dose levels of 300mg and 600mg are predicted to produce mean steady state aripiprazole concentrations of ~141 ng/ml and 281 ng/ml, respectively, compared to steady state concentrations of ~102 ng/ml and 304 ng/ml following oral aripiprazole doses of 10mg and 30mg, respectively. It is also predicted that 21 days of treatment with oral aripiprazole (15 mg/day) after the first injection will produce aripiprazole concentrations established for oral aripiprazole therapy within two weeks. Aripiprazole relative bioavailability (IM depot versus oral) is expected to be 100%.

Protocol for Trial ALK9072-002

Trial ALK9072-002 will examine the multiple dose pharmacokinetics and safety of ALKS 9072 in patients with chronic stable schizophrenia (age 18-55 years). Patients must have been on a stable antipsychotic drug regimen for at least two months before screening and agree to make no changes in this treatment unless deemed necessary by the investigator. CYP3A4 inducers and inhibitors and CYP2D6 inhibitors will be prohibited.

Patients will receive open-label oral aripiprazole 10mg qAM on an inpatient basis on days 1-5. This will be followed by a 28-day outpatient washout period. Patients will be readmitted on day 33 and remain inpatients through day 47. On day 34, patients will be randomly assigned to one of three treatment groups, with 32 patients in each group: ALKS 9072 300mg, 450mg, or 600mg. Patients will be sequentially assigned to the 300mg group first, then the 450mg group, and finally the 600mg group. Within each dose group, patients will be randomly assigned to IM ALKS 9072 or IM placebo in a 3:1 ratio. Study drug will be administered on days 34, 62, 90, and 118 (every 28 days). Patients will be readmitted to the clinic on day 117 for a 16-day inpatient stay (days 117 through 132). After discharge, they will return to the clinic on days 139, 146, 153, 160, 167, 174, 202, and 230.

Safety assessments will include inspection of the injection site, vital signs (including orthostatic pulse and blood pressure), clinical laboratory tests (including serum prolactin and urine pregnancy testing), 12-lead ECG's, the Extrapyramidal Symptom Rating Scale, and the Columbia-Suicide Severity Rating Scale (except during oral aripiprazole treatment). CYP genotype sampling will be done on day 33. Psychiatric clinical status will be monitored using the PANSS and CGI. Blood samples will be obtained for aripiprazole and metabolite levels during both oral and IM treatment. On day 118 (the final IM dose), samples will be collected one hour predose and 1, 4, 8, and 12 hours post-dose. Then, samples will be obtained once daily on days 119 through 132 and on days 139, 146, 153, 160, 167, 174, 202, and 230.

Protocol for Trial ALK9072-003

Trial ALK9072-003 will be a Phase 3 randomized, double-blind, placebo-controlled study of the safety and efficacy of ALKS 9072 in 540 patients with an acute exacerbation of schizophrenia. It will be conducted at approximately 60 centers in North America, Europe, and Asia and is expected to commence in December 2011. It is expected that 40% of subjects will be from U.S. sites and the remaining 60% will be from sites in Russia, Ukraine, Serbia, India, Malaysia, and the Philippines.

Patients will be in the age range 18-70 years and have a diagnosis of DSM-IV-TR schizophrenia for at least two years, with the acute exacerbation onset less than two months before screening. Inpatients must have been hospitalized for less than two weeks for the current exacerbation. The PANSS total score at screening and baseline must be between 70 and 120, with scores of 4 or greater on at least two of the following four items: delusions, conceptual disorganization, hallucinatory behavior, and suspiciousness/persecution. In addition, the CGI-severity score must be 4 or greater. Currently prescribed antipsychotics will be stopped before administration of study drug. Concomitant medications that are CYP3A4 inducers or inhibitors or CYP2D6 inhibitors will be prohibited.

Patients who have never taken aripiprazole will receive oral aripiprazole 5 mg/day for two days before randomization; patients who have taken and tolerated aripiprazole previously are excluded from this requirement. Patients will be randomized on day 1 in a 1:1:1 ratio to one of three IM treatment groups: placebo, ALKS 9072 300mg, or ALKS 9072 600mg (about 180/group). The injected volumes of the 300mg and 600mg doses are different; therefore, patients randomized to placebo will be further randomized in a 1:1 ratio to high or low volume placebo. IM placebo will contain Intralipid®, a sterile fat emulsion containing peanuts, soy, egg, and glycerol. The first IM dose will be given on day 1 by deep gluteal injection. In addition, patients will receive oral medication for the first three weeks after randomization: patients receiving ALKS 9072 will receive oral aripiprazole tablets 15 mg/day and patients receiving IM placebo will receive matching placebo capsules. Blinding will be maintained by overencapsulation of the aripiprazole tablets. Patients will remain on the inpatient unit for at least 14 days after the first dose. The second IM dose will be given on day 29 and the third and final IM dose will be given on day 57 (28 ±3 days between these doses). It is anticipated that the second and third doses will be administered on an outpatient basis. Double-blind evaluations will continue for four weeks after the last IM dose, with the final treatment period assessment on day 85. Follow-up visits will occur on days 113 and 141.

The primary efficacy endpoint will be the change from baseline to day 85 in the PANSS total score, which will be analyzed by Mixed Model with Repeated Measures (MMRM). Each ALKS 9072 group will be compared to placebo, with the Hommel procedure used to control the Type I error. The key secondary endpoint will be the mean change from baseline to day 85 in the PANSS positive subscale.

One unblinded interim analysis will be done by an independent statistical center on the primary endpoint when 50% of the patients have been randomized to re-estimate the final sample size, to a maximum of 230 patients per arm. The Type I error will be controlled using the CHW method.

Safety assessments will include physical examinations, vital signs, laboratory tests (hematology and chemistry panels and urinalysis), 12-lead ECG's, body weight, abnormal movement scales (AIMS, BARS, and SAS), and injection site evaluations. (b) (4) (b) (4) will be used to monitor suicidal thoughts or behavior during the trial.

A single blood sample for genotyping will be collected on day 1 for P450 enzymes and/or genes related to response or adverse events. Blood samples will be collected on various days throughout the study for determination of concentrations of ALKS 9072 and its metabolites.

2. DISCUSSION

2.1. Questions from the sponsor:

Question 1: To support the multiple fixed-dose pharmacokinetic clinical study (ALK9072-002) and Phase 3 clinical study (ALK9072-003), Alkermes will submit/will have already submitted ALKS 9072 final study reports for in vitro genetic toxicology studies, hERG evaluation, single-dose rat and dog studies with evaluation of safety pharmacology endpoints in dog, and 4-month rat and dog studies with evaluation of safety pharmacology endpoints in dog. Alkermes has initiated DART studies and will submit findings prior to the start of ALK9072-002 and ALK9072-003. Specifically, we plan to submit audited draft reports for the rat fertility, definitive rat embryo fetal development (EFD), and preliminary rabbit EFD studies. Findings from the definitive rabbit EFD study will be submitted subsequent to the IND Amendment.

Does the Agency agree that the nonclinical strategy supports ALK9072-002 and ALK9072-003 clinical studies?

FDA Response to Question 1: *Yes, in general your nonclinical program supports clinical studies ALK9072-002 and ALK9072-003. In addition, if the preliminary rabbit embryo-fetal development study demonstrates relevant drug-related adverse effects, the final or audited draft report of the definitive embryo-fetal development study in rabbit may be needed before initiation of studies ALKS 9072-002 (based on duration) and ALKS 9072-003 (based on number of subjects).*

Discussion at meeting:

No further discussion.

Question 2: Alkermes may elect to enroll subjects from study ALK9072-003 into an open-label safety extension trial (ALK9072-005) in which subjects will receive more than 4 monthly doses of ALKS 9072. To support ALK9072-005, we plan to submit a final audited draft report for the 6-month rat study and an audited interim draft for the 9-month dog study prior to exceeding 4 monthly doses in humans; the dog study report will contain all in-life and toxicokinetic data up to the first necropsy as well as full histopathology from the first necropsy. In addition, final study reports for the rat fertility, rat EFD, preliminary rabbit EFD, and definitive rabbit EFD studies will be submitted in an IND amendment prior to initiating ALK9072-005.

Does the Agency agree with the nonclinical strategy to support ALK9072-005?

FDA Response to Question 2: *Yes, we agree. However, if adverse histopathological changes are observed in the 4-month toxicity studies or in the first necropsy in the 9-month study in dogs, you will need to submit the results from the second necropsy for review prior to exceeding 4 monthly doses in humans.*

Discussion at meeting:

No further discussion.

Question 3: The nonclinical studies to support registration of ALKS 9072 are listed in Table 7. Under 505(b)(2), Alkermes will reference pertinent nonclinical safety studies for oral aripiprazole (Abilify Tablets, NDA 21-436) to support registration.

Does the Agency agree that the nonclinical safety studies outlined for ALKS 9072 support registration?

FDA Response to Question 3: *Yes, in general the studies appear adequate but we will also take into account circulating levels of prodrug and of intermediate in humans, and if they are significant we will look at levels in animals to see if there is adequate coverage, and if not, further studies may be needed. Although the level of ALKS 9072 was below the limit of detection in the first completed human study, levels of the N-hydroxymethyl aripiprazole intermediate were significant (mean total exposure of the intermediate was 10.4 and 7.5% of aripiprazole for C_{max} and AUC_{last} , respectively) following administration of 400 mg ALKS 9072. We note that an increase of the ALKS 9072 dose to 600 mg is planned in clinical trials, your method of N-hydroxymethyl aripiprazole intermediate measurement is not validated, and you plan to administer ALKS 9072 in a new formulation. Therefore, the level of human exposure to the ALKS 9072 and/or intermediate following multiple dose administration can be higher than that measured in the first completed single dose clinical study.*

Additional studies may be also needed if unexpected adverse effects are observed in any of the nonclinical or clinical studies. Carcinogenicity studies may be needed if preneoplastic lesions are seen in the long term toxicology studies.

Discussion at meeting:

Alkermes stated they will validate the method for measurement of the N-hydroxymethyl aripiprazole intermediate across species. Validation process for the rat has been completed and is ongoing in other species.

Question 4: To support the use of (b) (4) % w/v sorbitan monolaurate in planned clinical studies, Alkermes will submit the following nonclinical study reports: (1) final study reports for genetic toxicology studies (bacterial mutagenicity and chromosomal aberration) evaluating sorbitan monolaurate, (2) final study reports for 4-month rat and dog studies (with safety pharmacology endpoints included in the dog evaluation) to address local and systemic tolerability of (b) (4) % w/v and (b) (4) % w/v sorbitan monolaurate and (3) audited draft reports from the rat fertility, rat EFD, and preliminary rabbit EFD studies evaluating developmental and reproductive effects of (b) (4) % w/v sorbitan monolaurate. Audited data tables will be available from the in vivo micronucleus study and will be summarized in the IND amendment.

Does the Agency agree that the nonclinical qualification strategy outlined above supports the use of (b) (4) % w/v sorbitan monolaurate in the ALKS 9072 formulation in ALK9072-002 and ALK9072-003 clinical studies?

FDA Response to Question 4: *No. It may be difficult to assess the toxic potential of sorbitan monolaurate, since most of your nonclinical studies do not employ a control group not containing this compound. Some information on the effects of this compound may be obtained from dose-response data (i.e. you are using 2 dose levels), although in the absence of a concurrent control, any effects at the lower dose (and thus estimation of a safety margin for humans) cannot be conclusively determined. Some reliance may be placed on historical control data, although this is far from optimal. Information from published literature can be considered, but this will be a matter of review. Also, the need for some of these studies may be re-evaluated depending on the amount of the excipient (and its metabolites) circulating in humans after receiving the drug product.*

In addition to studies listed in your question, a HERG channel study is needed. If the preliminary rabbit embryo-fetal development study demonstrates relevant drug-related adverse effects you may need to conduct a definitive embryo-fetal development study in the rabbit with sorbitan monolaurate and submit draft audited or final report before initiation of clinical studies ALKS 9072-002 (based on duration) and ALKS 9072-003 (based on number of subjects) using the new formulation. We also ask that you submit information on the fate of sorbitan monolaurate at the injection site and its systemic exposure, metabolism, and elimination. Additional studies may be needed if unexpected adverse effects are observed in nonclinical or clinical studies. The nonclinical study reports supporting the use sorbitan monolaurate in the ALKS 9072 formulation in clinical trials must be submitted at least 30 days before initiation of clinical studies using this new formulation.

Discussion at meeting:

Alkermes indicated that sorbitan monolaurate (SML) and related fatty acid esters are orally bioavailable, used as food additives, and added to a wide variety of cosmetics. Alkermes also indicated that SML contains sorbitan, an anhydride of a common sugar, sorbitol, esterified to

lauric acid, a naturally occurring fatty acid. SML is part of a larger family of fatty acid conjugates of sorbitan including palmitate, oleate and stearate – known collectively as SPANs. SML has not been administered by the IM route so far, although some family members have been administered parenterally (i.e. sorbitan palmitate). Alkermes described the degradation pathway of SML by fatty acid catabolism and stated they will submit more information on this issue. Moreover, they stated that high endogenous levels of fatty acids are present in human and animal circulation. Therefore, it may be difficult to evaluate changes in circulating levels resulting from metabolism of SML following test article administration. At any rate, the Division indicated that the concern for toxicity will be less if endogenous levels of fatty acids are not significantly increased.

With regard to the lack of a concurrent control group not containing the SML, Alkermes indicated that some parameters were evaluated both pre- and post-treatment. The Division agreed that this, along with assessment of dose-relatedness of effects and historical background data, could be helpful in evaluating the toxicity of SML. The nonclinical information supporting the use of SML in the ALKS 9072 formulation in clinical trials will be submitted at least 30 days before the initiation of these trials.

The Division indicated that the HERG assay for SML was recommended based on applicable guidance documents for evaluation of new excipients. However, if scientific justification for not conducting a HERG assay for SML is provided by Alkermes, the Division will reconsider this recommendation. Alkermes stated that the need for the HERG channel study will be considered later during the development process.

Question 5: Alkermes plans to conduct the studies listed in Table 9 for sorbitan monolaurate prior to registration of ALKS 9072. In addition, Alkermes intends to reference public domain information as indicated in Section 2.1.1.5. This nonclinical qualification strategy is consistent with Guidance for Industry: Nonclinical Studies for the Safety Evaluation of Pharmaceutical Excipients, CDER/CBER (May, 2005).

Does the Agency agree that the nonclinical qualification studies and reference to publically available information for sorbitan monolaurate are sufficient for product registration?

The nonclinical studies to support registration of ALKS 9072 are listed in Table 7. Under 505(b)(2), Alkermes will reference pertinent nonclinical safety studies for oral aripiprazole (Abilify Tablets, NDA 21-436) to support registration.

Does the Agency agree that the nonclinical safety studies outlined for ALKS 9072 support registration?

FDA Response to Question 5: *On face, the listed studies appear to be sufficient. However, refer to Question #4 regarding the problem of lack of control group. Additional studies may be needed based on adverse effects observed in nonclinical and/or clinical studies. For example, carcinogenicity studies may be needed if preneoplastic lesions are seen in the long term toxicology studies.*

We ask that you to submit the publically available information for sorbitan monolaurate that you reference. Whether this information is sufficient to support product registration will be a matter for review.

Discussion at meeting:

No further discussion.

Question 6: It is anticipated that in studies ALK9072-001, ALK9072-002, ALK9072-003 and ALK9072-005 approximately 500 subjects will have received at least 1 dose of ALKS 9072, 240 will have received at least 3 monthly doses, 140 will have received at least 6 monthly doses, and 50 subjects will have received at least 12 monthly doses by the time of the NDA submission. In addition, the NDA under 505(b)(2) regulations will reference human safety experience with oral aripiprazole. The sponsor will provide additional human safety experience with patient exposure at the time of the 120 day NDA update.

Does the Agency agree that studies ALK9072-001, ALK9072-002, ALK9072-003 and ALK9072-005 together with referenced safety exposure with oral aripiprazole provide sufficient safety exposure to support NDA approval?

FDA Response to Question 6: *Assuming that the steady state concentrations of aripiprazole and dehydroaripiprazole after ALKS 9072 administration are within the ranges observed with the recommended maximum dose of oral aripiprazole (30 mg/day), we agree.*

Discussion at meeting:

No further discussion.

Question 7: The pharmacokinetic information obtained from the single-dose (ALK9072-001), multiple fixed-dose (ALK9072-002), and Phase 3 (ALK9072-003) studies will provide the clinical pharmacology information for ALKS 9072. PK modeling and simulation will be used to characterize the dose-exposure-response and will provide information on IM ALKS 9072 for labeling. The NDA will also reference clinical pharmacology studies performed with oral aripiprazole per 505(b)(2) regulations.

Does the Agency agree that Alkermes has satisfied the clinical pharmacology requirements for NDA approval?

FDA Response to Question 7: *You have single-dose PK information for oral aripiprazole and IM formulation from study ALK9072-001. You also plan to have sparse sampling from study ALK9072-003. Given that you already have a PK model developed, you can integrate the information collected from study ALK9072-003 to estimate the multiple-dose PK and characterize the dose/exposure-response relationship. Hence, we are unclear as to the additional information study ALK9072-002 will provide. We recognize that we suggested that you can conduct a separate multiple-dose study in parallel with the Phase 3 trial in our previous communication. However, we did not have the PK data from the 001 study and the modeling results at that point.*

Based on the structure, the prodrug is likely catalyzed by esterase to form the intermediate. We recommend that you characterize the conversion process, which may be important in determining the need for certain experiments or studies (eg: in-vitro drug-drug interaction).

Discussion at meeting:

No further discussion.

Question 8: The NDA will include data from a Phase 3 12-week efficacy study (ALK9072-003), and its long-term open-label safety extension study (ALK9072-005). The NDA will also reference the efficacy of oral aripiprazole per 505(b)(2) regulations.

Does the Agency agree that studies ALK9072-003 and ALK9072-005 together with referenced data for oral aripiprazole provide sufficient efficacy data to support NDA approval?

FDA Response to Question 8: *These data, on face, have the potential to meet the efficacy requirements for a 505(b)(2) submission. Whether the results will support an approval action will be a matter for review.*

Discussion at meeting:

No further discussion.

Question 9: Study ALK9072-003 is a multinational, multicenter, randomized, double-blind, placebo-controlled study designed to evaluate ALKS 9072 in subjects with schizophrenia experiencing an acute exacerbation of schizophrenia symptoms.

Does the Agency agree with the design of the Phase 3 study in subjects experiencing an acute exacerbation of schizophrenia symptoms (ALK9072-003)?

- a. Does the Agency agree with the oral and IM dosing, including oral test doses, oral lead-in and regimen to convert from oral to IM dosing with ALKS 9072?
- b. Does the Agency agree with the primary endpoint of change in total Positive and Negative Syndrome Score (PANSS) score, including the interim analysis for sample size re-estimation, analysis model (Mixed Multiple Regression Model [MMRM]), and Type-1 error control? Would the Agency alternatively accept the LOCF method of imputation instead of MMRM?
- c. Does the Agency agree with the secondary endpoints selected?
- d. Does the Agency agree with the pharmacokinetic sampling scheme and timing per protocol?
- e. Does the Agency agree with plans that approximately 40% of enrolled subjects be from US sites with the remaining 60% being from study sites in Russia, Ukraine, Serbia, India, Malaysia, and Philippines

FDA Response to Question 9: *We have the following comments regarding the design of trial ALK9072-003.*

1) *Given your plan to include a 3 week period of oral aripiprazole treatment after the first ALKS 9072 injection in the active treatment arms, we note that, should a subsequent application meet the standards for approval, the labeling would specify the need for such oral dosing as part of the instructions for use.*

2) *In addition, we request that the plasma concentration of the N-hydroxymethyl intermediate be determined at steady-state and that formaldehyde levels be measured at baseline and at steady-state in trial ALK9072-003 in addition to the concentrations of ALKS 9072 and its metabolites, as planned. This will require the development of a reliable assay for the intermediate by the time this trial is initiated.*

3) *Also, we recommend that trial ALK9072-003 use the Columbia-Suicide Severity Rating Scale (C-SSRS) to assess suicidal ideation and behavior during the trial.* (b) (4)

(b) (4)

Our responses to your other questions are as follows.

a. Based on the simulation results, 600 mg IM appears to give a mean steady-state concentration similar to a 30 mg oral daily dose. We agree that studying a lower IM dose of 300 mg is prudent.

b. The mean change from baseline to day 85 in the PANSS total score is acceptable as the primary efficacy endpoint.

You plan to conduct an unblinded interim analysis to re-estimate the final sample size based on the conditional power. Since the treatment efficacy will be assessed at the same time, you should allot a small portion of alpha for this interim look whether or not you plan to stop the trial for efficacy. By doing so, you would have a pre-specified criterion to make a decision in case DSMB strongly recommends early trial termination for efficacy, although we do not encourage early termination for efficacy in short-term trials such as this.

Your sample size estimation has already incorporated the expected overall dropout rate of 50%, which leads to 180 randomized patients per treatment arm. You also have a plan for possible sample size increase based on the interim data. Please note that when the sample size is increased greatly, it might lead to a significant p-value ($p < 0.05$, two sided) with a very small magnitude of treatment effect. In such a case, whether the observed treatment effect is clinically meaningful and acceptable will be a matter of review.

Since the dropout rate for a schizophrenia trial is not negligible, you should make every effort by design to reduce the dropout rate and pre-specify sensible sensitivity analyses to deal with the situation when the missing-data mechanism is not "missing at random". Please refer to the recent publication "The prevention and treatment of missing data in clinical trials" by the National Academies. We also encourage you to perform simulation studies to explore the impact

of differential dropouts (including the scenario you assumed for this trial) versus non-differential dropouts on the operating characteristics of the proposed MMRM analysis.

In addition to the detailed standard operating procedures in your DSMB charter, we also expect that you clearly address the trial logistics to ensure the trial integrity; for example, how will the analysis results of the unblinded sample size re-estimation be communicated internally or externally?

Regarding the proposed MMRM analysis, please pre-specify the region that you plan to include in the model (for example, what region category Russia would be assigned to). As for the LOCF imputation method, it requires a very strong assumption for the missing-data mechanism, so we discourage it from being used as the primary analysis unless you can justify its suitability in your case.

c. The PANSS positive subscale is not acceptable as the key secondary endpoint because it is subsumed by the primary efficacy endpoint, the PANSS total score. The CGI-improvement scale or the Sheehan Disability Scale would be acceptable as a key secondary endpoint.

d. Yes, we agree.

e. We do not object to the planned site locations, with only 40% of patients from U.S. sites. Please perform sensitivity analyses to examine the primary and key secondary efficacy endpoint results in the pool of U.S. sites.

Discussion at meeting:

3) (b) (4)

We currently recommend the C-SSRS. Nonetheless, the sponsor was invited to submit data that would justify the use of the (b) (4). We cautioned, however, that if they elect to use the (b) (4) and we do not accept this scale, a blinded coding of possible suicidal ideation and behavior data by experts may be necessary.

b) Alkermes shares our view on the dropout rates and responded by email in the following 4 bullets prior to the meeting:

- *Upon further review of the MMRM literature, we discovered that most of the simulation work has been done in the context of discontinuation rates in the range of 10 to 45%.*
- *However, expected discontinuation rates in placebo controlled trials of acute exacerbation of schizophrenia (especially trials of 12 weeks in duration) are usually*

greater than 50% and often as high as 70%. Therefore, Alkermes has performed more extensive simulations of MMRM and ANCOVA.LOCF under the typical conditions of acute placebo-controlled schizophrenia studies, in particular with 50% or more discontinuations, of which 30% or more are informative missing values. Under these conditions, we observed that the MMRM model performs less well than ANCOVA.LOCF in terms of accuracy, precision, power and type I error control.

- *ANCOVA/LOCF appears to be more reliable and predictable in preserving the accuracy of effect estimates as well as Type 1 error in comparison with MMRM under the circumstances expected in our proposed Phase 3 study.*
- *Alkermes would respectfully request that we submit our full simulation code and report to the Agency, followed by discussion on the specific topic of the most appropriate statistical analysis method for the ALK9072-003 trial.*

At the meeting, Alkermes clarified that they had conducted extensive simulations, assuming differential dropouts under different missing-data mechanisms and using different statistical analysis methods (such as LOCF ANCOVA, MMRM, MI, Pattern Mixture, WGEE). We agreed to review their results as well as the simulation codes before further discussion on the specific topic of the primary analysis.

Question 10: Alkermes regards the extended-release N-lauroyloxymethyl prodrug of aripiprazole, with an anticipated once-monthly dosing schedule, as offering significant advantages to patients with schizophrenia relative to currently available treatment options. These advantages as described in Section 1.1.1. As such, ALKS 9072 should be appropriate for Priority Review Designation.

Does the Agency have any comments regarding ALKS 9072 qualifying for Priority Review?

FDA Response to Question 10: *Currently available data do not demonstrate a clinically significant advantage of ALKS 9072 over marketed IM depot products. Unless such an advantage can be shown, it is unlikely that we would grant Priority Review Designation.*

Discussion at meeting:
No further discussion.

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/s/

THOMAS P LAUGHREN
09/29/2011



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

Sponsor Name:	ALKERMES, INC.
Application Number:	IND 107,249
Product Name:	ALKS 9072
Meeting Type:	Type B
Meeting Category:	Chemistry, Manufacturing, and Controls Meeting
Meeting Date and Time:	September 12, 2011; 3:00-4:00 p.m.
Meeting Location:	Food and Drug Administration White Oak Campus, Bldg 21 Rm. 1539, Silver Spring, MD
Briefing Package Dated	August 9, 2011

The following consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the meeting scheduled September 12, 2011, 3:00 – 4:00 p.m. ET, at the Food and Drug Administration, White Oak Campus, Silver Spring, MD between Alkermes, Inc. and the Center for Drug Evaluation and Research/Office of New Drug Quality Assessment. This material is shared to promote a collaborative and successful discussion at the meeting. The minutes of the meeting will reflect agreements, key issues, and any action items discussed during the formal meeting and may not be identical to these preliminary comments. If these answers and comments are clear to you and you determine that further discussion is not required, you have the option of canceling the meeting (contact Teshara G. Bouie, Regulatory Health Project Manager for Quality, (301) 796-1649). It is important to remember that some meetings, particularly milestone meetings, are valuable even if the premeeting communications are considered sufficient to answer the questions. **Please note that if there are any major changes to the questions (based on our responses herein), we may not be prepared to discuss or reach agreement on such changes at the meeting.** If any modifications to the development plan or additional questions for which you would like FDA feedback arise prior to the meeting, contact the Regulatory Health Project Manager for Quality to discuss the possibility of including these for discussion at the meeting.

Question 1:

As described in Section 6.3.4.2, drug substance is manufactured (b) (4)
(b) (4) is commercially available and is produced under
current Good Manufacturing Practice (cGMP) conditions. As part of the drug substance control
strategy Alkermes has assigned (b) (4)
Does the Agency agree (b) (4)
?

FDA Preliminary Response:

The agency does not agree (b) (4) You need to provide all relevant CMC information (b) (4) As provided in this briefing package, we recommend that you include a reference to a DMF which contains the relevant CMC information along with a letter of reference authorizing the Agency to review this DMF in support of their NDA.

Question 2:

The proposed drug substance control strategy, including specifications and test methods, is provided in Section 6.3.6, Section 6.3.6.2 and Section 6.5.2 and is designed in accordance with well established ICH guidance procedures to address all necessary attributes of the drug substance. Does the Agency agree with the proposed drug substance control strategy?

FDA Preliminary Response:

The proposed attributes for the drug substance specification are not acceptable as they do not provide adequate control of the drug substance. In addition to the tests included in this submission, the drug substance specification should include tests and acceptance criteria for water and heavy metals. Moreover, while the acceptability of the proposed acceptance criteria is a review issue and will be determined at the time of NDA submission, we note that the proposed acceptance criterion for the individual impurities is (b) (4) % which is not consistent with ICH Q3A. Finally, you reference the Ph. Eu. for most test. This is acceptable only if the Ph. Eu. tests are equivalent to or better than the USP tests. The sponsor should include the Ph. Eu. monographs in the NDA submission.

Question 3:

As provided in Section 6.4.3, Alkermes plans to scale-up (b) (4)

All scale-up and manufacturing activities are expected to occur at the same Alkermes' manufacturing site. Alkermes intends to use physical and chemical attributes, manufacturing process controls and in vitro drug release testing to demonstrate comparability of different scales, without further clinical characterization. Does the Agency agree with our plans for scale-up of the ALKS 9072 drug product manufacturing process?

FDA Preliminary Response:

Your proposal

(b) (4)

is acceptable.

However, your proposal to scale up to greater than (b) (4) post approval is not acceptable and will require the appropriate regulatory submission.

Question 4:

The proposed drug product control strategy, including specifications and test methods is provided in Section 6.4.4 and addresses all quality attributes of the drug product. Does the Agency agree with the proposed drug product control strategy?

FDA Preliminary Response:

Your proposed identification acceptance criterion for drug product specification is determined using an HPLC method. Identification solely by retention time is not regarded as being specific (refer ICH Q6A: Test procedures and acceptance Criteria for New Drug Substances and Drug Products). Include a specific identification test (e.g., Infrared spectroscopy) as part of the drug product specification. Your control strategy should include a test and acceptance criterion for particulate matter and a three-point particle size specification. All other tests are acceptable and the acceptability of the acceptance criteria is a review issue.

Question 5:

The proposed drug substance stability program, as provided in Section 6.5.2, is designed to address all necessary attributes to establish room temperature storage condition for an appropriate retest period, the length of which will be based on stability data. Does the Agency agree with the proposed drug substance stability proposal for NDA approval?

FDA Preliminary Response:

Drug substance stability plan appears to be acceptable.

Question 6:

The drug product registration stability proposal outlined in Section 6.5.3 is designed to address all necessary product attributes and is intended to establish room temperature storage condition for an appropriate expiry period which will be based on the stability data. Does the Agency agree with our drug product registration stability proposal for NDA approval?

FDA Preliminary Response:

The proposed stability plan is not acceptable. You should include a bracket (b) (4) as this is a representation of the possible best and worst case scenarios (see ICH Q1D).

Question 7:

As described in Section 6.5.4, in addition to the registration stability studies, Alkermes plans to conduct the following stability studies to justify a hold time of up to (b) (4) months for bulk

(b) (4) drug substance and provide justification for starting the drug product expiration dating period (b) (4)

- a) A (b) (4) bulk stability study with three lots stored for up to (b) (4) months at (b) (4) °C, and
- b) A drug product stability study (b) (4)

Does the Agency agree that the design of the proposed stability studies supports the start of the expiration period (b) (4)?

FDA Preliminary Response:

We agree that the design of the proposed stability studies support the start of the expiration period (b) (4) however, the sponsor should be advised that the reviewer will consider the data (b) (4) as the primary stability data.

Additional Biopharmaceutics Comments

In Vitro Drug Release Test:

Please provide the report for the proposed in vitro drug release test. This report should include the complete data that were collected during the development and validation of the proposed drug release method. A detailed description of the selected in vitro drug release methodology and the developmental parameters (i.e., solubility data for the drug substance, selection of the equipment/apparatus, in vitro release media, agitation/rotation speed, pH, assay, sink conditions, etc.) that were used to identify this method as most appropriate should be included in the report. The drug release profile should be complete and cover at least (b) (4)% of drug release or whenever a plateau (i.e., no increase over 3 consecutive time-points) is reached. We recommend using at least twelve samples per testing variable. The drug release data (individual, mean, SD, profiles) should be reported as the cumulative percentage of drug being released with time (the percentage is based on the product's label claim). The testing conditions used for each test should be clearly specified. Also, include the testing conducted to demonstrate the discriminating capability of the selected test as well as the validation data for the test method (i.e., method robustness, etc.) and analytical method (precision, accuracy, linearity, stability, etc.). The chosen method should be discriminating and sensitive enough to reject lots that would have less than acceptable clinical performance.

In Vitro Drug Release Acceptance Criteria:

We recommend that you collect complete drug release profile data from the bio-batches and primary (registration) stability batches of your product. These data will be used for the setting of the in vitro drug release acceptance criteria of your product (i.e., specification-sampling time point and specification values). For the setting of these criteria, the following points should be considered:

- The in vitro drug release profile should encompass the timeframe over which at least $(b)_{(4)}$ % of the drug is released or where the plateau of drug released is reached if incomplete release is occurring.
- Data from the lots used in the clinical trials and primary stability studies should be used.
- For extended release products the establishment of at least three specification time-points covering the initial, middle, and terminal phases of the complete drug release profile data should be set. The acceptance criteria ranges should be based on the overall release data generated at these times.
- In general, the selection of the specification ranges is based on mean target value $\pm (b)_{(4)}$ % and NLT $(b)_{(4)}$ % for the last specification time-point.
- The drug release acceptance criteria should be set in a way to ensure consistent performance from lot to lot and these criteria should not allow the release of any lots with release profiles outside those that were tested clinically.

{See appended electronic signature page}

Teshara G. Bouie
Regulatory Health Project Manager
Division of New Drug Quality Assessment I
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

{See appended electronic signature page}

Ramesh Sood, Ph.D.
Branch Chief
Branch I, Division of New Drug Quality Assessment I
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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/s/

TESHARA G BOUIE
09/09/2011

RAMESH K SOOD
09/09/2011

LATE-CYCLE COMMUNICATION
DOCUMENTS



NDA 207533

LATE-CYCLE MEETING MINUTES

Alkermes, Inc.
Attention: Ann Kurowski, M.S.
Associate Director, Regulatory Affairs
852 Winter Street
Waltham, MA 02451-2417

Dear Ms. Kurowski:

Please refer to your New Drug Application (NDA) dated August 22, 2014, submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for ARISTADA (aripiprazole lauroxil) extended release injectable suspension 441 mg, 662 mg, and 882 mg.

We also refer to the Late-Cycle Meeting (LCM) between representatives of your firm and the FDA on June 1, 2015.

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

If you have any questions, call Sharonjit Sagoo, Pharm.D., Regulatory Project Manager at (301) 796-0431.

Sincerely,

{See appended electronic signature page}

Mitchell V. Mathis, M.D.
CAPT, USPHS
Director
Division of Psychiatry Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure:
Late Cycle Meeting Minutes



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF LATE-CYCLE MEETING MINUTES

Meeting Date and Time: June 1, 2015 at 2:00PM – 3:30PM EST
Meeting Location: Teleconference

Application Number: 207533
Product Name: ARISTADA (aripiprazole lauroxil)
Applicant Name: Alkermes

FDA ATTENDEES

Mitchell Mathis, M.D.	Director, Division of Psychiatry Products (DPP)
Tiffany Farchione, M.D.	Deputy Director, DPP
Lucas Kempf, M.D.	Clinical Team Leader, DPP
Hao Zhu, Ph.D.	Clinical Pharmacology Team Leader, Office of Clinical Pharmacology (OCP)
Praveen Balimane, Ph.D.	Clinical Pharmacology Reviewer, OCP
Kevin Krudys, Ph.D.	Pharmacometrics Team Leader, OCP
Xiaofeng Wang, Ph.D.	Pharmacometrics Reviewer, OCP
Jeffrey Kraft, Ph.D.	Pharmacogenomics Reviewer, OCP
Amy Avila, Ph.D.	Pharmacology/Toxicology Reviewer, DPP
Aisar Atrakchi, Ph.D.	Pharmacology/Toxicology Supervisor, DPP
Jinglin Zhong, Ph.D.	Biometrics Reviewer
Peiling Yang, Ph.D.	Biometrics Team Leader
Wendy Wilson-Lee, Ph.D.	Branch Chief, Office of Pharmaceutical Quality
Ryan McGowan	Biomedical Engineer, Office of Device Evaluation, Center for Devices and Radiological Health
Juliette Toure, Pharm.D, R.A.C.	Associate Director of Labeling, DPP
Loretta Holmes, BSN, Pharm.D.	Reviewer, Division of Medication Error Prevention and Analysis (DMEPA)
Danny Gonzalez	Risk Management Analyst, Division of Risk Management
Martin Kwok, Pharm.D.	FDA Fellow,
Sharonjit Sagoo, Pharm.D.	Regulatory Project Manager

EASTERN RESEARCH GROUP ATTENDEES

Marc Goldstein, Independent Assessor

APPLICANT ATTENDEES

Elliot Ehrich, M.D.	Exec. VP, Research and Development and Chief Medical Officer
Srdjan Stankovic, M.D.	Sr. VP, Clinical Development and Medical Affairs
Georgianna Harris, Ph.D.	VP, Regulatory Affairs
Bernard Silverman, M.D.	VP, Clinical Science and Drug Safety
Paul Herbert, M. Eng.	VP, Process Development

Michael Palmieri, Ph.D.	Senior Director, Analytical Development
John Lally	Senior Director, Regulatory Affairs CMC
Magali Hickey, Ph.D.	Director, Formulation Development
Marjie Hard, Ph.D.	Associate Director, Translational Medicine
Ann Kurowski, M.S.	Director, Regulatory Affairs

1.0 BACKGROUND

NDA 207533 was submitted on August 22, 2014 for ARISTADA (aripiprazole lauroxil) extended-release injectable suspension.

Proposed indication: Schizophrenia

PDUFA goal date: August 22, 2015

FDA issued a Background Package in preparation for this meeting on May 14, 2015.

2.0 DISCUSSION

1. Introductory Comments

Welcome, Introductions, Ground rules, Objectives of the meeting

Discussion:

The conference call began at 2:05PM EST with:

- 1) *Welcome*
- 2) *Background information on application and meeting (NDA #; time allotted for meeting; purpose of LCM)*
- 3) *Materials referenced for meeting (LCM briefing document; DR letter; package insert labeling provided via email on 5/29/2015)*
- 4) *Introductions of attendees from FDA, Eastern Research Group, and Alkermes.*

2. Discussion of Substantive Review Issues

Product Quality

- (b) (4) drug substance bulk hold time
- Drug product shelf life, post-approval stability commitment, and photostability
- Drug product performance (b) (4)
- Proposed drug product dissolution acceptance criteria
- Proposed (b) (4) and proposed (b) (4) for drug product
- Drug product executed batch records
- Updated SPL data elements for package description

Discussion:

Alkermes responded to the quality discipline review letter dated April 29, 2015, in an amendment dated May 15, 2015. A preliminary review of the amendment found the responses adequate. The Division noted that the proposed bulk hold time for the (b) (4) drug substance and the need for a control for initial in vitro release were still under review. Alkermes provided additional justification for the proposed bulk hold time, (b) (4). The Division indicated that they would consider this circumstance when evaluating the bulk hold time proposal.

3. Additional Applicant Data

Alkermes asked for further clarification on the following items:

- 1) Are there any other issues we should plan for or address that would affect the timing of final approval of the ARISTADA NDA or the contents of our final labeling (e.g., unexpired exclusivity periods)?
- 2) On 27 March 2015, Alkermes responded to an Agency Email request for information dated 25 March 2015 (see attached) and asked the questions listed below. We have not received responses and would like to follow-up on these items at the Late Cycle Meeting.
 - a. In the NDA (section 3.2.S.3.2.) and in the March 6th response, Alkermes provided data for (b) (4) for the drug product and not drug substance. All results were less than (b) (4) ppm. As such, Alkermes proposed not to test for (b) (4) in either drug product or drug substance. Could the agency clarify that demonstrating the absence of (b) (4) in the drug product is not acceptable and requires a drug substance test and criterion?
 - b. We would like to clarify that we need to complete validation of the (b) (4) assay before we can include the updated specification, with a (b) (4) % limit, in the submission. We are therefore proposing to submit the updated specification via a CBE-0 post-approval. We will subsequently submit a tightened specification, via an annual report, after we have received and tested six (b) (4) batches.

Discussion:

- 1) *The Division stated that at this time, there are no issues we are aware of that would impact the timing of final approval.*
- 2) *a. The Division stated that a test and acceptance criterion for (b) (4) was not needed in the drug substance or drug product based on the data provided. The Division asked Alkermes to clarify if any future formulation or process changes would include an evaluation of the impact of the change on (b) (4) content in the drug substance and drug product. Alkermes indicated that any future formulation or process changes would include this evaluation.*
b. The Division indicated that the proposal to submit the updated specification and method validation information for (b) (4) assay as a CBE-30

supplement post-approval would need to be evaluated. Alkermes indicated that the method validation was near completion and that the information could be provided during the review cycle. The Division agreed to review the information during this review cycle if received by July 2015. Alkermes committed to submitting the method validation and updated specification as requested.

4. Information Requests

The following Information Request was issued 5/8/2015:

Center for Devices and Radiological Health

We acknowledge your commitment to continue performing on-going stability analysis to assess the mechanical reliability of the fully assembled device through the expiration date of the drug product using primary registration stability batches (Amendment 0015, submitted April 1, 2015). We would also like your commitment to submit evidence of completion of these activities to NDA annual reports.

Discussion:

We acknowledged the sponsor's acceptance of this commitment to submit evidence of completion of on-going stability analysis to NDA annual reports in an amendment dated May 15, 2015.

5. Major Labeling Issues

We will discuss the FDA draft labeling changes.

Alkermes requested clarification regarding the following FDA labeling revisions:

- 1) Addition [REDACTED] (b) (4) to the indication statement,
- 2) Removal [REDACTED] (b) (4) from the [REDACTED] (b) (4) Section,
- 3) Removal of language [REDACTED] (b) (4) and
- 4) Addition of dyslipidemia and weight gain to the Metabolic Changes Patient Counseling Section.

Discussion:

- 1) *The Division stated that, under the current labeling regulations, the indication statement should clarify [REDACTED] (b) (4). At this time, the Division will accept the sponsor's proposal [REDACTED] (b) (4).*

- 2) [REDACTED] (b) (4)

[REDACTED] (b) (4)
Your
[REDACTED] (b) (4)
proposed warning describes

- 3) *Per the Guidance for Industry: Dosage and Administration Section of Labeling for Human Prescription Drug and Biological Products – Content and Format, this section should provide information that is known and relevant to the safe and effective dosing and administration of the drug.* [REDACTED] (b) (4)

- 4) *The Agency explained that we have been removing clinically uninformative information from labeling; mean change from baseline data for metabolic parameters is considered uninformative. Quantifying the percent of the studied population that shifted to a clinically relevant state in the controlled trials is more informative.*

The Agency also stated that information a health care provider should convey to the patient or caregiver during a counseling session is required in Section 17, Patient Counseling. Section 17 generally includes major risks of the drug and how a person can mitigate or manage them. The language requested by the Agency is consistent with other antipsychotic labeling.

The sponsor stated that they understood and agreed with the above rationales.

6. Review Plans

We plan to complete our review and take action by the August 22, 2015 PDUFA goal date.

Discussion:

The Division reiterated our intent to review and take action on this application as scheduled. We indicated that we would inform Alkermes of any new information requests or review issues if they arise.

7. Wrap-up and Action Items

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

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/s/

TIFFANY R FARCHIONE
06/29/2015
On behalf of Mitchell Mathis, MD



NDA 207533

**LATE CYCLE MEETING
BACKGROUND PACKAGE**

Alkermes, Inc.
Attention: Ann Kurowski, M.S.
Associate Director, Regulatory Affairs
852 Winter Street
Waltham, MA 02451-2417

Dear Ms. Kurowski:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Aristada (aripiprazole lauroxil) extended release injectable suspension 441 mg, 662 mg, and 882 mg.

We also refer to the Late-Cycle Meeting (LCM) scheduled for May 21, 2015. Attached is our background package, including our agenda, for this meeting.

If you have any questions, call Sharonjit Sagoo, Pharm.D., Regulatory Project Manager, at (301) 796-0431.

Sincerely,

{See appended electronic signature page}

Mitchell V. Mathis, M.D.
CAPT, USPHS
Director
Division of Psychiatry Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

ENCLOSURE:
Late-Cycle Meeting Background Package

LATE-CYCLE MEETING BACKGROUND PACKAGE

Meeting Date and Time: June 1, 2015 at 2:00PM – 3:30PM EST
Meeting Location: White Oak, Building 22, Conference Room 1415

Application Number: NDA 207533
Product Name: Aristada (aripiprazole lauroxil)
Indication: Schizophrenia
Sponsor/Applicant Name: Alkermes

INTRODUCTION

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

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

BRIEF MEMORANDUM OF SUBSTANTIVE REVIEW ISSUES IDENTIFIED TO DATE

1. Discipline Review Letters

In addition to the contents of this background document, please refer to the following Discipline Review letters already provided to you:

Office of Pharmaceutical Quality – April 29, 2015

- Alkermes to respond by COB May 15, 2015

2. Substantive Review Issues

The following substantive review issues, communicated in the product quality discipline review letter (April 29, 2015), have been identified to date:

- The proposed (b) (4) drug substance bulk hold time is not supported by the data provided in the NDA submission.
- The proposed drug product shelf life is not supported by the data provided in the NDA submission.
- Additional executed batch records for drug product batches used to conduct the primary stability study are required.
- The proposed drug product dissolution acceptance criteria are not acceptable.
- Additional clarification on the (b) (4) and (b) (4) proposed as part of the drug product control strategy is required.
- Evidence of acceptable product performance in cases where (b) (4)
(b) (4)
- Additional information regarding drug product photostability is required.
- The proposed post-approval stability commitment for the drug product is not acceptable.
- Updates to the SPL data elements for package description are needed to identify the product as a pre-filled syringe.

ADVISORY COMMITTEE MEETING

An Advisory Committee meeting is not planned.

REMS OR OTHER RISK MANAGEMENT ACTIONS

No issues related to risk management have been identified to date.

LCM AGENDA

1. Introductory Comments – 4 minutes (RPM/CDTL)

Welcome, Introductions, Ground rules, Objectives of the meeting

2. Discussion of Substantive Review Issues – 50 minutes

Each issue will be introduced by FDA and followed by a discussion.

Product Quality

- (b) (4) drug substance bulk hold time
- Drug product shelf life, post-approval stability commitment, and photostability
- Drug product performance – (b) (4)
- Proposed drug product dissolution acceptance criteria
- Proposed (b) (4) and proposed (b) (4) for drug product
- Drug product executed batch records
- Updated SPL data elements for package description

3. Additional Applicant Data – 15 minutes (Applicant)

4. Information Request – 1 minute

The following Information Request is pending as of 5/8/2015:

Center for Devices and Radiological Health

We acknowledge your commitment to continue performing on-going stability analysis to assess the mechanical reliability of the fully assembled device through the expiration date of the drug product using primary registration stability batches (Amendment 0015, submitted April 1, 2015). We would also like your commitment to submit evidence of completion of these activities to NDA annual reports.

5. Major labeling issues – 15 minutes

We will discuss the FDA draft labeling changes.

6. Review Plans – 1 minute

We plan to complete our review and take action by the August 22, 2015 PDUFA goal date.

7. Wrap-up and Action Items – 4 minutes

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/s/

MITCHELL V Mathis
05/14/2015