

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**206038Orig1s000**

**ADMINISTRATIVE and CORRESPONDENCE  
DOCUMENTS**

## EXCLUSIVITY SUMMARY

NDA # 206038

SUPPL #

HFD #

Trade Name Orkambi

Generic Name lumacaftor/ivacaftor

Applicant Name Vertex Pharmaceuticals

Approval Date, If Known July 02, 2015

### **PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?**

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

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

YES  NO

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

505(b)1

c) 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:

d) Did the applicant request exclusivity?

YES  NO

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

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

YES  NO

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

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

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

YES  NO

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

## **PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES**

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

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

YES  NO

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

NDA#

NDA#

NDA#

2. Combination product.

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

YES  NO

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

NDA# 203188 ivacaftor

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.

*Orkambi (NDA 206038) contains lumacaftor, a new chemical entity, in combination with ivacaftor, a previously approved active moiety. Under the Agency's new interpretation of NCE exclusivity for certain fixed-combination drug products described in the Agency's Guidance for Industry, "New Chemical Entity Exclusivity for Certain Fixed-Combination Drug Products" (October 2014), a drug substance is eligible for 5-year exclusivity, provided it meets the regulatory definition of new chemical entity, regardless of whether that drug substance is approved in a single-ingredient drug product or in a fixed-combination with another drug substance that contains no previously approved active moiety, or in a fixed-combination with another drug substance that contains a previously approved active moiety. This NDA is thus eligible for 5-year new chemical entity exclusivity pursuant to the new interpretation.*

**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:

Trial 809-103  
Trial 809-104  
Trial 770-104

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

Investigation #3 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:

Trial 770-104 (Investigation #3 used to support NDA 203188.

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 checked="" type="checkbox"/>
Investigation #2	YES <input type="checkbox"/>	NO <input checked="" type="checkbox"/>
Investigation #3	YES <input type="checkbox"/>	NO <input checked="" 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"):

Trial 809-103  
Trial 809-104

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 # 74633	YES <input checked="" type="checkbox"/>	! NO <input type="checkbox"/>
		! Explain:
Investigation #2		!

IND # 74633

YES

!  
! NO   
! Explain:

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

Investigation #1

YES

Explain:

!  
!  
! NO   
! Explain:

Investigation #2

YES

Explain:

!  
!  
! NO   
! 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: Leila P. Hann

Title: Senior Regulatory Project Manager

Date: July 17, 2015

Name of Division Director signing form: Badrul A. Chowdhury, M.D., Ph.D.

Title: Division Director, DPARP

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

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

/s/  
-----

LEILA P HANN  
07/17/2015

BADRUL A CHOWDHURY  
07/17/2015

# ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION <sup>1</sup>		
NDA # 206038 BLA #	NDA Supplement # BLA Supplement #	If NDA, Efficacy Supplement Type: <i>(an action package is not required for SE8 or SE9 supplements)</i>
Proprietary Name: Orkambi Established/Proper Name: lumacaftor/ivacaftor Dosage Form: oral tablet		Applicant: Vertex Pharmaceuticals Agent for Applicant (if applicable):
RPM: Leila P. Hamm		Division: DPARP
NDA Application Type: <input checked="" type="checkbox"/> 505(b)(1) <input 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><b><u>For ALL 505(b)(2) applications, two months prior to EVERY action:</u></b></p> <ul style="list-style-type: none"> <li>Review the information in the 505(b)(2) Assessment and submit the draft<sup>2</sup> to CDER OND IO for clearance.</li> <li>Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)</li> </ul> <p><input 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"> <li>Proposed action</li> <li>User Fee Goal Date is <u>July 05, 2015</u></li> </ul>		<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> CR
<ul style="list-style-type: none"> <li>Previous actions (<i>specify type and date for each action taken</i>)</li> </ul>		<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 <a href="http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf">http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf</a> ). If not submitted, explain _____		<input type="checkbox"/> Received
❖ Application Characteristics <sup>3</sup>		

<sup>1</sup> 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.

<sup>2</sup> 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).

<sup>3</sup> 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. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

Review priority:  Standard  Priority  
 Chemical classification (new NDAs only): 1 and 4  
*(confirm chemical classification at time of approval)*

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

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:

<b>❖</b> 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
<b>❖</b> 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
<b>❖</b> Exclusivity	
• Is approval of this application blocked by any type of exclusivity (orphan, 5-year NCE, 3-year, pediatric exclusivity)?	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes
• If so, specify the type	
<b>❖</b> 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.
<b>CONTENTS OF ACTION PACKAGE</b>	
<b>Officer/Employee List</b>	
<b>❖</b> 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 <i>(including approval letter with final labeling)</i>	Action(s) and date(s) AP July 02, 2015
Labeling	
❖ Package Insert <i>(write submission/communication date at upper right of first page of PI)</i>	
<ul style="list-style-type: none"> <li>• Most recent draft labeling <i>(if it is division-proposed labeling, it should be in track-changes format)</i></li> </ul>	<input checked="" type="checkbox"/> Included
<ul style="list-style-type: none"> <li>• Original applicant-proposed labeling</li> </ul>	<input checked="" type="checkbox"/> Included
❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling <i>(write submission/communication date at upper right of first page of each piece)</i>	<input type="checkbox"/> Medication Guide <input checked="" type="checkbox"/> Patient Package Insert <input type="checkbox"/> Instructions for Use <input type="checkbox"/> Device Labeling <input type="checkbox"/> None
<ul style="list-style-type: none"> <li>• Most-recent draft labeling <i>(if it is division-proposed labeling, it should be in track-changes format)</i></li> </ul>	<input checked="" type="checkbox"/> Included
<ul style="list-style-type: none"> <li>• Original applicant-proposed labeling</li> </ul>	<input checked="" type="checkbox"/> Included
❖ Labels ( <b>full color</b> carton and immediate-container labels) <i>(write submission/communication date on upper right of first page of each submission)</i>	
<ul style="list-style-type: none"> <li>• Most-recent draft labeling</li> </ul>	<input checked="" type="checkbox"/> Included
❖ Proprietary Name	
<ul style="list-style-type: none"> <li>• Acceptability/non-acceptability letter(s) <i>(indicate date(s))</i></li> <li>• Review(s) <i>(indicate date(s))</i></li> </ul>	01/27/2015 01/22/2015
❖ Labeling reviews <i>(indicate dates of reviews)</i>	RPM: <input checked="" type="checkbox"/> None 12/22/2014 DMEPA: <input checked="" type="checkbox"/> None 05/28/2015 DMPP/PLT (DRISK): <input type="checkbox"/> None 06/11/2015 OPDP: <input type="checkbox"/> None 06/10/2015 SEALD: <input checked="" type="checkbox"/> None CSS: <input checked="" type="checkbox"/> None Other: <input checked="" type="checkbox"/> None
Administrative / Regulatory Documents	
❖ RPM Filing Review <sup>4</sup> /Memo of Filing Meeting <i>(indicate date of each review)</i>	12/31/2014
❖ All NDA 505(b)(2) Actions: Date each action cleared by 505(b)(2) Clearance Committee	<input checked="" type="checkbox"/> Not a (b)(2)
❖ NDAs only: Exclusivity Summary <i>(signed by Division Director)</i>	<input checked="" type="checkbox"/> Included
❖ Application Integrity Policy (AIP) Status and Related Documents <a href="http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm">http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</a>	
<ul style="list-style-type: none"> <li>• Applicant is on the AIP</li> </ul>	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No

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

<ul style="list-style-type: none"> <li>This application is on the AIP <ul style="list-style-type: none"> <li>If yes, Center Director's Exception for Review memo (<i>indicate date</i>)</li> <li>If yes, OC clearance for approval (<i>indicate date of clearance communication</i>)</li> </ul> </li> </ul>	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No  <input type="checkbox"/> Not an AP action
<ul style="list-style-type: none"> <li>Pediatrics (<i>approvals only</i>) <ul style="list-style-type: none"> <li>Date reviewed by PeRC _____ If PeRC review not necessary, explain: <u>orphan product</u></li> </ul> </li> </ul>	
<ul style="list-style-type: none"> <li>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, etc.) (<i>do not include previous action letters, as these are located elsewhere in package</i>)</li> </ul>	06/26/2015; 06/19/2015; 06/16/2015; 06/09/2015, 06/05/2015; 06/03/2015; 05/19/2015, 04/24/2015, 04/17/2015, 03/10/2015, 03/09/2015, 03/04/2015, 02/23/2015, 01/16/2015, 01/16/2015, 12/31/2014, 12/22/2014, 12/18/2014, 12/17/2014, 12/16/2014, 12/09/2014, 11/18/2014, 10/17/2014, 09/04/2014, 08/26/2014
<ul style="list-style-type: none"> <li>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)</li> </ul>	
<ul style="list-style-type: none"> <li>Minutes of Meetings <ul style="list-style-type: none"> <li>If not the first review cycle, any end-of-review meeting (<i>indicate date of mtg</i>)</li> <li>Pre-NDA/BLA meeting (<i>indicate date of mtg</i>)</li> <li>EOP2 meeting (<i>indicate date of mtg</i>)</li> <li>Mid-cycle Communication (<i>indicate date of mtg</i>)</li> <li>Late-cycle Meeting (<i>indicate date of mtg</i>)</li> <li>Other milestone meetings (e.g., EOP2a, CMC pilots) (<i>indicate dates of mtgs</i>)</li> </ul> </li> </ul>	<input checked="" type="checkbox"/> N/A or no mtg <input type="checkbox"/> No mtg 08/12/2014, 05/16/2014 <input type="checkbox"/> No mtg <input type="checkbox"/> N/A 02/19/2015 <input type="checkbox"/> N/A 04/29/2015
<ul style="list-style-type: none"> <li>Advisory Committee Meeting(s) <ul style="list-style-type: none"> <li>Date(s) of Meeting(s)</li> </ul> </li> </ul>	<input type="checkbox"/> No AC meeting May 12, 2015
<b>Decisional and Summary Memos</b>	
<ul style="list-style-type: none"> <li>Office Director Decisional Memo (<i>indicate date for each review</i>)</li> </ul>	<input type="checkbox"/> None 07/02/2015
<ul style="list-style-type: none"> <li>Division Director Summary Review (<i>indicate date for each review</i>)</li> </ul>	<input type="checkbox"/> None 06/25/2015
<ul style="list-style-type: none"> <li>Cross-Discipline Team Leader Review (<i>indicate date for each review</i>)</li> </ul>	<input type="checkbox"/> None 06/10/2015
<ul style="list-style-type: none"> <li>PMR/PMC Development Templates (<i>indicate total number</i>)</li> </ul>	<input type="checkbox"/> None 1
<b>Clinical</b>	
<ul style="list-style-type: none"> <li>Clinical Reviews <ul style="list-style-type: none"> <li>Clinical Team Leader Review(s) (<i>indicate date for each review</i>)</li> <li>Clinical review(s) (<i>indicate date for each review</i>)</li> <li>Social scientist review(s) (if OTC drug) (<i>indicate date for each review</i>)</li> </ul> </li> </ul>	<input checked="" type="checkbox"/> No separate review 06/02/2015, 12/17/2014 <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> )	06/02/2015 pgs 80-81
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers ( <i>indicate date of each review</i> )	<input type="checkbox"/> None 02/13/2015
❖ 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"> <li>REMS Documents and REMS Supporting Document (<i>indicate date(s) of submission(s)</i>)</li> <li>REMS Memo(s) and letter(s) (<i>indicate date(s)</i>)</li> <li>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>)</li> </ul>	<input type="checkbox"/> None 07/01/2015
❖ OSI Clinical Inspection Review Summary(ies) ( <i>include copies of OSI letters to investigators</i> )	<input type="checkbox"/> None requested 06/18/2015; 06/08/2015, 03/27/2015, 03/26/2015
<b>Clinical Microbiology</b> <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"/> None
<b>Biostatistics</b> <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 type="checkbox"/> None 06/02/2015, 06/01/2015, 12/31/2014
<b>Clinical Pharmacology</b> <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 type="checkbox"/> None 05/28/2015, 01/02/2015
❖ OSI Clinical Pharmacology Inspection Review Summary ( <i>include copies of OSI letters</i> )	<input checked="" type="checkbox"/> None requested
<b>Nonclinical</b> <input type="checkbox"/> None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> No separate review 06/17/2015
• Supervisory Review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> No separate review 06/04/2015
• Pharm/tox review(s), including referenced IND reviews ( <i>indicate date for each review</i> )	<input type="checkbox"/> None 06/16/2015; 06/04/2015; 05/05/2015, 11/24/2014, 11/20/2014
❖ 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 type="checkbox"/> No carc 11/20/2014
❖ ECAC/CAC report/memo of meeting	<input type="checkbox"/> None 11/19/2014
❖ OSI Nonclinical Inspection Review Summary ( <i>include copies of OSI letters</i> )	<input checked="" type="checkbox"/> None requested

<b>Product Quality</b> <input type="checkbox"/> None	
<b>❖ Product Quality Discipline Reviews</b>	
• ONDQA/OBP Division Director Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> No separate review
• Branch Chief/Team Leader Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> No separate review
• Product quality review(s) including ONDQA biopharmaceutics reviews <i>(indicate date for each review)</i>	<input type="checkbox"/> None 04/06/2015, 04/06/2015, 09/02/2014
<b>❖ Microbiology Reviews</b> ✓ NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) <i>(indicate date of each review)</i> <input type="checkbox"/> BLAs: Sterility assurance, microbiology, facilities reviews (OMPQ/MAPCB/BMT) <i>(indicate date of each review)</i>	<input type="checkbox"/> Not needed 12/11/2014
<b>❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer</b> <i>(indicate date of each review)</i>	<input type="checkbox"/> None 02/02/2015, 12/23/2014
<b>❖ Environmental Assessment (check one) (original and supplemental applications)</b>	
<input checked="" type="checkbox"/> Categorical Exclusion <i>(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)</i>	04/06/2015
<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>	
<b>❖ Facilities Review/Inspection</b>	
<input checked="" type="checkbox"/> NDAs: Facilities inspections (include EER printout or EER Summary Report only; do <b>NOT</b> include EER Detailed Report; date completed must be within <b>2 years</b> of action date) <i>(only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites<sup>5</sup>)</i>	Date completed: 06/23/2015 <input checked="" type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation <input type="checkbox"/> Not applicable
<input type="checkbox"/> BLAs: TB-EER (date of most recent TB-EER must be within <b>30 days</b> of action date) <i>(original and supplemental BLAs)</i>	Date completed: <input type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation
<b>❖ NDAs: Methods Validation</b> <i>(check box only, do not include documents)</i>	<input checked="" type="checkbox"/> Completed <input type="checkbox"/> Requested <input type="checkbox"/> Not yet requested <input type="checkbox"/> Not needed (per review)

<sup>5</sup> i.e., a new facility or a change in the facility, or a change in the manufacturing process in a way that impacts the Quality Management Systems of the facility.

Day of Approval Activities	
❖ For all 505(b)(2) applications: • Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)	<input type="checkbox"/> No changes <input type="checkbox"/> New patent/exclusivity ( <i>Notify CDER OND IO</i> )
• Finalize 505(b)(2) assessment	<input type="checkbox"/> Done
❖ Send a courtesy copy of approval letter and all attachments to applicant by fax or secure email	<input 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 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 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/  
-----

LEILA P HANN  
07/17/2015



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

---

---

**FACSIMILE TRANSMITTAL SHEET**

---

---

**DATE:** June 26, 2015

<b>To:</b> Rick Lilley Vice President, Regulatory Affairs	<b>From:</b> Leila P. Hann Senior Regulatory Project Manager
<b>Company:</b> Vertex Pharmaceuticals Inc.	Division of Pulmonary, Allergy, and Rheumatology Drug Products
<b>Fax number:</b> 617-961-7789	<b>Fax number:</b> 301-796-9728
<b>Secure Email:</b> Rick_Lilley@vrtx.com	<b>Phone number:</b> 301-796-3367

**Subject:** NDA 206038 (Orkambi) Information Request

---

**Total no. of pages including  
cover:** 18

---

**Comments:**

---

---

**Document to be mailed:**                      YES                      xNO

---

---

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.

If you are not the addressee, or a person authorized to deliver this document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please notify us immediately by telephone at (301) 796-2300. Thank you.

Your USPI for NDA 206038 submitted June 23, 2015, is currently under review. Attached is the FDA-edited label. We have the following explanatory comments:

1. We agree that for the time being, an EPC for lumacaftor will not be designated.
2. Highlights, Indication and Usage, Description, Clinical Pharmacology: We continue to believe the EPC “CFTR conformational stabilizer” is scientifically justified.
3. Warnings and Precautions, 5.4 Drug Interactions: In lieu of adding another Warning and Precaution related to menstrual abnormalities, we have added a statement regarding increased menstrual abnormalities in the drug interaction Warning and Precaution.
4. Adverse Reactions, 6: Liver related serious adverse reactions are labeled as such because they occurred more frequently in Orkambi treated patients (3) compared to placebo (0).
5. Drug Interactions, 7.11: The statement “Avoid concomitant use unless the benefit outweighs the risks” was added back in because women use hormonal contraceptives for reasons other than birth control and the benefit may not necessarily outweigh the risk.
6. Clinical Studies, 14: Minor edits made for clarification and consistency of language.

These are our current edits and there may be additional comments.

Submit revised draft labeling incorporating the attached changes.

Provide a response to the requests by email (Leila.Hann@fda.hhs.gov) or facsimile (301-796-9728), by 5pm, EST on Monday, June 30, 2015. Your response must also be submitted formally to the NDA shortly thereafter. If you have any questions, please contact Leila P. Hann, Regulatory Program Manager, at 301-796-3367.

APPEARS THIS WAY ON ORIGINAL

Drafted by: L. Hann/ June 22, 2015  
Cleared by: A. Shaw/ June 25, 2015  
C. Bertha/ June 25, 2015  
R. Lim/ June 25, 2015  
A. Durmowicz/ June 26, 2015  
L. Zeng/ June 25, 2015  
J. Chen/ June 25, 2015  
A. Marathe/ June 25, 2015  
S. Doddapaneni/ June 25, 2015  
S. Barnes/ June 26, 2015  
B. Chowdhury/ June 26, 2015  
Finalized by: L. Hann/ June 26, 2015

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

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

/s/  
-----

LEILA P HANN  
06/26/2015



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

**FACSIMILE TRANSMITTAL SHEET**

**DATE:** June 19, 2015

<b>To:</b> Rick Lilley Vice President, Regulatory Affairs	<b>From:</b> Leila P. Hann Senior Regulatory Project Manager
<b>Company:</b> Vertex Pharmaceuticals Inc.	Division of Pulmonary, Allergy, and Rheumatology Drug Products
<b>Fax number:</b> 617-961-7789	<b>Fax number:</b> 301-796-9728
<b>Secure Email:</b> Rick_Lilley@vrtx.com	<b>Phone number:</b> 301-796-3367

**Subject:** NDA 206038 (Orkambi) Information Request

**Total no. of pages including cover:** 21

**Comments:**

**Document to be mailed:**                    YES                    xNO

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.

If you are not the addressee, or a person authorized to deliver this document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please notify us immediately by telephone at (301) 796-2300. Thank you.

Your USPI for NDA 206038 submitted June 12, 2015, is currently under review. We have the following comments regarding the attached labeling. These are the preliminary edits and there may be additional comments.

1. Section 16 How Supplied: Provide the strength or potency of the dosage form. See 21CFR 201.57(c)(17).
2. Explain how the drug product is packaged in terms of the Inner Carton and the Outer Carton.
3. Highlights, Section 1, Indications and Usage, Section 11, Description, and Section 12, Clinical Pharmacology: Description of the drug has been modified to reflect lumacaftor (b) (4)
4. Section 5, Warnings and Precautions: Add “Menstrual Abnormalities” as an additional Warning and Precaution. Include the finding that the adverse reactions are especially relevant to women receiving oral contraceptives. Menstrual abnormalities should also be noted in the appropriate section of the Highlights section, Full Prescribing Information Contents, and Patient information Sheet (in the “What are the possible side effects of Orkambi” section).
5. Section 6.1, Clinical Trials Experience:
  - a. Pneumonia and cough added back in as these were greater than placebo and were reported as adverse reactions.
  - b. Reference to (b) (4) have been removed for reasons discussed with you extensively previously for the Kalydeco program/labeling.
6. Section 8, Use in Specific Populations:
  - a. Your proposed method for calculating nonclinical exposure margins is accepted. Certain values in Sections 8 and 13 were adjusted slightly based on rounding convention (to nearest 5 for values between 10-100).
  - b. Sections 8.8 and (b) (4) have been deleted; Section 8.8 has no role given the change in the Limitations of Use and Section (b) (4) for whom the Orkambi is clearly not indicated.
7. Section 10, Overdosage: The mention of the 600 mg dose of lumacaftor is not relevant given that the approved daily dose is actually higher.
8. Section 12, Clinical Pharmacology:
  - a. Clinical recommendations based on (b) (4) data should not be included in the clinical pharmacology section, e.g., (b) (4)

(b) (4) Similar edits have been made under specific populations of this section. Table 3 and (b) (4) are redundant. Choose one or the other for labeling purposes. Our opinion is that, overall, Table 3 is more informative.

9. Section 14, Clinical Studies:

- a. p-values added where appropriate.
- b. Reference to (b) (4) removed (b) (4).
- c. Reference to (b) (4) removed for reasons discussed in the past.

10. Section 17, Patient Counseling Information: Add patient counseling sections for “Use in Advanced Liver Disease” and “Menstrual Abnormalities”.

The Patient Labeling Team also reviewed the proposed label and have provided edits to the Patient Package Insert to reduce redundancy and improve readability.

Please provide a response to the requests by email (Leila.Hann@fda.hhs.gov) or facsimile (301-796-9728), by 5pm, EST on Tuesday, June 23, 2015. Your response must also be submitted formally to the NDA shortly thereafter. If you have any questions, please contact Leila P. Hann, Regulatory Program Manager, at 301-796-3367.

Drafted by: L. Hann/ June 10, 2015  
Cleared by: A. Shaw/ June 15, 2015  
C. Bertha/ June 15, 2015  
R. Lim/ June 19, 2015  
A. Durmowicz/ June 19, 2015  
L. Zeng/ June 17, 2015  
D. Petullo/ June 17, 2015  
J. Chen/ June 18, 2015  
A. Marathe/ June 18, 2015  
S. Doddapaneni/ June 18, 2015  
S. Barnes/ June 19, 2015  
B. Chowdury/ June 19, 2015  
Finalized by: L. Hann/ June 19, 2015

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

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

/s/  
-----

LEILA P HANN  
06/19/2015



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

---



---

**FACSIMILE TRANSMITTAL SHEET**

---



---

**DATE:** June 16, 2015

<b>To:</b> Rick Lilley Vice President, Regulatory Affairs	<b>From:</b> Leila P. Hann Senior Regulatory Project Manager
<b>Company:</b> Vertex Pharmaceuticals Inc.	Division of Pulmonary, Allergy, and Rheumatology Drug Products
<b>Fax number:</b> 617-961-7789	<b>Fax number:</b> 301-796-9728
<b>Secure Email:</b> Rick_Lilley@vrtx.com	<b>Phone number:</b> 301-796-3367

**Subject:** NDA 206038 (Orkambi) Information Request

**Total no. of pages including  
cover:** 4

**Comments:**

---

**Document to be mailed:**                      YES                      xNO

---



---

**THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.**

**If you are not the addressee, or a person authorized to deliver this document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please notify us immediately by telephone at (301) 796-2300. Thank you.**

You NDA 206038 dated November 5, 2014 is currently under review.

We have reviewed your communication dated June 15, 2015 regarding the determination of an Established Pharmacologic Class (EPC) for lumacaftor and have the following comments:

1. As previously communicated at the Late Cycle Meeting on April 29, 2015 and the teleconference on June 3, 2015, we are concerned with the use of the term (b) (4) to describe lumacaftor because it is too broad, potentially confusing and not meaningful in the context of the clinical data with lumacaftor. The Division has determined that the proposed (b) (4) are insufficient to overcome these concerns; therefore, any EPC containing the term (b) (4) would be unacceptable.
2. We note that in consultation with the Office of Prescription Drug Promotion (OPDP), they have also expressed concern regarding the use of the term (b) (4) to describe lumacaftor. OPDP stated that “promotional materials that would contain the term (b) (4) to describe either lumacaftor or Orkambi could be considered misleading (b) (4) OPDP recommends that the term (b) (4) not be included in the proposed PI for Orkambi.”
3. We continue to believe that the available data support the term “CFTR conformational stabilizer” for the following reasons:
  - a. The *F508del-CFTR* mutation leads to protein misfolding that affects the conformation, stability, and assembly of the domains of CFTR. This defective folding results in the processing and trafficking defect (e.g., retention in ER and degradation via ubiquitin-proteasome pathway) as well as impaired conformation, stability and function at the cell surface.<sup>1</sup>
  - b. Lumacaftor directly interacts with and stabilizes the MSD1 domain of F508del-CFTR, activity that is required for the “(b) (4) effect. Vertex study report K124 and the associated publication<sup>2</sup> conclude that “1) VX-809 biochemically stabilizes CFTR fragments that contain only MSD1. 2) VX-809 alters the conformation of MSD1 to protect it from proteolytic digestion with trypsin. 3) CFTR fragments fold to a conformation that is stabilized by VX-809 after biosynthesis of amino acid F374. F374 is located in the linker between MSD1 and NBD1 and helps stabilize MSD1 in conformation that is sensitive to VX-809...Data presented are consistent with the concept that (b) (4) such as VX-

809 modulate the conformation of a specific region of CFTR to enhance global protein folding and assembly.” These conclusions are supported by independent publications evaluating lumacaftor.<sup>3</sup>

- c. Lumacaftor treatment increases the stability of cell surface F508del-CFTR to closer to wild-type levels, an effect which was attributed to “(b)(4) of the defective protein conformation” in Vertex study report D146. Additional independent studies support the conclusion that lumacaftor has a stabilizing effect on cell surface F508del-CFTR.<sup>4</sup>

The totality of the available in vitro data support the conclusion that lumacaftor acts directly on F508del-CFTR to partially reverse the folding defects, resulting in increased processing and trafficking to the cell surface as well as increased stability and channel function at the cell membrane. The assignment of “CFTR conformational stabilizer” as the EPC reflects the knowledge of the molecular mechanism of action of lumacaftor. In addition, this EPC term distinguishing lumacaftor from other classes of compounds which have also been referred to as “(b)(4) and result in increased processing and trafficking of F508del-CFTR to the cell surface, but act via completely distinct and in some cases, non-specific, mechanisms (e.g., osmolytes, PDE5 inhibition, transcriptional regulation, PARP inhibition, modulation of proteostasis). Finally, we note that literature references to the notion of (b)(4) in the context of CFTR gene therapy occurred well before publication of the initial temperature correction paper, and in the ensuing years the term has been used to refer to a wide variety of mechanisms by which the underlying CFTR defect could be targeted.

If you have any questions, please contact Leila P. Hann, Senior Regulatory Program Manager, at 301-796-3367.

---

<sup>1</sup> Boyle (2013) *Lancet Resp Med*; Chiaw (2011), *Essays Biochem*; Lukacs (2012) *Trends Mol Med*; Du (2005) *Nat Struct Mol Bio*; Okiyoneda (2013) *Nat Chem Bio*; Farinha (2013) *FEBS Journal*; Baroni (2014) *Cell Mol Life Sci*; Pasyk (2015) *Proteomics*.

<sup>2</sup> Ren (2013) *Molecular Biology of the Cell*.

(b)(4)

---

Drafted by: L. Hann/ June 16, 2015  
Cleared by: A. Goodwin/ June 16, 2015  
T. Robison/ June 16, 2015  
A. Durmowicz/ June 16, 2015  
B. Chowdhury/ June 16, 2015  
S. Barnes/ June 16, 2015  
Finalized by: L. Hann/ June 16, 2015

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

/s/  
-----

LEILA P HANN  
06/16/2015



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

**FACSIMILE TRANSMITTAL SHEET**

**DATE:** June 09, 2015

<b>To:</b> Rick Lilley Vice President, Regulatory Affairs	<b>From:</b> Leila P. Hann Senior Regulatory Project Manager
<b>Company:</b> Vertex Pharmaceuticals Inc.	Division of Pulmonary, Allergy, and Rheumatology Drug Products
<b>Fax number:</b> 617-961-7789	<b>Fax number:</b> 301-796-9728
<b>Secure Email:</b> Rick_Lilley@vrtx.com	<b>Phone number:</b> 301-796-3367

**Subject:** NDA 206038 (Orkambi) Information Request

**Total no. of pages including cover:** 4

**Comments:**

**Document to be mailed:** YES xNO

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.

If you are not the addressee, or a person authorized to deliver this document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please notify us immediately by telephone at (301) 796-2300. Thank you.

Your NDA 206038 proposed labeling submitted May 26, 2015, is currently under review. We have the following comments and clarifications regarding labeling sent June 05, 2015.

Clinical pharmacology:

1. You stated that “The exposure (AUC) of lumacaftor is approximately 2 fold higher in healthy adult volunteers compared to exposure in patients with CF. The exposure of ivacaftor is similar between healthy adult volunteers and patients with CF.” Provide the source study/data to support the claim in the label (not just general “see summary of clinical pharmacology”).

2. Under distribution, you stated the (b) (4)  
(b) (4)  
for lumacaftor and ivacaftor.  
Replace this statement with  $Vd_{ss}$  in CF subjects.”

3. Provide a (b) (4)  
(b) (4)  
(b) (4)  
(b) (4)

(b) (4)

Please provide a response to the requests by email ([Leila.Hann@fda.hhs.gov](mailto:Leila.Hann@fda.hhs.gov)) or facsimile (301-796-9728), by Friday, June 12, 2015. Your response must also be submitted formally to the NDA shortly thereafter. If you have any questions, please contact Leila P. Hann, Senior Regulatory Program Manager, at 301-796-3367.

Drafted by: L. Hann/ June 09, 2015  
Cleared by: A. Goodwin/ June 08, 2015  
T. Robison/ June 08, 2015  
J. Chen/ June 09, 2015  
S. Doddapaneni/ June 09, 2015  
S. Barnes/ June 09, 2015  
Finalized by: L. Hann/ June 09, 2015

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

/s/  
-----

LEILA P HANN  
06/09/2015



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

---

---

***ELECTRONIC CORRESPONDENCE***

---

---

**Date:** June 5, 2015

<b>To:</b> Rick Lilley Vice President, Regulatory Affairs	<b>From:</b> Christine Ford, R.Ph. Regulatory Project Manager
<b>Company:</b> Vertex Pharmaceuticals, Inc.	Division of Pulmonary, Allergy, and Rheumatology Products
<b>Phone:</b> 617-961-7789	<b>Fax number:</b> 301-796-9728
<b>Email:</b> Rick_Lilley@vrtx.com	<b>Phone number:</b> 301-796-3420

**Subject:** NDA 206038 Orkambi (lumacaftor/ivacaftor) tablets  
FDA labeling comments

**Total no. of pages including cover:** 24

**Comments:** Please call or send an email to confirm receipt at [christine.ford@fda.hhs.gov](mailto:christine.ford@fda.hhs.gov)

*Submit response no later than close of business Friday, June 12, 2015*

---

**Document to be mailed:** YES  NO

---

---

**THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.**

If you are not the addressee, or a person authorized to deliver this document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please notify us immediately by telephone at (301) 796-3420. Thank you.

We refer to Orkambi NDA 206038 and have the following labeling edits provided in the attached marked up label. Additional labeling changes may be forthcoming.

FDA edits were made as tracked changes to the clean version of your proposed labeling submitted May 26, 2015. We also have the following general comments explaining the rationale for some of the edits:

- 1) Edits were made throughout the label to maintain consistency with the Kalydeco label where appropriate.
- 2) As discussed in the teleconference held on June 3, 2015, the EPC for lumacaftor is still under review. We will notify you as soon as a decision is made.
- 3) We have modified the "Limitations of Use" statement. (b) (4)  
(b) (4) (b) (4)
- 4) (b) (4) has been removed from section 6 (Adverse Reactions) of the label (b) (4)  
(b) (4)
- 5) Section 7 (Drug Interactions) was edited in order to improve readability.
- 6) In section 14 (Clinical Studies), dosing ranging information for lumacaftor and lumacaftor+ivacaftor from study 809-102 was added to provide a rationale for the doses explored in the studies 809-103 and 809-104.
- 7) Some edits we have made to numerical values may be slightly different from numbers you may have calculated. Please check any changes in numbers and justify any corresponding edits to them you may have.
- 8) Edits to the Patient Information Sheet to be consistent with the information in the Prescribing Information will be forthcoming

Any additional proposed changes you may have can be made in a similar fashion by using the clean Word version of the attached labeling and edit using tracked changes.

Submit revised draft labeling incorporating the requested changes to Leila Hann via secure email at [leila.hann@fda.hhs.gov](mailto:leila.hann@fda.hhs.gov) by June 12, 2015. Your response will subsequently need to be submitted officially to the NDA.

If you have any questions, please contact me today at 301-796-3420 or after today, Leila Hann at 301-796-3367.

Drafted by: RLim, ADurmowicz/ 6.05.2015  
cford/ 6.5.2015

Initialed by: SBarnes/ 6.5.2015  
ADurmowicz/ 6.5.2015

Finalized: cford/ 6.5.2015

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

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

/s/  
-----

CHRISTINE H CHUNG  
06/05/2015



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

**FACSIMILE TRANSMITTAL SHEET**

**DATE:** June 03, 2015

<b>To:</b> Rick Lilley Vice President, Regulatory Affairs	<b>From:</b> Leila P. Hann Senior Regulatory Project Manager
<b>Company:</b> Vertex Pharmaceuticals Inc.	Division of Pulmonary, Allergy, and Rheumatology Drug Products
<b>Fax number:</b> 617-961-7789	<b>Fax number:</b> 301-796-9728
<b>Secure Email:</b> Rick_Lilley@vrtx.com	<b>Phone number:</b> 301-796-3367

**Subject:** NDA 206038 (Orkambi) Information Request

**Total no. of pages including cover:** 10

**Comments:**

**Document to be mailed:**                    YES                    xNO

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.

If you are not the addressee, or a person authorized to deliver this document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please notify us immediately by telephone at (301) 796-2300. Thank you.

We are requesting your assistance in populating the attached tables for your New Molecular Entity, lumacaftor/ivacaftor, currently under review in the Division of Pulmonary, Allergy, and Rheumatology Products.

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](http://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

Please provide a response to the requests by email (Leila.Hann@fda.hhs.gov) or facsimile (301-796-9728), by Noon on Monday, June 15, 2015. Your response must also be submitted formally to the NDA shortly thereafter. If you have any questions, please contact Leila P. Hann, Regulatory Program Manager, at 301-796-3367.

Drafted by: L. Hann/ June 03, 2015  
Cleared by: N. Lowy/ June 01, 2015  
R. Lim/ June 02, 2015  
S. Barnes/ June 03, 2015  
Finalized by: L. Hann/ June 03, 2015

**Table 7.2.1-b. Baseline Demographics, Multiple Trials, Safety Population (complete only if safety p**

Demographic Parameters	809-103		809-104	
	Lumacaftor 400mg/Ivacaftor 250mg q12 (N=) n (%)*	Placebo (N=) n (%)*	Lumacaftor 400mg/Ivacaftor 250mg q12 (N=) n (%)*	Placebo (N=) n (%)*
<b>Sex</b>				
Male				
Female				
<b>Age</b>				
Mean years (SD)				
Median (years)				
Min, Max (years)				
<b>Age Group</b>				
<17 years				
>=17 - <65 years				
>=65 years				
>=75 years				
<b>Race</b>				
White				
Black or African American				
Asian				
American Indian or Alaska Native				
Native Hawaiian or Other Pacific Islander				
Other				
<b>Ethnicity</b>				
Hispanic or Latino				
Not Hispanic or Latino				
<b>Region</b>				
United States				
Rest of the World				
Canada				
South America				
Europe				
Asia				
Africa				

Source:

\* Percentages are calculated based on the total number of subjects in the respective arm.



**Table 6.1.2-b. Baseline Demographics, Trials 809-103 and 809-104**

Demographic Parameters	809-103		809-104
	Lumacaftor 400mg/Ivacaftor 250mg q12 (N=) n (%)*	Placebo (N=) n (%)*	Lumacaftor 400mg/Ivacaftor 250mg q12 (N=) n (%)*
<b>Sex</b>			
Male			
Female			
<b>Age</b>			
Mean years (SD)			
Median (years)			
Min, Max (years)			
<b>Age Group</b>			
<17 years			
>=17 - <65 years			
>=65 years			
>=75 years			
<b>Race</b>			
White			
Black or African American			
Asian			
American Indian or Alaska Native			
Native Hawaiian or Other Pacific Islander			
Other			
<b>Ethnicity</b>			
Hispanic or Latino			
Not Hispanic or Latino			
<b>Region</b>			
United States			
Rest of the World			
Canada			
South America			
Europe			
Asia			
Africa			

Source:

\* Percentages are calculated based on the total number of subjects in the respective arm.



**Table 6.1.7 Subgroup Analysis of Primary Endpoint, Pivotal Efficacy Trials (please complete this table twi**

Subgroup	Lumacaftor 400mg/Ivacaftor 250mg q12		Placebo	
	x (%)*	Total, n	x (%)*	Total, n
<b>Overall Response/All patients</b>				
<b>Sex</b>				
Male				
Female				
<b>Age Group</b>				
<17 years				
>=17 - <65 years				
>=65 years				
>=75 years				
<b>Race</b>				
White				
Black or African American				
Asian				
American Indian or Alaska Native				
Native Hawaiian or Other Pacific Islander				
Other				
<b>Ethnicity</b>				
Hispanic or Latino				
Not Hispanic or Latino				
<b>Region</b>				
United States				
Rest of the World				
Canada				
South America				
Europe				
Asia				
Africa				

Source:

\*Percentages are calculated based on the number of subjects in the subgroup per arm. For example, perce



**Table 7.5.3-a. Subgroup Analysis of AEs, Safety Population (pool 2 pivotal trials)**

Subgroup	Lumacaftor 400mg/Ivacaftor 250mg		Placebo	
	x (%)**	Total, n	x (%)**	Total, n
<b>Any TEAEs*</b>				
<b>Sex</b>				
Male				
Female				
<b>Age Group</b>				
<17 years				
>=17 - <65 years				
>=65 years				
>=75 years				
<b>Race</b>				
White				
Black or African American				
Asian				
American Indian or Alaska Native				
Native Hawaiian or Other Pacific Islander				
Other				
<b>Ethnicity</b>				
Hispanic or Latino				
Not Hispanic or Latino				
<b>Region</b>				
United States				
Rest of the World				
Canada				
South America				
Europe				
Asia				
Africa				

Source:

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

\*\* Percentages are calculated based on the number of subjects in the subgroup per arm. For example, percentage

esignated group of PTs)

ntage of males with TEAEs in treatment group = 25/30

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

/s/  
-----

LEILA P HANN  
06/03/2015



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

**FACSIMILE TRANSMITTAL SHEET**

**DATE:** May 19, 2015

<b>To:</b> Rick Lilley Vice President, Regulatory Affairs	<b>From:</b> Leila P. Hann Senior Regulatory Project Manager
<b>Company:</b> Vertex Pharmaceuticals Inc.	Division of Pulmonary, Allergy, and Rheumatology Drug Products
<b>Fax number:</b> 617-961-7789	<b>Fax number:</b> 301-796-9728
<b>Secure Email:</b> Rick_Lilley@vrtx.com	<b>Phone number:</b> 301-796-3367

**Subject:** NDA 206038 (Orkambi) Information Request

**Total no. of pages including cover:** 3

**Comments:**

**Document to be mailed:** YES xNO

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.

If you are not the addressee, or a person authorized to deliver this document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please notify us immediately by telephone at (301) 796-2300. Thank you.

Your NDA 206038 submitted November 05, 2014, is currently under review. We have the following initial comments regarding the label submitted March 18, 2015. These are the preliminary edits and there will be additional comments.

1. The drug product Orkambi refers only to the IVA 250/LUM 400 combination. (b) (4)  
All values and references to Orkambi in the label should be based on the IVA 250/LUM 400 group.
2. Formatting and wording of the parts of the Orkambi label that are in common with the Kalydeco label should use the agreed-to wording from the Kalydeco label.
3. Update your clinical pharmacology section based on the draft guidance “Clinical Pharmacology Labeling for Human Prescription Drug and Biological Products—Considerations, Content and Format.”  
(<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM109739.pdf>)

Please provide a response to the requests by email (Leila.Hann@fda.hhs.gov) or facsimile (301-796-9728), by Noon on Tuesday, May 26, 2015. Your response must also be submitted formally to the NDA shortly thereafter. If you have any questions, please contact Leila P. Hann, Regulatory Program Manager, at 301-796-3367.

Drafted by: L. Hann/ May 18, 2015  
Cleared by: A. Durmowicz/ May 18, 2015  
J. Chen/ May 19, 2015  
C. Jackson/ May 19, 2015  
Finalized by: L. Hann/ May 19, 2015

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

/s/  
-----

LEILA P HANN  
05/19/2015



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

**FACSIMILE TRANSMITTAL SHEET**

**DATE:** April 24, 2015

<b>To:</b> Rick Lilley Vice President, Regulatory Affairs	<b>From:</b> Leila P. Hann Senior Regulatory Project Manager
<b>Company:</b> Vertex Pharmaceuticals Inc.	Division of Pulmonary, Allergy, and Rheumatology Drug Products
<b>Fax number:</b> 617-961-7789	<b>Fax number:</b> 301-796-9728
<b>Secure Email:</b> Rick_Lilley@vrtx.com	<b>Phone number:</b> 301-796-3367

**Subject:** NDA 206038 (Orkambi) Information Request

**Total no. of pages including cover:** 4

**Comments:**

**Document to be mailed:** YES xNO

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.

If you are not the addressee, or a person authorized to deliver this document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please notify us immediately by telephone at (301) 796-2300. Thank you.

Your submissions to NDA 206038 dated November 5, 2014 and March 3, 2015 are under review and we have the following requests for information:

With regard to Vertex Study Report #D146:

1. We note that the data in the section entitled “Effects of VRT-826809 on the intrinsic channel gating activity of  $\Delta F508$ -CFTR” (e.g., Figure 8-5B) has been replaced in Version 2 (FRT cell model) compared to Version 1 (3T3 cell model). Provide the rationale for this amendment to the study report, and provide applicable methods details for the FRT experiments.
2. The FRT cell data in Figure 8-5B in Version 2 of the report includes results with the LUM-IVA combination, in contrast to the 3T3 cell data in Version 1. However, we note that similar 3T3 cell data (but with the addition of a LUM-IVA combination data point) appears in Figure 2-F of the 2011 Van Goor et al. *PNAS* publication. Clarify whether the 3T3 data in the Van Goor publication is from the same study as report D146 (Version 1) and provide an integrated assessment of the data generated in both cell lines.

With regard to Vertex Study Report #D143, and in the interest of comparing all available data of the effects on LUM, IVA and the combination on chloride transport in F508del CFTR HBE:

3. Provide summary data on the effects of LUM, IVA or the combination on chloride transport in F508del CFTR HBE, as shown in the example table below. This is a request to recapitulate the data from completed studies, and not a request for any new studies to be conducted. We acknowledge the limitations of cross-study comparisons and that each study included only some of the treatment conditions included in the table.

Include the mean  $\pm$  SEM for each data point as well as the number of wild-type and F508del CFTR donors represented in the study. If studies evaluated multiple doses, provide the data for LUM treatment at 3  $\mu$ M, acute IVA treatment at 1  $\mu$ M and/or extended IVA treatment at 0.1  $\mu$ M (or if this is not possible, note any deviation). The following studies should be included:

- a. D143, Table 8-3 “Study 1”
- b. D143, Table 8-3 “Study 2”
- c. Van Goor et al. (2011) *PNAS*. (Clarify if this is the same data as bullet “a”)
- d. B229. (Data from 4 donors summarized in Table 8-1, but the report suggests that F508del CFTR HBE from at least six donors were assessed).
- e. Van Goor et al. (2009) *PNAS*. We note that this study reported a mean increase of 4% of wild-type upon IVA treatment, with individual responses ranging up to 16% of wild-type, but detailed data was not included. Clarify if there is any overlap with the data presented in Study B229.

f. Any other relevant studies conducted by Vertex and/or published in the literature.

Study	Chloride Transport	WT HBE Control	<i>F508del CFTR</i> HBE					
			No treatment	LUM	IVA (acute)	IVA (24 hr)	LUM + IVA (acute)	LUM + IVA (24 hr)
	Raw data (uA/cm <sup>2</sup> )							
	% of WT							

Please provide a response to the requests by email (Leila.Hann@fda.hhs.gov) or facsimile (301-796-9728), by Noon on Friday, May 01, 2015. Your response must also be submitted formally to the NDA shortly thereafter. If you have any questions, please contact Leila P. Hann, Regulatory Program Manager, at 301-796-3367.

Drafted by: L. Hann/ April 22, 2015  
Cleared by: A. Goodwin/ April 22, 2015  
T. Robison/ April 22, 2015  
S. Barnes/ April 24, 2015  
Finalized by: L. Hann/ April 24, 2015

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

/s/  
-----

LEILA P HANN  
04/24/2015



NDA 206038

**MID-CYCLE COMMUNICATION**

Vertex Pharmaceuticals, Inc.  
50 Northern Avenue  
Boston, MA 02210

Attention: Rick Lilley  
Vice President, Regulatory Affairs

Dear Mr. Lilley:

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

We also refer to the teleconference between representatives of your firm and the FDA on February 19, 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) 796-3367.

Sincerely,

*{See appended electronic signature page}*

Leila P. Hann  
Senior Regulatory Project Manager  
Division of Pulmonary, Allergy, and Rheumatology  
Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

Enclosure:  
Mid-Cycle Communication



FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH

---

**MID-CYCLE COMMUNICATION**

**Meeting Date and Time:** February 19, 2015

**Application Number:** NDA 206038  
**Product Name:** Orkambi (lumacaftor/ivacaftor)  
**Indication:** cystic fibrosis patients 12yrs and older who are homozygous for the F508del mutation  
**Applicant Name:** Vertex Pharmaceuticals

**Meeting Chair:** Anthony Durmowicz, M.D.  
**Meeting Recorder:** Leila P. Hann

**FDA ATTENDEES**

Badrul A. Chowdhury, M.D., Ph.D., Director, Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)  
Anthony Durmowicz, M.D., Clinical Team Leader, DPARP  
Robert Lim, M.D., Clinical Reviewer, DPARP  
Timothy Robison, Ph.D., Non-Clinical Team Leader, DPARP  
Andrew Goodwin, Ph.D., Non-Clinical Reviewer, DPARP  
Satjit Brar, Ph.D., Team Leader, Division of Clinical Pharmacology II (DCPII)  
Jianmeng Chen, Ph.D., Clinical Pharmacology Reviewer, DCPII  
David Petullo, Ph.D., Team Leader, Division of Biostatistics II (DBII)  
Leila P. Hann, Regulatory Health Project Manager, DPARP

**APPLICANT ATTENDEES**

Jeffrey Chodakewitz, M.D., Executive Vice President & Chief Medical Officer  
Rick Lilley, Ph.D., Senior Vice President & Head of Regulatory Affairs  
Charlotte McKee, M.D., Vice President, Clinical Research  
David Waltz, M.D., Senior Director, Clinical Research  
Paul Panorchan, Ph.D., Director, Clinical Pharmacology  
Gemma Slade, 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**

No significant issues have been identified to date.

## **3.0 INFORMATION REQUESTS**

### **Biometrics**

Several discrepancies between the coding of the stratification variables and the clinical database were noted in your phase 3 trials. Additionally, we are requesting a quantitative analysis that evaluates the contribution of lumacaftor monotherapy to the combination product. An information request with specifics will be sent out within a week.

### **Clinical Pharmacology**

Clinical pharmacology reviewers requested the annotated label for section 7. Provide the rationale for the “Effect” and “Clinical comment” for each concomitant drug listed in section 7.

## **4.0 MAJOR SAFETY CONCERNS/RISK MANAGEMENT**

There are no major safety concerns identified at this time and there is currently no need for a REMS.

## **5.0 ADVISORY COMMITTEE MEETING**

A meeting with the Pulmonary-Allergy Drugs Advisory Committee is scheduled for May 12, 2015. The location has not been determined.

## **6.0 LATE-CYCLE MEETING /OTHER PROJECTED MILESTONES**

The Late-Cycle meeting is scheduled for April 29, 2015 from 12-1:30pm, EST.

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

/s/  
-----

LEILA P HANN  
03/17/2015



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

**FACSIMILE TRANSMITTAL SHEET**

**DATE:** March 10, 2015

<b>To:</b> Rick Lilley Vice President, Regulatory Affairs	<b>From:</b> Leila P. Hann Senior Regulatory Project Manager
<b>Company:</b> Vertex Pharmaceuticals Inc.	Division of Pulmonary, Allergy, and Rheumatology Drug Products
<b>Fax number:</b> 617-961-7789	<b>Fax number:</b> 301-796-9728
<b>Secure Email:</b> Rick_Lilley@vrtx.com	<b>Phone number:</b> 301-796-3367

**Subject:** NDA 206038 (Orkambi) Information Request

**Total no. of pages including cover:** 3

**Comments:**

**Document to be mailed:** YES xNO

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.

If you are not the addressee, or a person authorized to deliver this document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please notify us immediately by telephone at (301) 796-2300. Thank you.

Your NDA 206038 submitted November 05, 2014, is currently under review and we have the following requests for information:

1. As discussed in the T-con on February 19, 2015 submit annotated labeling for section 7 of the label submitted on February 6th 2015. Provide the rationale for the “Effect” and “Clinical comment” for each concomitant drug listed in section 7, such as a reference to a DDI study, a theoretical inference based on a specific metabolism pathway, etc.
2. Your response to the Information Request dated February 23, 2015 failed to provide an explanation for all discrepancies between the coding for stratification variables and the actual values for these measurements. The following is a complete list of subjects where the coding for the stratification variable percent predict FEV1 (ppFEV1) at screening was not in agreement with the value in the dataset ADSL. Clarify all discrepancies. Subjects noted with an asterisk were reported in the clinical study report and require no further clarification.
  - a. **Trial 103:** 03-008-07, 03-024-01\*, 03-045-13\*,03-057-03, 03-062-03\*, 03-081-10, 03-086-01\*, 03-089-14\*, 03-121-01\*, 03-312-06\*, 03-503-08, 03-701-17\*, 03-710-13, 03-805-07\*
  - b. **Trial 104:** 04-006-20, 04-010-08\*, 04-039-21, 04-055-05\*, 04-061-01, 04-064-05, 04-103-03, 04-410-04, 04-511-03, 04-531-02\*, 04-533-09\*, 04-704-13\*
3. Your response also failed to identify all subjects as shown below that were missing ppFEV1 values at screening yet were randomized. Clarify all discrepancies. If screening ppFEV1 assessments were indeed missing, justify why these subjects were randomized and how they were handled in your primary analysis. Subjects noted with an asterisk were explained in your previous response.
  - a. **Trial 103:** 03-021-03, 03-042-02, 03-043-11, 03-057-01, 03-071-04, 03-091-05, 03-101-04, 03-105-01\*, 03-201-05, 03-209-07, 03-309-04, 03-321-12, 03-321-18, 03-401-04, 03-502-06, 03-607-03, 03-712-02, 03-801-01, 03-803-02, 03-803-07
  - b. **Trial 104:** 04-007-01, 04-011-07, 04-028-04, 04-055-03, 04-067-02, 04-075-04, 04-097-03, 04-308-03, 04-308-04, 04-308-05, 04-308-06, 04-308-09, 04-512-06, 04-519-01\*, 04-522-01, 04-522-02

Please provide a response to the requests by email (Leila.Hann@fda.hhs.gov) or facsimile (301-796-9728), by Noon on Monday, March 16, 2015. Your response must also be submitted formally to the NDA shortly thereafter. If you have any questions, please contact Leila P. Hann, Regulatory Program Manager, at 301-796-3367.

APPEARS THIS WAY ON ORIGINAL

Drafted by: L. Hann/ March 09, 2015  
Cleared by: L. Zeng/ March 09, 2015  
D. Petullo/ March 09, 2015  
J. Chen/ March 09, 2015  
S. Doddapaneni/ March 09, 2015  
S. Barnes/ March 10, 2015  
Finalized by: L. Hann/ March 10, 2015

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

/s/  
-----

LEILA P HANN  
03/10/2015



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

**FACSIMILE TRANSMITTAL SHEET**

**DATE:** March 09, 2015

<b>To:</b> Rick Lilley Vice President, Regulatory Affairs	<b>From:</b> Leila P. Hann Senior Regulatory Project Manager
<b>Company:</b> Vertex Pharmaceuticals Inc.	Division of Pulmonary, Allergy, and Rheumatology Drug Products
<b>Fax number:</b> 617-961-7789	<b>Fax number:</b> 301-796-9728
<b>Secure Email:</b> Rick_Lilley@vrtx.com	<b>Phone number:</b> 301-796-3367

**Subject:** NDA 206038 (Orkambi) Information Request

**Total no. of pages including cover:** 3

**Comments:**

**Document to be mailed:** YES xNO

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.

If you are not the addressee, or a person authorized to deliver this document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please notify us immediately by telephone at (301) 796-2300. Thank you.

Your submission dated November 05, 2014 to NDA 206038 is currently under review. We have the following comments and requests for information.

Refer to the IND 79521 Type B meeting minutes dated March 20, 2013 in which you proposed to submit the NDA with only the transgenic mouse carcinogenicity data and the subsequent communication dated August 05, 2013 confirming that the proposal was acceptable. The second required carcinogenicity study in rats, which is currently in progress, will be handled as a post-marketing required (PMR) study. In that regard, please respond to this IR with a letter of intent to comply with the PMR guidelines and provide the following timelines:

1. Study Completion: MM/YY
2. Final Report Submission: MM/YY

Please provide a response to the requests by email (Leila.Hann@fda.hhs.gov) or facsimile (301-796-9728), by 5:00PM on Monday, March 16, 2015. Your response must also be submitted formally to the NDA shortly thereafter. If you have any questions, please contact Leila P. Hann, Regulatory Program Manager, at 301-796-3367.

Drafted by: L. Hann/ March 06, 2015  
Cleared by: L. Zeng/ March 06, 2015  
A. Goodwin/ March 06, 2015  
T. Robison/ March 06, 2015  
A. Durmowicz/ March 06, 2015  
S. Seymour/ March 06, 2015  
S. Barnes/ March 06, 2015  
Finalized by: L. Hann/ March 06, 2015

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

/s/  
-----

LEILA P HANN  
03/09/2015

**DOCUMENT INFORMATION PAGE**

**DARRTS COMMUNICATION**

This page is for FDA internal use only. Do NOT send this page with the letter.

**Application #(s):** NDA 206038

<b>Communication Type:</b>	Correspondence
<b>Communication Group:</b>	Information Request/Advice
<b>Communication Name:</b>	Information Request
<b>Communication ID:</b>	(COR-NDAIR-01)

<b>Drafted by:</b>	J. Duan, C. Cruz, V. Shah, S. Chatterjee, B. Kurtyka; Y. Liu
<b>Clearance history:</b>	R. Madurawe, C. Moore
<b>Finalized:</b>	Y. Liu
<b>Filename:</b>	

<b>Use Statement:</b>	Use to obtain clarifying information to assist in completing a review.
<b>Notes:</b>	BLA CMC Supplement Information Request – OBP RPM signs the letter NDA CMC Supplement Information Request – ONDQA RPM signs the letter

Version: DARRTS 06/05/2014

**END OF DOCUMENT INFORMATION PAGE**

The letter begins on the next page.



NDA 206038

**INFORMATION REQUEST**

Vertex Pharmaceuticals Incorporated  
Attention: Patricia Hurter, Ph.D., Senior Vice President  
CMC, Preclinical Development and Regulatory Affairs  
50 Northern Avenue  
Boston, MA 02210

Dear Dr. Hurter:

Please refer to your New Drug Application (NDA) submitted July 30, 2014 under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Lumacaftor/ivacaftor Tablets.

We are reviewing the CMC section of your submission and have the following comments and information requests. We request a prompt written response by March 17, 2015 in order to continue our evaluation of your NDA.

1. Reference is made to the 12/17/2014 Agency recommendation for the dissolution acceptance criterion and to your response dated 1/19/2015. We agree to a dissolution acceptance criterion of  $Q = \frac{(b)(4)}{(4)}\%$  at  $\frac{(b)(4)}{(4)}$  minutes for lumacaftor in FDC tablets for stability batches. However, we are concerned with the performance of the  $\frac{(b)(4)}{(4)}$  products when their initial criterion is set as  $Q = \frac{(b)(4)}{(4)}\%$  at  $\frac{(b)(4)}{(4)}$  minutes. Therefore, we reiterate the dissolution acceptance criterion for the product's initial release and RTRT be revised from " $Q = \frac{(b)(4)}{(4)}\%$  at  $\frac{(b)(4)}{(4)}$  minutes" to " $Q = \frac{(b)(4)}{(4)}\%$  at 20 minutes."
2. Reference is made to the 12/17/2014 Agency biopharmaceutics comments and to your response dated 1/19/2015. The responses you provided do not support your averaging approach. Although you may monitor dissolution inputs at a high frequency, some inputs are not IPC and they will not be translated to the dissolution monitoring before the model actually estimates dissolution. We reiterate our previous request: (b)(4)  
(b)(4)  
(b)(4). We recommend that you follow the principles of USP <711> stage 2 and propose a shorter period, during which the mean dissolution rates are predicted, and then report the average and the standard deviation for several periods (such as 12) within a batch."

3. Please provide references for the Noyes-Whitney equation you used as it is not in the usual form.
4. We accept your design space development and the criticality threshold limits which were used to define CPPs in P.2.3; the design space limits as specified in P.3.3, which include all the parameters that were demonstrated to impact drug product quality. We also accept your response to the Information Request dated 17 Oct 2014 where you stated "

(b) (4)



5. For the (b) (4) manufacturing processes, (b) (4)



(b) (4)

(b) (4)

8. The agency understands that the (b) (4)
9. Provide updated stability data for the three drug product batches manufactured at (b) (4)-Vertex.
10. Amend Section P.8.2 to include the statements of commitment for reporting the results of post approval studies and the actions to be taken if any batches fail stability.

Please note that the final CMC recommendation is pending satisfactory resolution of items #1, #2, and #4. You may request a teleconference, if so desired, to facilitate rapid resolution of these issues.

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

Sincerely,

Rapti D.  
Madurawe -A

Digitally signed by Rapti D. Madurawe -A  
DN: c=US, o=U.S. Government, ou=HHS,  
ou=FDA, ou=People,  
0.2.2.2.19290500.1061.1=1300220251,  
cn=Rapti D. Madurawe -A  
Date: 2015.03.04 16:09:37 -0500

Rapti Madurawe, Ph.D.  
Division Director (Acting)  
Office of Process and Facilities  
OPQ/CDER/FDA  
Center for Drug Evaluation and Research



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

**FACSIMILE TRANSMITTAL SHEET**

**DATE:** February 23, 2015

<b>To:</b> Rick Lilley Vice President, Regulatory Affairs	<b>From:</b> Leila P. Hann Senior Regulatory Project Manager
<b>Company:</b> Vertex Pharmaceuticals Inc.	Division of Pulmonary, Allergy, and Rheumatology Drug Products
<b>Fax number:</b> 617-961-7789	<b>Fax number:</b> 301-796-9728
<b>Secure Email:</b> Rick_Lilley@vrtx.com	<b>Phone number:</b> 301-796-3367

**Subject:** NDA 206038 (Orkambi) Information Request

**Total no. of pages including cover:** 4

**Comments:**

**Document to be mailed:**                    YES                    xNO

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.

If you are not the addressee, or a person authorized to deliver this document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please notify us immediately by telephone at (301) 796-2300. Thank you.

Your NDA 206038 submitted November 05, 2014, is currently under review and we have the following requests for information:

1. During the review of your application we noted several discrepancies between the coding for your stratification variables (age, gender, and percent predicted FEV<sub>1</sub> at screening) and the actual value for these measurements in your phase 3 trials (VX12-809-103 and VX12-809-104). Reference is made to the subject level dataset ADSL, stratification variables STRAT1, STRAT2, and STRAT3, and variables AGE, AAGE, SEX, and PPFEV1SN.

There were several subjects missing a screening percent predicted FEV<sub>1</sub> measurement but had values for the stratification variable STRAT3. For example, subjects 'VX12-809-103-03-105-01' and 'VX12-809-104-04-519-01' were missing screening values but had values for the stratification variable and were randomized. Additionally for several subjects, the values for stratification variable age (STRAT1: <18 years, >=18 years) do not agree with the values for AGE and AAGE. With respect to gender (STRAT2: male, female), and percent predicted FEV<sub>1</sub> at screening (STRAT3: <70%, >=70%), there are several cases where code for the stratification variable does not coincide with the values for SEX and PPFEV1SN.

The table below is an example of the discrepancies noted.

Subject ID	Stratification Code	Value
VX12-809-103-03-032-01	<18 years	18
VX12-809-104-04-522-02	<18 years	18
VX12-809-103-03-036-05	male	female
VX12-809-103-03-062-03	<70%	71.9%
VX12-809-104-04-531-02	≥70%	61.7%

Clarify these discrepancies in the datasets submitted for studies VX12-809-103 and VX12-809-104.

2. Your program is expected to show that lumacaftor makes a contribution to the claimed effect of your combination product. In section 1.4.2 of the Summary of Clinical Efficacy (page 15), you state, based on the results observed in study VX08-770-104, there was no clinically meaningful benefit of ivacaftor monotherapy after 16 weeks of treatment in subjects homozygous for the F508del-CFTR mutation. This conclusion was based on a difference between ivacaftor monotherapy and placebo of 1.7% in change from baseline in percent predicted FEV<sub>1</sub> over 16 weeks of treatment with a 95% confidence interval (CI) of [-0.6, 4.1]. In section 11.4.2.1 of the VX12-809-103 and VS12-809-104 study reports, you indicate that the effect size for the lumacaftor and ivacaftor combination (LUM 400 mg q12h/IVA 250 mg q12h) over placebo is 2.6% with a 95% CI of [1.2, 4.0] and 3.0% with a 95% CI of [1.6, 4.4], respectively. Provide a quantitative analysis that evaluates the contribution of lumacaftor monotherapy to the combination product, ivacaftor and lumacaftor, or provide other evidence to satisfy this request.

The contribution of ivacaftor does not need to be evaluated as lumacaftor monotherapy seems to decrease FEV1 and lumacaftor as a single ingredient product is not expected to be developed.

Please provide a response to the requests by email (Leila.Hann@fda.hhs.gov) or facsimile (301-796-9728), by Noon on Monday, March 02, 2015. Your response must also be submitted formally to the NDA shortly thereafter. If you have any questions, please contact Leila P. Hann, Regulatory Program Manager, at 301-796-3367.

Drafted by: L. Hann/ February 23, 2015  
Cleared by: L. Zeng/ February 23, 2015  
D. Petullo/ February 23, 2015  
R. Lim/ February 23, 2015  
A. Durmowicz/ February 23, 2015  
S. Barnes/ February 23, 2015  
Finalized by: L. Hann/ February 23, 2015

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

/s/  
-----

LEILA P HANN  
02/23/2015



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration  
Silver Spring, MD 20993

NDA 206038

**PROPRIETARY NAME REQUEST  
CONDITIONALLY ACCEPTABLE**

Vertex Pharmaceuticals Incorporated  
50 Northern Avenue  
Boston, MA 02210

ATTENTION: Rick Lilley, PhD  
Senior Vice President, Global Regulatory Affairs

Dear Dr. Lilley:

Please refer to your New Drug Application (NDA) dated and received July 4, 2014, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Lumacaftor/Ivacaftor Tablets, 200 mg/125 mg.

We also refer to your correspondence, dated and received November 5, 2014, requesting review of your proposed proprietary name, Orkambi.

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

If any of the proposed product characteristics as stated in your November 5, 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 Nichelle Rashid, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-3904. For any other information regarding this application, contact Leila Hann, Regulatory Project Manager in the Office of New Drugs, at (301) 796-3367.

Sincerely,

*{See appended electronic signature page}*

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

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

/s/  
-----

TODD D BRIDGES  
01/27/2015



NDA 206038

**MEETING DENIED**

Vertex Pharmaceuticals, Inc.  
50 Northern Avenue  
Boston, MA 02210

Attention: Rick Lilley  
Vice President, Regulatory Affairs

Dear Mr. Lilley:

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

We also refer to your January 09, 2015, correspondence requesting a type C meeting to discuss the 74 day letter, preparation for the Advisory Committee meeting, and amendments to the bio-analytical study reports. We are denying the meeting because it is premature to discuss the topics listed. There will be an opportunity to discuss the topics during our Mid-Cycle communication which will occur the week of February 17-20.

If you have any questions, call me at (301) 796-3367.

Sincerely,

*{See appended electronic signature page}*

Leila P. Hann  
Senior Regulatory Project Manager  
Division of Pulmonary, Allergy, and Rheumatology  
Products  
Office of Drug Evaluation II  
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/  
-----

LEILA P HANN  
01/16/2015



NDA 206038

**FILING COMMUNICATION -  
FILING REVIEW ISSUES IDENTIFIED**

Vertex Pharmaceuticals, Inc.  
50 Northern Avenue  
Boston, MA 02210

Attention: Rick Lilley  
Vice President, Regulatory Affairs

Dear Mr. Lilley:

Please refer to your New Drug Application (NDA) dated November 05, 2014, received November 05, 2014, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA), for Orkambi (lumacaftor/ivacaftor) oral tablet 200mg/125mg, (b) (4)

We also refer to your pre-submissions and amendments dated July 30, October 02, November 05, and 14, and December 12, 15, and 22, 2014, and January 05, 2014.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Priority**. This application is also subject to the provisions of “the Program” under the Prescription Drug User Fee Act (PDUFA) V (refer to: <http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm272170.htm> . Therefore, the user fee goal date is July 05, 2015.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing requirement/commitment requests by April 09, 2015.

In addition, the planned date for our internal mid-cycle review meeting is February 03, 2015. We are currently planning to hold an advisory committee meeting to discuss this application.

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

**Clinical:**

1. We note that the treatment effect observed in terms of percent predicted FEV1 in studies 103 and 104 was modest, with an effect size of 2.6% (95% CI: 1.2%, 4.0%) and 3.0% (95% CI: 1.6%, 4.4%), respectively. Whether or not this treatment effect represents a clinically meaningful improvement will be a review issue.
2. Inclusion of [REDACTED] <sup>(b)(4)</sup> of the label will be a review issue.

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application. If you respond to these issues during this review cycle, we may not consider your response before we take an action on your application.

**PRESCRIBING INFORMATION**

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

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

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

1. The labeling language for Section 7 (Drug Interactions) should reflect the concomitant medications used in the phase 3 trials. You should submit more specific language, addressing the recommendations for common CF concomitant medicines in Section 7 in the label.
2. In addition, you should include recommendations for managing concomitant administration of the following drug classes in Section 7 of the label:
  - a. Other Antacids/H2 blockers
  - b. Ibuprofen or other anti-inflammatory drugs

- c. Oral hypoglycemic
- d. Anti-depressants

We request that you resubmit labeling (in Microsoft Word format) that addresses these issues by February 06, 2015. The resubmitted labeling will be used for further labeling discussions. Use the SRPI checklist to correct any formatting errors to ensure conformance with the format items in regulations and guidances.

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

### **PROMOTIONAL MATERIAL**

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

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

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

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

### **REQUIRED PEDIATRIC ASSESSMENTS**

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

Because the drug for this indication has orphan drug designation, you are exempt from this requirement.

If you have any questions, call Leila P. Hann, Senior Regulatory Project Manager, at (301) 796-3367.

Sincerely,

*{See appended electronic signature page}*

Badrul A. Chowdhury, M.D., Ph.D.  
Director  
Division of Pulmonary, Allergy, and Rheumatology  
Products  
Office of Drug Evaluation II  
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/  
-----

LYDIA I GILBERT MCCLAIN

01/16/2015

Acting Division Director for Dr. Badrul Chowdhury



NDA 206038

**PRIORITY REVIEW DESIGNATION**

Vertex Pharmaceuticals, Inc.  
50 Northern Avenue  
Boston, MA 02210

Attention: Rick Lilley  
Vice President, Regulatory Affairs

Dear Mr. Lilley:

Please refer to your New Drug Application (NDA) dated November 05, 2014, received November 05, 2014, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA), for Orkambi (lumacaftor/ivacaftor) oral tablet at 200mg/125mg, [REDACTED] (b) (4) [REDACTED].

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application is considered filed 60 days after the date we received your application in accordance with 21 CFR 314.101(a). The review classification for this application is **Priority**. Therefore, the user fee goal date is July 05, 2015.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing requirement/commitment requests by April 09, 2015.

While conducting our filing review, we identified potential review issues and will communicate them to you on or before January 18, 2015.

If you have any questions, call Leila P. Hann, Senior Regulatory Project Manager, at (301) 796-3367.

Sincerely,

*{See appended electronic signature page}*

Badrul A. Chowdhury, M.D., Ph.D.  
Director  
Division of Pulmonary, Allergy, and Rheumatology  
Products  
Office of Drug Evaluation II  
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/  
-----

BADRUL A CHOWDHURY  
12/31/2014



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

**FACSIMILE TRANSMITTAL SHEET**

**DATE:** December 22, 2014

<b>To:</b> Rick Lilley Vice President, Regulatory Affairs	<b>From:</b> Leila P. Hann Senior Regulatory Project Manager
<b>Company:</b> Vertex Pharmaceuticals Inc.	Division of Pulmonary, Allergy, and Rheumatology Drug Products
<b>Fax number:</b> 617-961-7789	<b>Fax number:</b> 301-796-9728
<b>Secure Email:</b> Rick_Lilley@vrtx.com	<b>Phone number:</b> 301-796-3367

**Subject:** NDA 206038 (lumacaftor/ivacaftor) Information Request

**Total no. of pages including cover:** 5

**Comments:**

**Document to be mailed:** YES xNO

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.

If you are not the addressee, or a person authorized to deliver this document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please notify us immediately by telephone at (301) 796-2300. Thank you.

Your NDA 206038 submitted November 05, 2014, is currently under review and we have the following requests for information:

Provide the pooled dataset from combination therapy studies (VX12-809-103 and VX12-809-104) and VX08-770-104 (ivacaftor monotherapy study) with the following variables for ER analysis for efficacy. There should be one record for each unique ID.

1. Unique subject ID
2. Subject ID
3. Study ID
4. Lumacaftor PK metric (predicted steady state AUC, predicted steady state Ctrough, observed steady state Ctrough [one column for each PK metric]) for combination therapy studies (vx12-809-103 and vx12-809-104)
5. Ivacaftor PK metric (predicted steady state AUC, predicted steady state Ctrough, observed steady state Ctrough [one column for each PK metric]) for all studies
6. Baseline percent predicted FEV1
7. Percent predicted FEV1 at week 16 (all studies)
8. Percent predicted FEV1 at week 24 (combination therapy studies)
9. Absolute change from baseline in percent predicted FEV1 at Week 16 (all studies)
10. Absolute change from baseline in percent predicted FEV1 at Week 24 (combination therapy studies)
11. Average absolute change from baseline in percent predicted FEV1 at Week 16 and Week 24 (combination therapy studies)
12. Average relative change from baseline in percent predicted FEV1 at Week 16 and Week 24 (combination therapy studies)
13. Pulmonary Exacerbation (yes/no; 1/0) through week 24 (combination therapy studies)
14. Number of exacerbation events through week 24 (combination therapy studies)
15. Time to first pulmonary exacerbation (days) over 24 weeks (combination therapy studies)
16. Corresponding censoring variable for time-to-event analysis for above (item 15, data censoring at week 24)

17. Pulmonary Exacerbation (yes/no; 1/0) through week 16 (all studies)
18. Number of exacerbation events through week 16 (all studies)
19. Time to first pulmonary exacerbation (days) over 16 weeks (all studies)
20. Corresponding censoring variable for time-to-event analysis for above (item 19, data censoring at week 16)
21. Baseline BMI (all studies)
22. BMI at week 16 (all studies)
23. BMI at week 24 (combination therapy studies)
24. Absolute change from baseline in BMI at week 16 (all studies)
25. Absolute change from baseline in BMI at week 24 (combination therapy studies)
26. Baseline CFQ-R (all studies)
27. CFQ-R at week 16 (all studies)
28. CFQ-R at week 24 (combination therapy studies)
29. Absolute change from baseline in CFQ-R at week 16 (all studies)
30. Absolute change from baseline in CFQ-R at week 24 (combination therapy studies)
31. Planned treatment group
32. Actual treatment group
33. Full Analysis set flag
34. All demographics variable [one variable per column] including gender, body weight, race, age, age groups (<18, >=18 years) etc. Include any other stratification factor used in the study design. Include any demographic variable that is likely to affect PK or efficacy.

Please refer to the following pharmacometric data and models submission guidelines for your submission:

(<http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm180482.htm>)

Please provide a response to the requests by email ([Leila.Hann@fda.hhs.gov](mailto:Leila.Hann@fda.hhs.gov)) or facsimile (301-796-9728), by Noon on Monday, December 29, 2014. Your response must also be submitted formally to the NDA shortly thereafter. If you have any questions, please contact Leila P. Hann, Regulatory Program Manager, at 301-796-3367.

Drafted by: L. Hann/ December 22, 2014  
Cleared by: A. Marathe/ December 22, 2014  
L. Zhao/ December 22, 2014  
J. Chen/ December 22, 2014  
S. Barnes/ December 22, 2014  
Finalized by: L. Hann/ December 22, 2014

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

/s/  
-----

LEILA P HANN  
12/22/2014



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

**FACSIMILE TRANSMITTAL SHEET**

**DATE:** December 18, 2014

<b>To:</b> Rick Lilley Vice President, Regulatory Affairs	<b>From:</b> Leila P. Hann Senior Regulatory Project Manager
<b>Company:</b> Vertex Pharmaceuticals Inc.	Division of Pulmonary, Allergy, and Rheumatology Drug Products
<b>Fax number:</b> 617-961-7789	<b>Fax number:</b> 301-796-9728
<b>Secure Email:</b> Rick_Lilley@vrtx.com	<b>Phone number:</b> 301-796-3367

**Subject:** NDA 206038 (lumacaftor/ivacaftor) Information Request

**Total no. of pages including cover:** 3

**Comments:**

**Document to be mailed:** YES xNO

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.

If you are not the addressee, or a person authorized to deliver this document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please notify us immediately by telephone at (301) 796-2300. Thank you.

Your NDA 206038 submitted November 05, 2014, is currently under review and we have the following request for information:

1. Submit all related ECG waveforms with regard to the QT study report VX12-809-008 to the ECG warehouse at: [www.ecgwarehouse.com](http://www.ecgwarehouse.com)

Please provide a response to the requests by email ([Leila.Hann@fda.hhs.gov](mailto:Leila.Hann@fda.hhs.gov)) or facsimile (301-796-9728), by Noon on Tuesday, January 06, 2015. Your response must also be submitted formally to the NDA shortly thereafter. If you have any questions, please contact Leila P. Hann, Regulatory Program Manager, at 301-796-3367.

Drafted by: L. Hann/ December 18, 2014  
Cleared by: D. Kozeli/ December 15, 2014  
S. Barnes/ December 18, 2014  
Finalized by: L. Hann/ December 18, 2014

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

/s/  
-----

LEILA P HANN  
12/18/2014



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration  
Silver Spring MD 20993

NDA 206038

**INFORMATION REQUEST**

Vertex Pharmaceuticals Incorporated  
Attention: Patricia Hurter, Ph.D., Senior Vice President  
CMC, Preclinical Development and Regulatory Affairs  
50 Northern Avenue  
Boston, MA 02210

Dear Dr. Hurter:

Please refer to your New Drug Application (NDA) submitted July 30, 2014 under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Lumacaftor/ivacaftor Tablets.

We are reviewing the CMC section of your submission and have the following comments and information requests regarding the lumacaftor drug substance and the lumacaftor/ivacaftor fixed dose combination tablets (b) (4). Please provide a prompt written response by January 19, 2015 in order to continue our evaluation of your NDA.



(b) (4)

Sincerely,

Rapti D.  
Madurawe -A

Digitally signed by Rapti D. Madurawe -A  
DN: cn=US, o=U.S. Government, ou=HHS,  
ou=FDA, ou=People,  
0.9.2342.19200300.100.1.1=1300220251,  
cn=Rapti D. Madurawe -A  
Date: 2014.12.17 14:02:14 -05'00'

Rapti Madurawe, Ph.D.  
Branch Chief  
Division of New Drug Quality Assessment II  
Office of New Drug Quality Assessment  
Center for Drug Evaluation and Research



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

**FACSIMILE TRANSMITTAL SHEET**

**DATE:** December 16, 2014

<b>To:</b> Rick Lilley Vice President, Regulatory Affairs	<b>From:</b> Leila P. Hann Senior Regulatory Project Manager
<b>Company:</b> Vertex Pharmaceuticals Inc.	Division of Pulmonary, Allergy, and Rheumatology Drug Products
<b>Fax number:</b> 617-961-7789	<b>Fax number:</b> 301-796-9728
<b>Secure Email:</b> Rick_Lilley@vrtx.com	<b>Phone number:</b> 301-796-3367

**Subject:** NDA 206038 (lumacaftor/ivacaftor) Information Request

**Total no. of pages including cover:** 3

**Comments:**

**Document to be mailed:** YES xNO

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.

If you are not the addressee, or a person authorized to deliver this document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please notify us immediately by telephone at (301) 796-2300. Thank you.

Your NDA 206038 submitted November 05, 2014, is currently under review and we have the following request for information:

1. Regarding Trial VX12-809-103 and VX12-809-104, submit SAS programs that were used to generate tables and figures in your study report.

Please provide a response to the requests by email (Leila.Hann@fda.hhs.gov) or facsimile (301-796-9728), by Noon on Tuesday, December 23, 2014. Your response must also be submitted formally to the NDA shortly thereafter. If you have any questions, please contact Leila P. Hann, Regulatory Program Manager, at 301-796-3367.

Drafted by: L. Hann/ December 16, 2014  
Cleared by: L. Zeng/ December 16, 2014  
D. Petullo/ December 16, 2014  
S. Barnes/ December 16, 2014  
Finalized by: L. Hann/ December 16, 2014

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

/s/  
-----

LEILA P HANN  
12/16/2014



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

**FACSIMILE TRANSMITTAL SHEET**

**DATE:** December 09, 2014

<b>To:</b> Rick Lilley Vice President, Regulatory Affairs	<b>From:</b> Leila P. Hann Senior Regulatory Project Manager
<b>Company:</b> Vertex Pharmaceuticals Inc.	Division of Pulmonary, Allergy, and Rheumatology Drug Products
<b>Fax number:</b> 617-961-7789	<b>Fax number:</b> 301-796-9728
<b>Secure Email:</b> Rick_Lilley@vrtx.com	<b>Phone number:</b> 301-796-3367

**Subject:** NDA 206038 (lumacaftor/ivacaftor) Information Request

**Total no. of pages including cover:** 3

**Comments:**

**Document to be mailed:** YES xNO

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.

If you are not the addressee, or a person authorized to deliver this document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please notify us immediately by telephone at (301) 796-2300. Thank you.

Your NDA 206038 submitted November 05, 2014, is currently under review and we have the following requests for information:

1. Regarding Site 091 that participated in Study Protocol VX12-809-103, the study subject data listings should capture the following, as applicable:
  - a. Subject discontinuation (If applicable per treatment group: site subject number, screening visit date, randomization date (if applicable), date of first dose/last dose, date of discontinuation, reason for discontinuation).
  - b. Randomization list
  - c. Concomitant medication list (non-study medications).
  - d. All adverse events (If applicable per treatment group: preferred term/investigator entry, date start/stopped, severity/resolution, Serious Adverse Event (yes, no), death (yes/no)).
  - e. Primary efficacy endpoint [e.g., raw data for the forced expiratory volume in 1 second (FEV1) from baseline to Week 24/end-of-study visit (visit # and corresponding date)].
  - f. Protocol deviations or violations
2. In separate files per principal study investigator, please provide information similar to the information requested in comment 1 for Protocol Study Protocol VX12-809-104 (Site 006 and Site 009, respectively).
3. Provide the updated principal investigator names, physical addresses, and a contact e-mail/phone numbers.

Please provide a response to the requests by email (Leila.Hann@fda.hhs.gov) or facsimile (301-796-9728), by Noon on Friday, December 12, 2014. Your response must also be submitted formally to the NDA shortly thereafter. If you have any questions, please contact Leila P. Hann, Regulatory Program Manager, at 301-796-3367.

Drafted by: L. Hann/ December 08, 2014  
Cleared by: A. Orenca/ December 08, 2014  
R. Lim/ December 09, 2014  
A. Durmowicz/ December 09, 2014  
S. Barnes/ December 08, 2014  
Finalized by: L. Hann/ December 08, 2014

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

/s/  
-----

LEILA P HANN  
12/09/2014

## **Executive CAC**

**Date of Meeting:** November 18, 2014

**Committee:** Paul Brown, Ph.D., OND IO, Acting Chair  
Tim McGovern, Ph.D., OND IO, Member  
Ron Wange, Ph.D., DMEP, Alternate Member  
Timothy Robison, Ph.D., DPARP, Pharm Tox Team Leader  
Andrew Goodwin, Ph.D., DPARP, Presenting Reviewer  
Min Min, Ph.D., OB/DB-6, Observer (Statistics Reviewer)

Author of Minutes: Andrew Goodwin

The following information reflects a brief summary of the Committee discussion and its recommendations.

**NDA #** 206038

**IND #** 79521

**Drug Name:** Lumacaftor (VX-809)

**Sponsor:** Vertex Pharmaceuticals

### **Tg.rasH2 Mouse Carcinogenicity Study Final Results**

Lumacaftor (VX-809) is a proposed cystic fibrosis transmembrane conductance regulator (CFTR) in development for the treatment of cystic fibrosis patients homozygous for the  $\Delta F508$  mutation. NDA 206038 was submitted on November 5, 2014 seeking approval for a fixed-dose combination product containing lumacaftor and ivacaftor. A two-year rat carcinogenicity study is ongoing and will be completed as a post-marketing requirement.

VX-809 was negative for genotoxic potential in an in vitro bacterial reverse mutation assay, in vitro CHO cell chromosomal aberration assay, and in vivo mouse micronucleus assay.

In a six-month oral gavage carcinogenicity study in Tg.rasH2 mice, males received VX-809 at 200, 700, or 2000 mg/kg/day and females received VX-809 at 200, 500, or 1500 mg/kg/day. Two negative control groups received vehicle (0.5% methylcellulose (400 cps), 0.5% Tween 80, 0.05% simethicone in deionized water) or deionized water and a positive control group was administered urethane.

There were no effects on survival in VX-809 groups compared to the control groups. Dose-related clinical signs in males and females included hunched posture and rapid / shallow breathing. Additional findings in males included decreased motor activity, hyperactivity, ruffled

fur, and swelling. Males treated with VX-809 showed a slight trend towards decreased body weights at 700 and 2000 mg/kg/day (-7% vs. control, not statistically significant).

Females receiving VX-809 at 1500 mg/kg/day had an increased incidence of Harderian gland adenoma (4/25 = 16%) and carcinoma (1/25 = 4%) with a combined incidence of 5/25 or 20%. Data from 26 studies conducted at the test facility indicated historical control incidences in females of 2.8% (range 0-16%), 0.7% (range 0-8%), and 3.5% (range 0-24%) for Harderian gland adenoma, carcinoma, and combined incidence, respectively. Based on the fact that the incidence at the high-dose remained within the historical control range, these findings were not considered test article-related.

There were no notable tumor findings in males at doses up to 2000 mg/kg/day.

The urethane-treated positive control group exhibited lung adenomas, lung carcinomas and spleen hemangiosarcomas. These findings were generally consistent with historical control data for this known carcinogen.

Toxicokinetic analysis showed that VX-809 exposure increased less than dose-proportionally from 200 to 1500 (females) or 2000 (males) mg/kg/day and was greater in females vs. males. At Day 178, AUC<sub>0-24hr</sub> values at the highest doses tested were 1390 and 2090 ug\*hr/mL in males and females, respectively.

### **Executive CAC Recommendations and Conclusions**

Tg.rasH2 mouse:

- The Committee concurred that the study was acceptable, noting prior Exec CAC concurrence with the protocol.
- The Committee concurred that there were no drug-related neoplasms in the study.

Paul Brown, Ph.D.

Acting Chair, Executive CAC

cc:\

/Division File, DPARP  
/TRobison, DPARP  
/AGoodwin, DPARP  
/LHann, DPARP  
/ASeifried, OND IO

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

/s/  
-----

ADELE S SEIFRIED  
11/19/2014

PAUL C BROWN  
11/19/2014



NDA 206038

## NDA ACKNOWLEDGMENT

Vertex Pharmaceuticals, Inc.  
50 Northern Avenue  
Boston, MA 02210

Attention: Rick Lilley  
Vice President, Regulatory Affairs

Dear Mr. Lilley:

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

Name of Drug Product: Orkambi (lumacaftor/ivacaftor) oral tablet 200mg/125mg,  
(b) (4)

Date of Application: November 05, 2014

Date of Receipt: November 05, 2014

Our Reference Number: NDA 206038

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 January 04, 2014, in accordance with 21 CFR.

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).

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

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

You did not include such certification when you submitted this application. You may use Form FDA 3674, "Certification of Compliance, under 42 U.S.C. § 282(j)(5)(B), with Requirements of ClinicalTrials.gov Data Bank," [42 U.S.C. § 282(j)] to comply with the certification requirement. The form may be found at <http://www.fda.gov/opacom/morechoices/fdaforms/default.html>.

In completing Form FDA 3674, you should review 42 USC § 282(j) to determine whether the requirements of FDAAA apply to any clinical trial(s) referenced in this application. Please note that FDA published a guidance in January 2009, "Certifications To Accompany Drug, Biological Product, and Device Applications/Submissions: Compliance with Section 402(j) of The Public Health Service Act, Added By Title VIII of the Food and Drug Administration Amendments Act of 2007," that describes the Agency's current thinking regarding the types of applications and submissions that sponsors, industry, researchers, and investigators submit to the Agency and accompanying certifications. Additional information regarding the certification form is available at:

<http://www.fda.gov/RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticActFDCA/ct/SignificantAmendmentstotheFDCAAct/FoodandDrugAdministrationAmendmentsActof2007/ucm095442.htm>. Additional information regarding Title VIII of FDAAA is available at: <http://grants.nih.gov/grants/guide/notice-files/NOT-OD-08-014.html>. Additional information for registering your clinical trials is available at the Protocol Registration System website <http://prsinfo.clinicaltrials.gov/>.

When submitting the certification for this application, **do not** include the certification with other submissions to the application. Submit the certification within 30 days of the date of this letter. In the cover letter of the certification submission clearly identify that it pertains to **NDA 206038** submitted on November 05, 2014, and that it contains the FDA Form 3674 that was to accompany that application.

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

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

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

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, please see <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm>.

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

If you have any questions, call me at (301) 796-3367.

Sincerely,

*{See appended electronic signature page}*

Leila P. Hann  
Senior Regulatory Project Manager  
Division of Pulmonary, Allergy, and Rheumatology  
Products  
Office of Drug Evaluation II  
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/  
-----

LEILA P HANN  
11/18/2014



NDA 206038

**INFORMATION REQUEST**

Vertex Pharmaceuticals Incorporated  
Attention: Patricia Hurter, Ph.D., Senior Vice President  
CMC, Preclinical Development and Regulatory Affairs  
50 Northern Avenue  
Boston, MA 02210

Dear Dr. Hurter:

Please refer to your New Drug Application (NDA) submitted July 30, 2014 under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Lumacaftor/ivacaftor Tablets.

We are reviewing the CMC section of your submission and have the following comments and information requests. Please provide a prompt written response by November 14, 2014 in order to continue our evaluation of your NDA.

(b) (4)

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

Rapti D. Madurawe -A

Digitally signed by Rapti D. Madurawe -A  
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA,  
ou=People, 0.9.2342.19200300.100.1.1=1300220251,  
cn=Rapti D. Madurawe -A  
Date: 2014.10.17 17:57:08 -04'00'

*{See appended electronic signature page}*

Rapti Madurawe, Ph.D.  
Branch Chief  
Division of New Drug Quality Assessment II  
Office of New Drug Quality Assessment  
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/  
-----

YOUBANG LIU  
10/17/2014



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

**FACSIMILE TRANSMITTAL SHEET**

**DATE:** September 04, 2014

<b>To:</b> Patricia Hurter, Ph.D. Senior VP, CMC, Preclinical Development and Regulatory Affairs	<b>From:</b> Leila P. Hann Senior Regulatory Project Manager
<b>Company:</b> Vertex Pharmaceuticals, Inc.	Division of Pulmonary, Allergy, and Rheumatology Drug Products
<b>Fax number:</b> 617-341-6803	<b>Fax number:</b> 301-796-9728
<b>Secure Email:</b> patricia_hurter@vrtx.com	<b>Phone number:</b> 301-796-3367

**Subject:** NDA 206308 (ivacaftor/lumacaftor) Information Request

**Total no. of pages including  
cover:** 3

**Comments:**

**Document to be mailed:** YES xNO

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.

If you are not the addressee, or a person authorized to deliver this document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please notify us immediately by telephone at (301) 796-2300. Thank you.

Your NDA 206038 pre-submission received July 30, 2014, is currently under review and we have the following requests for information:

1. Provide dissolution profile comparisons between the to-be-marketed and the clinical formulations [REDACTED] (b) (4)
2. Provide information for the formulations used in study 007, including the formulation number, batch number, detailed composition, and the dissolution data.
3. Provide the raw data to support the following figures and tables in Section 3.2.P.2.3: Figure 4, Table 13, Table 14, Figure 7, Figure 12, Table 24, Table 25, Figure 13, Figure 14, Table 26, Table 27, Figure 15 – 20, Table 34 – 37, Table 43, Figure 24, Figure 30 – 34, Table 57 – 66 Please note that although the figures or tables only present the dissolution data at a specific time point ([REDACTED] (b) (4) minutes), the available dissolution data at other time points (such as [REDACTED] (b) (4) minutes) should be provided.
4. Provide data to support the alternative dissolution testing proposed for [REDACTED] (b) (4).
5. Provide the results of the investigations for the dissolution differences between different manufacturing sites.

If you have any questions, please contact Leila P. Hann, Regulatory Program Manager, at 301-796-3367.

Drafted by: L. Hann/ September 03, 2014  
Cleared by: C. Bertha/ September 03, 2014  
J. Duan/ September 04, 2014  
S. Barnes/ September 03, 2014  
Finalized by: L. Hann/ September 04, 2014

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

/s/  
-----

LEILA P HANN  
09/04/2014



IND79521

**MEETING MINUTES**

Vertex Pharmaceuticals  
50 Northern Avenue  
Boston, MA 02210-1862

Attention: Gemma Slade  
Director, Regulatory Affairs

Dear Ms. Slade:

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

We also refer to the meeting between representatives of your firm and the FDA on August 12, 2014. The purpose of the meeting was to discuss plans for submitting a NDA for lumacaftor /ivacaftor combination product for use in the treatment of Cystic Fibrosis.

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

If you have any questions, call me at (301) 796-2284.

Sincerely,

*{See appended electronic signature page}*

Angela Ramsey, MPH, MSN, RN  
Senior Program Management Officer  
Division of Pulmonary, Allergy, and Rheumatology  
Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

Enclosure:  
Meeting Minutes



**FOOD AND DRUG ADMINISTRATION**  
CENTER FOR DRUG EVALUATION AND RESEARCH

---

**MEMORANDUM OF MEETING MINUTES**

**Meeting Type:** Type B  
**Meeting Category:** IND

**Meeting Date and Time:** August 12, 2014 at 1:30- 3:00 pm EST  
**Meeting Location:** FDA White Oak, Building 22, Conference Room 1311

**Application Number:** 79521  
**Product Name:** lumacaftor  
**Indication:** Cystic Fibrosis  
**Sponsor/Applicant Name:** Vertex Pharmaceuticals

**Meeting Chair:** Badrul A. Chowdhury, MD  
**Meeting Recorder:** Angela Ramsey, MPH, MSN, RN

**FDA ATTENDEES**

Badrul A. Chowdhury, M.D., Ph.D., Division Director  
Anthony Durmowicz, M.D., Clinical Team Leader  
Timothy Robison, Ph.D., D.A.B.T., Non-Clinical Team Leader  
Andrew Goodwin, Ph.D., Non-Clinical Reviewer  
Gregory Levin, Ph.D., Statistical Reviewer  
David Petullo, M.S., Statistical Team Leader  
Satjit Brar, Ph.D., Clinical Pharmacology Supervisor  
Jianmeng Chen, Ph.D., Clinical Pharmacology Reviewer  
Craig Bertha, Ph.D., CMC Lead

**SPONSOR ATTENDEES**

Patricia Hurter, PhD, Senior Vice President, R&D Management, Regulatory Affairs  
Antoinette Paone, PhD, Vice President, Global Regulatory Affairs  
Gemma Slade, Director, Global Regulatory Affairs  
Sean McNiff, Senior Director, Global Regulatory Affairs  
Kate Jurcik, Associate Director, Global Regulatory Affairs  
Kiley Herrick, Senior Manager, Global Regulatory Affairs  
Jeffrey Chodakewitz, MD, Chief Medical Officer and Senior Vice President, Global Medicines  
David Waltz, MD, Senior Director, Clinical Development  
Dennis Dean, PhD, Senior Vice President, Exploratory Development  
Graeme Smith, PhD, Senior Director, Drug Safety Evaluation  
Mei-Hsiu Ling, PhD, Senior Director, Biostatistics

Xiaohong Huang, PhD, Associate Director, Biostatistics  
Paul Panorchan, PhD, Associate Director, Clinical Pharmacology  
Christopher Simard, MD, Senior Director, Global Patient Safety

## **BACKGROUND**

Vertex Pharmaceuticals submitted a Type B meeting request dated, June 6, 2014, to discuss plans for submitting a NDA for lumacaftor in combination with ivacaftor for treatment of patients with Cystic Fibrosis who are homozygous for the *F508* mutation in the *CFTR* gene.. Vertex submitted background material dated, July 31, 2014. Upon review of the material, the Division responded via secure email on August 11, 2014. Vertex requested to continue with the face-to-face meeting to discuss responses to question 1, 2, 4, 6, and additional comments 1, 2, and 3.

The content of the email is below. Any discussions that occurred during the meeting are captured directly under the relevant responses. The sponsor's questions are in bold italics; the Division responses are in italics; and discussion is in normal font. Vertex provided handouts during the meeting which are included at the end of the minutes.

## **DISCUSSION**

### **Question 1:**

***Ivacaftor is classified as a CFTR potentiator (see US Prescribing Information [USPI] for Kalydeco). Based on the mechanism of action, Vertex considers lumacaftor to be a***

(b) (4)

***In the proposed prescribing information for the lumacaftor and ivacaftor combination therapy product, Vertex proposes to identify the product (by trade name) first as a (b) (4) and thereafter to identify the active substances as a (b) (4) and potentiator, respectively. Does the Division agree?***

### **FDA Response:**

*We do not agree. Established pharmaceutical classes (EPCs) are associated with active moieties and therefore your proposal to assign an additional EPC to your combination product is not appropriate. Pharmaceutical classification of lumacaftor will be a review issue.*

### **Discussion:**

The Sponsor acknowledged and clarified the Division's guidance that a third pharmaceutical classification term would not be used to describe the combination product, as well as that the classification of lumacaftor would be a review issue. The Division requested that the Sponsor include pharmacology study reports in support of their proposed mechanism of action description in the NDA.

### **Question 2:**

***Does the Division agree that the NDA submission schedule, including the proposed inspection readiness dates, is acceptable?***

**FDA Response:**

*While your proposed submission schedule is generally acceptable, we have concerns regarding inspection site readiness. In general, all sites should be ready for inspection at the time of submission of final NDA elements (modules). To aid us in that regard, provide a timeline capturing critical PAI readiness items and their corresponding completion date. We would like explicit clarification regarding:*

- 1. Site readiness elements and activities that will be complete on November 7th*
- 2. Site readiness elements that will be complete on January 7*
- 3. Site readiness elements that will not be complete by January 7.*

*In addition, to expedite the review of the nonclinical elements of the NDA, if available, we encourage earlier submission of the data from the six-month mouse carcinogenicity study to the IND.*

**Discussion:**

Vertex referenced slide 43 in handout with proposed timelines for inspection and submission of mouse carcinogenicity data. The Division stated that the proposed plan appears reasonable.

**Question 3:**

***Does the Division agree that Studies 103 and 104 to support the demonstration of efficacy, and Studies 103, 104, and 105 to support safety in the target population, are considered the covered studies for this NDA under 21 CFR 54 for purposes of Financial Disclosure?***

**FDA Response:**

*Studies 103, 104 and 105 would be considered covered studies for this proposed NDA. Study 102, which includes the dose ranging information and initial findings of lumacaftor monotherapy (in which patients demonstrated a dose-dependent decrease in lung function when receiving lumacaftor alone), also constitutes a covered study under 21 CFR 54, because it provides data which “FDA would rely on to establish that the product is effective”.*

*In addition to the above studies, the protocol, study report, and data for your phase 2 study, 770-104, which evaluated ivacaftor 150 mg q12h monotherapy in CF patients homozygous for the F508del-CFTR mutation, should also be submitted as part your application.*

**Discussion:**

The Division noted that if Vertex was going to rely on study 101 for sweat chloride data, then it would also likely be considered a covered study.

**Question 4:**

***Does the Division agree that the proposed clinical data package is sufficient to support the NDA submission for lumacaftor and ivacaftor combination therapy for the proposed indication?***

FDA Response:

*We agree that your proposed clinical data package (as well as the data for study 770-104 requested in response to Question 3 above) would be sufficient for review. Whether this package is sufficient to support the NDA approval will be a review issue.*

*Additional Statistical comments:*

*Although your phase 3 studies demonstrated statistically significant improvements over placebo in percent predicted FEV<sub>1</sub>, several potential review issues have been identified.*

- 1. The estimated mean absolute percent predicted FEV<sub>1</sub> improvements over placebo for the proposed 400 mg q12h / 250 mg q12h dose of lumacaftor/ivacaftor in Studies 103 and 104 were 2.6% (95% CI: 1.2%, 4.0%) and 3.0% (95% CI: 1.6%, 4.4%), respectively. It will be important to consider if those relatively small mean improvements in FEV<sub>1</sub> are clinically relevant. This issue is especially relevant when looked at in the context of the results from Study 770-104 in the ivacaftor program, in which a mean absolute change from baseline in percent predicted FEV<sub>1</sub>, relative to placebo of 1.7% (95% confidence interval: -0.6%, +4.1%) was interpreted as not having a clinically meaningful treatment effect. Based on these results and other secondary endpoint data, the Limitations of Use section of the Kalydeco labeling indicates that Kalydeco is “Not effective in patients with CF who are homozygous for the F508del mutation in the CFTR gene.”*
- 2. In light of the results from your phase 2 study, 102, where results indicated a potential dose-dependent decrease in FEV<sub>1</sub> following treatment with lumacaftor monotherapy, it may be difficult to evaluate the contribution of lumacaftor in terms of efficacy for your combination product.*

Discussion:

Vertex acknowledged that the effect size noted for FEV<sub>1</sub> in the current combination program, Ivacaftor/lumacaftor, was similar to an effect size observed in the ivacaftor monotherapy program that was deemed ineffective, Study 770-104. However, Vertex stated that efficacy should be extended beyond FEV<sub>1</sub> to other clinically meaningful endpoints. As a result, when looking at the totality of data, i.e., primary and supportive secondary endpoints, they believe the combination product has a beneficial effect beyond that observed in Study 770-104.

The Division emphasized that the submission should address two issues: (1) the clinical relevance of the effect size in the phase 3 studies, especially taking into account results and labeling for the ivacaftor monotherapy in this population; and (2) the level of evidence from clinical data that lumacaftor contributes to the efficacy of the combination product, especially considering the trend toward a dose-dependent decrease in FEV<sub>1</sub> observed with the lumacaftor monotherapy. The Division also agreed that secondary endpoint data would be an important part of the overall evaluation of effectiveness.

Question 5:

*Does the Division agree with the planned population PK and PK/PD analysis?*

FDA Response:

*In general, the population PK and PK/PD approach is acceptable. In addition to the analysis based on model predicted PK parameters, PK/PD analysis based on the observed PK information (e.g., observed Ctrough) should also be provided.*

*Submit the data, NONMEM control streams, and scripts used to generate the final population PK model, PK/PD model, and associated plots. Data files should be submitted as SAS transport files with \*.xpt format (e.g. Data1.xpt) and other files be submitted as ASCII text files with \*.txt extension (e.g.:myfile\_ctl.txt, myfile\_out.txt).*

Discussion:

No discussion occurred.

**Question 6:**

***Does the Division agree that the proposal described below is sufficient for meeting the requirement for an ISE and ISS in the combination therapy NDA?***

FDA Response:

*Yes, your proposal is reasonable.*

*We note that page 28 of your amended meeting package describes that a “Study 106” will be included within the Safety Update, but no additional information/description is provided, nor is Study 106 included in your Appendix I, the list of 17 studies to be included within the NDA submission. Please clarify to which Study 106 you are referring (is this VX770-011-106, under IND 74,633, the lung clearance index study, or another under the VX-809 program?).*

Discussion:

Vertex clarified that the proposed Study 106 will be conducted in a population of patients with CF with more severe lung disease who otherwise would not be able to meet the inclusion/exclusion criteria of a typical clinical efficacy trial.

**Question 7:**

***If the NDA filing for the lumacaftor and ivacaftor combination therapy is granted Priority Review, Vertex is anticipating providing the safety update per 21 CFR 314.50(d)(5) to the Division 90 days after the initial NDA submission (as previously discussed with FDA in a Type B meeting on 08 January 2014). Does the Division agree with this timing for the safety update? Does the Division agree with the proposed content of the safety update?***

FDA Response:

*Yes, your proposal is acceptable.*

Discussion:

No discussion occurred.

**Question 8:**

***Does the Division agree with the Vertex plan to submit datasets in CDISC SDTM format? Analysis datasets will be in accordance with FDA eCTD Study Data Specifications. As a review aid, Vertex will provide the SAS programs used to derive the ADaM datasets. The code will be provided in bookmarked PDF format without links to the applicable domains. Is this plan acceptable to the Division?***

**FDA Response:**

*Your approach is acceptable.*

**Discussion:**

No discussion occurred.

**Question 9:**

***Vertex intends to file an NDA for lumacaftor and ivacaftor combination therapy in November 2014 following successful completion of the pivotal Phase 3 studies (Studies 103 and 104). Based on analyses of the individual studies and pooled data, Vertex considers the appropriate dose regimen for commercialization to be LUM 400 mg q12h/IVA 250 mg q12h and intends to file an NDA requesting approval of this regimen. Does the Division agree with the rationale proposed below?***

**FDA Response:**

*Your proposal appears reasonable, but the determination of efficacy and safety for the dose chosen cannot be determined until the data provided in the NDA is reviewed.*

**Discussion:**

No discussion occurred.

**Additional Comments:**

(b) (4)

**Discussion:**

No discussion occurred.

- *We remind you of our discussion during the Type B meeting under this IND, held January 8<sup>th</sup>, 2014, during which we discussed the importance of inclusion of pharmacodynamic sweat chloride data. From this package, it is not clear how much PD data you will submit within the NDA. While we acknowledged that sweat chloride was not actively*

*collected on all patients, the statistical discussion at the January meeting included options for evaluation of this data.*

Discussion:

Vertex mentioned that due to logistics and timing issues that sweat chloride data were not collected in Studies 103 or 104. For labeling purposes, they proposed that data from Study 101 may be acceptable.

- *Provide your justification/rationale why you believe that the decline in mature CF with chronic use of ivacaftor demonstrated in in vitro systems, described in recent publications in Science Translational Medicine (July 23, 2014 issue), does not apply to the F508del-CFTR homozygous patient population evaluated in Studies 103 and 104, and would not be responsible for a decline over time in functional CFTR in this patient population.*

Discussion:

Vertex pointed out that the results of studies conducted in *in vitro* systems can be very dependent on the conditions under which the studies are conducted. In this particular case, “long-term” *in vitro* exposure of cells used for in vitro studies was only for about 24 hrs. In addition, other similar studies conducted in *in vitro* systems have yielded results that conflict to those from the Science Translational Medicine piece.

- *We wish to notify you that there is potential that your Application may be determined to require an Advisory Committee meeting.*

Discussion:

No discussion occurred.

Additional Nonclinical comment:

*To facilitate statistical review of the 26-week TgrasH2 mouse carcinogenicity study, submit the tumor data sets in conformance to the electronic format specified in Study Data Specifications, Version 2.0 (July 18, 2012). This document is available at:*

*<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm>*

Additional Statistical Requests:

*You should submit any relevant DMC charters, and notes from all DMC meetings including any closed sessions as part of your application.*

**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](mailto:pdit@fda.hhs.gov). For further guidance on pediatric product development, please refer to: <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm>.

## **PRESCRIBING INFORMATION**

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

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

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

## **ATTACHMENTS AND HANDOUTS**

Vertex slides

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

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

/s/  
-----

ANGELA H RAMSEY  
09/02/2014



NDA 206038

**ACKNOWLEDGE NDA PRESUBMISSION**

Vertex Pharmaceuticals Incorporated  
50 Northern Avenue  
Boston, MA 02210

Attention: Patricia Hurter, Ph.D.  
Senior Vice President, CMC, Preclinical Development, and Regulatory Affairs

Dear Dr. Hurter:

We have received your pre-submission of product quality information for the following:

Name of Drug Product: lumacaftor/ivacaftor, (VX-809/VX-770) tablet at 200mg/125mg,  
(b) (4)

Date of Submission: July 30, 2014

Date of Receipt: July 30, 2014

Our Reference Number: NDA 206038

We will review this presubmission as resources permit. Pre-submissions are not subject to a review clock or to a filing decision by FDA until the application is complete.

Please cite the NDA listed above at the top of the first page of any communications concerning this supplemental application. Unless you are using the FDA Electronic Submissions Gateway (ESG), send all submissions by overnight mail or courier to the following address:

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

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

If you have any questions, call me at (301) 796-3367.

Sincerely,

*{See appended electronic signature page}*

Leila P. Hann  
Senior Regulatory Project Manager  
Division of Pulmonary, Allergy, and Rheumatology  
Products  
Office of Drug Evaluation II  
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/  
-----

LEILA P HANN  
08/26/2014



IND 79521

**MEETING MINUTES**

Vertex Pharmaceuticals Incorporated  
Attention: Stephanie Krogmeier, Ph.D.  
Director, Regulatory Affairs CMC  
130 Waverly Street  
Cambridge, MA 02139-4242

Dear Dr. Krogmeier:

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

We also refer to your March 21, 2014 correspondence requesting a Type B Pre-NDA CMC Meeting to discuss the implementation of a drug product continuous manufacturing process, relatively new technology, on an accelerated breakthrough therapy timeline. The meeting package was received on April 7, 2014.

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

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

Sincerely,

*{See appended electronic signature page}*

Eric P. Duffy, Ph.D.  
Division Director  
Division of New Drug Quality Assessment III  
Office of New Drug Quality Assessment  
Center for Drug Evaluation and Research

Enclosure:  
Meeting Minutes

## MEMORANDUM OF MEETING MINUTES

**Meeting Type:** Type B, Pre-NDA CMC  
**Meeting Category:** IND

**Meeting Date and Time:** May 16, 2014, 9:00 AM to 11:00 AM (ET)  
**Meeting Location:** CDER WO Bldg 22, Room 1419

**Application Number:** IND 79521  
**Product Name:** Lumacaftor  
**Indication:** Cystic Fibrosis  
**Sponsor/Applicant Name:** Vertex Pharmaceuticals, Inc.

**Meeting Chair:** Eric P. Duffy  
**Meeting Recorder:** Youbang Liu

### FDA ATTENDEES

Eric P. Duffy, Ph.D., Division Director, Division III, ONDQA  
Rapti Madurawe, Ph.D., Branch Chief, Branch V, ONDQA  
Sharmista Chatterjee, Ph.D., CMC Lead for QbD, ONDQA  
Craig Bertha, Ph.D., Acting CMC Lead, ONDQA  
Art Shaw, Ph.D., Senior CMC Reviewer, ONDQA  
Celia Cruz, Ph.D., Senior CMC Reviewer, ONDQA  
John Duan, Ph.D., Pharmacologist, ONDQA  
Youbang Liu, Ph.D., Regulatory Project Manager, ONDQA  
Mahesh Ramanadham, Branch Chief, OC,  
Anthony Durmowicz, M.D., Medical Officer, DPARP  
Ramon Martinez, Pre-Approval Manager, NEW-DO  
Rodriguez, Rebeca, Consumer Safety Officer, ORA

### EMA ATTENDEES (via phone)

Robert Bream  
Clement Lagalice  
Keith Pugh  
Andrea Ruggiero  
Oyvind Holte

### VERTEX ATTENDEES

Stephanie Krogmeier, Ph.D., Director, Regulatory Affairs CMC  
Tom Hansen, Ph.D., Associate Director, Regulatory Affairs CMC  
Antoinette Paone, M.S., MBA, Vice President, Regulatory Affairs  
Patricia Hurter, Ph.D., Sr. Vice President, Global Pharmaceutical Development and Acting Head of Regulatory Affairs  
Marco Verwijs, Ph.D., Associate Director, Formulation Development

Hayden Thomas, Ph.D., Vice President, Formulation Development  
Kelly Swinney, Ph.D., Director, Analytical Development  
David Nadig, Ph.D., Vice President, Analytical Development  
Patrick Connelly, Ph.D., Principal Scientific Fellow, Materials, Discovery, and Characterization  
Thomas Gandek, Ph.D., Vice President, Technical Operations  
Geny Doss, Sr. Director, Quality Assurance

## 1.0 BACKGROUND

Lumacaftor (VX 809; IND 79,521) is being developed clinically in combination with ivacaftor (VX 770; IND 74,633). Ivacaftor is approved as 150 mg tablets for use as a monotherapy in the United States (NDA 203,188) under the tradename Kalydeco™. Lumacaftor in combination with ivacaftor is indicated for the treatment of Cystic Fibrosis (CF) in patients aged 12 years and older who are homozygous for the F508del mutation in the CF transmembrane conductance regulator (CFTR) gene.

Vertex Pharmaceuticals, Inc. has developed a continuous manufacturing process for lumacaftor/ivacaftor drug product under a Quality by Design (QbD) paradigm and is currently preparing the marketing application. The purpose of this Type B Pre-NDA CMC Meeting is to seek for Agency feedback on the following:

- CMC submission plan
- Stability and shelf life
- Dissolution specification
- Control of Physical form
- Vertex [REDACTED] (b) (4)
- [REDACTED] (b) (4)

The FDA Meeting Preliminary Comments (including EMA's inputs) were sent to Vertex on May 14, 2014 (Attachment 1). Vertex provided a PowerPoint presentation (Attachment 2) to address Agency's comments and facilitate further discussion before the meeting.

EMA participated the meeting via phone and Adobe Connect.

## 2.0 DISCUSSION

After Dr. Eric Duffy's opening remarks, Vertex started presentation. The meeting discussions were primarily concentrated on the following areas that need clarification or further discussion.

**Question 6:** *Does the Agency agree with the proposed dissolution specification?*

**FDA Response to Question 6:** We noticed that you changed the proposed dissolution specification for lumacaftor from  $Q = \frac{(b)}{(4)}\%$  at 20 minutes to  $\frac{(b)}{(4)}$  minutes. The proposal has

to be justified. There are three issues to be resolved before the appropriate dissolution specifications can be set.

(b) (4)

**Additional Comment**

(b) (4)

**Meeting Discussion:**

Vertex acknowledged the three concerns raised in the FDA preliminary comments, and provided justification for the proposed lumacaftor dissolution specification. Vertex clarified that lot numbers used in the (b) (4) material for Question 6 were for clinical tablets (b) (4) while lot numbers used in the Stability and Shelf-life Update section of the (b) (4) material were for samples from the same tablet lots, which were (b) (4) for formal stability studies.

Vertex stated that dissolution data for both FDC formulations, for tablets dosed in the pivotal Phase 3 clinical studies, were given in the meeting information package. Example dissolution data were presented (slide 6) and discussed (b) (4) FDC tablets dosed in Phase 3, as justification for a lumacaftor dissolution specification of  $Q = \frac{(b)}{(4)}\%$  at  $\frac{(b)}{(4)}$  minutes.

FDA presented dissolution data analysis (Attachment 3). The data analysis raised concerns about variability between manufacturing sites.

(b) (4)

[Redacted] (b) (4)

Vertex noted that tablets manufactured at [Redacted] (b) (4)

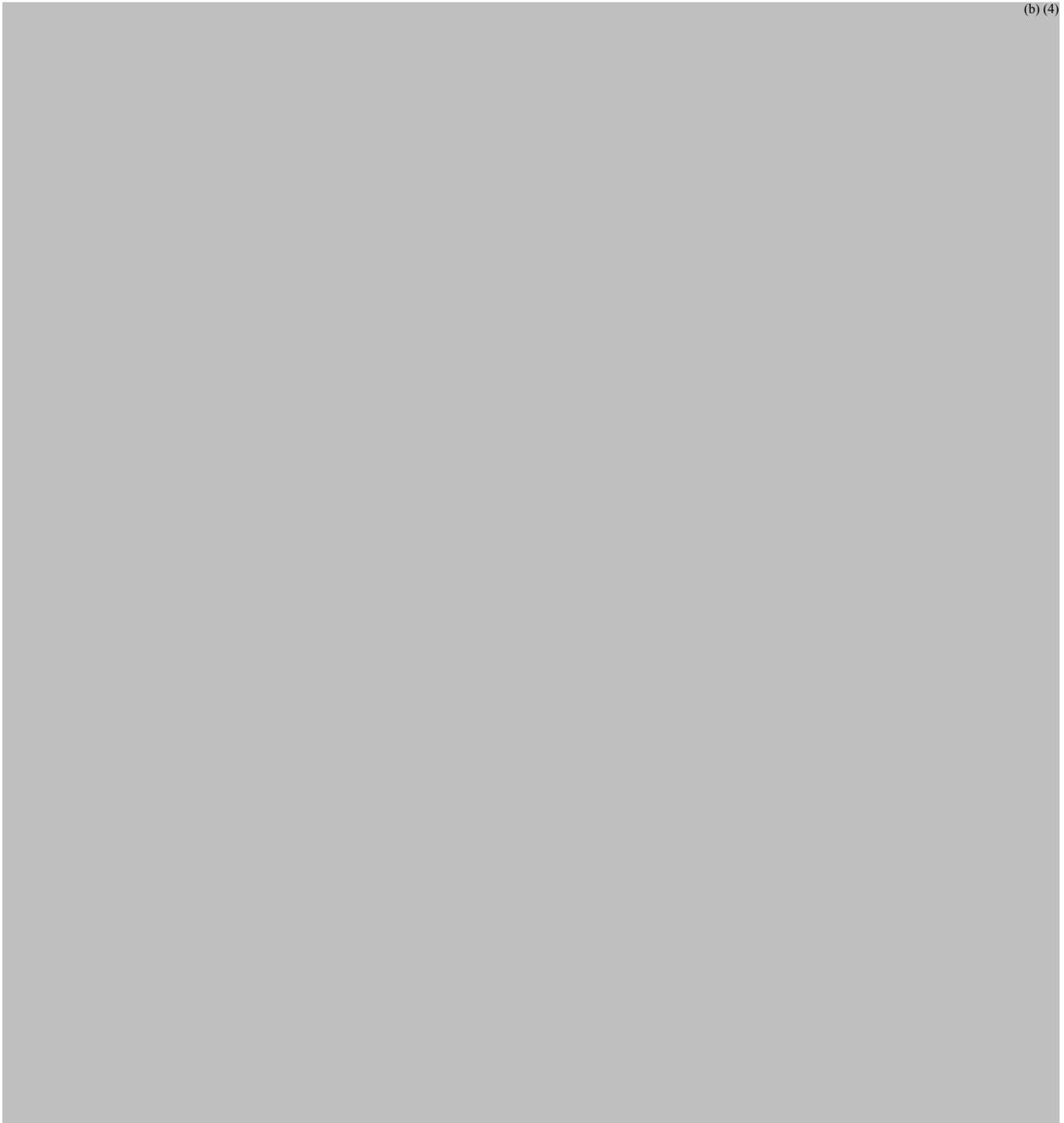
**Question 8:** Does the Agency agree that the Vertex (b) (4) control strategy is sufficient to satisfy GMP requirements and ensure product quality?

**Question 9:** Does the Agency agree with the (b) (4) testing strategy?

[Redacted] (b) (4)

***FDA Response to Question 8 and 9:*** Typically, adequacy of a control strategy is evaluated upon review and on an inspection. However, on review of the draft control strategy information provided within the meeting briefing package, we have the following comments for your consideration to facilitate implementation of (b) (4) and to assure drug product quality:

- 1) You have not provided adequate information on how you will control content variability and how you will determine the content uniformity of the batch manufactured via a continuous process:



(b) (4)

(b) (4)

**Question 3:** *Does the Agency agree with the proposed cross referencing strategy?*

**FDA Response to Question 3:** Yes, the Agency agrees. Please include a review guide clearly listing the referenced sections and location (submission number, date and page number) of the current information.

**Additional Comments:**

Please plan to provide a list of material attribute specifications for the incoming ivacaftor spray dried dispersions based on ranges acceptable for use in the current NDA. These should be incorporated in P.3.4.

**Meeting Discussion:**

(b) (4)

(b) (4)

**Notification Agency: Additional Manufacturing Site**

Vertex notified the Agency of the intention to include (b) (4) as an additional manufacturing site for supply chain risk mitigation. The impact on NDA submission is minor, and Vertex continues to plan on filing the CMC portion of the NDA in August, approximately 3 months ahead of the complete submission. (b) (4)

**EMA Post Meeting Comments**

EMA would like to notify Vertex that the (b) (4)

(b) (4)

**3.0 ISSUES REQUIRING FURTHER DISCUSSION**

None.

**4.0 ACTION ITEMS**

Action Item/Description	Owner	Due Date
N/A	N/A	N/A

**5.0 ATTACHMENTS AND HANDOUTS**

1. FDA Meeting Preliminary Comments
2. Vertex Presentation
3. FDA dissolution data analysis

## Attachment-1. FDA Meeting Preliminary Comments



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration  
Silver Spring MD 20993

IND 79521

### MEETING PRELIMINARY COMMENTS

Vertex Pharmaceuticals, Inc.  
Attention: Stephanie Krogmeier, Ph.D  
Director, Regulatory Affairs CMC  
130 Waverly Street  
Cambridge, MA 02139-4242

Dear Dr. Krogmeier:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for VX-809 (lumacaftor).

We also refer to your March 21, 2014 correspondence requesting a Type B Pre-NDA CMC Meeting to discuss the implementation of a drug product continuous manufacturing process, relatively new technology, on an accelerated breakthrough therapy timeline. The meeting package was received on April 7, 2014.

Our preliminary responses to your meeting questions are enclosed.

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

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

Sincerely,

*{See appended electronic signature page}*

Eric P. Duffy, Ph.D.  
Division Director  
Division of New Drug Quality Assessment III  
Office of New Drug Quality Assessment  
Center for Drug Evaluation and Research

ENCLOSURE:  
Preliminary Meeting Comments

Reference ID: 3506422

IND 79521  
Page 3

#### PRELIMINARY MEETING COMMENTS

**Meeting Type:** Type B, Pre-NDA CMC  
**Meeting Category:** IND

**Meeting Date and Time:** May 16, 2014, 9:00 AM to 11:00 AM (ET)  
**Meeting Location:** CDER WO Bldg 22, Room 1419

**Application Number:** IND 79521  
**Product Name:** Lumacaftor  
**Indication:** Cystic Fibrosis  
**Sponsor/Applicant Name:** Vertex Pharmaceuticals, Inc.

#### Introduction:

This material consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the meeting scheduled for May 16, 2014, in CDER WO Bldg 22, Room 1419 between Vertex Pharmaceuticals, Inc., FDA (U.S. Food and Drug Administration), and EMA (European Medicines Agency). We are sharing this material to promote a collaborative and successful discussion at the meeting. The meeting minutes will reflect agreements, important issues, and any action items discussed during the meeting and may not be identical to these preliminary comments following substantive discussion at the meeting. However, if these answers and comments are clear to you and you determine that further discussion is not required, you have the option of cancelling the meeting (contact the regulatory project manager (RPM)). If you choose to cancel the meeting, this document will represent the official record of the meeting. If you determine that discussion is needed for only some of the original questions, you have the option of reducing the agenda and/or changing the format of the meeting (e.g., from face to face to teleconference). It is important to remember that some meetings, particularly milestone meetings, can be valuable even if the pre-meeting communications are considered sufficient to answer the questions. Note that if there are any major changes to your development plan, the purpose of the meeting, or the questions based on our preliminary responses, we may not be prepared to discuss or reach agreement on such changes at the meeting although we will try to do so if possible. If any modifications to the development plan or additional questions for which you would like FDA/EMA feedback arise before the meeting, contact the RPM to discuss the possibility of including these items for discussion at the meeting.

#### 1.0 BACKGROUND

Lumacaftor (VX 809; IND 79,521) is being developed clinically in combination with ivacaftor (VX 770; IND 74,633). Ivacaftor is approved as 150 mg tablets for use as a monotherapy in the United States (NDA 203,188) under the tradename Kalydeco™. Lumacaftor in combination with ivacaftor is indicated for the treatment of Cystic Fibrosis

Reference ID: 3506422

IND 79521  
Page 4

(CF) in patients aged 12 years and older who are homozygous for the F508del mutation in the CF transmembrane conductance regulator (CFTR) gene.

Vertex Pharmaceuticals, Inc. has developed a continuous manufacturing process for lumacaftor/ivacaftor drug product under a Quality by Design (QbD) paradigm and is currently preparing the marketing application. The purpose of this Type B Pre-NDA CMC Meeting is to seek for Agency feedback on the following:

- CMC submission plan
- Stability and shelf life
- Dissolution specification
- Control of Physical form
- Vertex (b) (4) control strategy
- (b) (4) testing strategy

## 2.0 DISCUSSION

### 2.1 CMC Submission Plan

*Question 1: Does the Agency agree with filing the CMC portion of the NDA in August, approximately 3 months ahead of the complete submission?*

*FDA Response to Question 1: Yes, the agency agrees.*

*Additional Comment:*

(b) (4)

*Question 2: Does the Agency agree that amending Sections 3.2.P.8 and 2.3.P.8 in December with additional stability data following the complete submission (approximately 2 months into the review cycle) is acceptable and would not impact the PDUFA date?*

*FDA Response to Question 2: Yes, we agree. Since this is a breakthrough drug product, the addition of a new site (Vertex) with only three months of stability data is acceptable for review. However, (b) (4) data will be closely looked at and evaluated during the NDA review.*

Reference ID: 3506422

*Question 3: Does the Agency agree with the proposed cross referencing strategy?*

**FDA Response to Question 3:** Yes, the Agency agrees. Please include a review guide clearly listing the referenced sections and location (submission number, date and page number) of the current information.

**Additional Comments:**

Please plan to provide a list of material attribute specifications for the incoming ivacaftor spray dried dispersions based on ranges acceptable for use in the current NDA. These should be incorporated in P.3.4.

**2.2 Stability and Shelf-life Update**

*Question 4: Does the Agency agree with this approach to stability evaluation and the shelf-life prediction?*

**FDA Response to Question 4:** See response to Question 2 above.

*Question 5: Does the Agency agree that the proposed drug product plan supports a 24 month shelf life for material produced at the Vertex and (b) (4) manufacturing sites, assuming the data are supportive?*

**FDA Response to Question 5:** No, we do not agree; the determination of shelf-life is a review issue based upon the totality of the data and information provided in the submission.

**Additional Comments:**

In the NDA, please plan to explain a likely cause for the observed difference in (b) (4). In addition to the known (b) (4),

**2.3 Dissolution Specification**

*Question 6: Does the Agency agree with the proposed dissolution specification?*

**FDA Response to Question 6:** We noticed that you changed the proposed dissolution specification for lumacaftor from  $Q = \frac{(b)}{(4)}\%$  at 20 minutes to  $\frac{(b)}{(4)}$  minutes. The proposal has to be justified. There are three issues to be resolved before the appropriate dissolution specifications can be set.

(b) (4)

IND 79521  
Page 6



- 3) The applications of dissolution specifications: setting design space vs. regular quality control; (b) (4) release testing vs. stability testing; initial release vs. stability.

**Additional Comment**



**2.4 Control of Physical Form**

*Question 7: Does the Agency agree that in the form control (b) (4) method, a limit of (b) (4) % for the ivacaftor: (b) (4) is appropriate?*

*FDA Response to Question 7:* The approach is acceptable. However the acceptability of the limit will be a review issue.

**Additional Comments:**



**2.5 Vertex (b) (4) Control Strategy**

*Question 8: Does the Agency agree that the Vertex (b) (4) control strategy is sufficient to satisfy GMP requirements and ensure product quality?*

*FDA Response to Question 8:* Please see combined response for Question 8 and 9 below.

Reference ID: 3506422

2.6 (b) (4) Testing Strategy

*Question 9: Does the Agency agree with the real time release testing strategy?*

*FDA Response to Question 8 and 9:* Typically, adequacy of a control strategy is evaluated upon review and on an inspection. However, on review of the draft control strategy information provided within the meeting briefing package, we have the following comments for your consideration to facilitate implementation of (b) (4) and to assure drug product quality:

(b) (4)



Reference ID: 3506422

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

IND 79521  
Page 10

***Question 10:** Does the example method description and validation summary (Appendix 2) provide the appropriate level of detail for the NDA submission?*

***FDA Response to Question 10:** Adequacy of the NIR procedure would be evaluated during review and subsequent inspection. However, on evaluation of the method description information in Appendix 2, we have the following suggestions for your consideration:*

- 1) Provide details about external validation of the NIR calibration model. Compare the range of calibration and external validation data sets.
- 2) Data to show that the model is valid at the proposed commercial scale. Include a table comparing NIR predictions with HPLC. Validation information should also include sampling strategy for the reference analytical procedure.
- 3) Provide data to show estimation and rationale for the effective sample size (b) (4).
- 4) As regards model maintenance, it is understood that details would be maintained within the site's internal quality system. For review ease, include a summary in your NDA submission. Additionally, for regulatory communication of post approval changes of NIR procedure, determine reporting mechanism depending on the impact of the change.

**Additional Comments:**

- a. It is noted that as part of on-going performance verification and baseline correction the performance of the NIR spectrometer (b) (4).

(b) (4)

Reference ID: 3506422

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

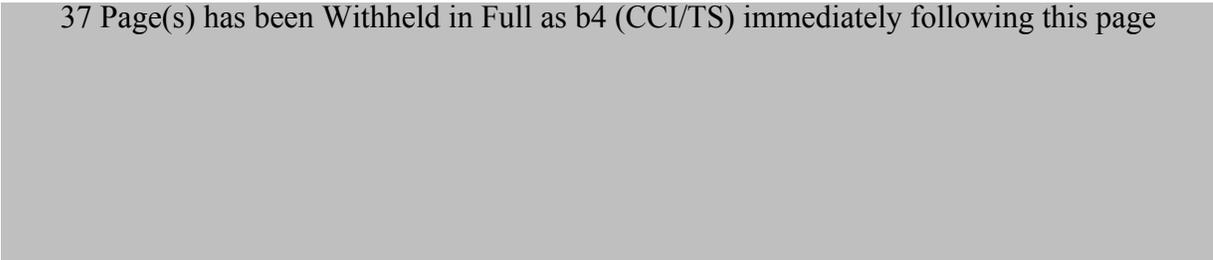
/s/  
-----

YOUBANG LIU  
05/14/2014

ERIC P DUFFY  
05/14/2014

Reference ID: 3506422

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



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

/s/  
-----

YOUBANG LIU  
06/13/2014

ERIC P DUFFY  
06/13/2014

**LATE-CYCLE COMMUNICATION**  
**DOCUMENTS**



NDA 206038

**LATE-CYCLE MEETING MINUTES**

Vertex Pharmaceuticals, Inc.  
50 Northern Avenue  
Boston, MA 02210

Attention: Rick Lilley  
Vice President, Regulatory Affairs

Dear Mr. Lilley:

Please refer to your New Drug Application (NDA) dated November 05, 2014, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Orkambi (lumacaftor/ivacaftor) oral tablet 200mg/125mg, (b) (4).

We also refer to the Late-Cycle Meeting (LCM) between representatives of your firm and the FDA on April 29, 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 Leila P. Hann, Senior Regulatory Project Manager at (301) 796-3367.

Sincerely,

*{See appended electronic signature page}*

Anthony Durmowicz, M.D.  
Cross Discipline Team Leader  
Division of Pulmonary, Allergy, and Rheumatology  
Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

Enclosure:  
Late Cycle Meeting Minutes



**FOOD AND DRUG ADMINISTRATION**  
CENTER FOR DRUG EVALUATION AND RESEARCH

---

**MEMORANDUM OF LATE-CYCLE MEETING MINUTES**

**Meeting Date and Time:** April 29, 2015, 12:00-01:30 PM, EST  
**Meeting Location:** FDA, White Oak 22, Room 1313

**Application Number:** NDA 206038  
**Product Name:** lumacaftor-ivacaftor (*Orkambi*)  
**Applicant Name:** Vertex Pharmaceuticals

**Meeting Chair:** Anthony Durmowicz, M.D.  
**Meeting Recorder:** Leila P. Hann

**FDA ATTENDEES – verify**

Mary Parks, Deputy Director, Office of Drug Evaluation II  
Badrul A. Chowdhury, M.D., Ph.D., Director, Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)  
Anthony Durmowicz, M.D., Clinical Team Leader, DPARP  
Robert Lim, M.D., Clinical Reviewer, DPARP  
Marcie Wood, Ph.D., Non-Clinical Supervisor, DPARP  
Timothy Robison, Ph.D., Non-Clinical Team Leader, DPARP  
Andrew Goodwin, Ph.D., Non-Clinical Reviewer, DPARP  
Jianmeng Chen, Ph.D., Clinical Pharmacology Reviewer, Division of Clinical Pharmacology II (DCPII)  
Anshu Marathe, Ph.D., Clinical Pharmacology Reviewer,  
David Petullo, Ph.D., Team Leader, Division of Biostatistics II (DBII)  
Lan Zeng, Ph.D., Biometrics Reviewer, DBII  
Craig Bertha, Ph.D.,  
Leila P. Hann, Regulatory Health Project Manager, DPARP  
Dipti Kalra, R.Ph., Safety Evaluator, Office of Safety Evaluation (OSE)  
Jasmine Gatti, M.D., OSE  
Kathy O'Connell, M.D., Ph.D., Rare Diseases Program

**EASTERN RESEARCH GROUP ATTENDEES**

(b) (4)

**APPLICANT ATTENDEES**

Jeffrey Chodakewitz M.D., Executive Vice President and Chief Medical Officer  
Rick Lilley Ph.D., Senior Vice President and Head of Global Regulatory Affairs  
Charlotte McKee M.D., Vice President and Head of Cystic Fibrosis Clinical Development  
Antoinette Paone M.B.A., Vice President, Global Regulatory Affairs  
Henry Seto M.D., Vice President, Global Patient Safety  
Dave Waltz M.D., Senior Director, Cystic Fibrosis Clinical Development

Graeme Smith Ph.D., Senior Director, Drug Safety Evaluation  
Fred Van Goor Ph.D., Principal Research Fellow  
Gemma Slade, Director, Global Regulatory Affairs  
Paul Panorchan Ph.D., Director, Clinical Pharmacology  
Michael P. Boyle, M.D., Vice President of Therapeutics Development, Cystic Fibrosis Foundation; Adjunct Professor of Medicine, Johns Hopkins University

## 1.0 BACKGROUND

NDA 206038 was submitted on November 05, 2014 for Orkambi (lumacaftor/ivacaftor).

Proposed indication(s): treatment of cystic fibrosis in patients 12yrs and older who are homozygous for *F508del* mutation

PDUFA goal date: July 05, 2014

FDA issued a Background Package in preparation for this meeting on April 17, 2015. Vertex submitted a power point presentation via email on April 28, 2015 and is attached below.

## 2.0 DISCUSSION

### 1. Introductory Comments – 5 minutes (RPM/CDTL)

Welcome, Introductions, Ground rules, Objectives of the meeting

**Discussion:** No discussion occurred.

### 2. Discussion of Substantive Review Issues – 20 minutes

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

Clinical

- The benefit lumacaftor/ivacaftor treatment over ivacaftor monotherapy

**Discussion:** The applicant requested clarification regarding the benefit:risk ratio of the combination product and the need for an Advisory Committee. The Division stated that based on the available clinical data, we cannot exclude that the combination offered no added clinical effect above ivacaftor alone. The Advisory Committee is being held to solicit input from non-conflicted parties.

Nonclinical

- Determination of the established pharmacologic class (EPC)

**Discussion:** The Division understands the term CFTR “(b) (4)” is widely used in the cystic fibrosis community. However, the term is potentially too broad given the criteria for

(b) (4) The Agency would welcome additional data from the applicant to support (b) (4) an EPC for lumacaftor.

3. Additional Applicant Data – 10 minutes (Applicant)

**Discussion:** No discussion occurred.

4. Information Requests – 5 minutes

Non-clinical

- Submit justification that supports the classification of lumacaftor (b) (4). Alternatively, submit an alternative EPC for lumacaftor for FDA consideration in accordance with the “Determining Established Pharmacologic Class” guidance noted above.

**Discussion:** See Discussion under agenda item 2.

5. Discussion of Upcoming Advisory Committee Meeting – 10 minutes

**Discussion:** The applicant expressed concern regarding Advisory Committee question 3. The concern was regarding the portion of the question asking for comment if an additional clinical trial should be conducted to compare the LUM/IVA FDC to ivacaftor alone. They were concerned as they perceived it as another voting question. The Agency clarified that that portion of the question was not meant as an additional voting question, but rather to elicit discussion.

6. Postmarketing Requirements/Postmarketing Commitments – 5 minutes

- 2-year carcinogenicity study with lumacaftor in rats

**Discussion:** No discussion occurred.

7. Review Plans – 5 minutes

- Review of responses to outstanding information requests
- Obtain feedback from Advisory Committee panel
- Completion of consults and tertiary reviews
- Completion of inspections
- Labeling discussions (as needed)

**Discussion:** No discussion occurred.

8. Wrap-up and Action Items – 5 minutes

**Discussion:** No discussion occurred.

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.

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

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

/s/  
-----

ANTHONY G DURMOWICZ  
05/29/2015



NDA 206038

**LATE CYCLE MEETING  
BACKGROUND PACKAGE**

Vertex Pharmaceuticals, Inc.  
50 Northern Avenue  
Boston, MA 02210

Attention: Rick Lilley  
Vice President, Regulatory Affairs

Dear Mr. Lilley:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Orkambi (lumacaftor/ivacaftor) oral tablet 200mg/125mg,

(b) (4).

We also refer to the Late-Cycle Meeting (LCM) scheduled for April 29, 2015. Attached is our background package, including our agenda, for this meeting.

If you have any questions, call Leila P. Hann, Senior Regulatory Project Manager, at (301) 796-3367.

Sincerely,

*{See appended electronic signature page}*

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

ENCLOSURE:  
Late-Cycle Meeting Background Package

## LATE-CYCLE MEETING BACKGROUND PACKAGE

**Meeting Date and Time:** April 29, 2015, 12:00-01:30 PM, EST  
**Meeting Location:** FDA, White Oak 22, Room 1313

**Application Number:** NDA 206038  
**Product Name:** lumacaftor-ivacaftor (*Orkambi*)  
**Indication:** treatment of cystic fibrosis in patients 12yrs and older who are homozygous for *F508del* mutation  
**Applicant Name:** Vertex Pharmaceuticals

### 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

No Discipline Review letters have been issued to date.

#### 2. Substantive Review Issues

The following substantive review issues have been identified to date:

##### Clinical

- As has been discussed previously with you, given the similar effect sizes observed in lumacaftor/ivacaftor studies (809-103 and 809-104) and ivacaftor monotherapy study 770-104, whether or not the proposed lumacaftor/ivacaftor combination provides an added benefit above ivacaftor alone continues to be a review issue.

### **Product Quality**

- Reports from manufacturing site inspections are pending.

### **Nonclinical**

Determination of the established pharmacologic class (EPC)

- Note that according to the Guidance for Industry and Review Staff: Labeling for Human Prescription Drug and Biological Products – Determining Established Pharmacologic Class for Use in the Highlights of Prescribing Information (October 2009), the EPC should indicate to health care professionals “what to expect from a drug and how it relates to other therapeutic options.” The EPC should be scientifically valid, clinically meaningful. It should be based on either the drug’s mechanism of action, physiologic effects, or chemical structure.

While acknowledging [REDACTED] (b) (4) based on review of the nonclinical and clinical data included in NDA 206038, our determination is that your proposal to classify lumacaftor [REDACTED] (b) (4) is not acceptable for the following reasons:

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

### **ADVISORY COMMITTEE MEETING**

**Date of AC meeting:** May 12, 2015

The Advisory Committee meeting briefing package will be sent under separate cover by the Division of Advisory Committee and Consultant Management on April 22, 2015.

**Potential questions and discussion topics for AC Meeting are listed below. Note that these may not represent the final questions for discussion.**

1. Discuss the efficacy data for LUM 400 mg/IVA 250 mg FDC twice daily in CF patients 12 years and older who are homozygous for the *F508del* mutation in the *CFTR* gene. Consider the following issues in the discussion: size of the treatment effect and contribution of lumacaftor in context to that for ivacaftor monotherapy.
2. Discuss the available efficacy data for ivacaftor monotherapy 150 mg twice daily in CF patients who are homozygous for the *F508del* mutation in the *CFTR* gene.
3. Do the data demonstrate that lumacaftor contributes to the clinical efficacy seen for the lumacaftor plus ivacaftor combination product in CF patients who are homozygous for the *F508del* mutation in the *CFTR* gene?

*Should a clinical study be conducted to compare the LUM/IVA combination to ivacaftor alone?*

4. Discuss the safety data for LUM 400 mg/IVA 250 mg FDC twice daily in CF patients 12 years and older who are homozygous for the *F508del* mutation in the *CFTR* gene.
5. Do the data support the safety of LUM 400 mg/IVA 250 mg FDC twice daily in CF patients 12 years and older who are homozygous for the *F508del* mutation in the *CFTR* gene.

*If not, what further data should be obtained?*

6. Do the efficacy and safety data support approval of the LUM 400 mg/IVA 250 mg fixed dose combination product twice daily in CF patients who are homozygous for the *F508del* mutation in the *CFTR* gene?

*If not, what further data should be obtained?*

We look forward to discussing our plans for the presentations of the data and issues for the upcoming AC meeting. Final questions for the Advisory Committee are expected to be posted two days prior to the meeting at this location:

<http://www.fda.gov/AdvisoryCommittees/Calendar/default.htm>

**REMS OR OTHER RISK MANAGEMENT ACTIONS**

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

## LCM AGENDA

1. Introductory Comments – 5 minutes (RPM/CDTL)  
Welcome, Introductions, Ground rules, Objectives of the meeting
2. Discussion of Substantive Review Issues – 20 minutes  
Each issue will be introduced by FDA and followed by a discussion.

### Clinical

- The benefit lumacaftor/ivacaftor treatment over ivacaftor monotherapy

### Nonclinical

- Determination of the established pharmacologic class (EPC)

3. Additional Applicant Data – 10 minutes (Applicant)
4. Information Requests – 5 minutes

### Non-clinical

- Submit justification that supports the classification of lumacaftor (b) (4)  
Alternatively, submit an alternative EPC for lumacaftor for FDA consideration in accordance with the “Determining Established Pharmacologic Class” guidance noted above.

5. Discussion of Upcoming Advisory Committee Meeting – 10 minutes
6. Postmarketing Requirements/Postmarketing Commitments – 5 minutes
  - 2-year carcinogenicity study with lumacaftor in rats
7. Review Plans – 5 minutes
  - Review of responses to outstanding information requests
  - Obtain feedback from Advisory Committee panel
  - Completion of consults and tertiary reviews
  - Completion of inspections
  - Labeling discussions (as needed)

8. Wrap-up and Action Items – 5 minutes

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

/s/  
-----

BADRUL A CHOWDHURY  
04/17/2015